NTNU
Norwegian University of
Science and Technology

CLINICAL STUDY REPORT

NTNU Intranasal Naloxone Trial

Double blinded, double dummy, randomised controlled trial of intranasal naloxone for pre- hospital use

Protocol Identification Number: NINA- 1
EudraCT Number: 2016-004072-22

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Clinical Study Report
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1 1. TITLE

NTNU Intranasal Naloxone Trial. Double blinded, double dummy, randomised controlled trial of intranasal naloxone for pre- hospital use (NINA-1)

2 2. SYNOPSIS

The following clinical study report is inspired by, but not strictly adherent ICH Topic E 3 Structure and Content of Clinical Study Reports.

The main publication from this trial is published in *Addiction(1)*.

Additional study documentation is available at:
Skulberg, Arne Kristian; Dale, Ola, 2020, "NTNU Intranasal Naloxone Trial (NINA-1) Study documents", https://doi.org/10.18710/ABRUWW, DataverseNO, V2

Aims
To measure and evaluate clinical response to nasal naloxone in opioid overdoses in the pre-hospital environment.

Design
Randomised, controlled, double-dummy, blinded, non-inferiority trial, and conducted at two centres.

Setting
Participants were included by ambulance staff in Oslo and Trondheim, Norway, and treated at the place where the overdose occurred.

Participants
Men and women age above 18 years with miosis, rate of respiration ≤8/min, and Glasgow Coma Score <12/15 were included. Informed consent was obtained through a deferred-consent procedure.

Intervention and comparator
A commercially available 1.4 mg/0.1 mL intranasal naloxone was compared with 0.8 mg/2 mL naloxone administered intramuscularly.

Measurements
The primary end-point was restoration of spontaneous respiration of ≥10 breaths/min within 10 minutes. Secondary outcomes included time to restoration of spontaneous respiration, recurrence of overdose within 12 hours and adverse events.

Findings
In total, 201 participants were analysed in the per-protocol population. Heroin was suspected in 196 cases. With 82% of the participants being men, 105 (97.2%) in the intramuscular group and 74 (79.6%) in the intranasal group returned to adequate spontaneous respiration within 10 minutes after one dose. The estimated risk difference was 17.5% (95% CI, 8.9%–26.1%) in favour of the intramuscular group. The risk of receiving additional naloxone was 19.4% (95% CI, 9.0%–29.7%) higher in the intranasal group. Adverse reactions were evenly distributed, except for drug withdrawal

reactions, where the estimated risk difference was 6.8% (95% CI, 0.2%–13%) in favour of the intranasal group in a post hoc analysis.

Conclusion
Intranasal naloxone (1.4 mg/0.1 mL) was less efficient than 0.8 mg intramuscular naloxone for return to spontaneous breathing within 10 minutes in overdose patients in the pre-hospital environment when compared head-to-head. Intranasal naloxone at 1.4 mg/0.1 mL restored breathing in 80% of participants after one dose and had few mild adverse reactions.

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4 4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AMIS	Akuttmedisinsk informasjonssystem (Acute Medical Information System). Computer program used by the emergency dispatch centres to document emergency 113 calls and allocate recourses. It registers patient details and times and recourses used. Equal in Oslo and Trondheim
ICH	Informed consent form
NoMA	Norwegian Medicine Agency
REC	Regional Ethics Committee
ISB,	Department of Circulation and Medical Imaging,
NTNU	Norwegian University of Science and Technology
GMP	Good manufacturing practice. This describes the minimum standard that a medicines manufacturer must meet in their production processes set by EMA.
EMA	European Medicines Agency
DnE	Den Norske Eterfabrikk
IMP	Investigational Medical Product
IV	Intravenous
IM	Intramuscular
IN	Intranasal
EMS	Emergency Medical Staff
AE	Adverse Event
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Event
DMSC	Data monitoring and Safety committee

5 ETHICS

5.1 Ethics Committee

The trial protocol and all amendments, including the patient information and the informed consent procedure were reviewed and approved in writing by Regional Committees for Medical and Health Research Ethics (REC) (2016/2000) after discussions that involved the The National Committee for Medical and Health Research Ethics (2017/44).

5.2 Ethical Conduct of the Study

This study was conducted in full accordance with the ICH guidelines for Good Clinical Practice (GCP) (CPMP/ICH/135/95), the Declaration of Helsinki of 1964, including the latest amendment of 2013 (Fortaleza, Brazil), and with local laws and regulations for Norway. The final study protocol and all amendments and the final version of the informed consent form (ICF) were approved by the Norwegian Medicine Agency (NoMA) and Regional Ethics Committee (REC) before enrolment of any subject into the study.

5.3 Patient Information and Consent

The NINA-1 trial had a differentiated model of oral consent after randomization and treatment with IMP, and a possibility to withdraw online or by telephone at any point.

The patient information consisted of two letters, one shorter for being handed out at the time of inclusion and a longer text available online. The aim of both letters were to provide information about the nature, purpose, possible risks and benefits of the trial. The investigator also explained to the patients that they were free to withdraw from it at any time. The Information incorporated wording that complies with relevant data protection and privacy legislation.

Both information letters are presented in Appendix 16.1.3.in the original Norwegian and a certified translation into English.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

6.1 Sponsor

Øystein Risa, Head of Department

Department of Circulation and Medical Imaging, Norwegian University of Science and Technology (ISB, NTNU)

For Protocol versions 1.0 Toril A Nagelhus Hernes were Head of Department of ISB

6.2 List of investigators

Name	Main affiliation	Role and time period
Arne Kristian Skulberg, MD, Ph.D.	• Department of Circulation and Medical Imaging, Faculty of medicine and health sciences, Norwegian University of Science and Technology, Trondheim, Norway • Department of Air ambulance Services, Division of Prehospital Services, Oslo University Hospital, Oslo; Norway	Investigator from 31st Oct 2016 until 1st May 2019 National coordinating investigator from 1st May 2019 until present
Ola Dale MD, Ph.D.	• Department of Circulation and Medical Imaging, Faculty of medicine and health sciences, Norwegian University of Science and Technology, Trondheim, Norway • Department of Research and Development, St. Olavs hospital, Trondheim University Hospital, Trondheim, Norway	National coordinating investigator from 31st Oct 2016 until 1st May 2019 Investigator from 1st May 2019 until present
Anne Cathrine Braarud, MD, Ph.D.	• Department of Ambulance Services, Division of Prehospital Services, Oslo University Hospital, Oslo; Norway	Principal investigator site Oslo University Hospital from 31st Oct 2016 until present
Jostein Dale, MD	• Clinic of Emergency Medicine and Prehospital Care, St. Olavs hospital, Trondheim University Hospital, Trondheim, Norway	Principal investigator site St. Olavs Hospital, Trondheim University Hospital from 31st December 2018 until present
Sindre Mellesmo MD	• Clinic of Emergency Medicine and Prehospital Care, St. Olavs hospital, Trondheim University Hospital, Trondheim, Norway	Principal investigator site St. Olavs Hospital, Trondheim University Hospital from 31st Oct 2016 until 31st December 2018
Ida Tylleskar MD, Ph.D.	• Department of Circulation and Medical Imaging, Faculty of medicine and health sciences, Norwegian University of Science and Technology, Trondheim, Norway	Investigator from 31st Oct 2016 until present

Fridtjof Heyerdahl, MD, Ph.D.	• Department of Air ambulance Services, Division of Prehospital Services, Oslo University Hospital, Oslo; Norway • Norwegian Air Ambulance Foundation, Oslo, Norway	Investigator from 31st Oct 2016 until present

6.3 List of local study coordinators

Tore Skålhegg, paramedic, Oslo University Hospital, Oslo; Norway

Jan Barstein, paramedic, St Olavs, Trondheim University Hospital, Trondheim, Norway

6.4 List of user participation board members

These were signatories to original ethics committee application 2016. The board has meet at different points during the study, with varying representation from different organizations within the field and user-representatives.

Torstein Bjordal, Member Foreningen Human Narkotikapolitikk

Heidi Hansen, RIO Rusmisbrukernes Interesseorganisasjon

Siri Getz Sollie LAR nett- Norge

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Fredrik Nillson RIO Rusmisbrukernes Interesseorganisasjon

Bettina Blakstad Landsforbundet Mot Stoffmisbruk

6.5 List of DSMC members

Per Farup, MD, PhD
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Akershus University Hospital

Øyvind Thomassen MD, PhD
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Marissa E. LeBlanc, PhD
Oslo Centre for Biostatistics and Epidemiology, Oslo University Hospital

6.6 Clinical Trial Unit

Not applicable

7 INTRODUCTION

7.1 Therapeutic Area and Disease Background

Opioid overdoses are a world-wide epidemic, affecting both users of illicit drugs and patients taking prescribed opioid painkillers. An estimated 69.000 people die worldwide annually (2), more than 250 of these in Norway (3). This is a high number- higher than deaths from road traffic accidents. The number of non-fatal opioid overdoses are manifold this. In Oslo and estimated 1000 code-red ambulance calls are made annually for this life-threatening condition. The majority of these patients live under dangerous and poor conditions and have numerous health problems.

Naloxone is an opioid antagonist, is a synthetic congener of oxymorphone. Naloxone is a competitive antagonist of μ, δ and κ-opioid receptors and it is most potent at the μ-receptor. It rapidly reverses the effect of morphine and other opioids, including pentazocine and nalorphine. Naloxone has not been shown to produce tolerance or to cause physical or psychological dependence. Naloxone has no abuse potential. Naloxone is on the WHO -list of essential drugs.

Those who inject heroin or other opioids are considered to have the highest risk for death from overdose. This project is a clinical, patient focused research project that concerns life-saving measures in such overdoses. It also aims to improve the safety of emergency medical staff and may contribute to public health measures for opioid users and those around them.

The indication for the administration of naloxone in the pre-hospital setting is complete or partial reversal of central nervous system and/ or respiratory depression, caused by natural or synthetic opioids. Without airway management, breathing support and naloxone the patient will go into cardiac arrest.

To resuscitate opioid overdoses, immediate treatment with a μ-opioid antagonist such as naloxone is vital. The antidote reverses the life-threatening respiratory depression rapidly with effect peak at 5 - 10 min (4, 5). and a half-life approximately 90 min with a duration of about 120 min (6).

Naloxone is traditionally licensed for intravenous, intramuscular and subcutaneous administration. Endotracheal and nebulized administration is described but these are rare and not relevant for routine clinical use (7-10). Naloxone is not suited for oral administration due to high first pass metabolism in the liver through glucuronidation. The drug is widely used in both pre-hospital medicine and inside hospitals. It has been available in various generic injectable forms for decades, most commonly in concentrations of 0.4 and 1.0 mg/mL and is considered being a low-cost drug (2).

The dose of naloxone needed to treat an opioid overdose varies. Titration, incremental increase in drug dosage to a level of optimal therapeutic effect, is the cornerstone of treatment with this antidote. It has a wide therapeutic window in that it is safe and non- toxic. However, in opioid dependent patents it can trigger acute withdrawal symptoms (11). Intramuscular administration gives less withdrawal than intravenous (IV) due to the lower maximum concentration and longer time to maximum concentration. The medical literature reflects this dosing range and titration principle with recommendations for starting dose ranging all the way between 0.02 and 2.0 mg IV (12). This

balancing act between too low and too high doses has implications both for local treatment protocols and also for new naloxone formulations or other treatment options to be investigated.

Naloxone is traditionally a prescription drug, although this is changing in some jurisdictions. As it has been available in injection-only formulations. Giving naloxone has required formal training and specialised equipment for parenteral administration. Over the last decades there has been a tendency of changing several medicines from being by prescription to over-the-counter drugs and put them directly in the hand of the patients or lay people. Examples such as adrenaline autoinjector, buccal midazolam and levonorgestrel for emergency contraception has proved safe and efficient (13-15). Naloxone is a safe antidote and is treatment for a potential life-threatening condition, there has been a considerable push to make it more available close to the overdoses. The aim has been a safe and simple form of administration through Take Home Naloxone (THN) programs. Take Home Naloxone has become widespread over the last 10 years, and is now part of large public health programs across the world, in contrast to the early resistance by policy makers and industry 20 years ago (16). A thorough review using the Bradford- Hill criteria for causation shows that THN programmes reduce overdose mortality among both programme participants and in the community, and have a low rate of adverse events (17). THN programs have used both naloxone for injection and for intranasal administration, with all IN naloxone use being “off-label”. Non-injection routes were early identified as a potential suitable alternative to injection of naloxone, as it requires little training and remove any risk of sharps-injury or exposure to blood. The intranasal route has been favoured due to its simplicity, but sublingual administration is also explored (18, 19).

The British Medical Journal mentioned distributing naloxone as a harm-reducing strategy in the early 1990´s, without discussing route of admnistration (20, 21). Activists and grass-root organizations in the addiction field started unofficial distribution of injectable naloxone at this time. In the next 20 years the field moved slowly, with several programs around the world handing out various naloxone formulation, commonly for IN use, to drug-users or others that may witness and opioid overdose. The “off- label” naloxone formulation had unknown absorption rate and bioavailability, onset and duration of action or type and frequency of adverse events. However, early studies indicated an effect (22). Such “off label” use is shown to increases adverse events and have implications for patent safety (23, 24). It also has ethical concerns exposing patients to undue risks (25). All the IN naloxone used were relatively low in concentration (1-2 mg/ mL) and realtively large in volume (1- 5 mL). Such large volumes are unsuitable for IN administration as the nose can only take 0,1-0,2 mL of fluid for systemic uptake (26). Intranasal naloxone needs to be high-concentration and low-volume to secure rapid enough uptake to reverse the respiratory depression and a duration long enough to reduce the risk of re-intoxication. Early studies indicated a very low bioavailability of IN naloxone, as little as 4% was reported in 2008 (27). However, the data was too weak to establish an authoritative nasal naloxone bioavailability. There was very little knowledge of the basic pharmacology of IN naloxone in opioid overdoses. Nevertheless, early epidemiological studies suggested a decrease in opioid mortality in areas IN naloxone were distributed to users (28) and open randomised trials of a dilute naloxone formulation in Australia showed it performed well compared to IM naloxone (22, 29). The WHO produced an expert rapport in 2014 (2) described key research questions in the field of naloxone treatment of opioid overdoses outside of hospital. They concluded: “People likely to witness an opioid overdose should have access to naloxone and be instructed in its administration…”. This recommendation was followed by calling for research regarding the optimal dosing and formulation

for the intranasal route of administration. The WHO concludes that this could be addressed by a pharmacokinetic study or tested in a randomised controlled trial. A recent review on the Pharmacokinetics and the Development of new non-injectable Naloxone is recently published(30).

The trial is related to the following MeSH terms:

Naloxone
Administration, Intranasal
Injections, Intramuscular
Narcotic Antagonists
Substance-Related Disorders
Drug Overdose
Chemically-Induced Disorders
Mental Disorders
Naloxone
Narcotic Antagonists
Physiological Effects of Drugs
Sensory System Agents
Peripheral Nervous System Agents

8 STUDY OBJECTIVES

The main objective of this study is to measure and evaluate clinical response to nasal naloxone in real opioid overdoses in the pre-hospital environment. By evaluating the core clinical parameter in opioid overdoses; the rate of respiration we want to compare the novel nasal formulation of naloxone with traditional IM treatment.

The primary endpoint:	1	The proportion of participants with a return of spontaneous respiration (≥10 breaths per minute) within 10 minutes of administrating the study drug
Secondary endpoints:	2.1	Time from administration of naloxone to respiration ≥10 breaths per minute
	2.2	Changes in oxygen saturation and level of consciousness measured by the Glasgow Coma Scale (GCS)
	2.3	Suitability of the spray device in a pre-hospital setting
	2.4	Overdose complications
	2.5	Opioid withdrawal reactions
	2.6	Adverse reactions to the naloxone formulation
	2.7	Need for rescue naloxone
	2.8	Rebound opioid intoxication within 12 hours of inclusion
	2.9	Reasons not to give rescue naloxone to non-responders
	2.10	Follow-up after care

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan-Description

The study is a phase III drugs trial of nasal naloxone. It is double blinded, double dummy, randomised control trial, multi- centre study, non- inferiority design.

Study Period	Estimated date of first patient enrolled: 1. January 2018 Anticipated recruitment period: 48 months Estimated date of last patient completed: 31. December 2021 **Actual dates for inclusions were:** Date of first patient in: 12th June 2018 Date of last patient in: 4th August 2020
Treatment Duration:	Approximately 40 minutes
Follow-up:	<u>Safety follow up:</u> Clinical status and adverse events will be recorded as described in the CRF. The duration of treatment is defined later, and the study ends when EMS is no longer in contact with the patient. The patient is therefore censored at this time, which will be recorded. Further treatment in the health service is not recorded, except it will be noted if the patient has received naloxone within 12 hours after inclusion. **Oslo and Trondheim:** The follow up will be identical in that included patients will be searched in AMIS at the local AMK. If they are found to have been in contact with the ambulance service within 24 hours after inclusion, the records of this second contact will be checked. If this includes the administration of naloxone in any form or dose, this will be recorded as described in the CRF. **Other follow up:** Through the user participation board (see section 16) and the information material handed out to participants and by other channels, the study team will be open to be contacted by included patients or other concerned parties. If contact is made regarding a specific study visit/ included patient, this will be recorded in the CRF in a free text field.

9.2 Discussion of Study Design, including the Choice of Control Groups

To assess the efficacy and safety of intranasal naloxone the a clinical trial in patients, rather that healthy volunteers are needed. The indication for the use of naloxone: immediate administration as emergency therapy for known or suspected opioid overdose as manifested by respiratory and/or central nervous system depression, in both non-medical and healthcare settings. Such patients will differ significantly from volunteers, both in terms of physiology; being hypoxic and hypercapnic and in terns of pharmacology as they will have concomitant opioid and possibly other drugs present. This forms the rationale for a trial in patients, even for medicines with approved marketing authorization.

Any superiority of intranasal naloxone lies in the route of administration itself; easy use with no risk of needle stick injury compared to injection. The efficacy of the medicine itself can therefore be examined in a non- inferiority design, with a suitable comparator.

As the indication for naloxone use in a life threatening emergency condition placebo studies would be unethical.

The most common route of naloxone administration in Norway is by the IM route, which I also advocated by the WHO(2). Regarding the dose to be administered there has been debates about the most suitable dose for start of titration, mainly between 0.4 mg and 0.8 mg naloxone hydrochloride. The 1.4 mg IMP in the current trial was tested against 0.8 mg in a volunteers study, and found to provide adequate systemic concentrations to treat opioid overdose compared with intramuscular 0.8 mg, without statistical difference on maximum plasma concentration, time to maximum plasma concentration or area under the curve.(31) Local data from the Oslo Ambulance Service showed that 0.8 mg IM was the most common dose to administer to overdoses in a severe clinical presentation.(32)

Based in this, and a decision to reduce the risk of non-response in the control group 0.8 mg naloxone IM was set as the comparator

9.3 Selection of Study Population

Participants were included among patients treated by the ambulance services at participating sites. For a patient to be assessed for inclusion at least to personnel with approved training as study works needed to present.

Inclusion were not limited to time of day, by location. The precise criteria are presented below.

9.3.1 Inclusion criteria

Inclusion criteria (all shall apply):

- Spontaneous respiration below or equal to 8 breaths per minute
- Glasgow Coma Scale score below 12/15
- Miosis
- Palpable carotid or radial arterial pulse

9.3.2 Exclusion criteria

Exclusion criteria (one criterion is enough for exclusion)

- Cardiac arrest
- Failure to assist ventilation using mask-bag technique
- Facial trauma, epistaxis or visible nasal blockage
- Iatrogenic opioid overdose
- Suspected participant below 18 years of age
- 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

9.3.3 Removal of patients from therapy or assessment

Not applicable

9.4 Treatments

9.4.1 Treatments administered

9.4.1.1 Single dose IN naloxone hydrochloride 1.4 mg:

This was administered as 100 µl 14.0 mg/ml (1.4 mg naloxone) by Aptar Unitdose device as one puff in one nostril.

9.4.1.2 Single dose IM naloxone hydrochloride 0.8 mg

This was administered as a 2 ml intramuscular injection (0.4 mg/ml naloxone hydrochloride) by hypodermic needle 21G or 23 G in the deltoid muscle.

9.4.1.3 Single dose IN Placebo

This was administered as 100 µl placebo nasal spray by Aptar Unitdose device as one puff in one nostril.

9.4.1.4 Single Dose IM Placebo

This was administered as a 2 ml intramuscular injection of sterile 9 mg/ml sodium chloride solution by hypodermic needle 21G or 23 G in the deltoid muscle.

9.4.2 Identity of investigational product and comparator

9.4.2.1 IMP: Nalokson DnE 14 mg/ml nasal spray:

The 14 mg/ ml IN formulation was manufactured by Sanivo Pharma, Oslo.

Naloxone hydrochloride was purchased directly from the manufacturer Siegfried AG in Switzerland. The active substance was manufactured in GMP approved facilities.
The nasal formulation contains the excipients polyvinyl pyrrolidone, glycerin, sodium edetate, benzalkonium chloride, citric acid monohydrate, sodium citrate dehydrate. Their concentrations are less than 1% (except for glycerin= 1.2%), varying from 0.02 to 0.28%.

An Investigational Medicinal Product Dossier was produced for this product.

Batch number used in the study: 18B069/1

9.4.2.2 IM Comparator:

Naloxone Hydrochloride Injection USP 4 mg/10 ml. Mylan Institutional LLC. Purchased and imported through Sanivo Pharma AS/Pharma Production AS Batch number 161204, 180401, 190301

9.4.2.3 IN Placebo

The IN placebo formulation was manufactured by Sanivo Pharma, Oslo. The nasal placebo spray contained no naloxone, but was otherwise similar to the IMP: Nalokson DnE 14 mg/ml nasal spray:

The nasal formulation contains the excipients polyvinyl pyrrolidone, glycerin, sodium edetate, benzalkonium chloride, citric acid monohydrate, sodium citrate dehydrate. Their concentrations are less than 1% (except for glycerin= 1.2%), varying from 0.02 to 0.28%.

An Investigational Medicinal Product Dossier was produced for this product.

Batch number used in the study 18B070

9.4.2.4 IM PLacebo

Sodium Chloride injection B. Braun 9 mg/ml x 10 ml, B. Braun. Purchased and imported through Hospital Pharmacy Trondheim

9.4.3 Method of assigning patients to treatment groups

Patient were assigned to treatment group by ambulance personnel at the scene. Each ambulance held one NINA-1 study kit at then time, and used the kit available at the dispatch that meet inclusion/ exclusion criteria. The kits were randomized to active IN or active IM. Kits were assigned to each ambulance in a random fashion, not by and particular order, and there were constantly between 6 and 10 ambulances with kits in circulation from the Oslo City Ambulance station. Which ambulance were sent at each dispatch were decided by the Emergency Dispatch Centre (AMK 113) by standard operational criteria and availability of resources, nit affected by the NINA-1 study.

9.4.4 Selection of doses in the study

9.4.4.1 Dose intramuscular naloxone comparator

The dosing of comparator, 0.8 mg IM, was based on the findings our examinations of dosing practises in Oslo (32) and from local treatment guidelines in the Oslo and St Olav's University Hospital ambulance services.

Our comparator is higher than the 0.4 mg IM often used in pharmacokinetic studies (33, 34), but well with international treatment guidelines and approved doing ranges from the various Summary of Product Characteristics of naloxone formulations.

The rationale for this increased comparator dose was participants safety, as our inclusion criteria selected patients in severe intoxication.

9.4.4.2 Dose intranasal naloxone

The dose of 1.4 mg/0.1 ml were chosen on the basis of a pharmacokinetic study in healthy volunteers(31). This study compared 1.4 mg IN to 0.8 mg IM naloxone and found Area under the curve from administration to last measured concentration (AUC0-last) for i.n. 1.4 mg and i.m. 0.8 mg were 2.62 ± 0.94 and 3.09 ± 0.64 h × ng/ml, respectively (P = 0.33). Maximum concentration (Cmax) was 2.36 ± 0.68 ng/ml for i.n. 1.4 mg and 3.73 ± 3.34 for i.m. 0.8 mg (P = 0.72). Two i.n. doses showed dose linearity and achieved a Cmax of 4.18 ± 1.53 ng/ml. Tmax was reached after 20.2 ± 9.4 minutes for i.n. 1.4 mg and 13.6 ± 15.4 minutes for i.m. 0.8 mg (P = 0.098). The absolute bioavailability for i.n. 1.4 mg was 0.49 (±0.24), while the relative i.n./i.m. bio- availability was 0.52 (±0.25). This trial concluded that Intranasal 1.4 mg naloxone provides adequate systemic concentrations to treat opioid overdose compared with intramuscular 0.8 mg, without statistical difference on maximum plasma concentration, time to maximum plasma concentration or area under the curve

9.4.5 Selection and timing of dose for each patient

All patients in this trial received the same doses of naloxone and placebo, as per randomization list.

The IMP was only administered once

The timing of the dosing were minutes after ambulance crew arrived at the scene and established first emergency response with bag/ mask ventilation, assessing the patient for inclusion/ exclusion criteria and preparing the administration by opening a kit, preparing the IM syringe and injection site. The spray/ injection should be administered simultaneously, or within30 seconds of each other with nasal spray was always administered first.

9.4.6 Blinding

Blinding refers to the concealment of group allocation in a clinical research study, it is impossible to blind study personnel to whether they give an injection or a nasal spray, and to reduce bias we therefor planned a "double dummy design". This means that after inclusion patients was given both a nasal spray and an intramuscular injection at the same time, one of these held naloxone and the other an inactive substance. This ensured that all patient receive naloxone- either by IN or the IM route.

The placebo IM and active IM fluid came in 10 mL glass vials, and was covered by the labels described in the protocol The vials were commercially available products, not specially designed for this trial and are therefore not 100 % identical. They differed in the colour of their plastic caps.

The naloxone product form Mylan is not available on the Norwegian market, and is unknown to ambulance staff in Norway. The sodium chloride bottle is available in Norway, but not used in the ambulance service today as they use plastic vials or bottles for their pre- hospital sodium chloride solution.

Unintentional unblinding was found to be unlikely as:
- the vials have their labels covered with the trial labelling described
- the labels used are light impermeable. To un-blind the individual vials study workers needed to forcibly remove these labels.
- Study workers have no opportunity to study the vials systematically. They never saw the vials together and directly compare them, neither in training nor during inclusion of participants.
- The study kits was be sealed and should only be opened in the actual treatment situation, which is during emergency treatment for overdose. Kits are to be returned immediately after completion of the study. This means that study workers will be busy treating the patients, including patients in the study and recording data.
- 318 study workers was recruited and trained in the two study centres, and each study worker was unlikely to include more than a few participants to the trial. The period between each time a study worker included a patient will in most cases be considerable, thus decreasing the risk of bias by remembering or forming an opinion of the contents in each vial.
- The fact that the EMS were not familiar with these vials on beforehand, and that the existing EMS naloxone and sodium chloride comes in different vials or ampoules.
- Another vial will be used in the training kits, so the study workers will not be exposed to the vials during the training.

9.4.7 Prior and concomitant therapy

No prior therapy were described in this trial

No concomitant medication were routinely administered by study personnel as part of this protocol. After administration of IMP ambulance personnel administered drugs in a few cases:

According to protocol ambulance staff may administer other drugs than naloxone to patients with suspected opioid overdoses, if medically indicated. Drugs such as for example nebulizes salbutamol cpuld be given as per local guidelines. All concomitant drugs administered by the EMS personnel during the treatment period was recorded in the study protocol.

The following grugs were administered within the study period of the NINA-1 trial

Site name	Subject Id	Medication name	ATC code	Dose per administration	Dose units	Route of administration
St. Olav's University Hospital	02-010	Flumazenil	V03AB25	0.2	milligram (mg)	intravenous (iv)
St. Olav's University Hospital	02-017	Midazolam	N05CD08	10	milligram (mg)	intrabuccal
Oslo University Hospital	01-619	Morphine	N02AA01	2	milligram (mg)	intravenous (iv)
Oslo University Hospital	01-677	Diazepam	N05BA01	5	milligram (mg)	intravenous (iv)
St. Olav's University Hospital	02-095	Flumazenil	V03AB25	0.3	milligram (mg)	intravenous (iv)

9.4.8 Treatment compliance

Not applicable, study personnel will administer all study drugs in the acute setting. Study drugs were administered only once.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and safety measurements assessed

Level	Outcome	Timeframe	Type
Primary	return of spontaneous respiration	During visit	Dichotomous
Secondary	Changes in Glasgow Coma Scale (GCS) in patients treated with study medicine for opioid overdose.	During visit	Continuous
	Changes in oxygen saturation (SpO2) in patients treated with study medicine for opioid overdose.	During visit	Continuous
	Time from administration of naloxone to respiration above or equal to 10 breaths per minute.	During visit	Time-to-event
	Opioid withdrawal reaction to naloxone reversal	During visit	Dichotomous
	Suitability of spray device in pre-hospital setting	During visit	Dichotomous
	Adverse reactions to naloxone formulation	During visit	
	Need for rescue naloxone	During visit	Dichotomous
	Recurrence of opioid overdose/ need for further pre-hospital naloxone within 12 hours of inclusion	12 hours	Dichotomous
	Follow up after care	During visit	Dichotomous

Safety variables measured were:

- Adverse reactions as described in protocol
- Overdose complications
- Opioid withdrawal reactions
- Receiving rescue naloxone

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9.5.2 Appropriateness of Measurements

Outcome	Appropriateness
Return of spontaneous respiration	The main symptom of opioid intoxication is a reduction of the rate of respiration. Together with miosis and reduced level of consciousness this forms the hallmarks of opioid agonism. The reduced rate of respiration leads to hypercapnia and hypoxia, leading to cardiac arrest and death. The measurement of rate of respiration is clinical and highly relevant both as a cardinal sign of opioid use and for clinicians in the discission weather or not to suspect opioid use as cause of acute illness. return of spontaneous respiration in our trial is defined as above or equal to 10 breaths per minute within 10 minutes of naloxone administration the counting of number of breath is the only appropriate measurement 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 minutes, the number of breaths were counted for 60 seconds. For awake, ambulatory patients, or patients speaking inn full sentences, the exact respiratory rate may be hard to count, and these will be classified as responders.
Changes in Glasgow Coma Scale (GCS) in patients treated with study medicine for opioid overdose.	Glasgow Coma Scale (GCS) is a well known measurement for level of consciousness with 3/15 being the lowest and 15/15 being fully awake. It is widely used by all pre- hospital practitioners and useful as a measurement dure to staffs familiarity with the scale.
Changes in oxygen saturation (SpO2) in patients treated with study medicine for opioid overdose.	SpO2 = oxygen saturation as measured by light absorption through a non-invasive pulse oximeter. It is the fraction of oxygen-saturated haemoglobin relative to total haemoglobin (unsaturated + saturated) in the blood. SpO2 is given as a percentage. It is a standard measurement of level of oxygenation in the prehospital field
Time from administration of naloxone to respiration above or equal to 10 breaths per minute.	This was measured using the provided stop watch. In emergency medicine and especially acute opioid intoxication the time from antidote administration to clinical effect is important to ensure rapid restoration of vital functions.
Opioid withdrawal reaction to naloxone reversal	Opioid withdrawal is a feared complication to naloxone administration in patients with tolerance to opioids. It is the main adverse reaction to naloxone, and therefore of special interest. We defined this as Adverse reactions defined as opioid withdrawal syndromes (MedDra lowest level term (LLT) 10030882). It includes responses subjectively described as abstinence, agitation or aggression.

	Nausea and vomiting was not included in the withdrawal definition as they may be separate adverse events
Suitability of spray device in pre-hospital setting	Study workers was asked an open ended question in the CRF if they found the device suitable for IN administration. This is important for implementation of any use of intranasal naloxone
Adverse reactions to naloxone formulation	Adverse reactions is a core measurement in all clinical drugs trial. In our study an adverse event deemed to have a certain, probable/likely or possible causal relationship to the IMP will be classified as an adverse reaction. The Causal relationship of the event to the study medication will be assessed later by the use of the WHO-UMC system for standardised case causality assessment(35).
Need for rescue naloxone	Naloxone is a drug of titration. Repeated dosing are therefor expected and all doses given in addition to study medicine of interest to evaluate the efficacy of the first dose.
Recurrence of opioid overdose/ need for further pre-hospital naloxone within 12 hours of inclusion	As naloxone has a shorter half life than many opioids there is a fear that the antagonistic effects wear off and an intoxication recurs, without additional administration of opioid agonist. To assess the efficacy of the nasal spray it was important to record any repeated need for naloxone within 12 hours. The time of 12 hours was chosen as any repeated naloxone beyond this time was likely to be because of repeated opioid use rather than effect of the dose causing the inclusion in the trial By looking up included patients in AMIS we will be able to record any use of pre-hospital naloxone within 12 hours after inclusion, and compare this between the groups. There may be a considerable time lag (days or weeks) between an actual occurrence of a recurrence and this coming to the attention of the study team. Recurrence is not defined as an Adverse Event of IMP. Its occurrence is after end of treatment period. It is the only information that will be recorded after the end of treatment period. Information recorded was: Participant details. Time and place of recurrence, dose and form of naloxone given, clinical response to naloxone (respiratory rate and GCS) and follow up.
Follow up after care	After pre- hospital treatment with naloxone several follow up options are available to patients. This ranges from hospital admission for patients without adequate clinical response to being left on sdite without further medical follow up. In this trial defined as the level of health care to which the patient is transferred after treatment by ambulance services, or if left at the scene. The variable contains the following categories: 1. Left at the scene of treatment. This represent patients who are not transported to further care or follow up after treatment with study drug. For ambulance personnel to choose this option patients should be physiologically normal with adequate level of consciousness,

	respiration and circulation, and to be fully competent to make informed decisions of their own. 2. Handed over to primary care. In Norway defined as general practitioners and Accident and Emergency Outpatient Clinic (Kommunal legevakt). For the sake of level of medical care, it also includes specialized in- patient addiction services that accept patient referred by ambulance personnel, such as Rusakutten-Aker in Oslo. These facilities accept patients without need for advanced emergency medical follow up. 3. Handed over to hospital. Patient is transferred to tertiary care, defined as hospitals with facilities for advanced medical investigations and treatment. 4. Others. Some patients are transferred to places not fitting any of these categories, such as drug-user shelters.

9.5.3 Primary efficacy variable(s)

- The primary efficacy variable measured was rate of respiration measured as number of breaths per minute.

9.5.4 Drug concentration measurements

Not applicable

9.6 Data Quality Assurance

Data was collected from ambulance records, the dispatch center callout system and study-specific case report forms. Data was manually entered into an electronic data management system (Viedoc, Uppsala, Sweden) from paper-based charts by trained study assistants and investigators. A risk-based data monitoring procedure was in place. This allowed for clinical trial monitoring by the Clinical Trials Unit of Oslo University Hospital fulfilling regulatory requirements and ICH–GCP guidelines, without the need for 100% source data verification of the patient data. The procedure involved performing a risk analysis to identify high-risk elements of the study concerning patient safety and primary endpoint data.

All study workers went through a comprehensive teaching and certification program to ensure intervention being performed in accordance to protocol and data collected in CRF in a uniform manner.

A Data Monitoring and Safety committee had oversight over the trial.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and analytical plans

There were no changes to the planned and performed analyses, and only one post- hoc analysis performed.

The null hypothesis is that the proportion of responders given intranasal naloxone is smaller by the 0.15 non-inferiority margin than given intramuscular naloxone

$$H_0: p_{IM} - p_{IN} >$$

and the alternative hypothesis is that the proportion of responders given intranasal naloxone is not smaller by the 0.15 non-inferiority margin compared to intramuscular naloxone

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

From this it follows that the upper bound of the 95% confidence interval of the difference between the groups shall not exceed 0.15 in order to reject H0 and confirm Ha

Decision Rule
This trial is designed to address a single primary outcome. Non-inferiority is claimed if the primary null hypothesis is rejected on the significance level (alpha) of 0.025 (one-sided). That is, if the upper limit of the 95% two-sided confidence interval for the treatment difference is less than 15%.

9.7.1.1 Subgroups

Subgroups were planned in the protocol:	Subgroups planned in statistical analysis plan and performed in final analysis	Comment
Place of treatment (differences between Sprøyterommet, public places indoor and outdoor, private homes and treatment facilities)	Place of treatment. Dichotomous variable: Safe injection facility (Sprøyterommet) or not.	
Different follow up: The various follow up after treatment will be compared between the groups		
Time of treatment (times during the day, day of the week and month/ season)		
Gender	Sex.	

	Dichotomous variable: Male/Female.	
Age	Age group. Dichotomous variable: Divided into two groups, below and above the mean age.	
Divided into those experiencing recurrence and those who do not experience recurrence		
Type of opioid consumed based on available information	Type of opioid consumed Dichotomous variable: Was benzodiasepines/GHB/Alcohol suspected as one of drugs taken by patient (yes/no)	
If treated with take-home naloxone prior to arrival of EMS		
Individuals included more than once during the study period if any		
Differences between study centres.		
	Baseline GCS Dichotomous variable (≤ 3/15, >3/15)	
	Baseline respiratory rate. Dichotomous variable (=0, >0 breaths per minute)	

9.7.1.2 Planned monitoring

The main statistical analysis was performed when all patients are included and after database lock. A feasibility analysis was be performed after 20 included participants and the results wasmade available to the DMSC. A similar analysis for the DMSC was made after 100 participants and included

- Summary of patient enrolment (number per site, age, gender and follow-up)
- Safety profile: adverse events, serious adverse events and SUSAR reported
- Interventions: The use of recue naloxone
- Follow up: The follow up after study treatment (Hospitalization, Left at the scene etc)
- Recurrence: The number of participants with recurring overdose within 12 hours after inclusion.
- Mortality: Any deaths by a trial participant during the duration of study time.

No interim analysis of the primary end-point was performed.

9.7.1.3 Data monitoring and Safety committee

An independent data monitoring and safety committee was in place. The members were :

Per Farup, MD, PhD, Faculty of Medicine, NTNU

Jørgen Dahlberg, MD, PhD, Akershus University Hospital

Øyvind Thomassen, MD, PhD, Dept. Emergency Medicine/ KSK Haukeland University Hospital

Marissa E. LeBlanc, PhD, Oslo Centre for Biostatistics and Epidemiology, Oslo University Hospital

The charter outline the work of the DMSC in included in appendix 16.1.1

The full statistical analysis plan is provided in Appendix 16.1.9

9.7.2 Determination of sample size

The aim was to investigate if administration of 1.4 mg intranasal naloxone hydrochloride was non-inferior to intramuscular administration of 0.8 mg naloxone hydrochloride. The primary endpoint was the proportion of participants with return of spontaneous respiration (≥10 breaths per minute) within 10 minutes of naloxone administration. It was expected that 88% of the patients on IM treatment (standard treatment) will be responders according to this criterion, and an equivalent dose intranasal administration is expected to result in a similar responder rate. The non-inferiority margin was set to Δ=15%.

A total of 200 cases was calculated to be needed to demonstrate that intranasal naloxone was non-inferior to intramuscular administration, assuming a two-sided significance level of 5% and a power of 90%.

9.7.3 Changes in the Conduct of the Study or Planned Analyses

- There were no changes to the planned analysis presented in the Statistical analysis plan.
- There was one post- hoc analysis estimating the risk difference of opioid withdrawal in the safety set.
- Protocol amendments and changes to the conduct of the study are presented below

Protocol version and date	Amendment/ Change
v. 1.0 31st Oct 2016	- Original protocol submission
v. 2.0 4th Oct 2017	- Change of producers of comparator active/placebo - Update on pharmacokinetic data in background section - Specifications regarding double dummy design and risk of unintentional unblinding - Changes to consent procedure in accordance with approval from NEC
v. 3.0 9th Jan 2018	- Adding prison as exclusion criterium *Please note this protocol version was current at first patient inclusion.*
v. 3.1 1st May 2019	- Change national coordinating investigator from Ola Dale to Arne Skulberg - Change PI Trondheim from Sindre Mellsemo to Jostein Dale - Change study statistician from Øyvind Salvensen to Morten Valberg - Updated contact information to CI, PI and others. - Align end-date to 31. Dec 2021 between protocol, REC approval and trial registrations
v. 3.2 2nd Sept 2019	- Adding 12.9 Safety reporting from participants with withdrawn consent
v 3.3 6th Mar 2020	- Change inclusion criteria <8 breaths per minutes to ≤8 breaths per minutes - Further specification relating to 12.9

10 STUDY PATIENTS

10.1 Disposition of Patients

Flow Charts

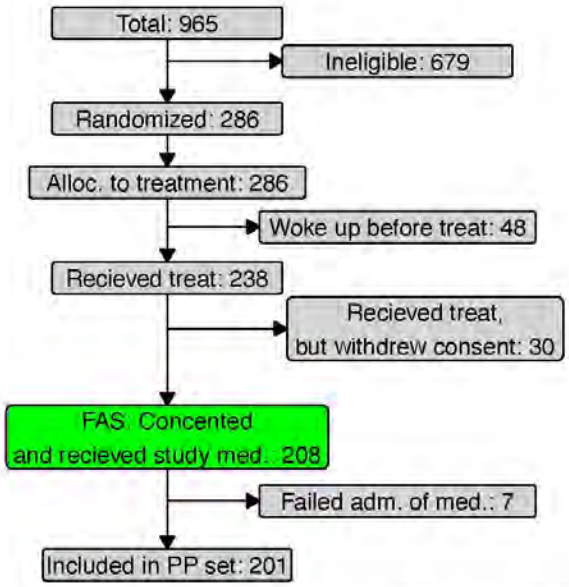

Figure 1: Study flow chart. Abbreviation: FAS, Full analysis set; PP, per protocol. NOTE: The numbers given are the number of overdoses, not the number of individuals.

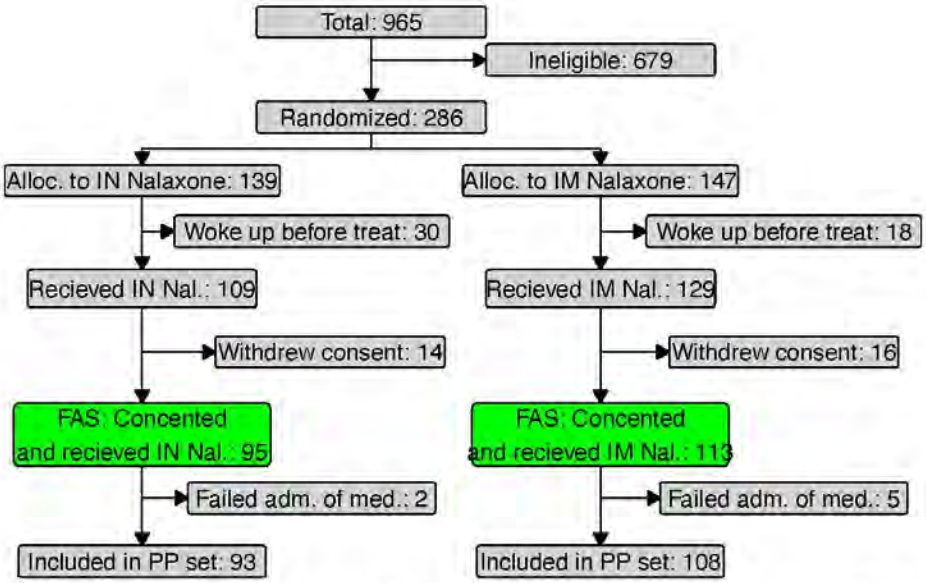

Figure 2: Study flow chart. Abbreviations: IN, intranasal; IM, Intramuscular; FAS, Full analysis set; PP, Per protocol. NOTE: The numbers given are the number of overdoses, not the number of individuals.

Oslo only

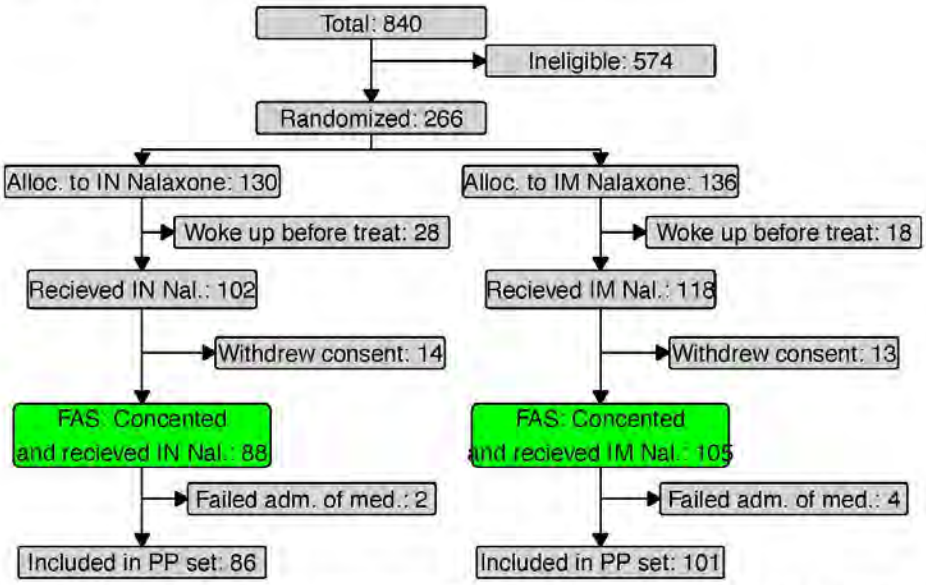

Figure 3: Study flow chart for Oslo. Abbreviations: IN, intranasal; IM, Intramuscular; FAS, Full analysis set; PP, Per protocol. NOTE: The numbers given are the number of overdoses, not the number of individuals.

Trondheim only

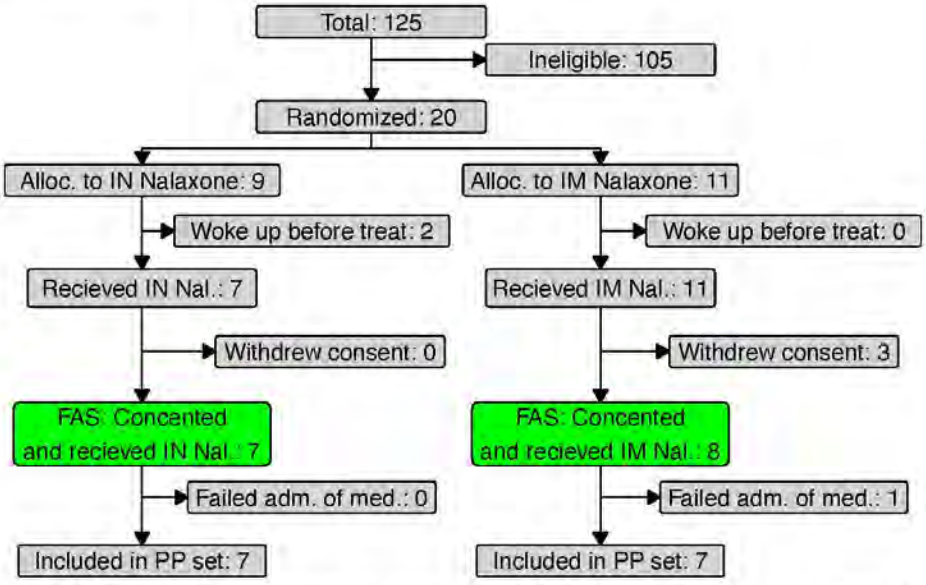

Figure 4: Study flow chart for Trondheim. Abbreviations: IN, intranasal; IM, Intramuscular; FAS, Full analysis set; PP, Per protocol. NOTE: The numbers given are the number of overdoses, not the number of individuals.

10.2 Protocol Deviations

SubjectId	SiteName	PDCAT	PDCATOTH	PDDESC
02-001	St Olav	Study procedure		Study workers tried to contact study team via study phone /OSlo AMK; were not passed on. Note fo file central level registered. See CTU admin NTF 005
01-018	OUH	Study procedure		Only 1 ml IM study drug administered
01-048	OUH	Selection criteria		RR 8/min. Patient could have been included based in this criteria after protocol version 3.3.
01-048	OUH	Selection criteria		GCS 12/15. Patient excluded as GCS should be below 12 to be included. This is a major deviation.
01-056	OUH	Study procedure		Only given 1 mL IM IMP
01-063	OUH	Study procedure		Given IM study medicine, but IN sprayed in the air by accident from kit 126. Treated with "normal" naloxone with good clinical response. Not asked for consent, despite given study medicine. Not AE reported. Registered in VieDoc as not consented. Study workers have not informed properly, despite patients being competent for oral consent as they have not given nasal IMP. This should have been done, but can not include in database without consent in patient with consent competency
01-068	OUH	Study procedure		IM and IN in different order, but within time
01-069	OUH	Selection criteria		Resp. frequency =8
01-136	OUH	AE/SAE/SUSAR reporting		Under AE says ? under hypothermia. EMS have made no mention in chart, or any actions against any hypothermia. Patient left at scene. Deemed not relevant and uncertain information.
01-136	OUH	Other	Database does not cover observation time interval	Chart har two clinical observation within 10 minutes, one at 18.07 and one at 18.08. As the database does not adequately cater for this, and they are very close in time I have recorded the last of the two (18.08) as these are the variables that leads to the patient being discharged at the scene.
01-137	OUH	Other	database response within 10 minutes	Two observation within 10 minutes, last (13.23) entered into database
01-200	OUH	AE/SAE/SUSAR reporting		AE form filled out by mistake. Patient is a non responder.
01-221	OUH	Selection criteria		3M freeze watch indicated kit exposed to frost prior to IMP, Study workers did a mistake and proceeded with inclusion
01-249	OUH	Other	Unable to connect kit to specific patient. IMP not administered due to freeze watch release	Unsure which patient kit opened in connection to
01-274	OUH	Study procedure		Given too little IM IMP
01-281	OUH	Study procedure		IM given before IN, but within 30 seconds. Discussed with DMC, minor deviation, should be included in Per protocol set
01-281	OUH	Study procedure		stoppeklokke fungerte ikke, ambulansepersonell brukte privat klokke
01-285	OUH	Study procedure		Longer than 30 seconds between IN spray and IM injection
01-288	OUH	Study procedure		Study drug administered despite freeze watch being activated. Information from Rune Wie confirms ambulance has been exposed to frost
01-308	OUH	Study procedure		patient woke up during treatment, only admnistered IMP IN, not intramuscular injection given. APtient woku up, and did not consent to use of data in trial. registered in anonymous safety set
01-336	OUH	Concent procedure		Not willing to receive written in formation, but gave oral consent. Discussed in study team and DMC, minor deviation, included in Per protocol set
01-337	OUH	Concent procedure		Included by staff at ambulance 255 (approved study workers), but after treatment transported to hospital by staff at 257 (not approved study workers). This meant that any questions medical team at Diakonhjemmet may have had could not be answered by EMS.
01-344	OUH	Concent procedure		Patient included with only one approved study worker. Case otherwise conducted due to protocol. Patient have given informed consent.
01-380	OUH	AE/SAE/SUSAR reporting		Paper CRF not fully filled inn in AE section, but ambulance journal does not report or indikcate AE, patient allowed to leave the scene.
01-592	OUH	Selection criteria		included despite kit being exposed to frost.
01-600	OUH	Study procedure		IM injection given in femoral muscle. This because he was wearing a lot of clothes and the deltoid muscle was hard to access
01-610	OUH	Study procedure		Not been able to trace which ambulance mission kit 300 was opened at. Nasal spray not activated. IM vial holds 8 mL (2 mL aspirated) Presumed not to be administered patient
01-617	OUH	Concent procedure		Participant not given information about inclusion. We have tried to call him at 93680417 5th Des 2019 with no answer. We will leave infomation in his file at the Safe Injection Facility and check that he has received info during the next weeks.
01-617	OUH	Concent procedure		Please see attached email and previous note to file regarding participant 01-617. We are confident he has received information about inclusion, and we will be included in the database. If he contacts us at a later point for withdrawal normal procedures will be followed.
01-649	OUH	Concent procedure		Patient not engaged in meaningful conversation with study crew, and ability consent must be questioned. He receive information and is given the opportunity to withdraw. He is included several times, and has never refused.
01-675	OUH	Study procedure		Comparator study medicine administered IV not IM.
01-675	OUH	Concent procedure		Patient not informed about inclusion by study workers, not given a chance to consent or not. Letter with study information sent to address and attempted to call by telephone, but no reply. We assume "non- consent" and include in anonymous safety set.
01-676	OUH	Concent procedure		Patient admitted to hospital, not given oral or written information regarding inclusion in trial
02-094	St Olav	Study procedure		period bweteen IN and IM admnistration is 45 seconds, 15 seconds longer than the time described in the protcol. This deviation had been discussed in the study team, and found to be minor and allow population assignment to "per protocol population"
02-094	St Olav	Study procedure		45 seconds between IN and IM
01-837	OUH	Concent procedure		Patient not informed orally and not given written information. Hence not being able to consent/ withdraw the patient is included in the anonymous dataset.

SubjectId	SiteName	PDCLAS	PDRISK	PDREOTH	PDCAPA
02-001	St Olav	Major	Patient safety		See CTU admin NTF 005
01-018	OUH	Minor	Scientific/data integrity		Increase training
01-048	OUH	Minor	Scientific/data integrity		No
01-048	OUH	Major	Scientific/data integrity		Teaching of study workers
01-056	OUH	Minor	Scientific/data integrity		teaching
01-063	OUH	Major	Scientific/data integrity		Informed study works about consent in all patient receiving any study drug.
01-068	OUH	Minor	Scientific/data integrity		Non
01-069	OUH	Major	Scientific/data integrity		Not included in PP analysis (subject to review with DMSC)
01-136	OUH	Minor	Other	No risk	Non taken
01-136	OUH	Minor	Other	Database	Non
01-137	OUH	Minor	Other	database	Non
01-200	OUH	Minor	Other	SAE form filled in without and AE bein present	Admitted to hospital - OUS-U
01-221	OUH	Major	Scientific/data integrity		Re education of stud workers in question and email to all stud workers nation wide reminding them of the frost indicator and inclusion criteria
01-249	OUH	Major	Other	Non	Non
01-274	OUH	Minor	Scientific/data integrity		Teaching
01-281	OUH	Minor	Scientific/data integrity		Non
01-281	OUH	Minor	Scientific/data integrity		ingen
01-285	OUH	Minor	Scientific/data integrity		Non
01-288	OUH	Major	Scientific/data integrity		<renew teaching regarding freeze watch
01-308	OUH	Major	Scientific/data integrity		teaching study staff to prepare injection site prior to administration of spray
01-336	OUH	Minor	Patients rights and welfare		Non
01-337	OUH	Minor	Other	Information at handover	Spoken to staff involved, Case will be distributed to all study workers in next info letter from study team,
01-344	OUH	Minor	Patients rights and welfare		EMS nr 3000 checked out as study worker, information regarding this reiterated in next newsletter.
01-380	OUH	Minor	Scientific/data integrity		Informed study workers on need to comply with training
01-592	OUH	Major	Scientific/data integrity		repeated teaching of study workers
01-600	OUH	Minor	Scientific/data integrity		Been in contact with ambulance worker 2702
01-610	OUH	Major	Scientific/data integrity		Remind study workers always to link kits to AMIS data/ ambulance mission
01-617	OUH	Major	Patients rights and welfare		Individuak EMS have been contacted
01-617	OUH	Major	Patients rights and welfare		Reminded not to leave info letter at Sprøyterommet
01-649	OUH	Minor	Patients rights and welfare		Explained study crew difficulty in assessing consent when not answering clearly
01-675	OUH	Minor	Scientific/data integrity		informed individual study workers
01-675	OUH	Major	Patients rights and welfare		Information to study workers
01-676	OUH	Major	Patients rights and welfare		Discussed procedure With study crew. Contacted Diakonhjemmet Hospital as soon as deviation seen to try to Reach patient, With no success
02-094	St Olav	Minor	Scientific/data integrity		Reminded study workers of protocol
02-094	St Olav	Major	Scientific/data integrity		non
01-837	OUH	Major	Patients rights and welfare		Spoken to study workers

SubjectId	SiteName	PDAPAYN	PDAPACOM	PDSTATYN	TreatGr	population
02-001	St Olav	No		No	Control	PP
01-018	OUH	Yes		No	Control	FAS
01-048	OUH	Yes	Personal communication Inge Christoffersen 12th July 2018	Yes	Active	FAS
01-048	OUH	Yes	Patient placed in Full Analysis Set, not Per Protocol population	No	Active	FAS
01-056	OUH	Yes		No	Active	Safety (no consent)
01-063	OUH	Yes		No	Active	Safety (no consent)
01-068	OUH	No	Has been discussed with DMC, as both are given within 30 seconds protocol divination is minor, and patient should be included in "per protocol analysis set"	No	Control	PP
01-069	OUH	Yes		No	Active	PP
01-136	OUH	No		No	Control	PP
01-136	OUH	No		No	Control	PP
01-137	OUH	No		No	Active	PP
01-200	OUH	No		No	Active	PP
01-221	OUH	Yes	To be discussed later if "full analysis" or removed because of major breech (GCP E9)	No	Control	FAS
01-249	OUH	Yes	ITT	No	Control	Woke up
01-274	OUH	Yes	Not per protocol analysis set	No	Control	FAS
01-281	OUH	No	See DMC discussion 19.05.2019	No	Active	PP
01-281	OUH	No	antar at privat klokke måler tid 0-10 minutter like presis som stoppeklokke	No	Active	PP
01-285	OUH	No		No	Active	Safety (no consent)
01-288	OUH	Yes		No	Control	Safety (no consent)
01-308	OUH	Yes		No	Active	Safety (no consent)
01-336	OUH	No		No	Control	PP
01-337	OUH	No	Discussed with DMC, should be included in Per Protocol set	No	Control	PP
01-344	OUH	No		No	Control	PP
01-380	OUH	No		No	Active	PP
01-592	OUH	Yes	not in per protocol st	No	Control	FAS
01-600	OUH	No		No	Active	PP
01-610	OUH	No		No	Control	Woke up
01-617	OUH	No		No	Active	PP
01-617	OUH	No		No	Active	PP
01-649	OUH	No		No	Control	PP
01-675	OUH	Yes	ITT	No	Control	Safety (no consent)
01-675	OUH	Yes		No	Control	Safety (no consent)
01-676	OUH	Yes	IS withdrawn from participation and placed in anonymous safetyset	No	Active	Safety (no consent)
02-094	St Olav	No		No	Control	FAS
02-094	St Olav	Yes	Case discussed at meeting of Safety Committee meeting 29th Sept 2020. Protocoldeviation deemed to be major, and that patient should be included in Full Analysis Set	Yes	Control	FAS
01-837	OUH	Yes		No	Active	Safety (no consent)

11 EFFICACY EVALUATION

11.1 Data Sets Analysed

Per protocol Set analysed for primary enbd point
Safety Set analysed for safety data

11.2 Demographic and Other Baseline Characteristics

Characteristics for overdoses in the Full analysis set (FAS) vs. those not in the FAS. Patients that did not give consent are not included, as their data are not included in the database. Column "n_var" gives the number of observations per variable. Mean (SD) of continuous variables are calculated for patients without missing values.

	n var		Excluded patients	Full Analysis set
n=			727	208
Centre (%)	935	Oslo University Hospital	620 (85.3)	193 (92.8)
		St. Olavs hospital	107 (14.7)	15 (7.2)
Sex (%)	935	Female	177 (24.3)	37 (17.8)
		Male	534 (73.5)	169 (81.2)
		Unknown	16 (2.2)	2 (1.0)
Age, years (mean (SD))	790		41.69 (14.12)	37.86 (10.56)
National Identity number known		Yes	Not applicable	183
		No	Not applicable	25
Follow up after treatment by emergency services	935	Admitted to hospital	206 (28.3)	22 (10.6)
		Left at the scene	287 (39.5)	137 (65.9)
		Oslo Accident and Emergency Outpatient Clinic (primary care facility)	208 (28.6)	44 (21.2)
		Addiction services Oslo University Hospital	11 (1.5)	5 (2.4)
		Trondheim Accident and Emergency Outpatient Clinic (primary care facility)	5 (0.7)	0 (0.0)
		Dead	1 (0.1)	0 (0.0)
		Other	9 (1.2)	0 (0.0)
Received Take Home Naloxone prior to ambulance arrival (%)	935	No	642 (88.3)	208 (100.0)
		Yes	85 (11.7)	0 (0.0)
Total dose naloxone given by ambulance (mean (SD))	724	milligram	0.55	Not applicable

Baseline characteristics of included individuals

	level	Overall
n		156
Sex (%)	Female	28 (17.9)
	Male	126 (80.8)
	Unknown	2 (1.3)
Age (earliest) (Mean (SD))		37.67 (11.20)
Number of adverse events in patient (%)	0	119 (76.3)
	1	29 (18.6)
	2	5 (3.2)
	3	1 (0.6)
	4	1 (0.6)
	5	1 (0.6)
Number of serious adverse events in patient (%)	0	155 (99.4)
	1	1 (0.6)
Vital status at end of study (%)	Alive	156 (100%)
At least one recurrence	No	149 (95.5)
	Yes	7 (4.5)
Number of recurrences	0	149 (95.5)
	1	6 (3.8)
	2	1 (0.6)
Rescue naloxone needed (ever) (%)	No	117 (75.0)
	Yes	39 (25.0)
Rescue naloxone received (ever) (%)	No	119 (76.3)
	Yes	37 (23.7)
Treatment received (%)	Intranasal naloxone	70 (44.9)
	Intramuscular naloxone	70 (44.9)
	Both	16 (10.3)
Number of times included (%)	1	131 (84.0)
	2	15 (9.6)
	3	6 (3.8)
	4	1 (0.6)
	5	2 (1.3)
	8	1 (0.6)

Patient characteristics for patients with overdoses included in the full analysis set
Note: 1) Patient characteristics for individual patients, not describing each event.
2) Serious Adverse Events (SAE) are included in Adverse Events (AE)

11.3 Measurements of Treatment Compliance

The investigator administered the investigational medicinal products and subjects' compliance was not assessed.

11.4 Efficacy Results and Tabulations of Individual Patient Data

Not provided

11.4.1 Analysis of efficacy

Please consult the attached document 11.4.1_Analysis of efficacy NiNa-1-FINAL-2020-10-30 for final analysis

11.4.2 Statistical/analytical issues

Please consult attached Statistical Analysis Plan

11.4.2.1 Adjustments for Covariates

See statistical analysis plan, document 11.4.1_Analysis of efficacy NiNa-1-FINAL-2020-10-30 and main publication

11.4.2.2 Handling of Dropouts or Missing Data

See statistical analysis plan, document 11.4.1_Analysis of efficacy NiNa-1-FINAL-2020-10-30 and main publication

11.4.2.3 Interim Analyses and Data Monitoring

See statistical analysis plan, document 11.4.1_Analysis of efficacy NiNa-1-FINAL-2020-10-30 and main publication

11.4.2.4 Multicentre Studies

See statistical analysis plan, document 11.4.1_Analysis of efficacy NiNa-1-FINAL-2020-10-30 and main publication

11.4.2.5 Multiple Comparisons/Multiplicity

See statistical analysis plan, document 11.4.1_Analysis of efficacy NiNa-1-FINAL-2020-10-30 and main publication

11.4.2.6 Use of an "Efficacy Subset" of Patients

See statistical analysis plan, document 11.4.1_Analysis of efficacy NiNa-1-FINAL-2020-10-30 and main publication

11.4.2.7 Active-Control Studies Intended to Show Equivalence

Not applicable

11.4.2.8 Examination of Subgroups

See statistical analysis plan, document 11.4.1_Analysis of efficacy NiNa-1-FINAL-2020-10-30 and main publication

11.4.3 Tabulation of individual response data

See statistical analysis plan, document 11.4.1_Analysis of efficacy NiNa-1-FINAL-2020-10-30 and main publication

11.4.4 Drug dose, drug concentration, and relationships to response

Not applicable

11.4.5 Drug-drug and drug-disease interactions

Not applicable

11.4.6 By-patient displays

Not applicable

11.4.7 Efficacy conclusions

Intranasal naloxone (1.4 mg/0.1 mL) was less efficient than 0.8 mg intramuscular naloxone for return to spontaneous breathing within 10 minutes in overdose patients in the pre-hospital environment when compared head-to-head. Intranasal naloxone at 1.4 mg/0.1 mL restored breathing in 80% of participants after one dose and had few mild adverse reactions.

12 SAFETY EVALUATION

12.1 Extent of Exposure

Participants were exposed to IMP once during the inclusion. Some individuals were included on multiple occasions.

The following table show that 20 individuals were exposed to IMP more than once

Number of times included	n=	Intranasal naloxone (Active IMP)	Intramuscular naloxone
1	68	1	0
1	63	0	1
2	8	1	1
2	5	0	2
2	2	2	0
3	4	2	1
3	1	0	3
3	1	1	2
4	1	1	3
5	1	0	5
5	1	2	3
8	1	1	7

The number of patients with the indicated treatment combination (for overdoses included in the Full analysis set).

12.2 Adverse Events (AEs)

12.2.1 Brief summary of adverse events
Consult main publication

12.2.2 Display of adverse events
Consult 16.2.7 Adverse event listings (each patient)

12.2.3 Analysis of adverse events
Consult main publication

12.2.4 Listing of adverse events by patient
Consult 16.2.7 Adverse event listings (each patient)

12.2.5 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events
Not applicable

12.2.6 Listing of deaths, other serious adverse events, and other significant adverse events
Not applicable

12.2.6.1 Deaths
Not applicable

12.2.6.2 Other Serious Adverse Events
Consult 16.2.7 Adverse event listings (each patient)

12.2.6.3 Other Significant Adverse Events
Not applicable

12.2.7 Narratives of deaths, other serious adverse events, and certain other significant adverse events
Not applicable

12.2.8 Analysis and discussion of deaths, other serious adverse events, and other significant adverse events
Not applicable

12.3 Clinical Laboratory Evaluation

12.3.1 Listing of individual laboratory measurements by patient (16.2.8) and each abnormal laboratory value (14.3.4)
Not applicable

12.3.2 Evaluation of each laboratory parameter
Not applicable

12.3.2.1 Laboratory Values Over Time
Not applicable

12.3.2.2 Individual Patient Changes
Not applicable

12.3.2.3 Individual Clinically Significant Abnormalities
Not applicable

12.4 Vital Signs, Physical Findings, and Other Observations Related to Safety
Consult main publication, especially primary end point

12.5 Safety Conclusions
Study drug has few and mild adverse reactions.

13 DISCUSSION AND OVERALL CONCLUSIONS
See main publication

14 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic Data
Not applicable

14.2 Efficacy Data
Not applicable

14.3 Safety Data
Not applicable

14.3.1 Displays of adverse events
Not applicable

14.3.2 Listings of deaths, other serious and significant adverse events
Not applicable

14.3.3 Narratives of deaths, other serious and certain other significant adverse events
Not applicable

14.3.4 Abnormal laboratory value listing (each patient)
Not applicable

15 REFERENCE LIST

1. Skulberg AK, Tylleskar I, Valberg M, Braarud AC, Dale J, Heyerdahl F, et al. Comparison of intranasal and intramuscular naloxone in opioid overdoses managed by ambulance staff: a double-dummy, randomised, controlled trial. Addiction. 2022.
2. World Health Organization. Management of Substance Abuse Team, World Health Organization. Community management of opioid overdose. Geneva: World Health Organization,; 2014.
3. Helsedirektoratet. «Ja visst kan du bli rusfri – men først må du overleve» [updated April 2014. Available from: http://helsedirektoratet.no/publikasjoner/nasjonal-overdosestrategi-20142017/.
4. Loimer N, Hofmann P, Chaudhry HR. Nasal administration of naloxone for detection of opiate dependence. J Psychiatr Res. 1992;26(1):39-43.
5. Loimer N, Hofmann P, Chaudhry HR. Nasal Administration of Naloxone Is as Effective as the Intravenous Route in Opiate Addicts. Int J Addict. 1994;29(6):819-27.
6. Tylleskar I, Skulberg AK, Skarra S, Nilsen T, Dale O. Pharmacodynamics and arteriovenous difference of intravenous naloxone in healthy volunteers exposed to remifentanil. Eur J Clin Pharmacol. 2018;74(12):1547-53.
7. Weber JM, Tataris KL, Hoffman JD, Aks SE, Mycyk MB. Can nebulized naloxone be used safely and effectively by emergency medical services for suspected opioid overdose? Prehosp Emerg Care. 2012;16(2):289-92.
8. Baumann BM, Patterson RA, Parone DA, Jones MK, Glaspey LJ, Thompson NM, et al. Use and efficacy of nebulized naloxone in patients with suspected opioid intoxication. Am J Emerg Med. 2013;31(3):585-8.
9. Tandberg D, Abercrombie D. Treatment of heroin overdose with endotracheal naloxone. Ann Emerg Med. 1982;11(8):443-5.
10. Health Products Regulatory Authority Ireland. Summary of Product Characteristics Naloxone B Braun [cited 2016 17 March]. Available from: http://www.webcitation.org/6g4edopWl
11. Clarke SF, Dargan PI, Jones AL. Naloxone in opioid poisoning: walking the tightrope. Emerg Med J. 2005;22(9):612-6.
12. Connors NJ, Nelson LS. The Evolution of Recommended Naloxone Dosing for Opioid Overdose by Medical Specialty. J Med Toxicol. 2016;12(3):276-81.
13. Sheikh A, Simons FER, Barbour V, Worth A. Adrenaline auto-injectors for the treatment of anaphylaxis with and without cardiovascular collapse in the community. Cochrane Database of Systematic Reviews. 2012(8).
14. McTague A, Martland T, Appleton R. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. The Cochrane database of systematic reviews. 2018;1:CD001905.
15. Shen J, Che Y, Showell E, Chen K, Cheng L. Interventions for emergency contraception. Cochrane Database of Systematic Reviews. 2017.
16. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Preventing opioid overdose deaths with take-home naloxone. European Monitoring Centre for Drugs and Drug Addiction; 2016.
17. McDonald R, Strang J. Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. Addiction. 2016;111(7):1177-87.
18. Strang J, McDonald R, Alqurshi A, Royall P, Taylor D, Forbes B. Naloxone without the needle - systematic review of candidate routes for non-injectable naloxone for opioid overdose reversal. Drug Alcohol Depend. 2016;163:16-23.
19. Preston KL, Bigelow GE, Liebson IA. Effects of sublingually given naloxone in opioid-dependent human volunteers. Drug Alcohol Depend. 1990;25(1):27-34.

20. Strang J, Darke S, Hall W, Farrell M, Ali R. Heroin overdose: the case for take-home naloxone. BMJ. 1996;312(7044):1435-6.
21. Strang J, Farrell M. Harm minimisation for drug misusers. BMJ. 1992;304(6835):1127-8.
22. Kelly AM, Kerr D, Dietze P, Patrick I, Walker T, Koutsogiannis Z. Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. Med J Aust. 2005;182(1):24-7.
23. Eguale T, Buckeridge DL, Verma A, Winslade NE, Benedetti A, Hanley JA, et al. Association of Off-label Drug Use and Adverse Drug Events in an Adult Population. JAMA Internal Medicine. 2016;176(1).
24. McCarthy M. Off-label drug use is associated with raised risk of adverse events, study finds. BMJ. 2015;351:h5861.
25. Dale O. Ethical issues and stakeholders matter. Addiction. 2016;111(4):587-9.
26. Costantino HR, Illum L, Brandt G, Johnson PH, Quay SC. Intranasal delivery: physicochemical and therapeutic aspects. Int J Pharm. 2007;337(1-2):1-24.
27. Dowling J, Isbister GK, Kirkpatrick CM, Naidoo D, Graudins A. Population pharmacokinetics of intravenous, intramuscular, and intranasal naloxone in human volunteers. Ther Drug Monit. 2008;30(4):490-6.
28. Walley AY, Xuan Z, Hackman HH, Quinn E, Doe-Simkins M, Sorensen-Alawad A, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. BMJ. 2013;346:f174.
29. Kerr D, Kelly A-M, Dietze P, Jolley D, Barger B. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. Addiction. 2009;104(12):2067-74.
30. Strang J, McDonald R, Campbell G, Degenhardt L, Nielsen S, Ritter A, et al. Take-Home Naloxone for the Emergency Interim Management of Opioid Overdose: The Public Health Application of an Emergency Medicine. Drugs. 2019;79(13):1395-418.
31. Skulberg AK, Asberg A, Khiabani HZ, Rostad H, Tylleskar I, Dale O. Pharmacokinetics of a novel, approved, 1.4-mg intranasal naloxone formulation for reversal of opioid overdose-a randomized controlled trial. Addiction. 2019;114(5):859-67.
32. Tylleskar I, Gjersing L, Bjornsen LP, Braarud AC, Heyerdahl F, Dale O, et al. Prehospital naloxone administration - what influences choice of dose and route of administration? BMC Emerg Med. 2020;20(1):71.
33. Krieter P, Chiang N, Gyaw S, Skolnick P, Crystal R, Keegan F, et al. Pharmacokinetic Properties and Human Use Characteristics of an FDA-Approved Intranasal Naloxone Product for the Treatment of Opioid Overdose. J Clin Pharmacol. 2016;56(10):1243-53.
34. McDonald R, Lorch U, Woodward J, Bosse B, Dooner H, Mundin G, et al. Pharmacokinetics of concentrated naloxone nasal spray for opioid overdose reversal: Phase I healthy volunteer study. Addiction. 2018;113(3):484-93.
35. Uppsala Monitoring Centre. The use of the WHO-UMC system for standardised case causality assessment [cited 2016 16th September]. Available from: http://www.webcitation.org/6kYn8ezcY

16 APPENDICES

16.1 Study Information

16.1.1 Protocol and protocol amendments

16.1.2 Sample case report form (unique pages only)

16.1.3 List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) - representative written information for patient and sample consent forms

Regional Committees for Medical and Health Research Ethics (REC) 2016/2000/REK sør-øst C

National Committee for Medical and Health Research Ethics. 2017/44 NEM

16.1.4 List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study

Name	Main affiliation	Role and time period	Training and background
Arne Kristian Skulberg, MD, Ph.D.	• Department of Circulation and Medical Imaging, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway • Department of Air ambulance Services, Division of Prehospital Services, Oslo University Hospital, Oslo, Norway	Investigator from 31 Oct 2016 until 1 May 2019 National coordinating investigator from 1 May 2019 until present	Medical doctor, consultant anesthetist
Ola Dale, MD, Ph.D.	• Department of Circulation and Medical Imaging, Faculty of Medicine and Health Sciences, Norwegian University of Science and	National coordinating investigator from 31 Oct 2016 until 1 May 2019 Investigator from 1 May 2019 until present	Medical doctor, consultant anesthetist, professor

	Technology, Trondheim, Norway • Department of Research and Development, St. Olavs hospital, Trondheim University Hospital, Trondheim, Norway		
Anne Cathrine Braarud, MD, Ph.D.	• Department of Ambulance Services, Division of Prehospital Services, Oslo University Hospital, Oslo; Norway	Principal investigator site Oslo University Hospital from 31 Oct 2016 until present	Medical doctor, consultant anesthetist
Jostein Dale, MD	• Clinic of Emergency Medicine and Prehospital Care, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway	Principal investigator site St. Olavs Hospital, Trondheim University Hospital from 31 Dec 2018 until present	Medical doctor, consultant
Sindre Mellesmo, MD	• Clinic of Emergency Medicine and Prehospital Care, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway	Principal investigator site St. Olavs Hospital, Trondheim University Hospital from 31 Oct 2016 until 31 Dec 2018	Medical doctor, consultant anesthetist
Ida Tylleskar, MD, Ph.D.	• Department of Circulation and Medical Imaging, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway	Investigator from 31 Oct 2016 until present	Medical student qualified as edical doctor,
Fridtjof Heyerdahl, MD, Ph.D.	• Department of Air ambulance Services, Division of Prehospital Services, Oslo University Hospital, Oslo; Norway • Norwegian Air Ambulance Foundation, Oslo, Norway	Investigator from 31st Oct 2016 until present	Medical doctor, consultant anesthetist

Tore Skålhegg, paramedic, Oslo University Hospital, Oslo; Norway	• Department of Ambulance Services, Division of Prehospital Services, Oslo University Hospital, Oslo; Norway	local study coordinator Oslo January 2018- December 2020	Qualified paramedic
Jan Barstein, paramedic, St Olavs, Trondheim University Hospital, Trondheim, Norway	• Clinic of Emergency Medicine and Prehospital Care, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway	local study coordinator Trondheim January 2018- December 2020	Qualified paramedic

16.1.5 Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement

16.1.6 Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used

Not made available

16.1.7 Randomisation scheme and codes (patient identification and treatment assigned)

16.1.8 Audit certificates (if available)

16.1.9 Documentation of statistical methods

16.1.10 Documentation of inter-laboratory standardisation methods and quality assurance procedures if used

Not applicable

16.1.11 Publications based on the study

16.1.12 Important references in the report

See last page

16.2 Patient Data Listings

16.2.1 Discontinued patients

Not applicable

16.2.2 Protocol deviations

See chapter 10.2

16.2.3 Patients excluded from the efficacy analysis

16.2.4 Demographic data

16.2.5 Compliance and/or Drug Concentration Data (if available)

Not applicable

16.2.6 Individual Efficacy Response data

Not made available

16.2.7 Adverse event listings (each patient)

16.2.8 Listing of individual laboratory measurements by patient, when required by regulatory authorities

Not applicable

16.3 CaseReportForms

16.3.1 CRFs of deaths, other serious adverse events and withdrawals for AE

In paper format, stored at site with ISF: Not avaliable

16.3.2 Other CRFs submitted

In paper format, stored at site with ISF: Not avaliable

16.4 Individual Patient Data Listings (US Archival Listing)

Not applicable

NINA-1 tables and analyses

30 October, 2020

Flow Charts

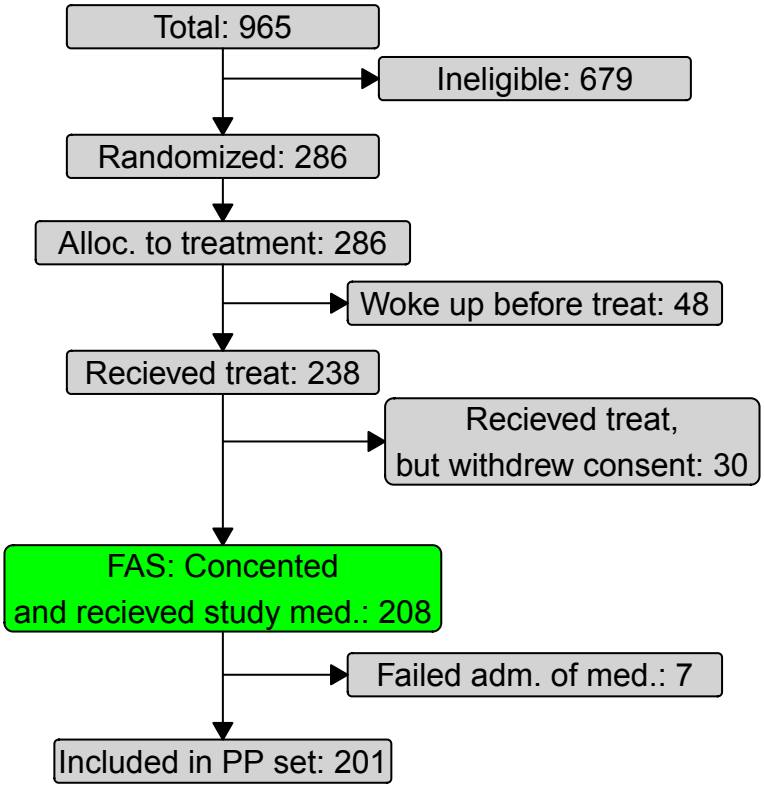

Figure 1: Study flow chart. Abbreviation: FAS, Full analysis set; PP, per protocol. NOTE: The numbers given are the number of overdoses, not the number of individuals.

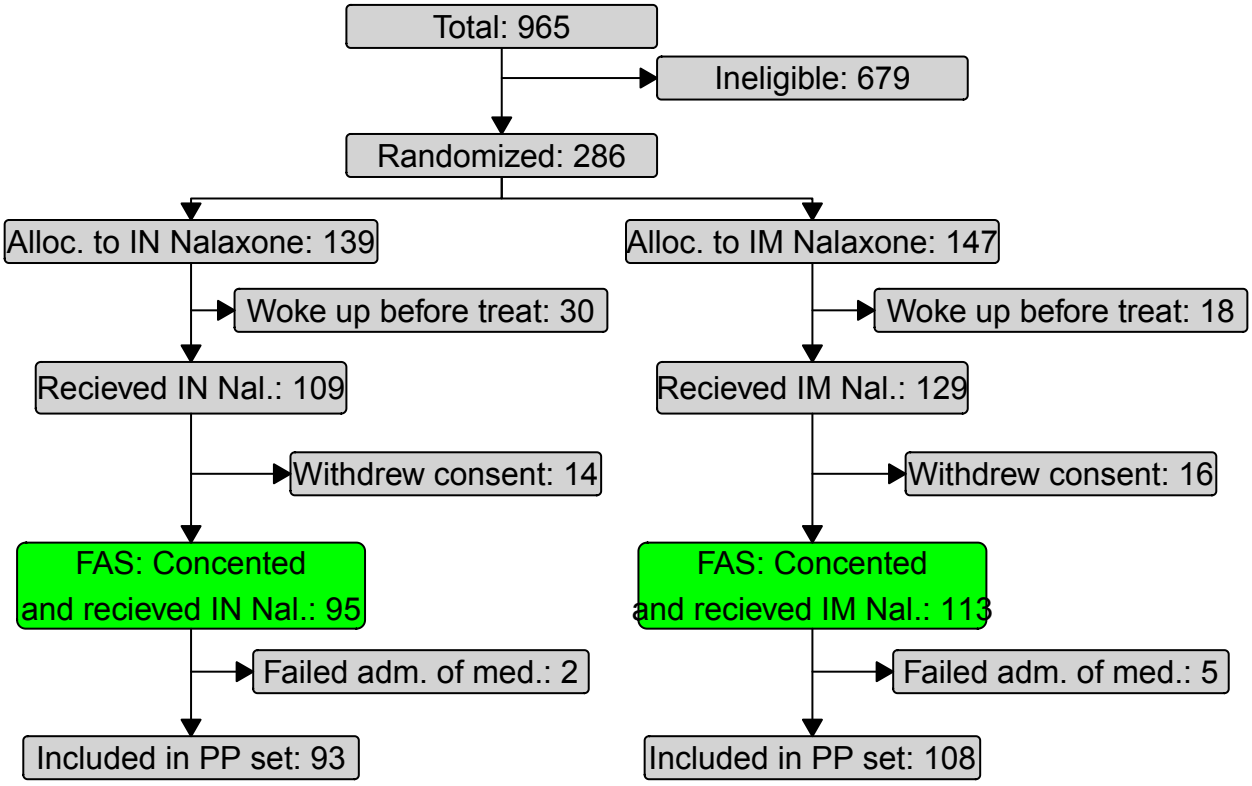

Figure 2: Study flow chart. Abbreviations: IN, intranasal; IM, Intramuscular; FAS, Full analysis set; PP, Per protocol. NOTE: The numbers given are the number of overdoses, not the number of individuals.

Oslo only

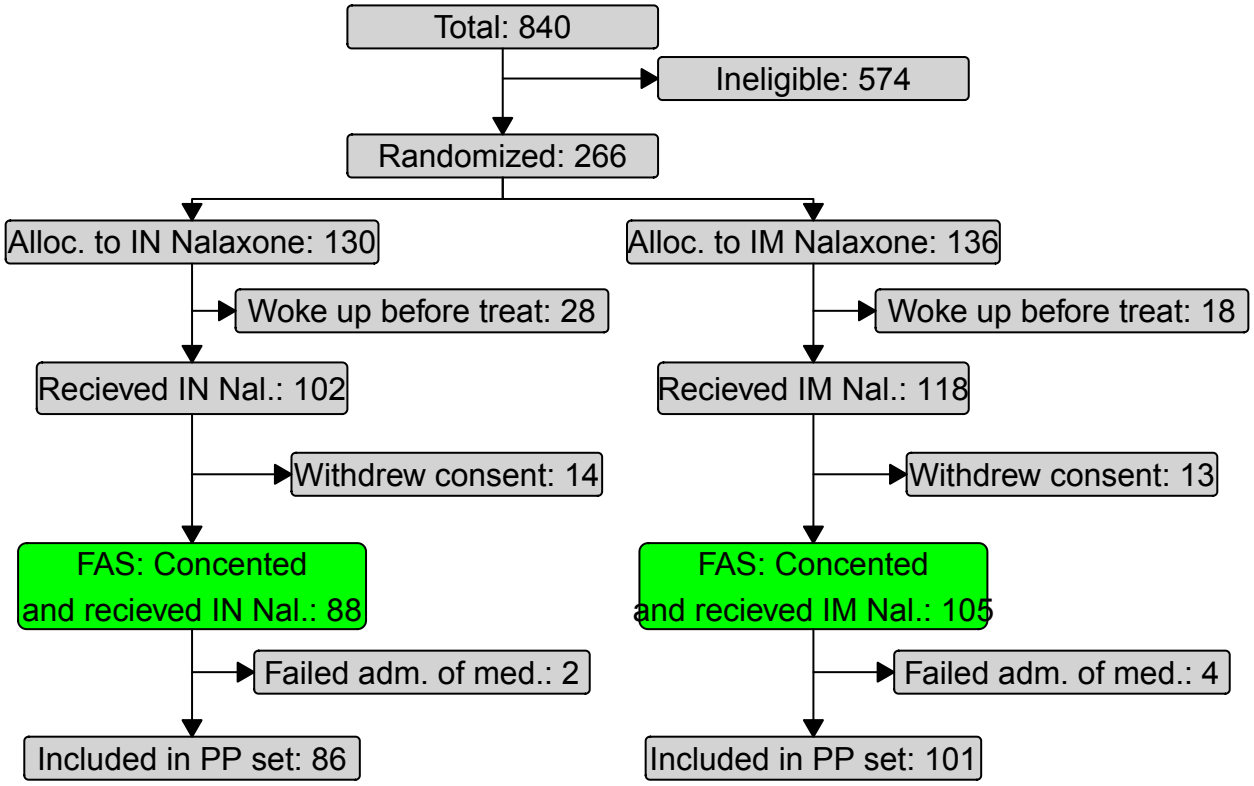

Figure 3: Study flow chart for Oslo. Abbreviations: IN, intranasal; IM, Intramuscular; FAS, Full analysis set; PP, Per protocol. NOTE: The numbers given are the number of overdoses, not the number of individuals.

Trondheim only

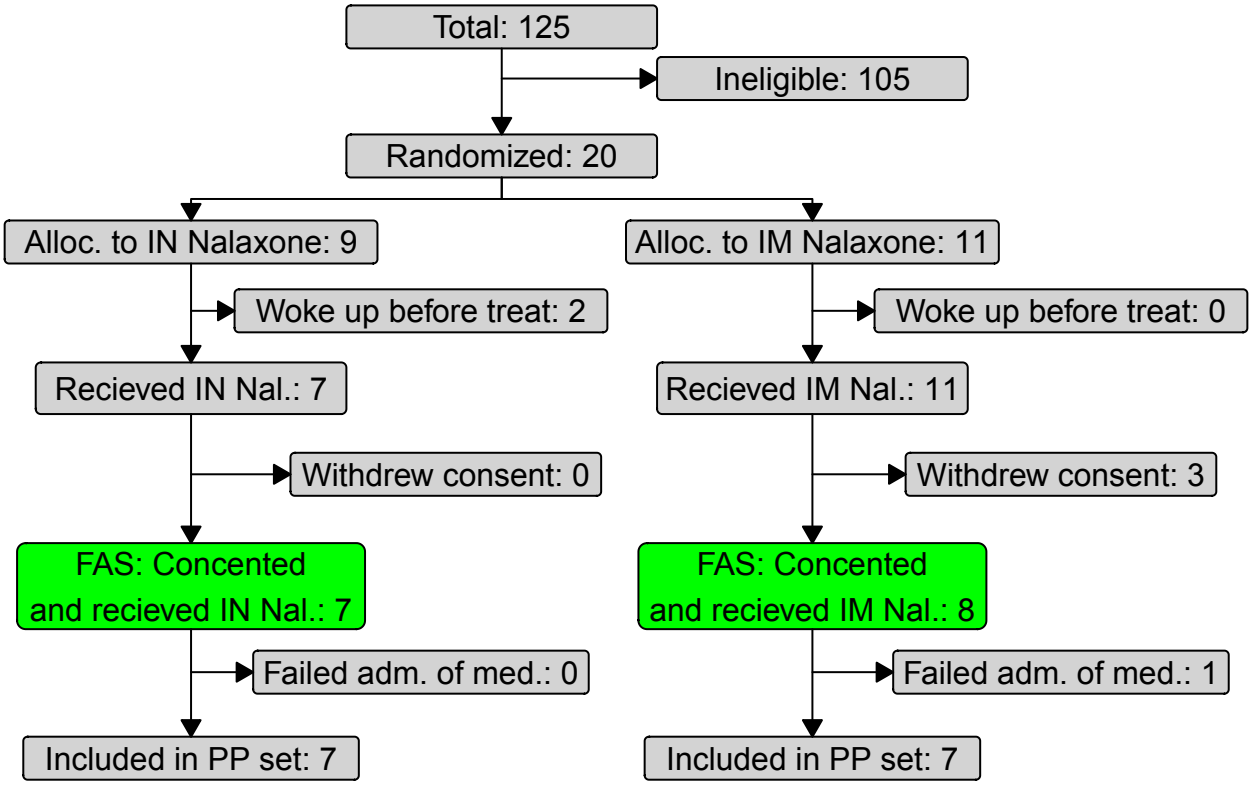

Figure 4: Study flow chart for Trondheim. Abbreviations: IN, intranasal; IM, Intramuscular; FAS, Full analysis set; PP, Per protocol. NOTE: The numbers given are the number of overdoses, not the number of individuals.

Summary data

FAS: Patient characteristics

Table 1: Overdose charactersistics for overdose events in the FAS (recieving study medication, see flow chart). Note: 1) the numbers represent overdose events, not individuals. 2) SAEs are included in AEs.

		Treatment Group		
		Control	Active	Overall
n		113	95	208
Center (%)	OUH	105 (92.9)	88 (92.6)	193 (92.8)
	St Olav's	8 (7.1)	7 (7.4)	15 (7.2)
Sex (%)	Female	20 (17.7)	17 (17.9)	37 (17.8)
	Male	92 (81.4)	77 (81.1)	169 (81.2)
	Unknown	1 (0.9)	1 (1.1)	2 (1.0)
No. of AEs in case (%)	0	91 (80.5)	78 (82.1)	169 (81.2)
	1	18 (15.9)	12 (12.6)	30 (14.4)
	2	3 (2.7)	3 (3.2)	6 (2.9)
	3	0 (0.0)	1 (1.1)	1 (0.5)
	4	0 (0.0)	1 (1.1)	1 (0.5)
	5	1 (0.9)	0 (0.0)	1 (0.5)
No. of SAEs in case (%)	0	113 (100.0)	94 (98.9)	207 (99.5)
	1	0 (0.0)	1 (1.1)	1 (0.5)
Rescue Nalaxone needed (%)	No	101 (89.4)	67 (70.5)	168 (80.8)
	Yes	12 (10.6)	28 (29.5)	40 (19.2)
Rescue Nalaxone used (%)	No	102 (90.3)	68 (71.6)	170 (81.7)
	Yes	11 (9.7)	27 (28.4)	38 (18.3)
Recurrence (%)	No	109 (96.5)	91 (95.8)	200 (96.2)
	Yes	4 (3.5)	4 (4.2)	8 (3.8)
Follow-up (%)	Adm. Hospital	9 (8.0)	13 (13.7)	22 (10.6)
	Left at scene	80 (70.8)	57 (60.0)	137 (65.9)
	Oslo Legevakt	22 (19.5)	22 (23.2)	44 (21.2)
	Rusakutten Aker	2 (1.8)	3 (3.2)	5 (2.4)
SUSAR (%)	0	113 (100.0)	95 (100.0)	208 (100.0)
Vital status (%)	Alive	113 (100.0)	95 (100.0)	208 (100.0)
Age (mean (SD))		37.30 (10.31)	38.55 (10.89)	37.86 (10.56)

Mean (sd) of continous variables are calculated for patients without missing values.

```
## [1] "No. of overdoses with missing information on age of patient: 18"
```

Table 2: Patient charactersistics for patients with overdoses included in the FAS (recieving study medication, see flow chart). Note: 1) Patients characteristics for indivdual patients, not describing each event. 2) SAEs are included in AEs.

	level	Overall
n		161
Sex (%)	Female	29 (18.0)
	Male	130 (80.7)
	Unknown	2 (1.2)
No. of AEs in patient (%)	0	122 (75.8)
	1	30 (18.6)
	2	6 (3.7)
	3	1 (0.6)
	4	1 (0.6)
	5	1 (0.6)
No. of SAEs in patient (%)	0	160 (99.4)
	1	1 (0.6)
At least one recurrence (%)	No	154 (95.7)
	Yes	7 (4.3)
No. of recurrences (%)	0	154 (95.7)
	1	6 (3.7)
	2	1 (0.6)
Rescue Nalaxone needed (ever) (%)	No	121 (75.2)
	Yes	40 (24.8)
Rescue Nalaxone used (ever) (%)	No	123 (76.4)
	Yes	38 (23.6)
Treatment recieved (%)	Active	71 (44.1)
	Both	17 (10.6)
	Control	73 (45.3)
No. of times included (%)	1	134 (83.2)
	2	17 (10.6)
	3	6 (3.7)
	4	1 (0.6)
	5	2 (1.2)
	8	1 (0.6)
Vital status (%)	Alive	161 (100.0)
Age (earliest) (mean (SD))		37.85 (11.31)

```
## [1] "No. of patients with missing information on age: 18"
```

Table 3: The number of patients with the indicated treatment combination (for overdoses included in the FAS).

No. times included	n	Active	Control
1	69	1	0
1	65	0	1
2	9	1	1
2	6	0	2
2	2	2	0
3	4	2	1
3	1	0	3
3	1	1	2
4	1	1	3
5	1	0	5
5	1	2	3
8	1	1	7

Per protocol: Patient characteristics

Table 4: Overdose charactersistics for overdose events in the PP set (see flow chart). Note: 1) the numbers represent overdose events, not individuals. 2) SAEs are included in AEs.

		Treatment Group		
		Control	Active	Overall
n		108	93	201
Center (%)	OUH	101 (93.5)	86 (92.5)	187 (93.0)
	St Olav's	7 (6.5)	7 (7.5)	14 (7.0)
Sex (%)	Female	19 (17.6)	17 (18.3)	36 (17.9)
	Male	88 (81.5)	75 (80.6)	163 (81.1)
	Unknown	1 (0.9)	1 (1.1)	2 (1.0)
No. of AEs in case (%)	0	88 (81.5)	76 (81.7)	164 (81.6)
	1	17 (15.7)	12 (12.9)	29 (14.4)
	2	2 (1.9)	3 (3.2)	5 (2.5)
	3	0 (0.0)	1 (1.1)	1 (0.5)
	4	0 (0.0)	1 (1.1)	1 (0.5)
	5	1 (0.9)	0 (0.0)	1 (0.5)
No. of SAEs in case (%)	0	108 (100.0)	92 (98.9)	200 (99.5)
	1	0 (0.0)	1 (1.1)	1 (0.5)
Rescue Nalaxone needed (%)	No	97 (89.8)	65 (69.9)	162 (80.6)
	Yes	11 (10.2)	28 (30.1)	39 (19.4)
Rescue Nalaxone used (%)	No	98 (90.7)	66 (71.0)	164 (81.6)
	Yes	10 (9.3)	27 (29.0)	37 (18.4)
Recurrence (%)	No	104 (96.3)	89 (95.7)	193 (96.0)
	Yes	4 (3.7)	4 (4.3)	8 (4.0)
Follow-up (%)	Adm. Hospital	7 (6.5)	13 (14.0)	20 (10.0)
	Left at scene	78 (72.2)	55 (59.1)	133 (66.2)
	Oslo Legevakt	21 (19.4)	22 (23.7)	43 (21.4)
	Rusakutten Aker	2 (1.9)	3 (3.2)	5 (2.5)
SUSAR (%)	0	108 (100.0)	93 (100.0)	201 (100.0)
Vital status (%)	Alive	108 (100.0)	93 (100.0)	201 (100.0)
Age (mean (SD))		37.27 (10.17)	38.54 (10.80)	37.85 (10.45)

Mean (sd) of continous variables are calculated for patients without missing values.

```
## [1] "No. of overdoses with missing information on age of patient: 18"
```

Table 5: Patient charactersistics for patients with overdoses included in the PP set (see flow chart). Note: 1) Patients characteristics for indivdual patients, not describing each event. 2) SAEs are included in AEs.

	level	Overall
n		156
Sex (%)	Female	28 (17.9)
	Male	126 (80.8)
	Unknown	2 (1.3)
No. of AEs in patient (%)	0	119 (76.3)
	1	29 (18.6)
	2	5 (3.2)
	3	1 (0.6)
	4	1 (0.6)
	5	1 (0.6)
No. of SAEs in patient (%)	0	155 (99.4)
	1	1 (0.6)
At least one recurrence (%)	No	149 (95.5)
	Yes	7 (4.5)
No. of recurrences (%)	0	149 (95.5)
	1	6 (3.8)
	2	1 (0.6)
Rescue Nalaxone needed (ever) (%)	No	117 (75.0)
	Yes	39 (25.0)
Rescue Nalaxone used (ever) (%)	No	119 (76.3)
	Yes	37 (23.7)
Treatment recieved (%)	Active	70 (44.9)
	Both	16 (10.3)
	Control	70 (44.9)
No. of times included (%)	1	131 (84.0)
	2	15 (9.6)
	3	6 (3.8)
	4	1 (0.6)
	5	2 (1.3)
	8	1 (0.6)
Vital status (%)	Alive	156 (100.0)
Age (earliest) (mean (SD))		37.67 (11.20)

```
## [1] "No. of patients with missing information on age: 18"
```

Table 6: The number of patients with the indicated treatment combination (for overdoses included in the PP set).

No. times included	n	Active	Control
1	68	1	0
1	63	0	1
2	8	1	1
2	5	0	2
2	2	2	0
3	4	2	1
3	1	0	3
3	1	1	2
4	1	1	3
5	1	0	5
5	1	2	3
8	1	1	7

AE data

Table 7: Adverse events (in FAS).

Center	SubjectId	Sex	AEno	EventType	Description	Severity	Action	Outcome	Relation	treatGr
OUH	01-021	Femal	1	Adverse Events	Vomits in ambulance during transport	Mild	None	Unknown	Possible	Active
OUH	01-021	Female	2	Adverse Events	Headache	Mild	None	Unknown	Possible	Active
St Olav's	02-009	Male	1	Adverse Events	hypothermia, cold and shivering, found lying on the floor	Moderate	Hospitalisation	Unknown	Unlikely	Control
OUH	01-069	Male	1	Adverse Events	aggression, agitation. Also previously described in AMK database. known for aggression- jumping angrily around. Not conistent With opioid withdrawal reatcion	Mild	Other	Unknown	Unlikely	Active
OUH	01-122	Male	1	Adverse Events	Aggression	Moderate	None	Unknown	Certain	Control
OUH	01-125	Male	1	Adverse Events	Nausea	Mild	None	Unknown	Possible	Control
OUH	01-140	Male	1	Adverse Events	Nausea	Mild	None	Unknown	Possible	Active
OUH	01-140	Male	2	Adverse Events	Vomiting	Mild	None	Unknown	Possible	Active
OUH	01-140	Male	3	Adverse Events	Patient described as spastic, hypertonic and transported to Diakonhjemmet Hospital. Not described as seizures, and not treated as seizure by EMS. Suspected GHB intoxication.	Moderate	Hospitalisation	Unknown	Unlikely	Active
OUH	01-140	Male	4	Adverse Events	Crossed off for agitated, interpreted as opioid withdrawal	Moderate	None	Unknown	Probable/ Likely	Active

Table 7: Adverse events (in FAS). *(continued)*

Center	SubjectId	Sex	AEno	EventType	Description	Severity	Action	Outcome	Relation	treatGr
OUH	01-151	Male	1	Adverse Events	Patient described as aggressive and not willing to engage in meaningful discussion regarding consent. Offered follow up declines.	Mild	None	Unknown	Certain	Active
OUH	01-194	Male	1	Adverse Events	Chart describe rhinorrea form opposite nostril to IMP administration during inclusion. They speculate if this is stomach content, but not sure. Patient wakes up without signs of aspiration, nausea or vomiting	Mild	None	Resolved	Unlikely	Control
OUH	01-202	Male	1	Adverse Events	EMS have crossed out for headache, but not described severity. Patient deemed competent and somatically well enough to be admitted to Rusakutten not Legevakt or Hospital	Mild	None	Unknown	Possible	Active
St Olav's	02-033	Male	1	Adverse Events	Patient expressed nausea during transport, transient and short lasting. Relieved by entering the emergency room. No vomiting. Cannot rule our car-sickness.	Mild	None	Resolved	Possible	Control
OUH	01-235	Male	1	Adverse Events	EMS marked out nausea as symptom, not described severity, but patient deemed well enough to remain at Sprøyterommet.	Mild	None	Unknown	Possible	Active
OUH	01-235	Male	2	Adverse Events	Crossed off as agitated + abstinent after inclusion. Not further described in chart	Moderate	None	Unknown	Certain	Active

Table 7: Adverse events (in FAS). *(continued)*

Center	SubjectId	Sex	AEno	EventType	Description	Severity	Action	Outcome	Relation	treatGr
OUH	01-253	Male	1	Adverse Events	headache, severity not described, but patient deemed fit to remain at the scene without follow up.	Mild	None	Unknown	Possible	Control
OUH	01-253	Male	2	Adverse Events	Dizziness, light-headedness described in chart, severity not described, but patient deemed fit to remain at the scene without follow-up.	Mild	None	Unknown	Possible	Control
OUH	01-263	Femal	1	Adverse Events	Nausea	Mild	None	Resolved	Possible	Active
OUH	01-333	Female	1	Adverse Events	Crossed off for aggression in chart.	Moderate	None	Unknown	Certain	Control
OUH	01-373	Femal	1	Adverse Events	Headache	Mild	None	Unknown	Possible	Control
OUH	01-373	Female	2	Adverse Events	nausea	Mild	None	Unknown	Possible	Control
OUH	01-388	Male	1	Adverse Events	Crossed off for aggression in CRF	Mild	None	Unknown	Certain	Active
OUH	01-389	Male	1	Adverse Events	Described as agitated, but not violent by EMS. Does cooperate	Mild	None	Unknown	Certain	Control
OUH	01-395	Male	1	Adverse Events	Crossed off for nausea at paper CRF, not described in more detail	Mild	None	Unknown	Possible	Active
OUH	01-402	Male	1	Adverse Events	Headache described in paper CRF	Mild	None	Unknown	Possible	Control
OUH	01-410	Male	1	Adverse Events	Headache, not described more closely	Mild	None	Unknown	Possible	Active
OUH	01-411	Male	1	Adverse Events	Aspiration. Patient has vomited and aspirated prior to the arrival of ambulance crew	Moderate	None	Unknown	Unlikely	Control

Table 7: Adverse events (in FAS). *(continued)*

Center	SubjectId	Sex	AEno	EventType	Description	Severity	Action	Outcome	Relation	treatGr
OUH	01-417	Femal	1	Adverse Events	Describes as aggressive, agitated and abstinent by ambulance workers. These three are all expressions of the same clinical syndrome of opioid abstinence, and coded as one AE for this patient	Moderate	None	Unknown	Certain	Control
OUH	01-443	Male	1	Adverse Events	Aggression, leaves ambulance, interpreted as abstinence	Moderate	None	Unknown	Certain	Active
OUH	01-583	Male	2	Adverse Events	Nausea, crossed off at paper CRF, not described more closely	Mild	None	Unknown	Possible	Active
OUH	01-592	Male	1	Adverse Events	CRF describes headache. no further information	Mild	None	Unknown	Possible	Control
OUH	01-619	Male	1	Adverse Events	Nausea/ vomiting crossed off in CRF	Mild	None	Unknown	Possible	Control
OUH	01-619	Male	2	Adverse Events	Symptoms of abstinence. Allieviated when morfin iv was administered due to pain after bystander CPR	Moderate	None	Resolved	Certain	Control
OUH	01-619	Male	3	Adverse Events	Hypothermia. Was cold after lying outside for 30 minutes prior to AMK alerted. It was wintertime. Warmed up when entering ambulance	Moderate	Other	Resolved	Unlikely	Control
OUH	01-619	Male	4	Adverse Events	Aspiration, described in study chart as crackles at auscultation and respiratory distress. No vomiting and aspiration is described occurring after EMS came to the scene, so presumed happening prior of arrival and prior to administration if IMP	Moderate	None	Unknown	Unlikely	Control

Table 7: Adverse events (in FAS). *(continued)*

Center	SubjectId	Sex	AEno	EventType	Description	Severity	Action	Outcome	Relation	treatGr
OUH	01-619	Male	5	Adverse Events	Pain in chest after bystander CPR. Relieved by administered morphine (se concomitant medication this patient)	Moderate	Medical Intervention	Unknown	Unlikely	Control
OUH	01-630	Male	1	Adverse Events	Study personell crossed off for aggression/agitation and abstinence. Not well described in chart	Mild	None	Unknown	Certain	Control
OUH	01-658	Male	1	Adverse Events	Crossed off for abstinence	Mild	None	Unknown	Certain	Control
OUH	01-673	Male	1	Adverse Events	Patient shivering and cold, being outside and wet	Moderate	Other	Unknown	Unlikely	Control

Table 7: Adverse events (in FAS). *(continued)*

Center	SubjectId	Sex	AEno	EventType	Description	Severity	Action	Outcome	Relation	treatGr
OUH	01-677	Femal	1	Adverse Events	Patient included as per protocol. A few minutes into observation period study workers experiences masseter spasm. She had Guedel airway in place at the time, and no ventilation issues occurred. EMS contacted physician backup, administered 0.4 mg IV naloxone and 5 mg diazepam IV as per local protocol. Patient a a few minutes bradycardia 28-40 beats/minute. No sign of hypotension of hypoxia. No skin reaction/ bronchospasm described. Bradycardia self limited. Patient regained spontaneous respiration, bur remained unconscious at GCS =9/15. Admitted to Lovisenberg Hospital. She was administered repeat dose naloxone at hospital with no reaction and observed for 14 hours prior to being discharged to home with no sequelae. As described bradycardia is main reaction. Masseter spasm is more unclear in description and aetiology, and may be seen in relation to Guedel airway	Severe	Hospitalisation	Resolved	Possible	Active

Table 7: Adverse events (in FAS). *(continued)*

Center	SubjectId	Sex	AEno	EventType	Description	Severity	Action	Outcome	Relation	treatGr
OUH	01-677	Female	2	Adverse Events	Masseter spasm is more unclear in description and aetiology, and may be seen in relation to Guedel airway . See AE no 1 for closer description of jaw spasm	Mild	Medical Intervention	Resolved	Unlikely	Active
OUH	01-677	Female	3	Adverse Events	patient was cold. temprature measured (infrared at tympanic membrane) to 35,1 degrees celcius	Moderate	None	Resolved	Unlikely	Active
OUH	01-694	Male	1	Adverse Events	paper CRF states agitation, but patient calms Down when explained what happens. Explicitly stated in patient chart that he does not seem to suffer from opioid abstinence/ withdrawal	Mild	None	Resolved	Unlikely	Control
OUH	01-700	Male	1	Adverse Events	Headache described in chart, no mention of severity or duration. No medical intervention and left on site	Mild	None	Unknown	Possible	Control
St Olav's	02-094	Female	1	Adverse Events	nausea crossed off in chart, not described in more detail. no vomiting, no medical intervention for nausea	Mild	None	Unknown	Possible	Control
St Olav's	02-094	Female	2	Adverse Events	crossed of for agitation, not described in detail. interpreted as possible withdrawal.	Mild	None	Unknown	Certain	Control
OUH	01-706	Male	1	Adverse Events	Study workers indicated nausea in paper CRF, no more information available	Mild	None	Unknown	Possible	Active
St Olav's	02-095	Male	1	Adverse Events	Nausea described in chart, no intervention	Mild	None	Unknown	Possible	Active

Table 7: Adverse events (in FAS). *(continued)*

Center	SubjectId	Sex	AEno	EventType	Description	Severity	Action	Outcome	Relation	treatGr
St Olav's	02-095	Male	2	Adverse Events	Study workers describe irrregular pulse while palpating, not ECG changes recorded. Circulatory stable. NO intervention. Not reason for hospital admission	Mild	None	Unknown	Unassessable/ Unclasssifi-able	Active
OUH	01-796	Male	1	Adverse Events	patient found outside, body temprature measured to 34,2 degrees by infrared measurement tympanic membrane	Moderate	Other	Unknown	Unlikely	Active
OUH	01-803	Male	1	Adverse Events	Staff crossed off for opioid abstinence reaction in CRF, not described more closely	Mild	None	Unknown	Certain	Control
OUH	01-817	Femal	1	Adverse Events	Patient found outside, described as cold and hypothermic by crew, no temperature measured	Moderate	Other	Unknown	Unlikely	Active
OUH	01-819	Male	1	Adverse Events	Described in chart as hypothermic, no temperature measured. Found utside in the street	Moderate	Other	Unknown	Unlikely	Control

Table 8: Adverse events for overdoses where the patient refused or withdrew consent.

Center	SubjectId	Sex	AEno	EventType	Description	Severity	Action	Outcome	Relation	treatGr
OUH	01-057	Unknown	1	Adverse Events	Angry and verbally abusive, interpreted as abstinence reaction	Moderate	None	Unknown	Certain	Control
St Olav's	02-012	Male	1	Adverse Events	Aggression. Did not want naloxone. Goes after EMS staff.	Moderate	Other	Resolved	Certain	Control
OUH	01-264	Female	1	Adverse Events	Aggression, immedeatly injects heroin while EMS still present. Interpreted as opioid withdrawal	Moderate	None	Unknown	Certain	Control
OUH	01-287	Male	1	Adverse Events	Patient describes light head-ache, EMS not recorded severity, but patient allowed to remain at the scene. Must be considered not serious or require medical attention.	Mild	None	Unknown	Possible	Active
OUH	01-329	Male	1	Adverse Events	aggressive, interpreted as abstinence	Moderate	None	Unknown	Certain	Control
OUH	01-607	Female	1	Adverse Events	Aggressive and agitated.	Moderate	None	Unknown	Certain	Control
St Olav's	02-088	Male	1	Adverse Events	Aggression and withdrawal reaction. Wakes up 4 minutes after study drug administration. Upset that he was given naloxone and that the opioid effect was taken from him. Described as "mildt utaggerende" (mildly challenging?), spitting and kicking.	Moderate	None	Unknown	Certain	Control
St Olav's	02-096	Male	1	Adverse Events	Freeze and shakes, no intervention except taken into warm ambulance	Moderate	None	Unknown	Unlikely	Control

Table 9: Number and proportion of cases (among all recieving treatment, see flow chart) with adverse events by system organ class (SOC) and preferred term (PT).

		Treatment Group		Overall
SOC	PT	Active	control	
n		109	129	238
Cardiac disorders	Arrhythmia (%)	1 (0.9)	0 (0.0)	1 (0.4)
	Bradycardia (%)	1 (0.9)	0 (0.0)	1 (0.4)
Gastrointestinal disorders	Nausea (%)	7 (6.4)	5 (3.9)	12 (5.0)
	Vomiting (%)	2 (1.8)	0 (0.0)	2 (0.8)
General disorders and administration site conditions	Drug withdrawal syndrome (%)	5 (4.6)	15 (11.6)	20 (8.4)
	Hypothermia (%)	3 (2.8)	5 (3.9)	8 (3.4)
	Non-cardiac chest pain (%)	0 (0.0)	1 (0.8)	1 (0.4)
Musculoskeletal and connective tissue disorders	Trismus (%)	1 (0.9)	0 (0.0)	1 (0.4)
Nervous system disorders	Dizziness (%)	0 (0.0)	1 (0.8)	1 (0.4)
	Headache (%)	4 (3.7)	5 (3.9)	9 (3.8)
	Hypertonia (%)	1 (0.9)	0 (0.0)	1 (0.4)
Psychiatric disorders	Aggression (%)	1 (0.9)	0 (0.0)	1 (0.4)
	Agitation (%)	0 (0.0)	1 (0.8)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	Aspiration (%)	0 (0.0)	2 (1.6)	2 (0.8)
	Rhinorrhoea (%)	0 (0.0)	1 (0.8)	1 (0.4)

Table 10: Number and proportion of cases (among all recieving treatment, see flow chart) with adverse reactions by system organ class (SOC) and preferred term (PT).

		Treatment Group		Overall
SOC	PT	Active	control	
n		109	129	238
Cardiac disorders	Bradycardia (%)	1 (0.9)	0 (0.0)	1 (0.4)
Gastrointestinal disorders	Nausea (%)	7 (6.4)	5 (3.9)	12 (5.0)
	Vomiting (%)	2 (1.8)	0 (0.0)	2 (0.8)
General disorders and administration site conditions	Drug withdrawal syndrome (%)	5 (4.6)	15 (11.6)	20 (8.4)
Nervous system disorders	Dizziness (%)	0 (0.0)	1 (0.8)	1 (0.4)
	Headache (%)	4 (3.7)	5 (3.9)	9 (3.8)

Rescue Nalaxone

```
## [1] "No. of overdoses in FAS where rescue Nalaxone was needed:  40"
```

Table 11: Use of rescue Nalaxone in FAS.

	Center	SubjectId	Sex	treatGr	Needed	Recieved	overdoseTime	studyMedTime	rescueNalaxoneTime	TimeSinceStudyDrugAdm	TimeNB	Reason	Reason_not_give
1	OUH	01-019	Male	Active	Yes	Yes	Unknown	2018-06-19 07:19	2018-06-19 07:35	16		Not adequately increased GCS	
2	OUH	01-021	Female	Active	Yes	Yes	Unknown	2018-06-19 17:53	2018-06-19 18:03	10		Not adequately increased GCS	
3	OUH	01-030	Male	Active	Yes	Yes	2018-06-20 09:33	Unknown	Unknown	10		Not adequately increased GCS	
4	OUH	01-031	Male	Active	Yes	Yes	2018-06-20 17:25	Unknown	Unknown	Unknown	not stated in ambulance journal	Not adequately increased GCS	
5	OUH	01-053	Male	Control	Yes	Yes	2018-06-28 11:57	Unknown	Unknown	10.5		Not adequately increased GCS	
8	OUH	01-065	Male	Control	Yes	Yes	2018-07-04 19:45	Unknown	Unknown	Unknown	Can only see after 20.20 and prior to 20.23	Not adequately increased GCS	
9	OUH	01-133	Male	Active	Yes	Yes	2018-09-04 17:38	Unknown	2018-09-04 18:08	Unknown	By EMS file	Not adequately increased GCS	
10	OUH	01-140	Male	Active	Yes	Yes	2018-09-17 01:21	Unknown	Unknown	10		Not adequately increased GCS	
11	OUH	01-200	Male	Active	Yes	Yes	2018-11-13 12:15	Unknown	2018-11-13 12:55	Unknown	see chart	Not adequately increased GCS	
12	OUH	01-202	Male	Active	Yes	No	2018-11-16 20:15	Unknown	Unknown	Unknown		not breathing more than 10/ min at 10 minutes	Adequately responded shortly after 10 minutes (at 12 minutes)
13	OUH	01-221	Male	Control	Yes	Yes	2018-12-06 16:16	Unknown	2018-12-06 16:46	Unknown	see chart	Not adequately increased GCS	
14	OUH	01-230	Female	Control	Yes	Yes	Unknown	2018-12-26 01:00	2018-12-26 01:10	10		Respiratory rate 5/ minute after 5 minutes. Not increased level of conciseness	
15	OUH	01-259	Male	Control	Yes	Yes	Unknown	2019-01-25 04:44	Unknown	11		Not adequately increased GCS	
16	OUH	01-263	Female	Active	Yes	Yes	2019-01-30 07:45	Unknown	Unknown	Unknown	Not verfiel	Not adequately increased GCS	
17	OUH	01-273	Unknown	Active	Yes	Yes	2019-02-22 00:27	Unknown	Unknown	Unknown	not specified	Not adequately increased GCS	
20	OUH	01-335	Male	Active	Yes	Yes	2019-04-17 20:37	Unknown	2019-04-17 21:01	Unknown	By Chart	Not adequately increased GCS	
21	OUH	01-337	Female	Control	Yes	No	2019-04-20 21:07	Unknown	Unknown	Unknown		Not adequately increased GCS	Adequate response to naloxone on respiration, wanted calm patient during transport to hospital for evaluation and treatment of continued low GCS. In hospital responded to flumazenil.
22	OUH	01-374	Male	Control	Yes	Yes	2019-05-17 07:42	Unknown	Unknown	Unknown	Not noted in chart	Not adequately increased GCS	
23	OUH	01-388	Male	Active	Yes	Yes	Unknown	2019-05-25 13:56	2019-05-25 14:15	19		Not adequately increased GCS	
24	OUH	01-395	Male	Active	Yes	Yes	2019-05-26 22:51	Unknown	Unknown	10.0833333333333		No effect on RR	
25	OUH	01-410	Male	Active	Yes	Yes	2019-06-07 14:08	Unknown	Unknown	Unknown	Nt verified	Not adequately increased GCS	
26	OUH	01-463	Male	Control	Yes	Yes	Unknown	2019-08-04 NK:NK	Unknown	10		Not adequately increased GCS	
27	OUH	01-486	Male	Active	Yes	Yes	2019-08-15 13:38	Unknown	2019-08-15 14:10	Unknown	As stated in paper ambulance journal	Not adequately increased GCS	
28	OUH	01-503	Female	Active	Yes	Yes	2019-08-26 02:05	Unknown	2019-08-26 03:05	Unknown	In medical chart	Not adequately increased GCS	
29	OUH	01-671	Male	Active	Yes	Yes	2020-02-05 10:48	Unknown	Unknown	10		Not adequately increased GCS	
32	OUH	01-677	Female	Active	Yes	Yes	2020-02-12 03:25	Unknown	Unknown	Unknown	See chart	Deterioration in clinical state	
33	OUH	01-696	Male	Active	Yes	Yes	Unknown	2020-03-18 09:30	2020-03-18 09:44	14		Not adequately increased GCS	
34	OUH	01-699	Male	Active	Yes	Yes	2020-03-21 14:45	Unknown	Unknown	Unknown	Unknown	Not adequately increased GCS	
35	OUH	01-760	Male	Active	Yes	Yes	2020-05-26 17:41	Unknown	Unknown	10		Not adequately increased GCS	
36	OUH	01-782	Male	Active	Yes	Yes	2020-06-19 14:07	Unknown	Unknown	10		Not adequately increased GCS	
37	OUH	01-803	Male	Control	Yes	Yes	Unknown	2020-06-26 03:08	Unknown	10		Not adequately increased GCS	
38	OUH	01-819	Male	Control	Yes	Yes	2020-07-07 06:22	Unknown	2020-07-07 07:01	Unknown	Stated clearly in chart	Not adequately increased GCS	
39	St Olav's	02-009	Male	Control	Yes	Yes	Unknown	2018-06-29 NK:NK	2018-06-29 19:42	Unknown	Chart St. Olavs, see comments section VieDoc	Not adequately increased GCS	
40	St Olav's	02-010	Female	Control	Yes	Yes	2018-07-10 15:17	Unknown	Unknown	Unknown	More than 10 minutes after IMP, see study form	Not adequately increased GCS	
41	St Olav's	02-034	Male	Active	Yes	Yes	Unknown	2018-11-03 12:45	Unknown	12		Not adequately increased GCS	
42	St Olav's	02-060	Male	Active	Yes	Yes	Unknown	2019-05-28 12:34	Unknown	14		Not adequately increased GCS	
43	St Olav's	02-061	Female	Active	Yes	Yes	2019-06-08 19:03	Unknown	Unknown	10		Not adequately increased GCS	
44	St Olav's	02-086	Male	Active	Yes	Yes	2019-11-20 23:15	Unknown	Unknown	11		Not adequately increased GCS	
45	St Olav's	02-095	Male	Active	Yes	Yes	Unknown	2020-04-05 14:45	2020-04-05 15:06	21		Deterioration in clinical state	
46	St Olav's	02-107	Male	Active	Yes	Yes	2020-05-14 18:46	Unknown	Unknown	10		Not adequately increased GCS	

TimeSinceStudyDrugAdm = Time since study drug administration in minutes.

Table 12: Timing of rescue Nalaxone in those that recieved rescue naloxone (FAS and witdrawed patients).

	level	Control	Active
n		15	31
Rescue Nalaxone given >= 10 min. (%)	Unknown	10 (66.7)	15 (48.4)
	Yes	5 (33.3)	16 (51.6)

Table 13: Use of rescue Nalaxone in patients that refused or withdrew consent.

Center	SubjectId	Sex	treatGr	Needed	Recieved	overdoseTime	studyMedTime	rescueNalaxoneTime	TimeSinceStudyDrugAdm	TimeNB	Reason	Reason_not_give
OUH	01-057	Unknown	Control	Yes	Yes	Unknown	Unknown	Unknown	Unknown	see chart	Not adequately increased GCS	
OUH	01-063	Female	Active	Yes	Yes	Unknown	Unknown	Unknown	Unknown	see chart	Only given IMP IM, given non-IMP for safety	
OUH	01-287	Male	Active	Yes	Yes	Unknown	Unknown	Unknown	Unknown	see chart	Not adequately increased GCS	
OUH	01-288	Male	Control	Yes	Yes	Unknown	Unknown	Unknown	Unknown	Time unknown	Not adequately increased GCS	
OUH	01-675	Male	Control	Yes	Yes	Unknown	Unknown	Unknown	Unknown	see chart, not stated in database du to anonymization	IMP not given correctly Injection given IV,	
OUH	01-676	Female	Active	Yes	Yes	Unknown	Unknown	2020-01-23 18:07	Unknown	Stated clearly in chart	Not adequately increased GCS	

Study medication not according to protocol

Table 14: Study medication given, but protocol deviations.

SiteName	SubjectId	treatmentGr	drugAccordingProtocol	intramuscularAsPlanned	intranasalAsPlanned	muscularNote	nasalNote
OUH	01-018	Control	No	No	Yes	1 ml. given. Due to chart - chaotic environment	
OUH	01-048	Active	No	Yes	Yes		
OUH	01-068	Control	Yes	No	No	Injection was given prior to nasal spray	Injection was given prior to nasal spray
OUH	01-221	Control	No	Yes	Yes		
OUH	01-274	Control	No	No	Yes	given 1.0 ml IM study medicine	
OUH	01-281	Active	Yes	No	No	IM injection given 10 sec. prior to nasal injection	Nasal injection given 10 sec. after IM
OUH	01-592	Control	No	Yes	Yes		
OUH	01-600	Active	Yes	No	Yes	Given in femoral muscle, note to file written, discussed in study team	
OUH	01-686	Active	No	No	Yes	Spoils some fluid from leak between syringe and needle.	
St Olav's	02-094	Control	No	No	Yes	Given 45 seconds after IN	

Table 14 continued.

SiteName	SubjectId	treatmentGr	noteOther	population
OUH	01-018	Control		FAS
OUH	01-048	Active	RF 8/min + GCS = 12	FAS
OUH	01-068	Control		PP
OUH	01-221	Control	Freeze watch released prior to drug administration. Patient should have been excluded.	FAS
OUH	01-274	Control	Given 1.0 ml IM	FAS
OUH	01-281	Active		PP
OUH	01-592	Control	Freeze watch was cracked. Study workers did not notice. Kit used.	FAS
OUH	01-600	Active		PP
OUH	01-686	Active	Spoils some fluid from leak between syringe and needle.	FAS
St Olav's	02-094	Control	IM 45 seconds after IN, too long	FAS

Exclusions

Table 15: Reasons for exclusions.

Reason	Freq
Cardiac arrest, EMS staff without training as study workers	1
Deemed unfit for inclusion due to any other cause by study personnel at the scene; such as unsafe work environment for EMS	43
EMS staff without training as study workers	38
EMS staff without training as study workers, Deemed unfit for inclusion due to any other cause by study personnel at the scene; such as unsafe work environment for EMS	5
Failure to assist ventilation using maskbag technique	2
Failure to assist ventilation using maskbag technique, Deemed unfit for inclusion due to any other cause by study personnel at the scene; such as unsafe work environment for EMS	1
Failure to assist ventilation using maskbag technique, Participant that have received nasal naloxone by any route in the current overdose	1
Glasgow Coma Scale (GCS) below 12 and	28
Glasgow Coma Scale (GCS) below 12 and, Deemed unfit for inclusion due to any other cause by study personnel at the scene; such as unsafe work environment for EMS	5
Glasgow Coma Scale (GCS) below 12 and, EMS staff without training as study workers	3
Glasgow Coma Scale (GCS) below 12 and, Latrogenic opioid overdose when opioid is administered inhospital, or by EMS or other health care workers in the pre hospital setting	2

Table 15 continued: Reasons for exclusions.

Reason	Freq
Glasgow Coma Scale (GCS) below 12 and, Participant that have received nasal naloxone by any route in the current overdose	1
Latrogenic opioid overdose when opioid is administered inhospital, or by EMS or other health care workers in the pre hospital setting	2
Latrogenic opioid overdose when opioid is administered inhospital, or by EMS or other health care workers in the pre hospital setting, EMS staff without training as study workers	1
Miosis	3
Miosis, Deemed unfit for inclusion due to any other cause by study personnel at the scene; such as unsafe work environment for EMS	2
Miosis, Glasgow Coma Scale (GCS) below 12 and	1
Miosis, Palpable carotid or radial arterial pulse, EMS staff without training as study workers	1
No study drug available	2
Palpable carotid or radial arterial pulse, Cardiac arrest	4
Palpable carotid or radial arterial pulse, Cardiac arrest, Participant that have received nasal naloxone by any route in the current overdose	1
Participant in prison or custody by police	1
Participant in prison or custody by police, EMS staff without training as study workers	1
Participant that have received nasal naloxone by any route in the current overdose	34
Participant that have received nasal naloxone by any route in the current overdose, Deemed unfit for inclusion due to any other cause by study personnel at the scene; such as unsafe work environment for EMS	1
Participant that have received nasal naloxone by any route in the current overdose, EMS staff without training as study workers	1
Participant that have received nasal naloxone by any route in the current overdose, Participant in prison or custody by police	1
Reduced (below 8 breaths per minute) or absent spontaneous respiration	195
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Deemed unfit for inclusion due to any other cause by study personnel at the scene; such as unsafe work environment for EMS	14
Reduced (below 8 breaths per minute) or absent spontaneous respiration, EMS staff without training as study workers	29
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Facial trauma or epistaxis or visible nasal blockage	2
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Failure to assist ventilation using maskbag technique, EMS staff without training as study workers	1

Table 15 continued: Reasons for exclusions.

Reason	Freq
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Glasgow Coma Scale (GCS) below 12 and	125
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Glasgow Coma Scale (GCS) below 12 and, Deemed unfit for inclusion due to any other cause by study personnel at the scene; such as unsafe work environment for EMS	5
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Glasgow Coma Scale (GCS) below 12 and, EMS staff without training as study workers	7
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Glasgow Coma Scale (GCS) below 12 and, Latrogenic opioid overdose when opioid is administered inhospital, or by EMS or other health care workers in the pre hospital setting	4
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Glasgow Coma Scale (GCS) below 12 and, Latrogenic opioid overdose when opioid is administered inhospital, or by EMS or other health care workers in the pre hospital setting, EMS staff without training as study workers	2
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Glasgow Coma Scale (GCS) below 12 and, No study drug available	1
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Glasgow Coma Scale (GCS) below 12 and, Participant in prison or custody by police	1
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Glasgow Coma Scale (GCS) below 12 and, Participant in prison or custody by police, Deemed unfit for inclusion due to any other cause by study personnel at the scene; such as unsafe work environment for EMS	1
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Glasgow Coma Scale (GCS) below 12 and, Participant that have received nasal naloxone by any route in the current overdose	17
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Glasgow Coma Scale (GCS) below 12 and, Participant that have received nasal naloxone by any route in the current overdose, EMS staff without training as study workers, Deemed unfit for inclusion due to any other cause by study personnel at the scene; such as unsafe work environment for EMS	1
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Latrogenic opioid overdose when opioid is administered inhospital, or by EMS or other health care workers in the pre hospital setting	2
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Miosis	33

Table 15 continued: Reasons for exclusions.

Reason	Freq
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Miosis, Deemed unfit for inclusion due to any other cause by study personnel at the scene; such as unsafe work environment for EMS	1
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Miosis, EMS staff without training as study workers	5
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Miosis, EMS staff without training as study workers, Deemed unfit for inclusion due to any other cause by study personnel at the scene; such as unsafe work environment for EMS	1
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Miosis, Failure to assist ventilation using maskbag technique, Facial trauma or epistaxis or visible nasal blockage, EMS staff without training as study workers, Deemed unfit for inclusion due to any other cause by study personnel at the scene; such as unsafe work environment for EMS	1
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Miosis, Glasgow Coma Scale (GCS) below 12 and	9
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Miosis, Glasgow Coma Scale (GCS) below 12 and, Deemed unfit for inclusion due to any other cause by study personnel at the scene; such as unsafe work environment for EMS	2
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Miosis, Glasgow Coma Scale (GCS) below 12 and, EMS staff without training as study workers	1
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Miosis, Glasgow Coma Scale (GCS) below 12 and, Latrogenic opioid overdose when opioid is administered inhospital, or by EMS or other health care workers in the pre hospital setting	2
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Miosis, Glasgow Coma Scale (GCS) below 12 and, Palpable carotid or radial arterial pulse, Deemed unfit for inclusion due to any other cause by study personnel at the scene; such as unsafe work environment for EMS	2
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Miosis, Glasgow Coma Scale (GCS) below 12 and, Palpable carotid or radial arterial pulse, EMS staff without training as study workers	1

Table 15 continued: Reasons for exclusions.

Reason	Freq
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Miosis, Glasgow Coma Scale (GCS) below 12 and, Palpable carotid or radial arterial pulse, Participant that have received nasal naloxone by any route in the current overdose	1
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Miosis, Glasgow Coma Scale (GCS) below 12 and, Participant that have received nasal naloxone by any route in the current overdose	4
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Miosis, Latrogenic opioid overdose when opioid is administered inhospital, or by EMS or other health care workers in the pre hospital setting, Participant that have received nasal naloxone by any route in the current overdose, Deemed unfit for inclusion due to any other cause by study personnel at the scene; such as unsafe work environment for EMS	1
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Miosis, Palpable carotid or radial arterial pulse, Failure to assist ventilation using maskbag technique, EMS staff without training as study workers	1
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Miosis, Palpable carotid or radial arterial pulse, Latrogenic opioid overdose when opioid is administered inhospital, or by EMS or other health care workers in the pre hospital setting, EMS staff without training as study workers	1
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Miosis, Participant that have received nasal naloxone by any route in the current overdose	2
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Palpable carotid or radial arterial pulse, Latrogenic opioid overdose when opioid is administered inhospital, or by EMS or other health care workers in the pre hospital setting	1
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Participant in prison or custody by police	1
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Participant that have received nasal naloxone by any route in the current overdose	12
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Participant that have received nasal naloxone by any route in the current overdose, Deemed unfit for inclusion due to any other cause by study personnel at the scene; such as unsafe work environment for EMS	1
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Participant that have received nasal naloxone by any route in the current overdose, EMS staff without training as study workers	2
Reduced (below 8 breaths per minute) or absent spontaneous respiration, Suspected participant below 18 years of age	1
TOTAL	679

Table 16: Number of times each exclusion criteria was used (items marked * are inclusion criterias (No. of times not satisfied)).

Criterion	Frequency
Reduced (below 8 breaths per minute) or absent spontaneous respiration*	493
Miosis*	75
Glasgow Coma Scale (GCS) below 12*	226
Palpable carotid or radial arterial pulse*	13
Cardiac arrest	6
Failure to assist ventilation using mask- bag technique	7
Facial trauma or epistaxis or visible nasal blockage	3
Latrogenic opioid overdose when opioid is adm. in-hospital, by EMS or other health care workers in the pre hospital setting	18
Suspected participant below 18 years of age	1
Suspected or visibly pregnant participant	0
Participant that have received naloxone by any route in the current overdose	81
Participant in prison or custody by police	6
EMS staff without training as study workers	104
No study drug available	3
Study drug frozen as indicated by Freeze Watch in kit or past its expiry date	0
Deemed unfit for inclusion due to any other cause by study personnel at the scene; such as unsafe work environment for EMS	87

Table 17: Overdose charactersistics for overdoses in the FAS (see flow chart) vs. those not in the FAS (those that are ineligible or woke up before treatment was given, i.e. thos who exited the flow chart prior to the FAS). Patients that did not give consent are not included. Column n_var gives the number of observations per variable. Mean (sd) of continous variables are calculated for patients without missing values.

			In FAS		Overall
	n_var		No	Yes	
n			727	208	935
Center (%)	935	OUH	620 (85.3)	193 (92.8)	813 (87.0)
		St Olav's	107 (14.7)	15 (7.2)	122 (13.0)
Sex (%)	935	Female	177 (24.3)	37 (17.8)	214 (22.9)
		Male	534 (73.5)	169 (81.2)	703 (75.2)
		Unknown	16 (2.2)	2 (1.0)	18 (1.9)
Follow-up (%)	935	Adm. hospital	206 (28.3)	22 (10.6)	228 (24.4)
		Dead	1 (0.1)	0 (0.0)	1 (0.1)
		Left at scene	287 (39.5)	137 (65.9)	424 (45.3)
		Oslo Legevakt	208 (28.6)	44 (21.2)	252 (27.0)
		Other	9 (1.2)	0 (0.0)	9 (1.0)
		Rusakutten Aker	11 (1.5)	5 (2.4)	16 (1.7)
		Trondheim Legevakt	5 (0.7)	0 (0.0)	5 (0.5)
OD location (%)	935	Drug Consumption Room "Sprøyterommet"	141 (19.4)	82 (39.4)	223 (23.9)
		Health institution, medical office	27 (3.7)	0 (0.0)	27 (2.9)
		Other venue	11 (1.5)	3 (1.4)	14 (1.5)
		Private home	129 (17.7)	31 (14.9)	160 (17.1)
		Public place, indoor e.g. car park	88 (12.1)	19 (9.1)	107 (11.4)
		Public place, outdoor	275 (37.8)	68 (32.7)	343 (36.7)
		Shelter, other drug-user facility	49 (6.7)	5 (2.4)	54 (5.8)
		Unknown	7 (1.0)	0 (0.0)	7 (0.7)
Take-home nal. adm. (%)	935	No	642 (88.3)	208 (100.0)	850 (90.9)
		Yes	85 (11.7)	0 (0.0)	85 (9.1)
Route of non-IMP nal. adm. (%)	935	IM	631 (86.8)	0 (0.0)	631 (67.5)
		IV	37 (5.1)	0 (0.0)	37 (4.0)
		Not relevant (in FAS)	0 (0.0)	208 (100.0)	208 (22.2)
		Other	56 (7.7)	0 (0.0)	56 (6.0)
		Unknown	3 (0.4)	0 (0.0)	3 (0.3)
Age (mean (SD))	790		41.69 (14.12)	37.86 (10.56)	40.77 (13.44)
Primary non-IMP nal. dose (mean (SD))	724		0.48 (0.24)	NaN (NA)	0.48 (0.24)
Total non-IMP nal. dose (mean (SD))	724		0.55 (0.31)	NaN (NA)	0.55 (0.31)

Table 18: Dose of non-IMP naloxone. Column n_var gives the number of observations per variable. Mean (sd) of continous variables are calculated for patients without missing values.

		Take-home naloxone	
	n_var	No	Yes
n		642	85
Primary dose (mean (SD))	724	0.50 (0.22)	0.35 (0.32)
Additional dose (mean (SD))	727	0.07 (0.18)	0.06 (0.21)

Table 19: Dose of non-IMP naloxone. Column n_var gives the number of observations per variable. The 25th, 50th (median), 75th and 90th percentile is presented for those who had gotten take-home naloxone.

		Take-home naloxone							
		No				Yes			
	n_var	25%	50%	75%	90%	25%	50%	75%	90%
Primary dose (indicated percentile)	724	0.4	0.4	0.8	0.8	0	0.4	0.8	0.8
Additional dose (indicated percentile)	727	0	0	0	0.4	0	0	0	0

Table 20: Whether or not non-IMP naloxone is given.

		Take-home naloxone	
	level	No	Yes
n		642	85
Primary dose given (%)	No	22 (3.4)	33 (38.8)
	Unknown	3 (0.5)	0 (0.0)
	Yes	617 (96.1)	52 (61.2)
Additional dose given (%)	No	538 (83.8)	78 (91.8)
	Yes	104 (16.2)	7 (8.2)

Table 21: Mean (sd) of primary dose of non-IMP naloxone given by EMS for those who recieved a dose.

	Take-home naloxone	
level	No	Yes
n	617	52
Primary dose (mean (SD))	0.52 (0.21)	0.57 (0.21)

Table 22: Mean (sd) of additional doses of non-IMP naloxone given by EMS for those who recieved one or more additional doses.

	Take-home naloxone	
level	No	Yes
n	104	7
Additional dose (mean (SD))	0.45 (0.17)	0.69 (0.30)

Table 23: Mean (sd) of total doses of non-IMP naloxone given by EMS for those who recieved at least one dose of non-IMP naloxone

	Take-home naloxone	
level	No	Yes
n	617	52
Total dose (mean (SD))	0.59 (0.27)	0.66 (0.36)

Routes of administration and dose of naloxone in events of opioid overdose (not in the FAS) and subsequent administration of naloxone after the initial dose

```
## [1] "Routes of administration and initial naloxone treatment given by EMS (not in FAS):"
```

```
##              Stratified by EXROUTE
##               level IM            IV           Other        Unknown
##   n           ""    "631"         "37"         "56"         "3"
##   EXDOSE (%) "0"   "  0 ( 0.0) " " 0 ( 0.0) " "55 (98.2) " "0 (  0.0) "
##              "0.1" "  1 ( 0.2) " " 3 ( 8.1) " " 0 ( 0.0) " "0 (  0.0) "
##              "0.2" " 38 ( 6.0) " " 7 (18.9) " " 0 ( 0.0) " "0 (  0.0) "
##              "0.3" "  3 ( 0.5) " " 1 ( 2.7) " " 0 ( 0.0) " "0 (  0.0) "
##              "0.4" "361 (57.2) " "23 (62.2) " " 1 ( 1.8) " "0 (  0.0) "
##              "0.6" "  5 ( 0.8) " " 1 ( 2.7) " " 0 ( 0.0) " "0 (  0.0) "
##              "0.8" "223 (35.3) " " 2 ( 5.4) " " 0 ( 0.0) " "0 (  0.0) "
##              NA    "  0 ( 0.0) " " 0 ( 0.0) " " 0 ( 0.0) " "3 (100.0) "
```

```
## [1] "Routes of administration and subsequent naloxone treatment given by EMS (not in FAS):"
```

```
##              Stratified by EX2ROUTE
##               level IM           IN           IV           None
##   n           ""    "61"         "1"          "48"         "616"
##   addDose (%) "0"   " 0 ( 0.0) " "0 (  0.0) " " 0 ( 0.0) " "616 (100.0) "
##               "0.1" " 0 ( 0.0) " "0 (  0.0) " " 1 ( 2.1) " "  0 (  0.0) "
##               "0.2" " 3 ( 4.9) " "0 (  0.0) " " 3 ( 6.2) " "  0 (  0.0) "
##               "0.4" "49 (80.3) " "1 (100.0) " "34 (70.8) " "  0 (  0.0) "
##               "0.6" " 2 ( 3.3) " "0 (  0.0) " " 1 ( 2.1) " "  0 (  0.0) "
##               "0.8" " 5 ( 8.2) " "0 (  0.0) " " 8 (16.7) " "  0 (  0.0) "
##               "1.2" " 2 ( 3.3) " "0 (  0.0) " " 1 ( 2.1) " "  0 (  0.0) "
##              Stratified by EX2ROUTE
##               Other
##   n           "1"
##   addDose (%) "0 (  0.0) "
##               "0 (  0.0) "
##               "0 (  0.0) "
##               "1 (100.0) "
##               "0 (  0.0) "
##               "0 (  0.0) "
##               "0 (  0.0) "
```

Nalxone given by by EMS in patients treated with bystander naloxone prior to EMS arrival

```
## [1] "Primary route and dose:"
```

```
##              Stratified by EXROUTE
##               level IM           IV           Other
##   n           ""    "49"         "3"          "33"
##   EXDOSE (%) "0"   " 0 ( 0.0) " "0 (  0.0) " "33 (100.0) "
##              "0.2" " 2 ( 4.1) " "0 (  0.0) " " 0 (  0.0) "
##              "0.4" "24 (49.0) " "3 (100.0) " " 0 (  0.0) "
##              "0.8" "23 (46.9) " "0 (  0.0) " " 0 (  0.0) "
```

```
## [1] "Subsequent route and dose:"
```

```
##               Stratified by EX2ROUTE
##                level IM          IV          None
##   n            ""    "2"         "5"         "78"
##   addDose (%) "0"   "0 ( 0.0) " "0 ( 0.0) " "78 (100.0) "
##                "0.4" "1 (50.0) " "2 (40.0) " " 0 (  0.0) "
##                "0.8" "1 (50.0) " "2 (40.0) " " 0 (  0.0) "
##                "1.2" "0 ( 0.0) " "1 (20.0) " " 0 (  0.0) "
```

Note that for the route for the subsequent dose “addDose” (which is EX2DOSE+EX3DOSE), the variable EX2ROUTE (route of second) is used. If the patient recieved a third dose, the route of the third dose might be different than the one listed in the above tables.

Concomitant Medication

Variable names and associated lables:

- CMMED: Medication name.
- CMATC: ATC code.
- CMMEDOTH:Medication name -other.
- CMOTHATC: ATC code (for other medications).
- CMDOS: Dose per administration.
- CMDOSU: Dose units.
- CMROUT: Route of administration.
- CMROUTOT: Other route specification.
- CMINDC: Medical intervention during study.
- CMINDCO: Concomitant disease specification.
- CMINDOTH: Concomitant disease specification -other.

Table 24: Concomitant Medication.

SubjectId	SiteName	CMMED	CMATC	CMMEDOTH	CMOTHATC	CMDOS	CMDOSU	CMROUT	CMROUTOT	CMINDC	CMINDCO	CMINDOTH	TreatGr
02-010	St Olav	Flumazenil	V03AB25	NA	NA	0.2	milligram (mg)	intravenous (iv)		Other		Not adequate GCS response. Given in the hospital	Control
02-017	St Olav	Midazolam	N05CD08	NA	NA	10.0	milligram (mg)	other	intrabuccal	Concomitant disease	epilepsy		NA
01-619	OUH	Morfin	N02AA01	NA	NA	2.0	milligram (mg)	intravenous (iv)		Concomitant disease	Pain after chest compression		Control
01-677	OUH	Stesolid	N05BA01	NA	NA	5.0	milligram (mg)	intravenous (iv)		Adverse Event, please specify AE no.			Active
02-095	St Olav	Flumazenil	V03AB25	NA	NA	0.3	milligram (mg)	intravenous (iv)		Other		Recuded conciousness, suspected benzodiazepines	Active

Protocol deviations

Variable names and associated lables:

- PDCAT: PD category.
- PDCATOTH: PD category -other.
- PDDESC: Description of deviation.
- PDCLAS: PD classification.
- PDRISK: Risk evaluation.
- PDREOTH: Risk evaluation -other.
- PDCAPA: Corrective and preventive action.
- PDAPAYN: Effect on analysis population assignment.
- PDAPACOM: Comment to analysis population assignment.
- PDSTATYN: Is the statistician consulted?

```
## [1] "Numper of protocol deviations (total, incl. if multiple per OD): 36"
## [1] "Numper of OD events with protocol deviations: 30"
## [1] "Numper in fas: 208"
## [1] "Proportion of OD events with (at least one) PD: 0.144230769230769"
## [1] "Active gr.: 14 PDs (at least one) in 95 ODs. Proportion:0.147368421052632"
## [1] "Control gr.: 16 PDs (at least one) in 113 ODs. Proportion:0.141592920353982"
```

Table 25: Protocol deviations.

SubjectId	SiteName	PDCAT	PDCATOTH	PDDESC
02-001	St Olav	Study procedure		Study workers tried to contact study team via study phone /OSlo AMK; were not passed on. Note fo file central level registered. See CTU admin NTF 005
01-018	OUH	Study procedure		Only 1 ml IM study drug administered
01-048	OUH	Selection criteria		RR 8/min. Patient could have been included based in this criteria after protocol version 3.3.
01-048	OUH	Selection criteria		GCS 12/15. Patient excluded as GCS should be below 12 to be included. This is a major deviation.
01-056	OUH	Study procedure		Only given 1 mL IM IMP
01-063	OUH	Study procedure		Given IM study medicine, but IN sprayed in the air by accident from kit 126. Treated with "normal" naloxone with good clinical response. Not asked for consent, despite given study medicine. Not AE reported. Registered in VieDoc as not consented. Study workers have not informed properly, despite patients being competent for oral consent as they have not given nasal IMP. This should have been done, but can not include in database without consent in patient with consent competency
01-068	OUH	Study procedure		IM and IN in different order, but within time
01-069	OUH	Selection criteria		Resp. frequency =8
01-136	OUH	AE/SAE/SUSAR reporting		Under AE says ? under hypothermia. EMS have made no mention in chart, or any actions against any hypothermia. Patient left at scene. Deemed not relevant and uncertain information.
01-136	OUH	Other	Database does not cover observation time interval	Chart har two clinical observation within 10 minutes, one at 18.07 and one at 18.08. As the database does not adequately cater for this, and they are very close in time I have recorded the last of the two (18.08) as these are the variables that leads to the patient being discharged at the scene.
01-137	OUH	Other	database response within 10 minutes	Two observation within 10 minutes, last (13.23) entered into database
01-200	OUH	AE/SAE/SUSAR reporting		AE form filled out by mistake. Patient is a non responder.
01-221	OUH	Selection criteria		3M freeze watch indicated kit exposed to frost prior to IMP, Study workers did a mistake and proceeded with inclusion
01-249	OUH	Other	Unable to connect kit to specific patient. IMP not administered due to freeze watch release	Unsure which patient kit opened in connection to
01-274	OUH	Study procedure		Given too little IM IMP
01-281	OUH	Study procedure		IM given before IN, but within 30 seconds. Discussed with DMC, minor deviation, should be included in Per protocol set
01-281	OUH	Study procedure		stoppeklokke fungerte ikke, ambulansepersonell brukte privat klokke
01-285	OUH	Study procedure		Longer than 30 seconds between IN spray and IM injection
01-288	OUH	Study procedure		Study drug administered despite freeze watch being activated. Information from Rune Wie confirms ambulance has been exposed to frost
01-308	OUH	Study procedure		patient woke up during treatment, only admnistered IMP IN, not intramuscular injection given. APtient woku up, and did not consent to use of data in trial. registered in anonymous safety set
01-336	OUH	Concent procedure		Not willing to receive written in formation, but gave oral consent. Discussed in study team and DMC, minor deviation, included in Per protocol set
01-337	OUH	Concent procedure		Included by staff at ambulance 255 (approved study workers), but after treatment transported to hospital by staff at 257 (not approved study workers). This meant that any questions medical team at Diakonhjemmet may have had could not be answered by EMS.
01-344	OUH	Concent procedure		Patient included with only one approved study worker. Case otherwise conducted due to protocol. Patient have given informed consent.
01-380	OUH	AE/SAE/SUSAR reporting		Paper CRF not fully filled inn in AE section, but ambulance journal does not report or indikcate AE, patient allowed to leave the scene.
01-592	OUH	Selection criteria		included despite kit being exposed to frost.
01-600	OUH	Study procedure		IM injection given in femoral muscle. This because he was wearing a lot of clothes and the deltoid muscle was hard to access
01-610	OUH	Study procedure		Not been able to trace which ambulance mission kit 300 was opened at. Nasal spray not activated. IM vial holds 8 mL (2 mL aspirated) Presumed not to be administered patient
01-617	OUH	Concent procedure		Participant not given information about inclusion. We have tried to call him at 93680417 5th Des 2019 with no answer. We will leave infomation in his file at the Safe Injection Facility and check that he has received info during the next weeks.
01-617	OUH	Concent procedure		Please see attached email and previous note to file regarding participant 01-617. We are confident he has received information about inclusion, and we will be included in the database. If he contacts us at a later point for withdrawal normal procedures will be followed.
01-649	OUH	Concent procedure		Patient not engaged in meaningful conversation with study crew, and ability consent must be questioned. He receive information and is given the opportunity to withdraw. He is included several times, and has never refused.
01-675	OUH	Study procedure		Comparator study medicine administered IV not IM.
01-675	OUH	Concent procedure		Patient not informed about inclusion by study workers, not given a chance to consent or not. Letter with study information sent to address and attempted to call by telephone, but no reply. We assume "non- consent" and include in anonymous safety set.
01-676	OUH	Concent procedure		Patient admitted to hospital, not given oral or written information regarding inclusion in trial
02-094	St Olav	Study procedure		period bweteen IN and IM admnistration is 45 seconds, 15 seconds longer than the time described in the protcol. This deviation had been discussed in the study team, and found to be minor and allow population assignment to "per protocol population"
02-094	St Olav	Study procedure		45 seconds between IN and IM
01-837	OUH	Concent procedure		Patient not informed orally and not given written information. Hence not being able to consent/ withdraw the patient is included in the anonymous dataset.

Table 25 continued: Protocol deviations.

SubjectId	SiteName	PDCLAS	PDRISK	PDREOTH	PDCAPA
02-001	St Olav	Major	Patient safety		See CTU admin NTF 005
01-018	OUH	Minor	Scientific/data integrity		Increase training
01-048	OUH	Minor	Scientific/data integrity		No
01-048	OUH	Major	Scientific/data integrity		Teaching of study workers
01-056	OUH	Minor	Scientific/data integrity		teaching
01-063	OUH	Major	Scientific/data integrity		Informed study works about consent in all patient receiving any study drug.
01-068	OUH	Minor	Scientific/data integrity		Non
01-069	OUH	Major	Scientific/data integrity		Not included in PP analysis (subject to review with DMSC)
01-136	OUH	Minor	Other	No risk	Non taken
01-136	OUH	Minor	Other	Database	Non
01-137	OUH	Minor	Other	database	Non
01-200	OUH	Minor	Other	SAE form filled in without and AE bein present	Admitted to hospital - OUS-U
01-221	OUH	Major	Scientific/data integrity		Re education of stud workers in question and email to all stud workers nation wide reminding them of the frost indicator and inclusion criteria
01-249	OUH	Major	Other	Non	Non
01-274	OUH	Minor	Scientific/data integrity		Teaching
01-281	OUH	Minor	Scientific/data integrity		Non
01-281	OUH	Minor	Scientific/data integrity		ingen
01-285	OUH	Minor	Scientific/data integrity		Non
01-288	OUH	Major	Scientific/data integrity		<renew teaching regarding freeze watch
01-308	OUH	Major	Scientific/data integrity		teaching study staff to prepare injection site prior to administration of spray
01-336	OUH	Minor	Patients rights and welfare		Non
01-337	OUH	Minor	Other	Information at handover	Spoken to staff involved, Case will be distributed to all study workers in next info letter from study team,
01-344	OUH	Minor	Patients rights and welfare		EMS nr 3000 checked out as study worker, information regarding this reiterated in next newsletter.
01-380	OUH	Minor	Scientific/data integrity		Informed study workers on need to comply with training
01-592	OUH	Major	Scientific/data integrity		repeated teaching of study workers
01-600	OUH	Minor	Scientific/data integrity		Been in contact with ambulance worker 2702
01-610	OUH	Major	Scientific/data integrity		Remind study workers always to link kits to AMIS data/ ambulance mission
01-617	OUH	Major	Patients rights and welfare		Individuak EMS have been contacted
01-617	OUH	Major	Patients rights and welfare		Reminded not to leave info letter at Sprøyterommet
01-649	OUH	Minor	Patients rights and welfare		Explained study crew difficulty in assessing consent when not answering clearly
01-675	OUH	Minor	Scientific/data integrity		informed individual study workers
01-675	OUH	Major	Patients rights and welfare		Information to study workers
01-676	OUH	Major	Patients rights and welfare		Discussed procedure With study crew. Contacted Diakonhjemmet Hospital as soon as deviation seen to try to Reach patient, With no success
02-094	St Olav	Minor	Scientific/data integrity		Reminded study workers of protocol
02-094	St Olav	Major	Scientific/data integrity		non
01-837	OUH	Major	Patients rights and welfare		Spoken to study workers

Table 25 continued: Protocol deviations.

SubjectId	SiteName	PDAPAYN	PDAPACOM	PDSTATYN	TreatGr	population
02-001	St Olav	No		No	Control	PP
01-018	OUH	Yes		No	Control	FAS
01-048	OUH	Yes	Personal communication Inge Christoffersen 12th July 2018	Yes	Active	FAS
01-048	OUH	Yes	Patient placed in Full Analysis Set, not Per Protocol population	No	Active	FAS
01-056	OUH	Yes		No	Active	Safety (no consent)
01-063	OUH	Yes		No	Active	Safety (no consent)
01-068	OUH	No	Has been discussed with DMC, as both are given within 30 seconds protocol divination is minor, and patient should be included in "per protocol analysis set"	No	Control	PP
01-069	OUH	Yes		No	Active	PP
01-136	OUH	No		No	Control	PP
01-136	OUH	No		No	Control	PP
01-137	OUH	No		No	Active	PP
01-200	OUH	No		No	Active	PP
01-221	OUH	Yes	To be discussed later if "full analysis" or removed because of major breech (GCP E9)	No	Control	FAS
01-249	OUH	Yes	ITT	No	Control	Woke up
01-274	OUH	Yes	Not per protocol analysis set	No	Control	FAS
01-281	OUH	No	See DMC discussion 19.05.2019	No	Active	PP
01-281	OUH	No	antar at privat klokke måler tid 0-10 minutter like presis som stoppeklokke	No	Active	PP
01-285	OUH	No		No	Active	Safety (no consent)
01-288	OUH	Yes		No	Control	Safety (no consent)
01-308	OUH	Yes		No	Active	Safety (no consent)
01-336	OUH	No		No	Control	PP
01-337	OUH	No	Discussed with DMC, should be included in Per Protocol set	No	Control	PP
01-344	OUH	No		No	Control	PP
01-380	OUH	No		No	Active	PP
01-592	OUH	Yes	not in per protocol st	No	Control	FAS
01-600	OUH	No		No	Active	PP
01-610	OUH	No		No	Control	Woke up
01-617	OUH	No		No	Active	PP
01-617	OUH	No		No	Active	PP
01-649	OUH	No		No	Control	PP
01-675	OUH	Yes	ITT	No	Control	Safety (no consent)
01-675	OUH	Yes		No	Control	Safety (no consent)
01-676	OUH	Yes	IS withdrawn from participation and placed in anonymous safetyset	No	Active	Safety (no consent)
02-094	St Olav	No		No	Control	FAS
02-094	St Olav	Yes	Case discussed at meeting of Safety Committee meeting 29th Sept 2020. Protocoldeviation deemed to be major, and that patient should be included in Full Analysis Set	Yes	Control	FAS
01-837	OUH	Yes		No	Active	Safety (no consent)

Timeframes of ambulance dispatchment

Dispatch time (time from AMK alerted to arrival at scene) and total time (time from AMK alerted to dispatch finished) FAS:

```
## [1] "No. events in FAS: 208"
```

```
## [1] "No. left at scene FAS: 137"
```

```
## [1] "No. not left at scene FAS: 71"
```

```
##                                          n_var level Control
## n                                        ""    ""    "  113"
## responseTime (mean (SD))                 "207" ""    " 5.50 (3.57)"
## totalTime (mean (SD))                    "206" ""    "64.79 (20.64)"
## timeTreatStartToHandover (mean (SD))     "71"  ""    "34.15 (15.01)"
## timeTreatStartToLeftAtScene (mean (SD)) "135" ""    "49.95 (17.89)"
##                                          Active          Overall
## n                                        "   95"         "  208"
## responseTime (mean (SD))                 " 6.22 (4.49)"  " 5.83 (4.03)"
## totalTime (mean (SD))                    "72.94 (27.28)" "68.55 (24.22)"
## timeTreatStartToHandover (mean (SD))     "44.82 (15.17)" "39.86 (15.92)"
## timeTreatStartToLeftAtScene (mean (SD)) "51.60 (17.69)" "50.64 (17.76)"
```

Where

“responseTime” = Dispatch time, time from AMK alerted to arrival at scene.

“totalTime” = Time from AMK alerted to dispatch finished.

“timeTreatStartToHandover” = Time from arrival at scene to minimum of time of handover time and time of dispatch finished.For patients that were not left at scene.

“timeTreatStartToLeftAtScene” = Time from arrival at scene to minimum of time of departure from scene and time of dispatch finished. For patients that were left at scene.

The same table for the PP set:

```
## [1] "No. events in PP: 201"
```

```
##                                          n_var level Control
## n                                        ""    ""    "  108"
## responseTime (mean (SD))                 "200" ""    " 5.45 (3.55)"
## totalTime (mean (SD))                    "199" ""    "64.22 (20.61)"
## timeTreatStartToHandover (mean (SD))     "68"  ""    "33.53 (14.77)"
## timeTreatStartToLeftAtScene (mean (SD)) "131" ""    "49.70 (18.05)"
##                                          Active          Overall
## n                                        "   93"         "  201"
## responseTime (mean (SD))                 " 6.15 (4.44)"  " 5.78 (3.99)"
## totalTime (mean (SD))                    "73.01 (27.56)" "68.33 (24.44)"
## timeTreatStartToHandover (mean (SD))     "44.82 (15.17)" "39.84 (15.92)"
## timeTreatStartToLeftAtScene (mean (SD)) "51.29 (17.94)" "50.37 (17.95)"
```

Inclusion rate: Full analysis set (FAS)

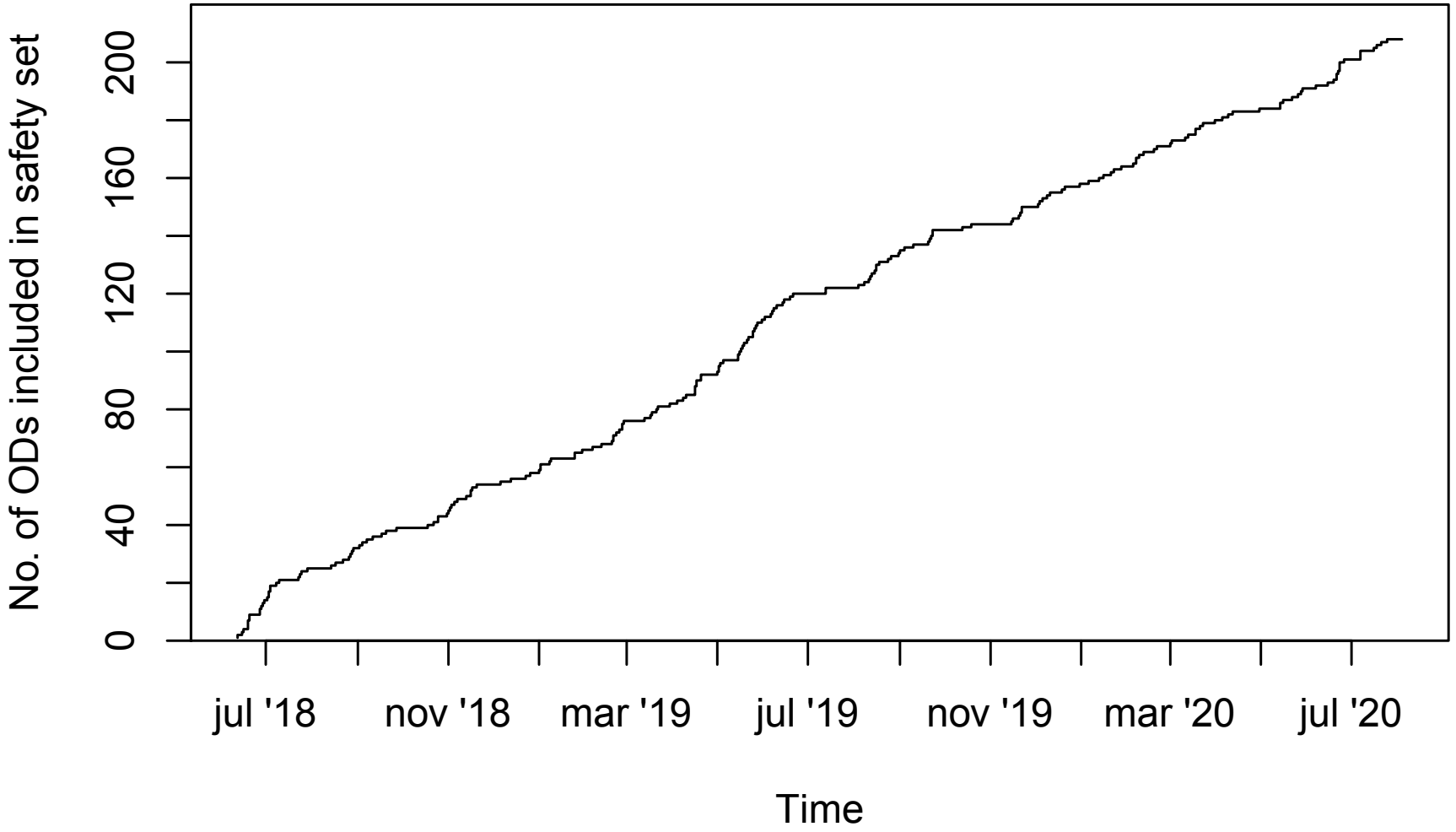

Figure 5: Inclusion of overdoses (in FAS, see flow chart).

FAS: First and last patient

```
## [1] "Total number (of overdoses): 208"
## [1] "Date of first patient in: 2018-06-12"
## [1] "Date of last patient in: 2020-08-04"
```

Inclusion rate: Per Protocol Set

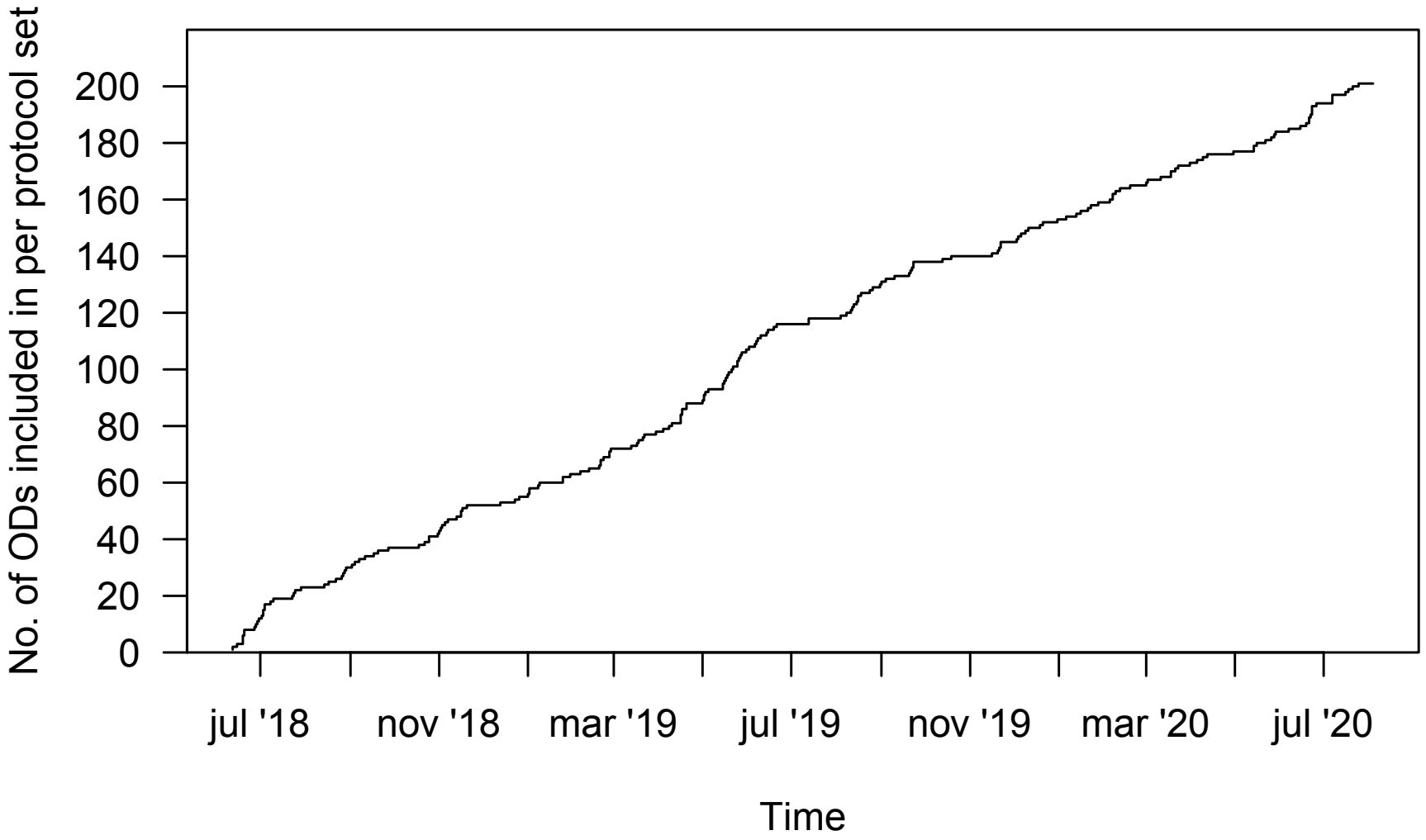

Figure 6: Inclusion of patients (in per protocol, see flow chart). Note that the numbers represents overdoses, not individuals.

PP: First and last patient

```
## [1] "Total number (of overdoses): 201"
## [1] "Date of first patient in: 2018-06-12"
## [1] "Date of last patient in: 2020-08-04"
```

Primary analyses (per protocol)

The analyses in this report complices with the Statistical analysis plan (SAP) of the NINA-1 study. The primary analysis of the primary and secondary endpoint is conducted in the per protocol (PP) population. Sensitivity analyses will be conducted in the Full analysis set (FAS).

Baseline overdose characteristics

Baseline characteristics are given in Table 26.

Table 26: Baseline overdose event charactersistics. Column n_var gives the number of observations per variable.

			Treatment Group		
	n_var		Control	Active	Overall
n			108	93	201
Center (%)	201	OUH	101 (93.5)	86 (92.5)	187 (93.0)
		St Olav's	7 (6.5)	7 (7.5)	14 (7.0)
Sex (%)	201	Female	19 (17.6)	17 (18.3)	36 (17.9)
		Male	88 (81.5)	75 (80.6)	163 (81.1)
		Unknown	1 (0.9)	1 (1.1)	2 (1.0)
Season (%)	201	Autumn	17 (15.7)	20 (21.5)	37 (18.4)
		Spring	28 (25.9)	26 (28.0)	54 (26.9)
		Summer	39 (36.1)	31 (33.3)	70 (34.8)
		Winter	24 (22.2)	16 (17.2)	40 (19.9)
Time of week (%)	201	Mon-Thu	70 (64.8)	57 (61.3)	127 (63.2)
		Fri-Sun	38 (35.2)	36 (38.7)	74 (36.8)
Time of day (%)	201	Day (7:00-17:59)	56 (51.9)	57 (61.3)	113 (56.2)
		Evening (18:00-23:59)	34 (31.5)	21 (22.6)	55 (27.4)
		Night (00-6:59)	18 (16.7)	15 (16.1)	33 (16.4)
Baseline GCS (%)	201	<=3	86 (79.6)	71 (76.3)	157 (78.1)
		>3	22 (20.4)	22 (23.7)	44 (21.9)
Baseline resp. rate (%)	201	0	30 (27.8)	26 (28.0)	56 (27.9)
		>0	78 (72.2)	67 (72.0)	145 (72.1)
OD location (%)	201	Safe env. (sprøyterommet)	51 (47.2)	29 (31.2)	80 (39.8)
		Unsafe env.	57 (52.8)	64 (68.8)	121 (60.2)
Primary suspected drug (%)	201	Heroin	106 (98.1)	90 (96.8)	196 (97.5)
		Methadone	0 (0.0)	1 (1.1)	1 (0.5)
		Other opioids	2 (1.9)	2 (2.2)	4 (2.0)
Route of prim. susp. drug (%)	201	IV	106 (98.1)	88 (94.6)	194 (96.5)
		PO	0 (0.0)	1 (1.1)	1 (0.5)
		Unknown	2 (1.9)	4 (4.3)	6 (3.0)
Benz./GHB/Alc. one of drugs (%)	201	No	89 (82.4)	77 (82.8)	166 (82.6)
		Yes	19 (17.6)	16 (17.2)	35 (17.4)
Identity known (%)	201	Yes	100 (92.6)	83 (89.2)	183 (91.0)
		No	8 (7.4)	10 (10.8)	18 (9.0)
Dispatch time in min. (mean (SD))	200		5.45 (3.55)	6.15 (4.44)	5.78 (3.99)
Baseline oxygen sat. (mean (SD))	159		75.32 (18.21)	79.20 (17.65)	77.05 (18.01)
Age (mean (SD))	183		37.27 (10.17)	38.54 (10.80)	37.85 (10.45)

Mean (sd) of continous variables are calculated for patients without missing values.

```
## [1] "No. of overdose events with missing information on age of patient: 18"
```

```
## [1] "No. of overdose events with missing information on baseline oxygen sat.: 42"
```

```
## [1] "OD location expanded (numbers):"
```

```
##
## Drug Consumption Room "Sprøyterommet"                          Other venue
##                                    80                                    3
##                           Private home    Public place, indoor e.g. car park
##                                    31                                   17
##                 Public place, outdoor     Shelter, other drug-user facility
##                                    66                                    4
```

```
## [1] "OD location expanded (percentage):"
```

```
##
## Drug Consumption Room "Sprøyterommet"                          Other venue
##                               39.800995                             1.492537
##                           Private home    Public place, indoor e.g. car park
##                               15.422886                             8.457711
##                 Public place, outdoor     Shelter, other drug-user facility
##                               32.835821                             1.990050
```

Primary endpoint

The primary endpoint on the NINA-1 trial is the return to spontaneous respiration (above or equal to 10 breaths per minute) within 10 minutes og naloxone administration. The experimental arm of the trial recieves naloxone intranasal (IN), and the control arm recieves the naloxone intramuscular (IM). These two groups will be referred to either as Active or IN and Control or IM, respectively.

This is a non-inferiority trial, where the non-inferiority margin is set to $\Delta = 0.15$. That is, non-inferiority is claimed if the risk difference of having a positive outcome ($p_{IM} - p_{IN}$) has a 95% confidence interval with an upper bound less than 0.15. Hence, the null hypothesis is

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

and the alternative hypothesis is that

$$H_1 : p_{IM} - p_{IN} \leq \Delta.$$

The primary hypothesis is assessed by analysing the primary endpoint by a logistic regression model, adjusting the treatment variable for study center (which was the stratification variable used in the randomization). To take into account that the same individual may have had several overdoses and may thus have been included several times in the trial, the model is fitted using generelized estimating equations with exchangable working correlation. The `geepack` in `R` was used. From the model, the difference in the marginal predicted probabilities between the groups are calculated. The upper bound of the confidence interval of this risk difference is then compared to Δ.

The result of the primary analysis of the primary endpoint is given in Figure 7 and in Table 27.

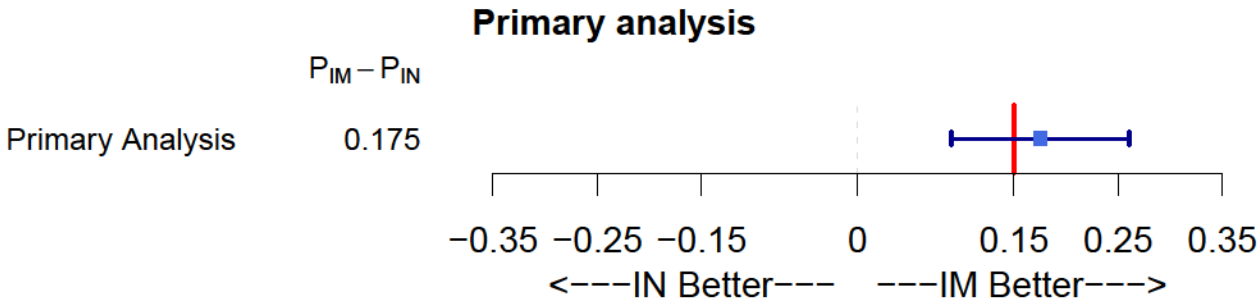

Figure 7: Results of the primary analysis of the primary endpoint. The risk difference with 95% CI is dispalyed. The red vertical lines represents the non-inferiority margin.

Subgroup analyses

Several subgroup analyses was specified in the SAP. Each of these were analyzed in a similar way as the primary analysis of the primary endpoint, with the addition of the inclusion of an interaction term between the variable in question and the treatment variable. The results from these analyses is given in Figure 8 and Table 27.

Because of a low number of non-events (i.e. those with a negative outcome), there could be problems when calcualting CIs for the subgroups. There could be problems with the following variables:

```
## [1] "Sex"                "OD Location"        "Age 2 cat."
## [4] "Benz/GHB/Alc"       "GCS"                "Resp. rate baseline"
```

Table 27: Results from primary and subgroup analyses of the primary endpoint. The risk difference (Control - Active) of returning to spontaneous breathing within 10 minutes is given with 95% confidence intervals. [1] Exchangable correlation structure not possible due to separation issues, independent correlation structure used instead. [2] Adjustment for centre not possible due to separation issues.

	Risk difference			Risk in control gr.			Risk in active gr.		
	Margin	Lower CI (95%)	Upper CI (95%)	Margin	Lower CI (95%)	Upper CI (95%)	Margin	Lower CI (95%)	Upper CI (95%)
Primary	0.1752933	0.0898525	0.2607340	0.9713654	0.9393895	1	0.7960721	0.7159867	0.8761576
Sex: Male	0.1753369	0.0804881	0.2701857	0.9762847	0.9439227	1	0.8009477	0.7109335	0.8909620
Sex: Female	0.1864132	-0.0207350	0.3935613	0.9490755	0.8494363	1	0.7626624	0.5806729	0.9446518
Location: Safe env. (Sprøyterommet) [1,2]	0.1034483	-0.0571476	0.2640442	1.0000000	1.0000000	1	0.8965517	0.7595951	1.0000000
Location: Unsafe env./other [1,2]	0.1973684	0.0296315	0.3651054	0.9473684	0.8926929	1	0.7500000	0.5767620	0.9232380
Age (2 cat.): <= mean [1]	0.1890272	0.0450619	0.3329924	0.9455756	0.8842921	1	0.7565484	0.6254422	0.8876546
Age (2 cat.): > mean [1]	0.2142081	0.1017760	0.3266403	1.0000000	1.0000000	1	0.7857919	0.6733597	0.8982240
Benz/GHB/Alc one of drugs: No	0.1786582	0.0833782	0.2739381	0.9762712	0.9440578	1	0.7976130	0.7078082	0.8874179
Benz/GHB/Alc one of drugs: Yes	0.1619351	-0.0238430	0.3477132	0.9512326	0.8547358	1	0.7892975	0.6205228	0.9580721
Baseline GCS <= 3 [1]	0.1801344	0.0767148	0.2835539	0.9618866	0.9193249	1	0.7817522	0.6866627	0.8768417
Baseline GCS > 3 [1]	0.1577872	-0.0038764	0.3194509	1.0000000	1.0000000	1	0.8422128	0.6805491	1.0000000
Baseline resp. rate: 0	0.0861230	-0.0601902	0.2324363	0.9629736	0.8928478	1	0.8768505	0.7465889	1.0000000
Baseline resp. rate: >0	0.2082601	0.1042937	0.3122265	0.9742120	0.9388950	1	0.7659519	0.6668727	0.8650311

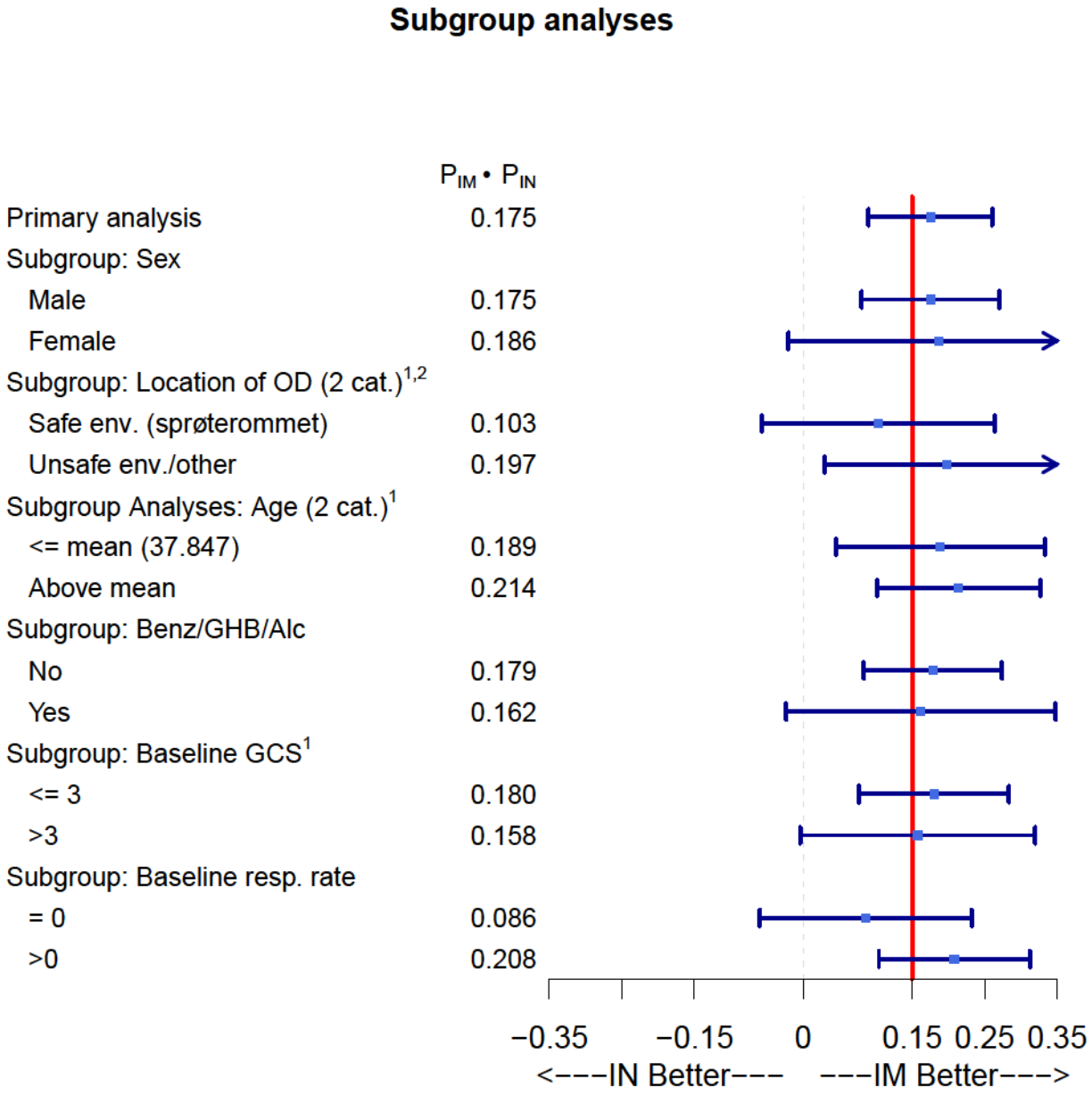

Figure 8: Results of the subgroup analysis of the primary endpoint. The result of the primary analysis is included for completeness. [1]Exchangable correlation structure not possible due to separation issues, independent correlation structure used instead. [2]Adjustment for centre not possible due to separation issues.

Sensitivity of Missingness in subgroup analyses For some of the variables displayed in Figure 8 and listed in table 27, there are missing values. The number of missing values are given in table 28.

Table 28: No. of overdoses with missing values for variables used in subgroup analyses.

Variable	Missing
Sex	2
Age	18

For the age variable, sensitivity analyses are done by setting all the missing values to each age group, respectively. For the sex variable, sensitivity analyses are done by setting all the missing values to male and female, respectively. Results of these sensitivity analyses are given in Table 29.

Table 29: Sensitivity of missingness in subgroup analyses. For the age variable an exchangable correlation structure was not possible due to separation issues, independent correlation structure used instead.

	Margin	Lower CI (95%)	Upper CI (95%)
Sex-missing set to Male: Male	0.1729947	0.0792531	0.2667363
Sex-missing set to Male: Female	0.1864171	-0.0205111	0.3933454
Sex-missing set to Female: Male	0.1751953	0.0803769	0.2700137
Sex-missing set to Female: Female	0.1761519	-0.0223892	0.3746930
Age2cat-missing set to lowest: <= mean	0.1465566	0.0261578	0.2669554
Age2cat-missing set to lowest: > mean	0.2139572	0.0787233	0.3491910
Age2cat-missing set to highest: <= mean	0.1888770	0.0451242	0.3326299
Age2cat-missing set to highest: > mean	0.1719239	0.0772696	0.2665781

Raw data for primary endpoint and variables in subgroup analyses (contigency tables)

Primary endpoint

```
##              Outcome
## Treatment gr.   0   1
##       Control   3 105
##       Active   19  74
```

Soubgroups: Sex

```
## , , Sex = Female
##
##              Outcome
## Treatment gr.  0  1
##       Control  1 18
##       Active   4 13
##
## , , Sex = Male
##
##              Outcome
## Treatment gr.  0  1
##       Control  2 86
##       Active  15 60
##
## , , Sex = Unknown
##
##              Outcome
## Treatment gr.  0  1
##       Control  0  1
##       Active   0  1
```

Soubgroups: Location of OD

```
## , , OD location = 0
##
##              Outcome
## Treatment gr.  0  1
##       Control  0 51
##       Active   3 26
##
## , , OD location = 1
##
##              Outcome
## Treatment gr.  0  1
##       Control  3 54
##       Active  16 48
```

```
## [1] "(0 : Sprøyterommet/Safe, 1: All other/Unsafe)"
```

Soubgroups: Age (2 cat.)

```
## , , Age cat. = 0
##
##              Outcome
## Treatment gr.  0  1
##       Control  3 52
##       Active  10 31
##
## , , Age cat. = 1
##
##              Outcome
## Treatment gr.  0  1
##       Control  0 45
##       Active   9 33
```

```
## [1] "(0 : <= mean age, 1: > mean age)"
```

Soubgroups: Benz/GHB/Alc

```
## , , Benz/GHB/Alc. = 0
##
##              Outcome
## Treatment gr.  0  1
##       Control  2 87
##       Active  15 62
##
## , , Benz/GHB/Alc. = 1
##
##              Outcome
## Treatment gr.  0  1
##       Control  1 18
##       Active   4 12
```

```
## [1] "(0 : No, 1: Yes)"
```

Soubgroups: Baseline GCS

```
## , , Baseline GCS = 0
##
##              Outcome
## Treatment gr.  0  1
##       Control  3 83
##       Active  15 56
##
## , , Baseline GCS = 1
##
##              Outcome
## Treatment gr.  0  1
##       Control  0 22
##       Active   4 18
```

```
## [1] "(0 : <= 3, 1: >3)"
```

Soubgroups: Baseline Resp. rate

```
## , , Baseline resp. rate = 0
##
##              Outcome
## Treatment gr.  0  1
##       Control  1 29
##       Active   3 23
##
## , , Baseline resp. rate = 1
##
##              Outcome
## Treatment gr.  0  1
##       Control  2 76
##       Active  16 51
```

```
## [1] "(0 : = 0, 1: >0)"
```

Secondary endpoint: Time to return to satisfactory respiration

A secondary endpoint is the time from naloxone administration to respiration above or equal to 10 breaths per minute. If a patient did not reach this endpoint within 10 minutes, the time is cencored at 10 minutes. A Kaplan-Meier plot of the time to satisfactory respiration is given in Figure 9.

The treatment groups are compared by estimating the difference in the restricted mean survival times (RMSTs) at each miniute after nalaxone administration, up to 10 minutes. The `SurvRM2` package in `R` is used to calculate the adjusted (for study centre) RMST differences. To take into account the clustering in the data (several ODs in the same indiviual), the Jackknife, where in each Jackknife sample one individual (rather than OD) is left out, are used to calculate the 95% confidence intervals of the RMST differences. The results are given in Table 30 and in Figure 10.

The RMST is interpreted as average time-to-event up to a given time point. That is, the average time to satisfactory breathing within e.g. 10 minutes. In Table 30 results are presented as "Control - Active". Thus, a value of 1 of the RMST difference at 10 minutes, can be interpreted as that, within 10 minutes, patients in the active group on average returns to satisfactory breathing 1 minutes earlier than those in the control group.

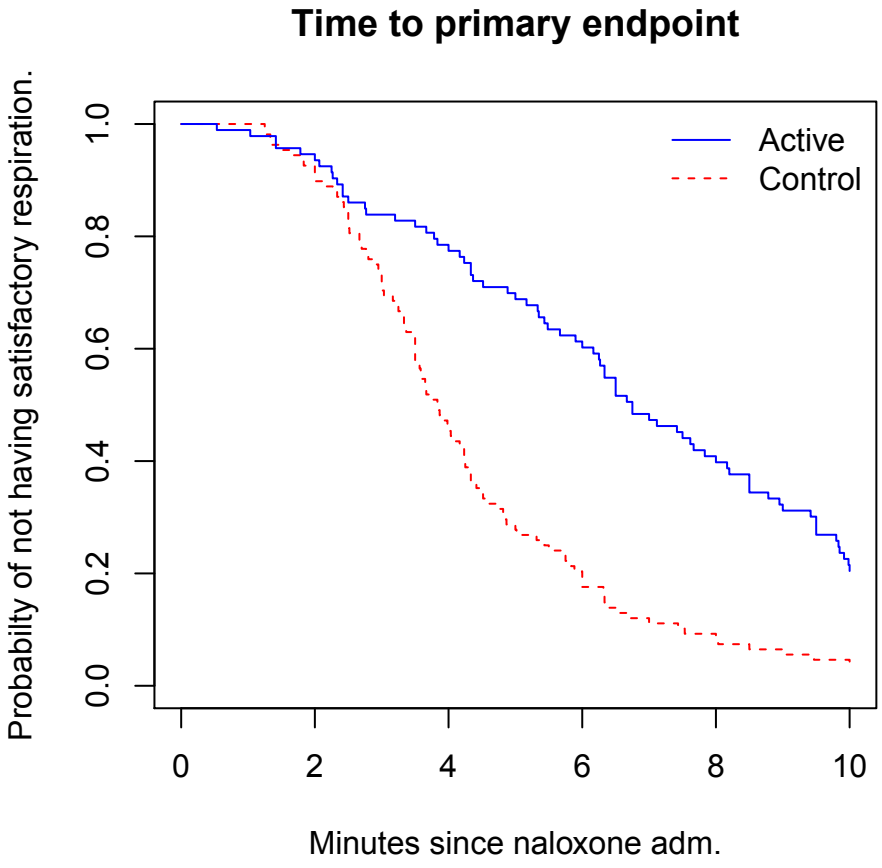

Figure 9: Kaplan-Meier plot (unadjusted for study centre) showing the probability of not having reached satisfactory respiration (10 breaths per minute).

Table 30: The difference in restricted mean survival time (RMST) between the two groups, with 95% confidence intervals based on the Jackknife. Result are displayed as control group minus active group, unadjusted and adjusted for study site

	Unadj. for site			Adj. for site		
	Estimate	CI95Lower	CI95Upper	Estimate	CI95Lower	CI95Upper
RMST diff. at 1 min	0.0050179	-0.0049241	0.0149600	0.0050461	-0.0049533	0.0150460
RMST diff. at 2 min	0.0035394	-0.0457070	0.0527874	0.0032850	-0.0464713	0.0530513
RMST diff. at 3 min	-0.0471227	-0.1801495	0.0859049	-0.0481702	-0.1825159	0.0862055
RMST diff. at 4 min	-0.2723268	-0.5088184	-0.0358418	-0.2744678	-0.5125711	-0.0363239
RMST diff. at 5 min	-0.6455446	-0.9757471	-0.3153591	-0.6485814	-0.9804721	-0.3166490
RMST diff. at 6 min	-1.0490741	-1.4698458	-0.6283189	-1.0528398	-1.4756143	-0.6300183
RMST diff. at 7 min	-1.4424432	-1.9408856	-0.9440122	-1.4462966	-1.9476072	-0.9449349
RMST diff. at 8 min	-1.7833732	-2.3599659	-1.2067838	-1.7870724	-2.3674764	-1.2066134
RMST diff. at 9 min	-2.0749104	-2.7217940	-1.4280232	-2.0778206	-2.7295636	-1.4260163
RMST diff. at 10 min	-2.3070888	-3.0158762	-1.5982933	-2.3086612	-3.0232956	-1.5939581

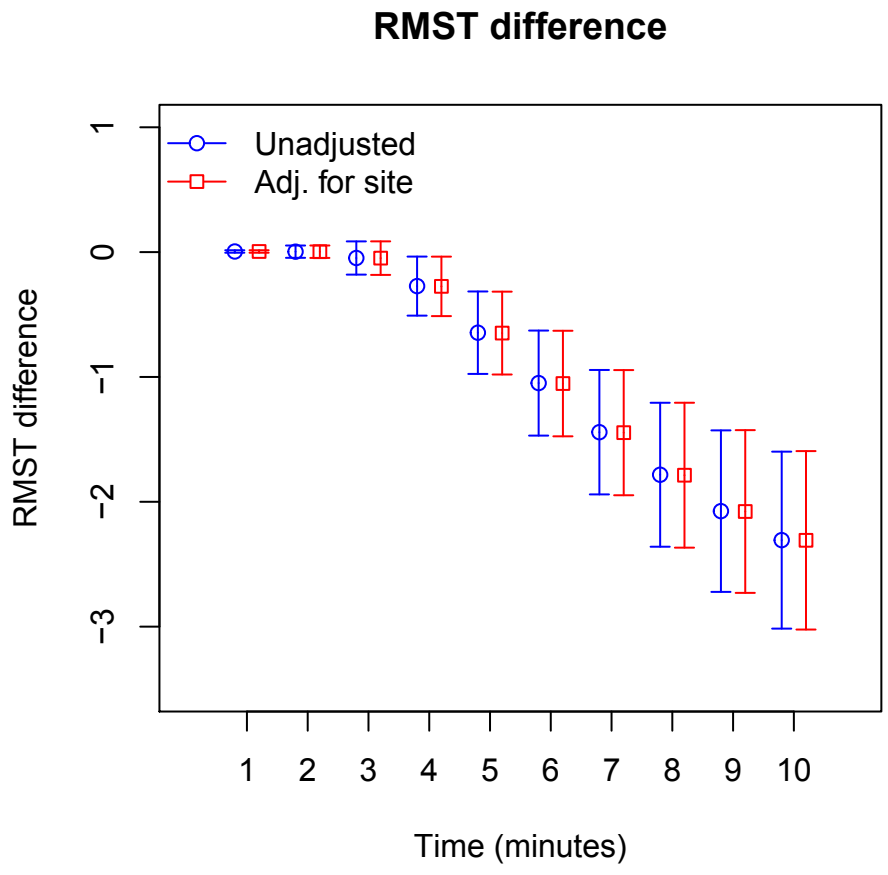

Figure 10: RMST difference (control minus active) at each minute of the follow-up time, from one to ten minutes. Both adjusted (for study site) and unadjusted RMST differences are presented.

Secondary endpoint: Complications

A secondary endpoint is whether or not a patient had a overdose complicaiton. This is a dichotomous endpoint, and is analyzed in the same way as the primary endpoint.

The number of ODs where there were at least one complication:

```
## [1] "No. ODs with at least one complication: 12"
```

The result is (difference in risk of having at least one complication, control - active):

```
##       Margin Lower CI (95%) Upper CI (95%)
## 1 0.01200031    -0.05308568     0.07708631
```

The marginal predicted risks of having at least one complication are:

```
##             Margin Lower CI (95%) Upper CI (95%)
## Control 0.06687398    0.019355696      0.1143923
## Active  0.05487367    0.008468722      0.1012786
```

Secondary endpoint: Adverse reactions

A secondary endpoint is whether or not a patient had a adverse reaction (AR). This is a dichotomous endpoint, and is analyzed in the same way as the primary endpoint.

The number of ODs where there were at least one AR:

```
## [1] "No. ODs with at least one AR: 28"
```

The result is (difference in risk of having at least one AR, control - active):

```
##        Margin Lower CI (95%) Upper CI (95%)
## 1 -0.02214548     -0.1155482     0.07125721
```

The marginal predicted risks of having at least one AR are:

```
##            Margin Lower CI (95%) Upper CI (95%)
## Control 0.1265320     0.06825242      0.1848117
## Active  0.1486775     0.07696285      0.2203922
```

Secondary endpoint: Opioid withdrawal reaction to naloxone reversal

A secondary endpoint is whether or not a patient had an opioid withdrawal reaction to naloxone reversal. This is a dichotomous endpoint, and is analyzed in the same way as the primary endpoint.

The number of ODs with opioid withdrawal:

```
## [1] "No. ODs with opioid withdrawal: 13"
```

The result is (difference in risk of having opioid withdrawal, control - active):

```
##       Margin Lower CI (95%) Upper CI (95%)
## 1 0.01984607     -0.0456453     0.08533743
```

The marginal predicted risks of having opioid withdrawal are:

```
##             Margin Lower CI (95%) Upper CI (95%)
## Control 0.07326612    0.027410871     0.11912137
## Active  0.05342005    0.007684955     0.09915515
```

Secondary endpoint: Problems with spray device.

A secondary endpoint is whether or not there was a practical problem of using the spray device in the pre-hospital setting. As this is not suspected to be affected by the treatment allocaton, no analysis will be done, and only a summary is given in Table 31.

Table 31: Problems with spray device.

	OUH		St. Olav		Total	
	No	Yes	No	Yes	No	Yes
Control	101	0	7	0	108	0
Active	86	0	7	0	93	0
Total	187	0	14	0	201	0

Secondary endpoint: Follow-up

The distribution of follow-up after care is:

```
## , ,  = Control
##
##
##             Adm. Hospital Left at scene Oslo Legevakt Rusakutten Aker
##   OUH                   3            75            21               2
##   St Olav's             4             3             0               0
##
## , ,  = Active
##
##
##             Adm. Hospital Left at scene Oslo Legevakt Rusakutten Aker
##   OUH                   8            53            22               3
##   St Olav's             5             2             0               0
```

A secondary endpoint is whether a patient is followed up at a hospital or not. This is a dichotomous endpoint, and is analyzed in the same way as the primary endpoint. The result is (difference in risk of follow-up at hospital, control - active):

```
##        Margin Lower CI (95%) Upper CI (95%)
## 1 -0.06824802      -0.141729    0.005232969
```

The marginal predicted risks of follow-up at hospital are:

```
##             Margin Lower CI (95%) Upper CI (95%)
## Control 0.06936738     0.02810129      0.1106335
## Active  0.13761540     0.07518448      0.2000463
```

For the Trondheim (St. Olav) center, the possible follow-ups are effectively “Adm. to hospital” and “Left at scene”. For the Oslo (OUH) centre, patients could also be followed-up at “Legevakt” or “Rusakutten” (emergency room).

Combining the follow-up in hospital and at emergency rooms into one endpoint, yeilds the following result (difference in risk of follow-up at emergency room or hospital, control - active):

```
##       Margin Lower CI (95%) Upper CI (95%)
## 1 -0.1123503     -0.2372552     0.01255462
```

The marginal predicted risks of follow-up at emergency room or hospital are:

```
##            Margin Lower CI (95%) Upper CI (95%)
## Control 0.3095770      0.2198762      0.3992779
## Active  0.4219273      0.3228821      0.5209726
```

Secondary endpoint: Rescue Naloxone

A secondary endpoint is whether or not a patient recieved rescue naloxone. This is a dichotomous endpoint, and is analyzed in the same way as the primary endpoint.

The result is (difference in risk of recieving rescue naloxone, control - active):

```
##       Margin Lower CI (95%) Upper CI (95%)
## 1 -0.1936404     -0.2974789    -0.08980186
```

The marginal predicted risks of needing rescue naloxone are:

```
##             Margin Lower CI (95%) Upper CI (95%)
## Control 0.09468496     0.03821025      0.1511597
## Active  0.28832535     0.20203903      0.3746117
```

The number of patients that needed and that actually recieved rescue naloxone is given in Table 32. Details on timing and reasons why rescue naloxone was needed or not given can be found in Table 11.

Table 32: Rescue naloxone needed/recieved.

	Rescue nalaxone recieved	
	No	Yes
Rescue naloxone not needed	162	0
Rescue naloxone needed	2	37

Secondary endpoint: Recurrence

A secondary endpoint is whether or not a patient had a recurrence of opioid overdose within 12 hours of inclusion.

The result is (difference in risk of having a recurrence, control - active):

```
##         Margin Lower CI (95%) Upper CI (95%)
## 1 -0.001907082    -0.06705669     0.06324253
```

The marginal predicted risks of having recurrence are:

```
##             Margin Lower CI (95%) Upper CI (95%)
## Control 0.03527844  -0.0004379514     0.07099484
## Active  0.03718552  -0.0112632803     0.08563433
```

Detailed information about the recurrences is given in Table 33.

Table 33: Recurrences in the PP set.

SubjectId	treat	ROMEDDTC	ROMEDHRS	RODOSE	ROROUTE	ROROTH	RO2DOSE	RO2ROUTE	ROCOMM	ROINCYN
01-031	Active	2018-06-20 20:10	1	0.4	Other	unkown	NA		recurrence registered as excluded 01-024	No
01-240	Control	2019-01-09 17:13	4	0.4	IM		NA		Recurence is dokumentet as not included file# 01-241 / 176. Papers is copied and archived in this file too	No
01-263	Active	2019-01-30 18:00	8	1.4	Other	titrated IV doses over 6 hours	0.4	IM	Given 0.2 mg naloxone IV x 7 from 11.00-18.00 and 0.4 mg IM x 1 at 18.00 at Lovisenberg Hospital	No
01-374	Control	2019-05-17 12:00	3	0.2	IM		NA		admnistered 0.2 mg IM naloxone at OKL see AMIS no 6144, transferred to Ullevål hospital for further observation	No
01-410	Active	2019-06-07 23:40	8	0.4	IM		NA		Gitt ved OKL, ingen respons	No
01-481	Control	2019-08-08 09:26	5	0.4	IM		NA		01-497	No
01-617	Active	2019-12-04 08:36	11	NA			NA		Study KIT.	Yes
01-797	Control	2020-06-23 17:40	2	0.0	IN		0.0	IM	Incuded again KIT 1429	Yes

Secondary endpoint: Change in Glasgow Coma Scale (GCS), baseline - 10min

A secondary endpoint is the change in GCS from before intervention to the GSC value at 10 minutes (at the end of the intervention). This is a continous endpoint. Overview of missing values for the GCS variable is given in Table 34.

Missing values were imputed using multiple imputation with chained equations (the `mice` package in `R` is used). Variables used in the multiple imputation is age, sex, study center, oxygen saturation (baseline and 10-minute value) and time to respiration above or equal to 10 breaths per minute. We imputed 100 datasets, and a linear model was fitted to each of the imputed datasets, with GCS change as the outcome variable. The treatment variable was adjusted by study center and initial GSC. The model was fitted using generalized estimating equations, the `geepack` in `R`, to take into account that the same individual may have had several overdoses and may thus have been included several times in the trial. The result from fitting this model to each of the imputed datasets was then pooled (using the `R` package `mitools`).

The resulting mean difference (adjusted for study center and initial GCS) is (control-active):

```
##   mean_diff CI95lower CI95upper
## 1  1.855723 0.6584139  3.053033
```

The estimated marginal means in each group are:

```
##   Treatment   EmMean CI95lower CI95upper
## 1   Control 8.500404  7.224759  9.776050
## 2    Active 6.644681  5.200189  8.089173
```

Table 34: Missingness (no. of ODs with missing information) in the GCS variable; the initial value prior to intervention, the 10-minute value, and the change from the initial to the 10-minute value.

GCS_initial	GCS_10min	GCS_change
0	23	23

The distribution of the GCS change is skewed, as displayed in figure 11. A sensitivity analysis testing for a difference in distribution is done by using a version of Wilcoxon rank sum test for clustered data (see SAP). The resulting p-value of the test is (a large p-value indicates no difference in distribution between groups):

```
##
##  Clustered Wilcoxon rank sum test using Datta-Satten method
##
## data:  GCSbefore10minChange; group: treat_num; cluster: clusterId; (from dataset)
## number of observations: 178;  number of clusters: 136
## Z = 2.2835, p-value = 0.0224
## alternative hypothesis: true difference in locations is not equal to 0
```

```
## [1] "p-value:  0.0223997939479608"
```

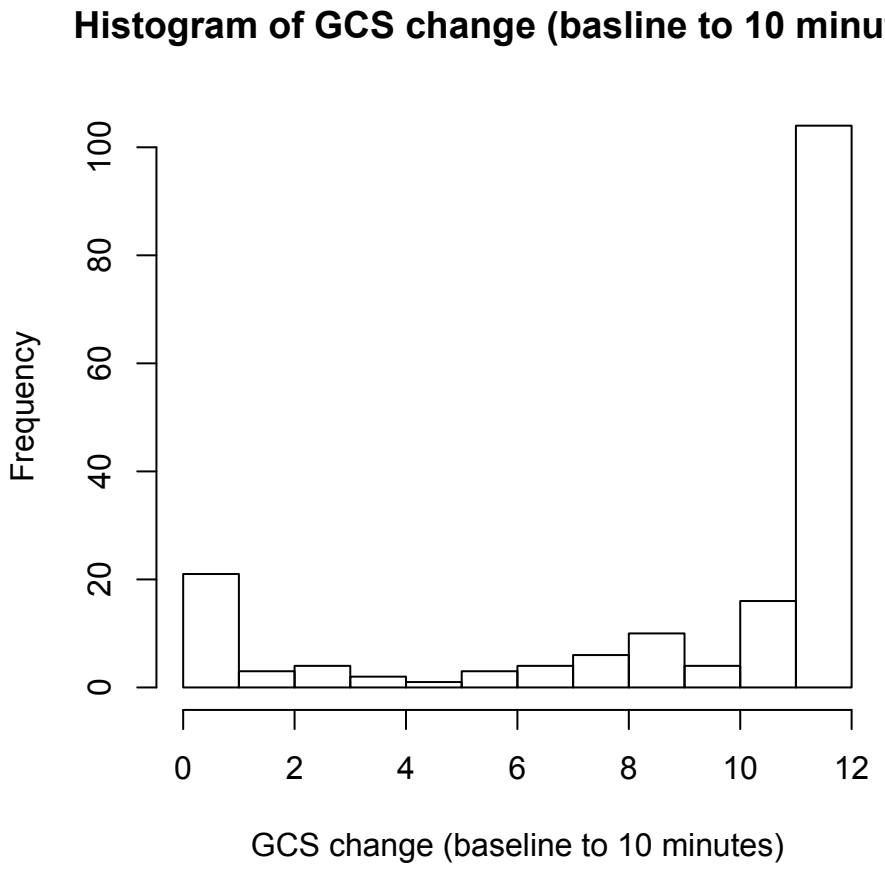

Figure 11: Histogram of GCS change from baseline to 10 minutes.

Secondary endpoint: Change in Glasgow Coma Scale (GCS), baseline - max

A secondary endpoint is the change in GCS from before intervention to the maximum GSC value in the extended follow-up of 40 minutes. This is a continous endpoint. Overview of missing values for the GCS variable is given in Table 35.

Missing values were imputed using multiple imputation with chained equations (the `mice` package in `R` is used). Variables used in the multiple imputation is age, sex, study center, oxygen saturation (baseline and 10-minute value) and time to respiration above or equal to 10 breaths per minute. We imputed 100 datasets, and a linear model was fitted to each of the imputed datasets, with GCS change as the outcome variable. The treatment variable was adjusted by study center and initial GSC. The model was fitted using generalized estimating equations, the `geepack` in `R`, to take into account that the same individual may have had several overdoses and may thus have been included several times in the trial. The result from fitting this model to each of the imputed datasets was then pooled (using the `R` package `mitools`).

The resulting mean difference (adjusted for study center and initial GCS) is (control-active):

```
##   mean_diff  CI95lower CI95upper
## 1 0.3530443 -0.3901497  1.096238
```

The estimated marginal means in each group are:

```
##   Treatment   EmMean CI95lower CI95upper
## 1   Control 9.658635  8.607325  10.70995
## 2    Active 9.305591  8.158261  10.45292
```

Table 35: Missingness (no. of ODs with missing information) in the GCS variable; the initial value prior to intervention, the maximum value during the intervention, and the change from the initial to the maximum.

GCS_initial	GCS_max	GCS_change
0	1	1

The distribution of the GCS change is skewed, as displayed in figure 12. A sensitivity analysis testing for a difference in distribution is done by using a version of Wilcoxon rank sum test for clustered data (see SAP). The resulting p-value of the test is (a large p-value indicates no difference in distribution between groups):

```
##
##  Clustered Wilcoxon rank sum test using Datta-Satten method
##
## data:  changeGCSFirstMax; group: treat_num; cluster: clusterId; (from dataset)
## number of observations: 200;  number of clusters: 155
## Z = 0.86891, p-value = 0.3849
## alternative hypothesis: true difference in locations is not equal to 0
```

```
## [1] "p-value:  0.384894098442066"
```

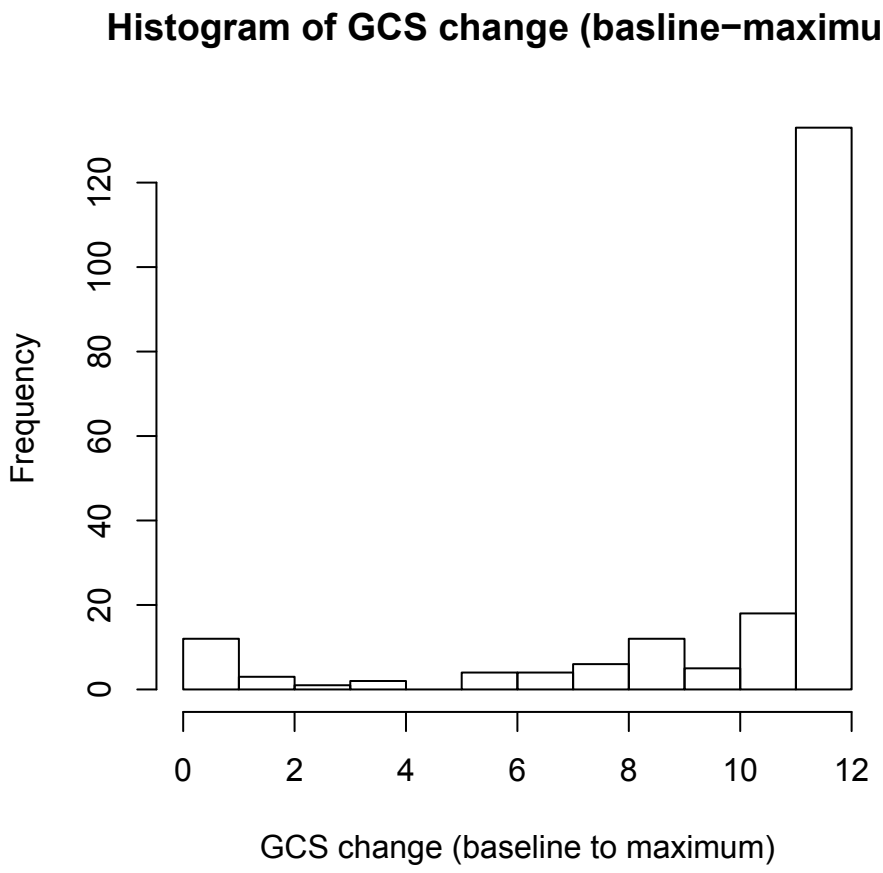

Figure 12: Histogram of GCS change from baseline maximum value in the extended follow-up.

Secondary endpoint: Oxygen saturation, baseline - 10 min

A secondary endpoint is the change in oxygen saturation from before intervention to the level of oxygen saturation at 10 minutes (at the end of the intervention). This is a continous endpoint. Overview of missing values for the oxygen saturation variable is given in Table 36.

Missing values were imputed using multiple imputation with chained equations (the `mice` package in `R` is used). Variables used in the multiple imputation is age, sex, study center, GCS (baseline and 10-minute value) and time to respiration above or equal to 10 breaths per minute. We imputed 100 datasets, and a linear model was fitted to each of the imputed datasets, with oxygen saturation change as the outcome variable. The treatment variable was adjusted by study center and initial oxygen saturation. The model was fitted using generalized estimating equations, the `geepack` in `R`, to take into account that the same individual may have had several overdoses and may thus have been included several times in the trial. The result from fitting this model to each of the imputed datasets was then pooled (using the `R` package `mitools`).

The resulting mean difference (adjusted for study center and initial oxygen saturation) is (control-active):

```
##    mean_diff CI95lower CI95upper
## 1 -0.3316978 -11.07221  10.40881
```

The estimated marginal means in each group are:

```
##   Treatment   EmMean CI95lower CI95upper
## 1   Control 21.75703  14.70521  28.80885
## 2    Active 22.08873  18.29857  25.87889
```

Table 36: Missingness (no. of ODs with missing information) in the oxygen saturation variable; the initial value prior to interventoin, the 10-minute value, and the change from the initial to the 10-minute value.

OxSat_initial	OxSat_10min	OxSat_change
42	75	91

Secondary endpoint: Oxygen saturation, baseline - max

A secondary endpoint is the change in oxygen saturation from before intervention to the maximum level of oxygen saturation mesured in the extended follow-up (up to 40 minutes after IMP administration). This is a continous endpoint. Overview of missing values for the oxygen saturation variable is given in Table 37.

Missing values were imputed using multiple imputation with chained equations (the `mice` package in `R` is used). Variables used in the multiple imputation is age, sex, study center, GCS (baseline and 10-minute value) and time to respiration above or equal to 10 breaths per minute. We imputed 100 datasets, and linear model was fitted to each of the imputed datasets, with oxygen saturation change as the outcome variable. The treatment variable was adjusted by study center and initial oxygen saturation. The model was fitted using generalized estimating equations, the `geepack` in `R`, to take into account that the same individual may have had several overdoses and may thus have been included several times in the trial. The result from fitting this model to each of the imputed datasets was then pooled (using the `R` package `mitools`).

The resulting mean difference (adjusted for study center and initial oxygen saturation) is (control-active):

```
##    mean_diff CI95lower CI95upper
## 1 -0.4970397  -1.47474 0.4806611
```

The estimated marginal means in each group are:

```
##   Treatment   EmMean CI95lower CI95upper
## 1   Control 22.09221  21.30768  22.87674
## 2    Active 22.58925  21.96031  23.21819
```

Table 37: Missingness (no. of ODs with missing information) in the oxygen saturation variable; the initial value prior to intervention, the maximum value during the intervention, and the change from the initial to the maximum.

OxSat_initial	OxSat_max	OxSat_change
42	54	76

Sensitivity analysis (Full analysis set)

The analysis done on the FAS is the exact same analysis that was done for the PP set above.

Baseline overdose characteristics

Baseline characteristics are given in Table 38.

Table 38: Baseline overdose event charactersistics. Column n_var gives the number of observations per variable.

			Treatment Group		
	n_var		Control	Active	Overall
n			113	95	208
Center (%)	208	OUH	105 (92.9)	88 (92.6)	193 (92.8)
		St Olav's	8 (7.1)	7 (7.4)	15 (7.2)
Sex (%)	208	Female	20 (17.7)	17 (17.9)	37 (17.8)
		Male	92 (81.4)	77 (81.1)	169 (81.2)
		Unknown	1 (0.9)	1 (1.1)	2 (1.0)
Season (%)	208	Autumn	18 (15.9)	20 (21.1)	38 (18.3)
		Spring	29 (25.7)	26 (27.4)	55 (26.4)
		Summer	40 (35.4)	32 (33.7)	72 (34.6)
		Winter	26 (23.0)	17 (17.9)	43 (20.7)
Time of week (%)	208	Mon-Thu	71 (62.8)	58 (61.1)	129 (62.0)
		Fri-Sun	42 (37.2)	37 (38.9)	79 (38.0)
Time of day (%)	208	Day (7:00-17:59)	57 (50.4)	59 (62.1)	116 (55.8)
		Evening (18:00-23:59)	35 (31.0)	21 (22.1)	56 (26.9)
		Night (00-6:59)	21 (18.6)	15 (15.8)	36 (17.3)
Baseline GCS (%)	208	<=3	91 (80.5)	72 (75.8)	163 (78.4)
		>3	22 (19.5)	23 (24.2)	45 (21.6)
Baseline resp. rate (%)	208	0	31 (27.4)	27 (28.4)	58 (27.9)
		>0	82 (72.6)	68 (71.6)	150 (72.1)
OD location (%)	208	Safe env. (sprøyterommet)	52 (46.0)	30 (31.6)	82 (39.4)
		Unsafe env.	61 (54.0)	65 (68.4)	126 (60.6)
Primary suspected drug (%)	208	Heroin	111 (98.2)	92 (96.8)	203 (97.6)
		Methadone	0 (0.0)	1 (1.1)	1 (0.5)
		Other opioids	2 (1.8)	2 (2.1)	4 (1.9)
Route of prim. susp. drug (%)	208	IV	111 (98.2)	90 (94.7)	201 (96.6)
		PO	0 (0.0)	1 (1.1)	1 (0.5)
		Unknown	2 (1.8)	4 (4.2)	6 (2.9)
Benz./GHB/Alc. one of drugs (%)	208	No	93 (82.3)	79 (83.2)	172 (82.7)
		Yes	20 (17.7)	16 (16.8)	36 (17.3)
Identity known (%)	208	Yes	105 (92.9)	85 (89.5)	190 (91.3)
		No	8 (7.1)	10 (10.5)	18 (8.7)
Dispatch time in min. (mean (SD))	207		5.50 (3.57)	6.22 (4.49)	5.83 (4.03)
Baseline oxygen sat. (mean (SD))	163		75.00 (18.12)	79.40 (17.61)	76.94 (17.98)
Age (mean (SD))	190		37.30 (10.31)	38.55 (10.89)	37.86 (10.56)

Mean (sd) of continous variables are calculated for patients without missing values.

```
## [1] "No. of overdose events with missing information on age of patient: 18"
```

```
## [1] "No. of overdose events with missing information on baseline oxygen sat.: 45"
```

Primary endpoint

The result of the analysis of the primary endpoint is given in Figure 13 and in Table 39.

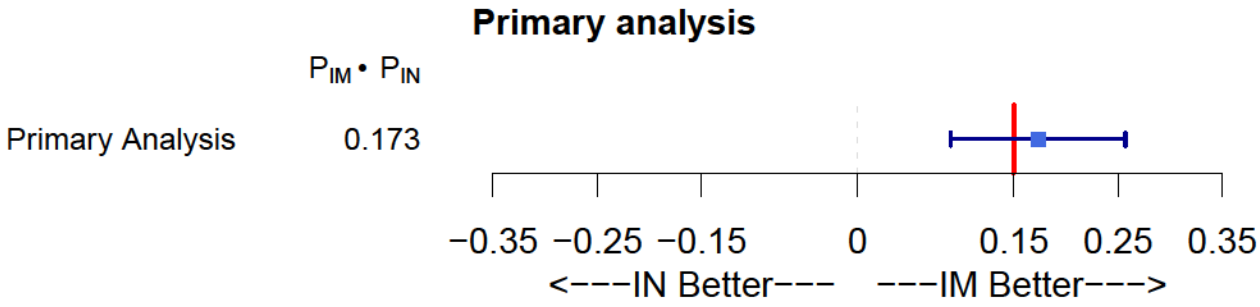

Figure 13: Results of the analysis of the primary endpoint in the FAS. The risk difference with 95% CI is dispalyed. The red vertical lines represents the non-inferiority margin.

Subgroup analyses

Several subgroup analyses was specified in the SAP. Each of these were analyzed in a similar way as the analysis of the primary endpoint, with the addition of the inclusion of an interaction term between the variable in question and the treatment variable. The results from these analyses is given in Figure 14 and Table 39.

Because of a low number of non-events (i.e. those with a negative outcome), there could be problems when calcualting CIs for the subgroups. There could be problems with the following variables:

```
## [1] "Sex"                 "OD Location"         "Age 2 cat."
## [4] "Benz/GHB/Alc"        "GCS"                 "Resp. rate baseline"
```

Table 39: Results from primary and subgroup analyses of the primary endpoint. The risk difference (Control - Active) of returning to spontaneous breathing within 10 minutes is given with 95% confidence intervals. [1] Exchangable correlation structure not possible due to separation issues, independent correlation structure used instead. [2] Adjustment for centre not possible due to separation issues.

	Risk difference			Risk in control gr.			Risk in active gr.		
	Margin	Lower CI (95%)	Upper CI (95%)	Margin	Lower CI (95%)	Upper CI (95%)	Margin	Lower CI (95%)	Upper CI (95%)
Primary	0.1730784	0.0892991	0.2568577	0.9728065	0.9423615	1.0000000	0.7997281	0.7209843	0.8784720
Sex: Male	0.1718054	0.0791736	0.2644373	0.9772281	0.9461682	1.0000000	0.8054227	0.7174171	0.8934282
Sex: Female	0.1914957	-0.0131678	0.3961592	0.9537642	0.8615196	1.0000000	0.7622686	0.5799203	0.9446168
Location: Safe env. (Sprøyterommet) [1,2]	0.1000000	0.1000000	0.1000000	1.0000000	1.0000000	1.0000000	0.9000000	0.9000000	0.9000000
Location: Unsafe env./other [1,2]	0.1969735	0.1969735	0.1969735	0.9508197	0.9508197	0.9508197	0.7538462	0.7538462	0.7538462
Age (2 cat.): <= mean [1]	0.1876475	0.0473823	0.3279126	0.9490926	0.8913089	1.0000000	0.7614451	0.6329352	0.8899550
Age (2 cat.): > mean [1]	0.2100511	0.0506545	0.3694478	1.0000000	1.0000000	1.0000000	0.7899489	0.6305522	0.9493455
Benz/GHB/Alc one of drugs: No	0.1752212	0.0820073	0.2684351	0.9775137	0.9469205	1.0000000	0.8022926	0.7143130	0.8902721
Benz/GHB/Alc one of drugs: Yes	0.1646002	-0.0200187	0.3492190	0.9532429	0.8611130	1.0000000	0.7886427	0.6197937	0.9574918
Baseline GCS <= 3 [1]	0.1804574	0.0786991	0.2822157	0.9645450	0.9250489	1.0000000	0.7840876	0.6898540	0.8783213
Baseline GCS > 3 [1]	0.1529501	0.0242874	0.2816127	1.0000000	1.0000000	1.0000000	0.8470499	0.7183873	0.9757126
Baseline resp. rate: 0	0.0830199	-0.0587135	0.2247533	0.9641721	0.8961521	1.0000000	0.8811521	0.7550344	1.0000000
Baseline resp. rate: >0	0.2067633	0.1045094	0.3090173	0.9756289	0.9421150	1.0000000	0.7688656	0.6710458	0.8666853

```
## [1] "Risk difference, ignoring clusters, location of OD = sproyterommet:"
```

```
##      Margin Lower CI (95%) Upper CI (95%)
## 1 0.1042734   -0.007737859      0.2162847
```

```
## [1] "Risk difference, ignoring clusters, location of OD = unsafe:"
```

```
##     Margin Lower CI (95%) Upper CI (95%)
## 1 0.194855     0.07870785      0.3110021
```

```
## [1] "Risks, ignoring clusters, location of OD = sproyterommet:"
```

```
##             Label    Margin Lower CI (95%) Upper CI (95%)
## 1 treat = Control 1.0000000      0.9999902       1.000010
## 2  treat = Active 0.8957266      0.7837153       1.007738
```

```
## [1] "Risks, ignoring clusters, location of OD = unsafe:"
```

```
##             Label    Margin Lower CI (95%) Upper CI (95%)
## 1 treat = Control 0.9525636      0.8998491      1.0052782
## 2  treat = Active 0.7577087      0.6536106      0.8618068
```

Subgroup analyses

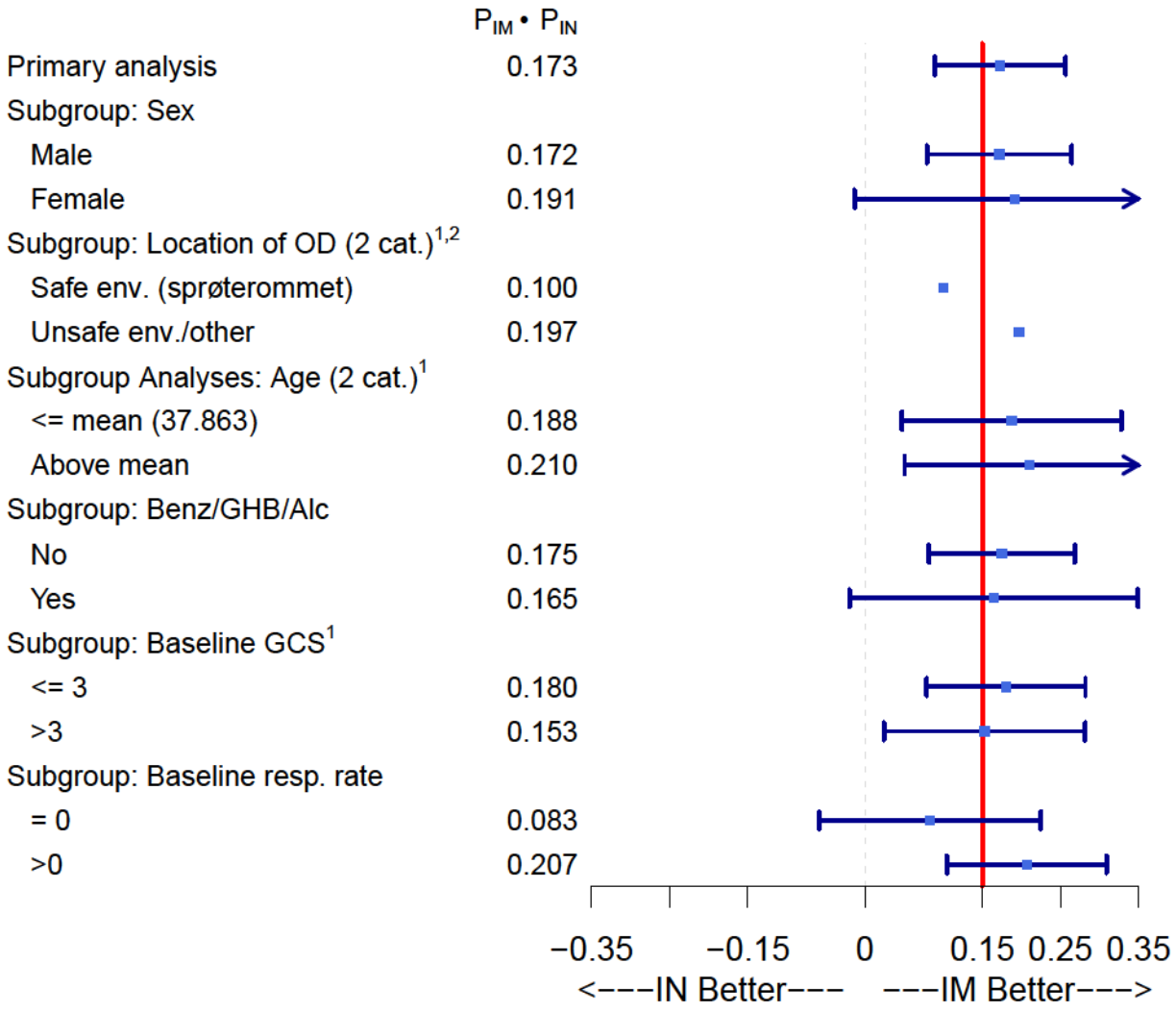

Figure 14: Results of the subgroup analysis of the primary endpoint. The result of the primary analysis is included for completeness. [1]Exchangable correlation structure not possible due to separation issues, independent correlation structure used instead. [2]Adjustment for centre not possible due to separation issues.

Sensitivity of Missingness in subgroup analyses For some of the variables displayed in Figure 14 and listed in table 39, there are missing values. The number of missing values are given in table 40.

Table 40: No. of overdoses with missing values for variables used in subgroup analyses.

Variable	Missing
Sex	2
Age	18

For the age variable, sensitivity analyses are done by setting all the missing values to each age group, respectively. For the sex variable, sensitivity analyses are done by setting all the missing values to male and female, respectively. Results of these sensitivity analyses are given in Table 41.

Table 41: Sensitivity of missingness in subgroup analyses. For the age variable an exchangable correlation structure not possible due to separation issues, independent correlation structure used instead.

	Margin	Lower CI (95%)	Upper CI (95%)
Sex-missing set to Male: Male	0.1695748	0.0779924	0.2611572
Sex-missing set to Male: Female	0.1915337	-0.0128853	0.3959528
Sex-missing set to Female: Male	0.1716766	0.0790750	0.2642782
Sex-missing set to Female: Female	0.1808758	-0.0154305	0.3771821
Age2cat-missing set to lowest: <= mean	0.1462357	0.0286376	0.2638337
Age2cat-missing set to lowest: > mean	0.2097217	0.0973404	0.3221030
Age2cat-missing set to highest: <= mean	0.1873219	0.0472859	0.3273579
Age2cat-missing set to highest: > mean	0.1692992	0.0762067	0.2623918

Raw data for primary endpoint and variables in subgroup analyses (contigency tables)

Primary endpoint

```
##              Outcome
## Treatment gr.   0   1
##       Control   3 110
##       Active   19  76
```

Soubgroups: Sex

```
## , , Sex = Female
##
##              Outcome
## Treatment gr.  0  1
##       Control  1 19
##       Active   4 13
##
## , , Sex = Male
##
##              Outcome
## Treatment gr.  0  1
##       Control  2 90
##       Active  15 62
##
## , , Sex = Unknown
##
##              Outcome
## Treatment gr.  0  1
##       Control  0  1
##       Active   0  1
```

Soubgroups: Location of OD

```
## , , OD location = 0
##
##              Outcome
## Treatment gr.  0  1
##       Control  0 52
##       Active   3 27
##
## , , OD location = 1
##
##              Outcome
## Treatment gr.  0  1
##       Control  3 58
##       Active  16 49
```

```
## [1] "(0 : Sprøyterommet/Safe, 1: All other/Unsafe)"
```

Soubgroups: Age (2 cat.)

```
## , , Age cat. = 0
##
##              Outcome
## Treatment gr.  0  1
##       Control  3 55
##       Active  10 32
##
## , , Age cat. = 1
##
##              Outcome
## Treatment gr.  0  1
##       Control  0 47
##       Active   9 34
```

```
## [1] "(0 : <= mean age, 1: > mean age)"
```

Soubgroups: Benz/GHB/Alc

```
## , , Benz/GHB/Alc. = 0
##
##              Outcome
## Treatment gr.  0  1
##       Control  2 91
##       Active  15 64
##
## , , Benz/GHB/Alc. = 1
##
##              Outcome
## Treatment gr.  0  1
##       Control  1 19
##       Active   4 12
```

```
## [1] "(0 : No, 1: Yes)"
```

Soubgroups: Baseline GCS

```
## , , Baseline GCS = 0
##
##              Outcome
## Treatment gr.  0  1
##       Control  3 88
##       Active  15 57
##
## , , Baseline GCS = 1
##
##              Outcome
## Treatment gr.  0  1
##       Control  0 22
##       Active   4 19
```

```
## [1] "(0 : <= 3, 1: >3)"
```

Soubgroups: Baseline Resp. rate

```
## , , Baseline resp. rate = 0
##
##              Outcome
## Treatment gr.  0  1
##       Control  1 30
##       Active   3 24
##
## , , Baseline resp. rate = 1
##
##              Outcome
## Treatment gr.  0  1
##       Control  2 80
##       Active  16 52
```

```
## [1] "(0 : = 0, 1: >0)"
```

Secondary endpoint: Time to return to satisfactory respiration

A secondary endpoint is the time from naloxone administration to respiration above or equal to 10 breaths per minute. If a patient did not reach this endpoint within 10 minutes, the time is cencored at 10 minutes. A Kaplan-Meier plot of the time to satisfactory respiration is given in Figure 15.

The treatment groups are compared by estimating the difference in the restricted mean survival times (RMSTs) at each minute after nalaxone administration, up to 10 minutes. The `SurvRM2` package in `R` is used to calculate the adjusted (for study centre) RMST differences. To take into account the clustering in the data (several ODs in the same indiviual), the Jackknife, where in each Jackknife sample one individual (rather than OD) is left out, are used to calculate the 95% confidence intervals of the RMST differences. The results are given in Table 42 and in Figure 16.

The RMST is interpreted as average time-to-event up to a given time point. That is, the average time to satisfactory breathing within e.g. 10 minutes. In Table 42 results are presented as "Control - Active". Thus, a value of 1 of the RMST difference at 10 minutes, can be interpreted as that, within 10 minutes, patients in the active group on average returns to satisfactory breathing 1 minutes earlier than those in the control group.

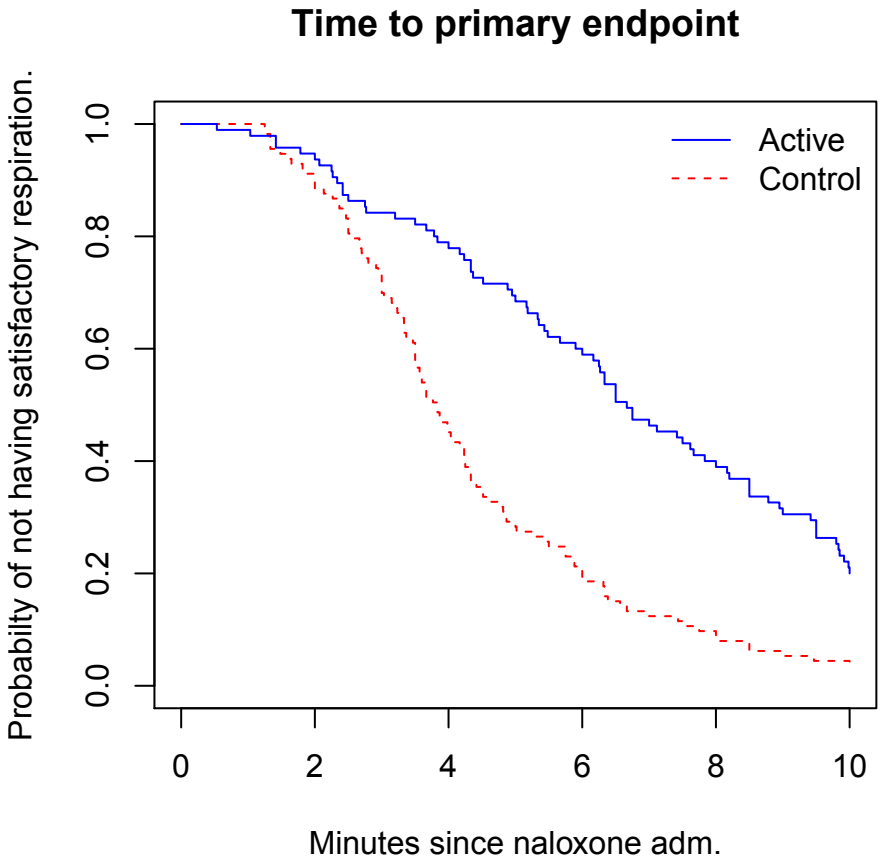

Figure 15: Kaplan-Meier plot (unadjusted for study centre) showing the probability of not having reached satisfactory respiration (10 breaths per minute).

Table 42: The difference in restricted mean survival time (RMST) between the two groups, with 95% confidence intervals based on the Jackknife. Result are displayed as control group minus active group, unadjusted and adjusted for study site

	Unadj. for site			Adj. for site		
	Estimate	CI95Lower	CI95Upper	Estimate	CI95Lower	CI95Upper
RMST diff. at 1 min	0.0049123	-0.0048176	0.0146422	0.0049194	-0.0048257	0.0146650
RMST diff. at 2 min	-0.0052523	-0.0546351	0.0441317	-0.0053848	-0.0550514	0.0442927
RMST diff. at 3 min	-0.0685701	-0.2009132	0.0637732	-0.0690664	-0.2022050	0.0641054
RMST diff. at 4 min	-0.3047865	-0.5402104	-0.0693686	-0.3056819	-0.5419041	-0.0694137
RMST diff. at 5 min	-0.6812358	-1.0098792	-0.3526067	-0.6824473	-1.0118480	-0.3529969
RMST diff. at 6 min	-1.0661885	-1.4833124	-0.6490770	-1.0676335	-1.4858285	-0.6493803
RMST diff. at 7 min	-1.4369275	-1.9314866	-0.9423746	-1.4384274	-1.9348390	-0.9419499
RMST diff. at 8 min	-1.7575485	-2.3302491	-1.1848459	-1.7590344	-2.3344562	-1.1835396
RMST diff. at 9 min	-2.0401413	-2.6813881	-1.3988858	-2.0414290	-2.6864322	-1.3963452
RMST diff. at 10 min	-2.2686058	-2.9694881	-1.5677109	-2.2695459	-2.9752291	-1.5637743

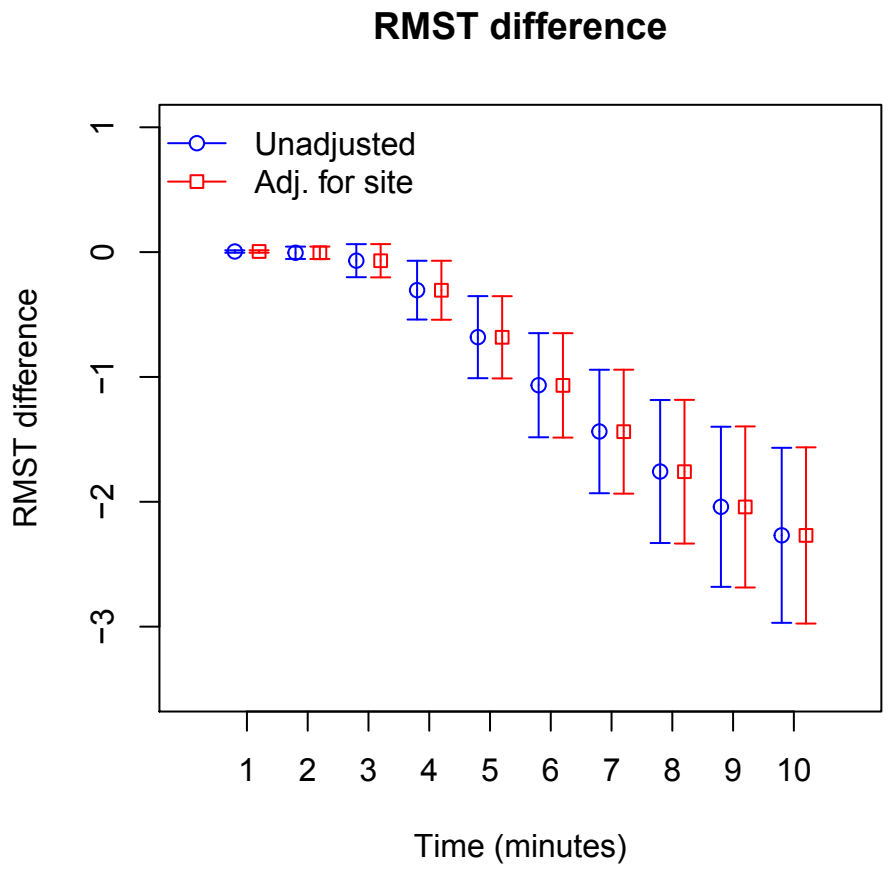

Figure 16: RMST difference (control minus active) at each minute of the follow-up time, from one to ten minutes. Both adjusted (for study site) and unadjusted RMST differences are presented.

Secondary endpoint: Complications

A secondary endpoint is whether or not a patient had a overdose complicaiton. This is a dichotomous endpoint, and is analyzed in the same way as the primary endpoint.

The number of ODs where there were at least one complication:

```
## [1] "No. ODs with at least one complication: 12"
```

The result is (difference in risk of having at least one complication, control - active):

```
##       Margin Lower CI (95%) Upper CI (95%)
## 1 0.01004962    -0.05268936     0.07278859
```

The marginal predicted risks of having at least one complication are:

```
##             Margin Lower CI (95%) Upper CI (95%)
## Control 0.06375524    0.018432376      0.1090781
## Active  0.05370563    0.008357152      0.0990541
```

Secondary endpoint: Adverse reactions

A secondary endpoint is whether or not a patient had a adverse reaction (AR). This is a dichotomous endpoint, and is analyzed in the same way as the primary endpoint.

The number of ODs where there were at least one AR:

```
## [1] "No. ODs with at least one AR: 30"
```

The result is (difference in risk of having at least one AR, control - active):

```
##        Margin Lower CI (95%) Upper CI (95%)
## 1 -0.00700332     -0.1002191     0.08621249
```

The marginal predicted risks of having at least one AR are:

```
##            Margin Lower CI (95%) Upper CI (95%)
## Control 0.1386669     0.07862132      0.1987125
## Active  0.1456702     0.07524970      0.2160908
```

Secondary endpoint: Opioid withdrawal reaction to naloxone reversal

A secondary endpoint is whether or not a patient had an opioid withdrawal reaction to naloxone reversal. This is a dichotomous endpoint, and is analyzed in the same way as the primary endpoint.

The number of ODs with opioid withdrawal:

```
## [1] "No. ODs with opioid withdrawal: 14"
```

The result is (difference in risk of having opioid withdrawal, control - active):

```
##       Margin Lower CI (95%) Upper CI (95%)
## 1 0.02713096    -0.03861503     0.09287695
```

The marginal predicted risks of having opioid withdrawal are:

```
##             Margin Lower CI (95%) Upper CI (95%)
## Control 0.07920528    0.031907239     0.12650331
## Active  0.05207432    0.007413019     0.09673561
```

Secondary endpoint: Problems with spray device.

A secondary endpoint is whether or not there was a practical problem of using the spray device in the pre-hospital setting. As this is not suspected to be affected by the treatment allocaton, no analysis will be done, and only a summary is given in Table 43.

Table 43: Problems with spray device.

	OUH		St. Olav		Total	
	No	Yes	No	Yes	No	Yes
Control	105	0	8	0	113	0
Active	88	0	7	0	95	0
Total	193	0	15	0	208	0

Secondary endpoint: Follow-up

The distribution of follow-up after care is:

```
## , ,  = Control
##
##
##             Adm. Hospital Left at scene Oslo Legevakt Rusakutten Aker
##   OUH                   4            77            22               2
##   St Olav's             5             3             0               0
##
## , ,  = Active
##
##
##             Adm. Hospital Left at scene Oslo Legevakt Rusakutten Aker
##   OUH                   8            55            22               3
##   St Olav's             5             2             0               0
```

A secondary endpoint is whether a patient is followed up at a hospital or not. This is a dichotomous endpoint, and is analyzed in the same way as the primary endpoint. The result is (difference in risk of follow-up at hospital, control - active):

```
##        Margin Lower CI (95%) Upper CI (95%)
## 1 -0.05447467     -0.1280153       0.019066
```

The marginal predicted risks of follow-up at hospital are:

```
##             Margin Lower CI (95%) Upper CI (95%)
## Control 0.08319549     0.03985908      0.1265319
## Active  0.13767016     0.07623916      0.1991012
```

For the Trondheim (St. Olav) center, the possible follow-ups are effectively “Adm. to hospital” and “Left at scene”. For the Oslo (OUH) centre, patients could also be followed-up at “Legevakt” or “Rusakutten” (emergency room).

Combining the follow-up in hospital and at emergency rooms into one endpint, yeilds the following result (difference in risk of follow-up at emergency room or hospital, control - active):

```
##        Margin Lower CI (95%) Upper CI (95%)
## 1 -0.09352351     -0.2155376      0.0284906
```

The marginal predicted risks of follow-up at emergency room or hospital are:

```
##            Margin Lower CI (95%) Upper CI (95%)
## Control 0.3215099      0.2339588      0.4090610
## Active  0.4150334      0.3177464      0.5123204
```

Secondary endpoint: Rescue Naloxone

A secondary endpoint is whether or not a patient recieved rescue naloxone. This is a dichotomous endpoint, and is analyzed in the same way as the primary endpoint.

The result is (difference in risk of needing rescue naloxone, control - active):

```
##       Margin Lower CI (95%) Upper CI (95%)
## 1 -0.1860185     -0.2886496    -0.08338747
```

The marginal predicted risks of recieving rescue naloxone are:

```
##             Margin Lower CI (95%) Upper CI (95%)
## Control 0.09843686     0.04181633      0.1550574
## Active  0.28445538     0.19958823      0.3693225
```

The number of patients that needed and that actually recieved rescue naloxone is given in Table 50. Details on timing and reasons why rescue naloxone was needed or not given can be found in Table 11.

Table 44: Rescue naloxone needed/recieved.

	Rescue nalaxone recieved	
	No	Yes
Rescue naloxone not needed	168	0
Rescue naloxone needed	2	38

Secondary endpoint: Recurrence

A secondary endpoint is whether or not a patient had a recurrence of opioid overdose within 12 hours of inclusion.

The result is (difference in risk of having a recurrence, control - active):

```
##        Margin Lower CI (95%) Upper CI (95%)
## 1 -0.00223992    -0.06542866     0.06094883
```

The marginal predicted risks of having recurrence are:

```
##             Margin Lower CI (95%) Upper CI (95%)
## Control 0.03384657  -0.0004780356     0.06817118
## Active  0.03608649  -0.0111228492     0.08329583
```

Detailed information about the recurrences is given in Table 45.

Table 45: Recurrences in the FAS.

SubjectId	treat	ROMEDDTC	ROMEDHRS	RODOSE	ROROUTE	ROROTH	RO2DOSE	RO2ROUTE	ROCOMM	ROINCYN
01-031	Active	2018-06-20 20:10	1	0.4	Other	unkown	NA		recurrence registered as excluded 01-024	No
01-240	Control	2019-01-09 17:13	4	0.4	IM		NA		Recurence is dokumentet as not included file# 01-241 / 176. Papers is copied and archived in this file too	No
01-263	Active	2019-01-30 18:00	8	1.4	Other	titrated IV doses over 6 hours	0.4	IM	Given 0.2 mg naloxone IV x 7 from 11.00-18.00 and 0.4 mg IM x 1 at 18.00 at Lovisenberg Hospital	No
01-374	Control	2019-05-17 12:00	3	0.2	IM		NA		admnistered 0.2 mg IM naloxone at OKL see AMIS no 6144, transferred to Ullevål hospital for further observation	No
01-410	Active	2019-06-07 23:40	8	0.4	IM		NA		Gitt ved OKL, ingen respons	No
01-481	Control	2019-08-08 09:26	5	0.4	IM		NA		01-497	No
01-617	Active	2019-12-04 08:36	11	NA			NA		Study KIT.	Yes
01-797	Control	2020-06-23 17:40	2	0.0	IN		0.0	IM	Incuded again KIT 1429	Yes

Secondary endpoint: Glasgow Coma Scale (GCS), baseline - 10 min

A secondary endpoint is the change in GCS from before intervention to the GSC value at 10 minutes (at the end of the intervention). This is a continous endpoint. Overview of missing values for the GCS variable is given in Table 46.

Missing values were imputed using multiple imputation with chained equations (the `mice` package in `R` is used). Variables used in the multiple imputation is age, sex, study center, oxygen saturation (baseline and 10-minute value) and time to respiration above or equal to 10 breaths per minute. We imputed 100 datasets, and linear model was fitted to each of the imputed datasets, with GCS change as the outcome variable. The treatment variable was adjusted by study center and initial GSC. The model was fitted using generalized estimating equations, the `geepack` in `R`, to take into account that the same individual may have had several overdoses and may thus have been included several times in the trial. The result from fitting this model to each of the imputed datasets was then pooled (using the `R` package `mitools`).

The resulting mean difference (adjusted for study center and initial GCS) is (control-active):

```
##   mean_diff CI95lower CI95upper
## 1  1.859455 0.6664186  3.052492
```

The estimated marginal means in each group are:

```
##   Treatment   EmMean CI95lower CI95upper
## 1   Control 8.484566  7.324956  9.644176
## 2    Active 6.625111  5.224038  8.026184
```

Table 46: Missingness (no. of ODs with missing information) in the GCS variable; the initial value prior to intervention, the maximum value during the intervention, and the change from the initial to the maximum.

GCS_initial	GCS_10min	GCS_change
0	23	23

The distribution of the GCS change is skewed, as displayed in figure 17. A sensitivity analysis testing for a difference in distribution is done by using a version of Wilcoxon rank sum test for clustered data (see SAP). The resulting p-value of the test is (a large p-value indicates no difference in distribution between groups):

```
##
##  Clustered Wilcoxon rank sum test using Datta-Satten method
##
## data:  GCSbefore10minChange; group: treat_num; cluster: clusterId; (from dataset)
## number of observations: 185;  number of clusters: 141
## Z = 2.297, p-value = 0.02162
## alternative hypothesis: true difference in locations is not equal to 0
```

```
## [1] "p-value:  0.0216184771483393"
```

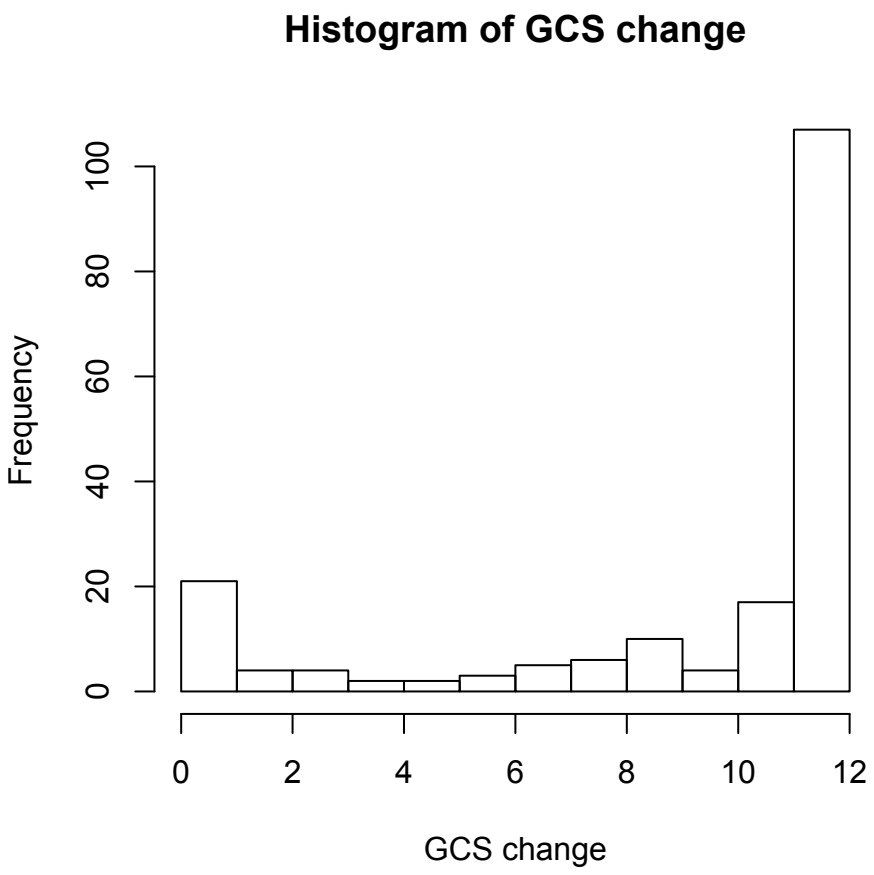

Figure 17: Histogram of GCS change from baseline to 10 minutes.

Secondary endpoint: Change in Glasgow Coma Scale (GCS), baseline - max

A secondary endpoint is the change in GCS from before intervention to the maximum GSC value in the extended follow-up of 40 minutes. This is a continous endpoint. Overview of missing values for the GCS variable is given in Table 47.

Missing values were imputed using multiple imputation with chained equations (the `mice` package in `R` is used). Variables used in the multiple imputation is age, sex, study center, oxygen saturation (baseline and 10-minute value) and time to respiration above or equal to 10 breaths per minute. We imputed 100 datasets, and a linear model was fitted to each of the imputed datasets, with GCS change as the outcome variable. The treatment variable was adjusted by study center and initial GSC. The model was fitted using generalized estimating equations, the `geepack` in `R`, to take into account that the same individual may have had several overdoses and may thus have been included several times in the trial. The result from fitting this model to each of the imputed datasets was then pooled (using the `R` package `mitools`).

The resulting mean difference (adjusted for study center and initial GCS) is (control-active):

```
##   mean_diff  CI95lower CI95upper
## 1 0.3142306 -0.4149577  1.043419
```

The estimated marginal means in each group are:

```
##   Treatment   EmMean CI95lower CI95upper
## 1   Control 9.621019  8.659209  10.58283
## 2    Active 9.306789  8.215902  10.39768
```

Table 47: Missingness (no. of ODs with missing information) in the GCS variable; the initial value prior to intervention, the maximum value during the intervention, and the change from the initial to the maximum.

GCS_initial	GCS_max	GCS_change
0	1	1

The distribution of the GCS change is skewed, as displayed in figure 18. A sensitivity analysis testing for a difference in distribution is done by using a version of Wilcoxon rank sum test for clustered data (see SAP). The resulting p-value of the test is (a large p-value indicates no difference in distribution between groups):

```
##
##  Clustered Wilcoxon rank sum test using Datta-Satten method
##
## data:  changeGCSFirstMax; group: treat_num; cluster: clusterId; (from dataset)
## number of observations: 207;  number of clusters: 160
## Z = 0.87359, p-value = 0.3823
## alternative hypothesis: true difference in locations is not equal to 0
```

```
## [1] "p-value:  0.382341247749671"
```

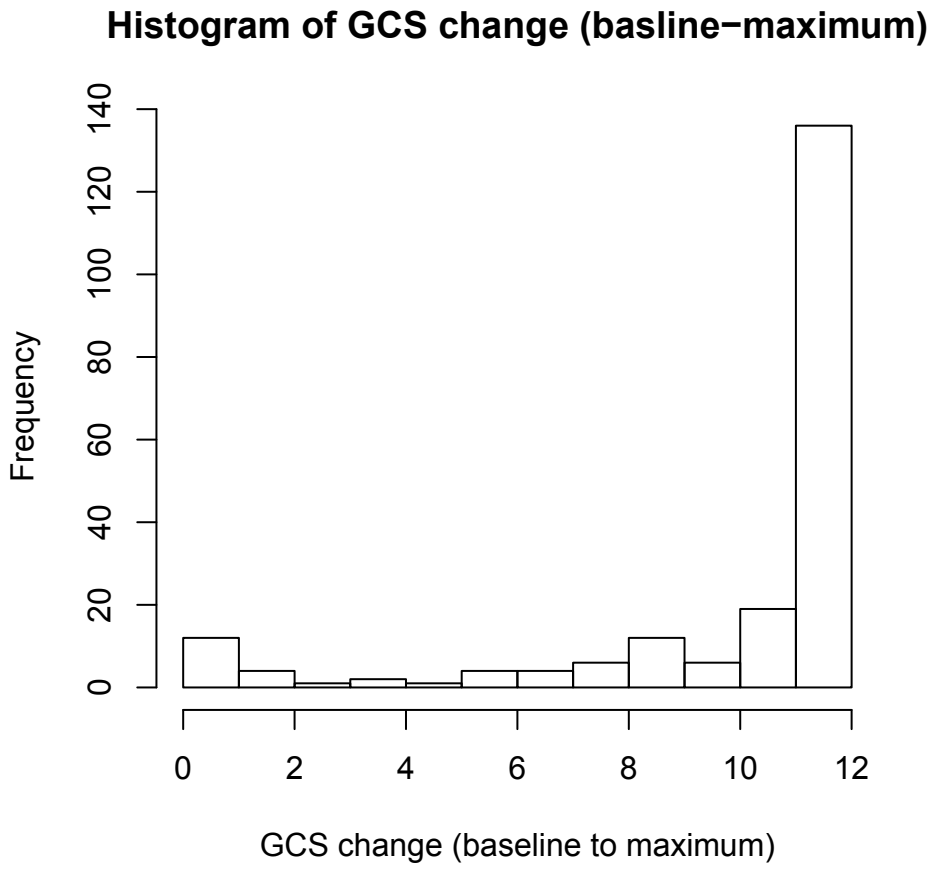

Figure 18: Histogram of GCS change from baseline maximum value in the extended follow-up.

Secondary endpoint: Oxygen saturation, baseline - 10 min

A secondary endpoint is the change in oxygen saturation from before intervention to the level of oxygen saturation at 10 minutes (at the end of the intervention). This is a continous endpoint. Overview of missing values for the oxygen saturation variable is given in Table 48.

Missing values were imputed using multiple imputation with chained equations (the `mice` package in `R` is used). Variables used in the multiple imputation is age, sex, study center, GCS (baseline and 10-minute value) and time to respiration above or equal to 10 breaths per minute. We imputed 100 datasets, and linear model was fitted to each of the imputed datasets, with oxygen saturation change as the outcome variable. The treatment variable was adjusted by study center and initial oxygen saturation. The model was fitted using generalized estimating equations, the `geepack` in `R`, to take into account that the same individual may have had several overdoses and may thus have been included several times in the trial. The result from fitting this model to each of the imputed datasets was then pooled (using the `R` package `mitools`).

The resulting mean difference (adjusted for study center and initial oxygen saturation) is (control-active):

```
##    mean_diff  CI95lower CI95upper
## 1 -0.2823734 -0.9385368 0.3737901
```

The estimated marginal means in each group are:

```
##   Treatment   EmMean CI95lower CI95upper
## 1   Control 21.77694  21.08754  22.46634
## 2    Active 22.05932  21.35936  22.75927
```

Table 48: Missingness (no. of ODs with missing information) in the oxygen saturation variable; the initial value prior to interventoin, the maximum value during the intervention, and the change from the initial to the maximum.

OxSat_initial	OxSat_10min	OxSat_change
45	79	95

Secondary endpoint: Oxygen saturation, baseline - max

A secondary endpoint is the change in oxygen saturation from before intervention to the maximum level of oxygen saturation mesured in the extended follow-up (up to 40 minutes after IMP administration). This is a continous endpoint. Overview of missing values for the oxygen saturation variable is given in Table 49.

Missing values were imputed using multiple imputation with chained equations (the `mice` package in `R` is used). Variables used in the multiple imputation is age, sex, study center, GCS (baseline and 10-minute value) and time to respiration above or equal to 10 breaths per minute. We imputed 100 datasets, and linear model was fitted to each of the imputed datasets, with oxygen saturation change as the outcome variable. The treatment variable was adjusted by study center and initial oxygen saturation. The model was fitted using generalized estimating equations, the `geepack` in `R`, to take into account that the same individual may have had several overdoses and may thus have been included several times in the trial. The result from fitting this model to each of the imputed datasets was then pooled (using the `R` package `mitools`).

The resulting mean difference (adjusted for study center and initial oxygen saturation) is (control-active):

```
##    mean_diff CI95lower CI95upper
## 1 -0.5302186 -1.192454  0.132017
```

The estimated marginal means in each group are:

```
##   Treatment   EmMean CI95lower CI95upper
## 1   Control 21.86332  21.12760  22.59903
## 2    Active 22.39354  21.77798  23.00910
```

Table 49: Missingness (no. of ODs with missing information) in the oxygen saturation variable; the initial value prior to interventoin, the maximum value during the intervention, and the change from the initial to the maximum.

OxSat_initial	OxSat_max	OxSat_change
45	57	79

Post hoc analyses of safety endpoints

The analyses of the endpoints in this section is done in the Safety Set, that is all patietnts in the FAS and all patients that withdrew consent (all patients that recieved study medication). These endpoints are dichotomous, and is analyzed in the same way as the primary endpoints.

Complications

A safety endpoint is whether or not a patient had an overdose complicaiton. This is a dichotomous endpoint, and is analyzed in the same way as the primary endpoint.

The number of ODs where there were at least one complication:

```
## [1] "No. ODs with at least one complication: 13"
```

The result is (difference in risk of having at least one complication, control - active):

```
##      Margin Lower CI (95%) Upper CI (95%)
## 1 0.0154126    -0.04069854     0.07152375
```

The marginal predicted risks of having at least one complication are:

```
##             Margin Lower CI (95%) Upper CI (95%)
## Control 0.06251544    0.021317288     0.10371360
## Active  0.04710284    0.007215589     0.08699009
```

Adverse reactions

A safety endpoint is whether or not a patient had a adverse reaction (AR). This is a dichotomous endpoint, and is analyzed in the same way as the primary endpoint.

The number of ODs where there were at least one AR:

```
## [1] "No. ODs with at least one AR: 37"
```

The result is (difference in risk of having at least one AR, control - active):

```
##    Margin Lower CI (95%) Upper CI (95%)
## 1 0.02879    -0.06028951      0.1178695
```

The marginal predicted risks of having at least one AR are:

```
##            Margin Lower CI (95%) Upper CI (95%)
## Control 0.1666983     0.10540507      0.2279915
## Active  0.1379083     0.07337198      0.2024446
```

Opioid withdrawal reaction to naloxone reversal

A safety endpoint is whether or not a patient had an opioid withdrawal reaction to naloxone reversal. This is a dichotomous endpoint, and is analyzed in the same way as the primary endpoint.

The number of ODs with opioid withdrawal:

```
## [1] "No. ODs with opioid withdrawal: 20"
```

The result is (difference in risk of having opioid withdrawal, control - active):

```
##       Margin Lower CI (95%) Upper CI (95%)
## 1 0.06822835    0.002384108      0.1340726
```

The marginal predicted risks of having opioid withdrawal are:

```
##             Margin Lower CI (95%) Upper CI (95%)
## Control 0.11426872    0.061730148     0.16680730
## Active  0.04604038    0.006494522     0.08558623
```

Rescue Naloxone recieved

A safety endpoint is whether or not a patient recieved rescue naloxone. This is a dichotomous endpoint, and is analyzed in the same way as the primary endpoint.

The result is (difference in risk of needing rescue naloxone, control - active):

```
##       Margin Lower CI (95%) Upper CI (95%)
## 1 -0.1735285     -0.2714002    -0.07565678
```

The marginal predicted risks of recieving rescue naloxone are:

```
##            Margin Lower CI (95%) Upper CI (95%)
## Control 0.1072064     0.05150645      0.1629064
## Active  0.2807349     0.20110365      0.3603662
```

The number of patients that needed and that actually recieved rescue naloxone is given in Table 50. Details on timing and reasons why rescue naloxone was needed or not given can be found in Table 11.

Table 50: Rescue naloxone needed/recieved.

	Rescue nalaxone recieved	
	Yes	No
Rescue naloxone not needed	0	192
Rescue naloxone needed	44	2

Rescue Naloxone doses in Safety Set

Table 51: Dose and route of rescue naloxone for overdoses in the Safety Set. Column n_var gives the number of observations per variable. Mean (sd) of continous variables are calculated for patients without missing values. Note that one overdose had missing route of primary dose, for which the route of secondary dose was used.

			Treatment		
	n_var		Control	Active	Overall
n			129	109	238
Recieved rescue naloxone (%)	238	Yes	14 (10.9)	30 (27.5)	44 (18.5)
		No	115 (89.1)	79 (72.5)	194 (81.5)
Route of primary dose of rescue naloxone (%)	238	IM	11 (8.5)	20 (18.3)	31 (13.0)
		IV	3 (2.3)	7 (6.4)	10 (4.2)
		Non given	115 (89.1)	79 (72.5)	194 (81.5)
		Other	0 (0.0)	2 (1.8)	2 (0.8)
		Unknown	0 (0.0)	1 (0.9)	1 (0.4)
Total dose of rescue naloxone (mean (SD))	237		0.07 (0.21)	0.16 (0.34)	0.11 (0.28)

Table 52: Dose and route of rescue naloxone for overdoses in the Safety Set, where patients actually recieved rescue naloxone. Column n_var gives the number of observations per variable. Mean (sd) of continous variables are calculated for patients without missing values. Note that one overdose had missing route of primary dose, for which the route of secondary dose was used.

			Treatment		
	n_var		Control	Active	Overall
n			14	30	44
Route of primary dose of rescue naloxone (%)	44	IM	11 (78.6)	20 (66.7)	31 (70.5)
		IV	3 (21.4)	7 (23.3)	10 (22.7)
		Other	0 (0.0)	2 (6.7)	2 (4.5)
		Unknown	0 (0.0)	1 (3.3)	1 (2.3)
Total dose of rescue naloxone (mean (SD))	43		0.60 (0.30)	0.61 (0.38)	0.61 (0.35)

Rescue Naloxone doses in FAS

Table 53: Dose and route of rescue naloxone for overdoses in the FAS. Column n_var gives the number of observations per variable. Mean (sd) of continous variables are calculated for patients without missing values. Note that one overdose had missing route of primary dose, for which the route of secondary dose was used.

			Treatment		
	n_var		Control	Active	Overall
n			113	95	208
RescueNalaxoneGot (%)	208	Yes	11 (9.7)	27 (28.4)	38 (18.3)
		No	102 (90.3)	68 (71.6)	170 (81.7)
Route of primary dose of rescue naloxone (%)	208	IM	8 (7.1)	17 (17.9)	25 (12.0)
		IV	3 (2.7)	7 (7.4)	10 (4.8)
		Non given	102 (90.3)	68 (71.6)	170 (81.7)
		Other	0 (0.0)	2 (2.1)	2 (1.0)
		Unknown	0 (0.0)	1 (1.1)	1 (0.5)
Total dose of rescue naloxone (mean (SD))	207		0.05 (0.16)	0.18 (0.35)	0.11 (0.27)

Table 54: Dose and route of rescue naloxone for overdoses in the FAS, where patients actually recieved rescue naloxone. Column n_var gives the number of observations per variable. Mean (sd) of continous variables are calculated for patients without missing values. Note that one overdose had missing route of primary dose, for which the route of secondary dose was used.

			Treatment		
	n_var		Control	Active	Overall
n			11	27	38
Route of primary dose of rescue naloxone (%)	38	IM	8 (72.7)	17 (63.0)	25 (65.8)
		IV	3 (27.3)	7 (25.9)	10 (26.3)
		Other	0 (0.0)	2 (7.4)	2 (5.3)
		Unknown	0 (0.0)	1 (3.7)	1 (2.6)
Total dose of rescue naloxone (mean (SD))	37		0.51 (0.19)	0.64 (0.40)	0.60 (0.35)

NTNU
Norwegian University of
Science and Technology

NTNU INTRANASAL NALOXONE TRIAL
Double blinded, double dummy, randomised controlled trial of intranasal naloxone for pre- hospital use

Protocol Identification Number: NINA- 1
EudraCT Number: 2016-004072-22

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PROTOCOL VERSION NO. 3.3
Date: 06.03.2020

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1.1 Signature page

Title	NTNU Intranasal Naloxone Trial Double blinded, double dummy, randomised controlled trial of intranasal naloxone for pre-hospital use
Protocol ID no:	NINA-1
EudraCT no:	2016-004072-22
Protocol version and date:	No 3.3, 6Th March 2020

I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements:

Name	Title	Role	Signature	Date
Øystein Risa	Director	Sponsor		
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Ola Dale	Professor, MD, PhD	Investigator		
Ida Tylleskar	MD	Investigator		
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Morten Valberg	PhD	Statistician		

Protocol version and date	Amendment/ Change	Approved Ethics Committee	Approved Medicines Agency
Protocol versions with all changes marked in yellow between versions are kept in the Trial Master File			
v. 1.0 31st Oct 2016	- Original protocol submission	20th Dec 2016 Regional Ethics Committee (REC) approved with condition of consent prior to randomisation 7th Mar 2017 National Ethics committee (NEC) approved without consent prior to randomisation (reference: NEM 2017/44)	Not approved
v. 2.0 4th Oct 2017	- Change of producers of comparator active/placebo - Update on pharmacokinetic data in background section - Specifications regarding double dummy design and risk of unintentional unblinding - Changes to consent procedure in accordance with approval from NEC	REC 31st Oct 2017	NoMA 7th Dec 2017
v. 3.0 9th Jan 2018	- Adding prison as exclusion criterium ***Please note this protocol version was current at first patient inclusion.***	REC 5th Feb 2018	NoMA 12th Jan 2018
v. 3.1 1st May 2019	- Change national coordinating investigator from Ola Dale to Arne Skulberg - Change PI Trondheim from Sindre Mellsemo to Jostein Dale - Change study statistician from Øyvind Salvensen to Morten Valberg - Updated contact information to CI, PI and others. - Align end-date to 31. Dec 2021 between protocol, REC approval and trial registrations	REC 20th Jun 2019	NoMA 1st Jun 2019
v. 3.2 2nd Sept 2019	- Adding 12.9 Safety reporting from participants with withdrawn consent	REC 15th Nov 2019	NoMA 2nd Oct 2019
v 3.3 6th Mar 2020	- Change inclusion criteria <8 breaths per minutes to ≤8 breaths per minutes - Further specification relating to 12.9		

2 PROTOCOL SYNOPSIS

NTNU INTRANASAL NALOXONE TRIAL

DOUBLE BLINDED, DOUBLE DUMMY, RANDOMISED CONTROLLED TRIAL OF INTRANASAL NALOXONE FOR PRE- HOSPITAL USE

Sponsor	Øystein Risa, Head of Department Department of Circulation and Medical Imaging, Norwegian University of Science and Technology
Phase and study type	Double blinded, double dummy, randomised controlled clinical trial, non- inferiority study, phase III drug trial
Investigational Medical Product (IMP):	**IMP:** **Nasal spray:** Nasal naloxone DNE 14 mg/ml **Comparator:** **IM injection:** Naloxone Hydrochloride Injection USP 4 mg/10 ml. Mylan Institutional LLC. **Placebo:** **Nasal spray:** Nasal spray DNE without naloxone **IM Injection:** Natriumklorid B. Braun 9 mg/ml x 10 ml, B. Braun. (Sodium Chloride injection)
Centres:	Oslo University Hospital, Pre- hospital Division St. Olav's University Hospital, Department for Emergency Medicine and Prehospital Services
Study Period:	Estimated date of first patient enrolled: 1. January 2018 Anticipated recruitment period: 48 months Estimated date of last patient: 31. December 2021
Treatment Duration:	Approximately 40 minutes

Follow-up:	Observed by by Emergency Medical Staff (EMS) until end of treatment. At later data search in Acute Medical Information System (AMIS) to record subsequent contact with emergency medical services, only incidences involving further use of naloxone within 12 hours after inclusion will be recorded.
Objectives	Measure and evaluate clinical response to nasal naloxone in real opioid overdoses in the pre- hospital environment.
Endpoints:	**Primary endpoint:** • Proportion of patients with return of spontaneous respiration (above or equal to 10 breaths per minute) within 10 minutes of naloxone administration in pre-hospital opioid overdose. **Secondary endpoint:** • Changes in Glasgow Coma Scale (GCS) and oxygen saturation (SaO2) in patients treated with study medicine for opioid overdose. • Overdose complications (e.g. aspiration, cardiac arrest, death) • Time from administration of naloxone to respiration above or equal to 10 breaths per minute. • Opioid withdrawal reaction to naloxone reversal • Suitability of spray device in pre-hospital setting • Adverse reactions to naloxone formulation • Need for rescue naloxone, dose and route of administration during study visit • Recurrence of opioid overdose/ need for further pre-hospital naloxone within 12 hours of inclusion • Data regarding reasons not to give rescue naloxone to non-responders • Follow up after care
Study Design:	Double blinded, double dummy, randomised control trial, multi-centre study, non-inferiority design.

Main Inclusion Criteria:	– Suspected opioid overdose clinically diagnosed by EMS based on the following criteria 1. Reduced (below or equal to 8 breaths per minute) or absent spontaneous respiration 2. Miosis 3. GCS below 12 and – Palpable carotid or radial arterial pulse
Main Exclusion Criteria:	– Cardiac arrest – Failure to assist ventilation using mask-bag technique – Facial trauma or epistaxis or visible nasal blockage – Iatrogenic opioid overdose when opioid is administered in-hospital, or by EMS or other health care workers in the pre-hospital setting – Suspected participant below 18 years of age – Suspected or visibly pregnant participant – Participant that have received naloxone by any route in the current overdose – Participant in prison or custody by police – EMS staff without training as study workers – No study drug available – Study drug frozen as indicated by Freeze Watch in kit or past its expiry date – Deemed unfit for inclusion due to any other cause by study personnel at the scene; such as unsafe work environment for EMS.
Sample Size:	200 patients included
Efficacy Assessments:	Responders will be participants that achieve a respiratory rate above 10 breaths per minute within 10 minutes after the administration of study medicine. For awake, ambulatory patients, or patients speaking inn full sentences, the exact respiratory rate may be hard to count, and these will be classified as responders. Non- responders are defined as patients not achieving spontaneous respiration rate above 10 breaths per minute Rescue naloxone is IV/IM naloxone given at 10 minutes or more to non-responders. For non-responders, the dose of rescue naloxone required will be compared between the groups. If clinical deterioration occurs, or the EMS experience loss of ventilation control prior to 10 minutes, treatment as per local guideline- including naloxone will be administered and recorded in CRF.

Safety Assessments:	Treatment will only be given by trained EMS staff. Assessment will follow local guidelines by the Oslo or Trondheim Ambulance Service and the standard of care required normally when treating opioid overdoses in the field. They assessment after the Airway Breathing Circulation Disability Environment/Exposure principles of resuscitation (ABCDE) principles of emergency medicine (1) include clinical observation of respiratory rate, oxygen saturation, pulse, GCS and skin colour. Electrocardiogram and non- invasive blood pressure will be measured if deemed necessary and feasible at the scene. The normal treatment and observational period by EMS for this condition is normally approximately 30 minutes, unless the patient needs follow up by other medical services, typically Oslo Kommunale Legevakt (OKL) or St Olav's Hospital. Patients are never left alone, but are often left at the scene with agency staff at for example Sprøyterommet (Drug Consumption Room) or others such as friends or family to look after them. All patients are offered follow up, but many decline further treatment. This wish is respected if the patient is considered to be informed and able to care for him/ her self. As per local guideline all patients will be offered transport to further health services for further observation after an opioid overdose or assessment/ treatment of concurrent medical or conditions. Opioid overdoses are common, and have very low mortality when EMS are present at the scene. Our data show that out of 1054 cases where naloxone was administered in Oslo City Centre in 2014 and 2015 only one fatality occurred (2). EMS will double as study workers and pre- hospital health care providers in this study. All EMS staff in our definition have standing orders permitting them to administer naloxone (and a number of other prescription drugs) as injection prior to being trained and accepted as study workers.

3 Index

4 List of Abbreviations and Definitions of Terms

Abbreviation/ term	Explanation
ABC or ABCDE	Airway Breathing Circulation Disability Environment/Exposure principles of resuscitation
AE	Adverse Event
AMIS	Akuttmedisinsk informasjonssystem (Acute Medical Information System). Computer program used by the emergency dispatch centres to document emergency 113 calls and allocate recourses. It registers patient details and times and recourses used. Equal in Oslo and Trondheim
AMK	Akuttmedisinsk Kommunikasjons Sentral (Emergency Medical Dispatch Centre).
Bpm	Breaths per minute
Cmax	Maximum concentration
CPR	Cardio- Pulmonary Resuscitation
CRF	Case Report Form (electronic/paper)
CRS	Department of clinical research support
CSA	Clinical Study Agreement
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation due to Adverse Event
DMSC	Data Monitoring and Safety Committee
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electro Cardio Gram
EMS	Emergency Medical Service. In Norway, this includes paramedic, fagarbeider, ambulansearbeider and lærling 2. It also includes medical doctors working in the ambulance service. Investigators with ambulance and/ or medical training will also be considered EMS in this protocol
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IM	Intramuscular
IMP	Investigational Medicinal Product (includes active comparator and placebo)
IMPD	Investigational Medicinal Product Dossier
IN	Intranasal
IND	Investigational New Drug
ISF	Investigator Site File
IV	Intravenous

MOM	Medisinsk Operativ Manual (Treatment guidelines Oslo Ambulance Service)
NTNU	Norwegian University of Science and Technology
OKL	Oslo Kommunale Legevakt: Oslo Accident and Emergency Outpatient Clinic, Storgata 44, 0182 Oslo.
OUS	Oslo University Hospital
PK	Pharmacokinetic
SAE	Serious Adverse Event
SDV	Source data verification
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
Sprøyterommet (SIF)	Safe Injection Facility run by Oslo Municipality, located at Storgata 36C, 0182 Oslo
T1/2	Half Life
Tmax	Time to maximum concentration
TMF	Trial Master File

5 Introduction

5.1 Background

Opioid overdoses have for the last decade counted for about 250 untimely deaths annually in Norway (3). The government is currently implementing a strategy for combating this epidemic (4). Among the actions promoted in this strategy is the distribution of naloxone for intranasal administration. Such administration of naloxone is currently being implemented and tried out around the world, but very little have been done to pharmacologically study this new route of administration of this well- known drug, and only 3 open label RCTs have been conducted (5-7). A recent guideline from the WHO on community management of opioid overdoses is a comprehensive review of many of the aspects we cover in our research regarding both dosage, routes of administration of naloxone and care of these patients in the pre- hospital setting (8). The WHO also focuses on the current wide spread off label use of nasal naloxone as a problem and identifies several research questions of critical importance and very low evidence. This research project aims to answer several of these, such as time to opioid reversal and opioid withdrawal reactions to naloxone.
The current study, together with our research group's previous and future studies aims to provide data for the development of a formulation of naloxone for intranasal administration with full marketing authorisation for use in pre-hospital overdoses and to improve the safety for those administering naloxone. It may contribute to public health measures for opioid users and those around them.
It must be emphasized that the indication for administering naloxone by EMS staff is respiratory depression or respiratory arrest in an unconscious patient. Without airway management and breathing support, the primary intervention, the patient will go into cardiac arrest. This makes research challenging, but with good professional control of the respiration (bag- mask ventilation) the time to naloxone administration is of less importance.
To resuscitate opioid overdoses, immediate supportive treatment with a μ-opioid antagonist such as naloxone is vital. The antidote reverses the life threatening respiratory depression rapidly with effect peak at 5 -10 min (9), a duration of action of approximately 90 min (10), and previous pharmacokinetic (PK) studies report an elimination half-life of about 1 hour (range 30-81 min) (11). Usually naloxone is administered IV and/ or IM, the former requires considerable skill, and the latter have a slower onset of action. IN naloxone has been suggested as an alternative for emergency teams (5, 12-14) and possibly also by lay people or peers (15). The justification for IN administration is the elimination of the hazard of needle stick injuries and blood exposure from a risk population. Moreover, cannulation of IV drug users can be very technically challenging (13).
However, IN naloxone in this setting is not well established. The first IN formulation with marketing authorization was approved by the Food and Drug Administration for the US market in November 2015 (16). This is a 40 mg/ml naloxone formulation, delivering 4 mg naloxone in a 0,1 mL in an Aptar Unitdose spray device. It is produced by Adapt Pharma(17). There has never been conducted a blinded RCT asking if intra nasal naloxone is equal to intramuscular and/or intravenous administration of naloxone in acute opioid overdoses. This study, however, has been extensively called for internationally (14). The WHO remarks that there is low evidence for most of the recommendation in its own report, and that research questions regarding naloxone time and ease of administration, adverse events, overdose mortality and morbidity and time to overdose reversal are all critical and needs answering (8).
This protocol relates to out of hospital opioid overdoses (also referred to as community overdoses (8)). These are different from in- hospital or iatrogenic overdoses in several ways. The most important difference is that in hospital over dosage with opioids commonly occur in controlled settings in a hospital ward, often in relation to a patient receiving anaesthesia, or for pain relief. This means that patients are overdosed on a known opioid at a known dose. This makes reversal controlled and easy. A pre- hospital overdose on the other hand is a function of the dosage of the opioid taken, other drugs consumed (particularly sedatives and alcohol) and a variety of other factors such as tolerance, somatic illness etc. Normally all of these factors are unknown in the out of hospital setting (8). The recommended dose and titration guidelines for opioid overdoses in the community lies between 0,4 and 2,0 mg naloxone (18). In in-hospital reversal of iatrogenic over dosage the recommended doses are much lower, from IV 0,08 mg postoperatively (19) to 0,1-0,2 mg naloxone as described in the Summary of Product Characteristics (SPC) for naloxone from B. Braun (20).

5.2 Our research group

The present research group has significant experience with nasal formulations and with pharmacokinetic studies of nasally administered opioids and sedatives (21-26). In addition EUDRA CT: 2013-000050-22 is submitted for publication. The Oslo ambulance Service also has considerable experience with clinical studies and RCTs in the emergency setting in the Oslo area (27-30). In Oslo there is extensive experience with RCTs in the pre- hospital settings, and a leading academic group in cardiac arrest research (31, 32). We have participated in research meetings and discussions with these experienced research colleagues and will continue this close cooperation throughout the study period.

5.3 Background - Therapeutic Information

The emergency management of opioid overdoses is first the diagnosis of the condition, this is based on reduced or arrested respiration, reduced level of consciousness and miosis. This is often, but not always accompanied by a clinical suspicion based on the setting where the patient is found and findings of narcotics, injection equipment etc. at the scene, but not always. Further management follows Airway, Breathing Circulation Disability Exposure (ABCDE) principles with airway management, breathing and circulation assessment, and management and administration of naloxone (8, 18). The following describes two medical guidelines used in the EMS in Oslo and Trondheim, respectively.

Oslo: Medisinsk Operativ Manual (MOM) (Appendix 12)

Standard treatment for opioid overdoses in Oslo today is described in Medisinsk Operativ Manual (Medical Operative Manual, MOM)(33). This document was last updated in August 2016. The MOM describes the symptoms of an opioid overdose: reduced/ loss of consciousness and/or reduced/arrested respiration and miosis. Management is first to establish and maintain free airways, positive pressure ventilation using a bag- mask and then treatment with naloxone. EMS are authorised to administer naloxone by 0,4 mg/ml injection. Two dosing regimens for opioid overdoses exist. The first describes iatrogenic overdoses by morphine hydrochloride. The dosing in this instance is 0,1 mg naloxone IV titrated to effect. This regimen is not the subject of this study, it is one of the main exclusion criteria. The dosage guidelines for reversal of opioid in the community have two modalities based on the presumed body weight of the patient, below or above 70 kg. For patient presumed to be below 70 kg the guideline is first to give 0,4 mg naloxone IM and then 0,4 mg naloxone IV. For patients above 70 kg, the guideline is first to give 0,8 mg naloxone IM and then 0,4 mg naloxone IV. Irrespective of the patient body weight, the guideline is to repeat the dosage every 3 minutes until satisfactory effect, up to a maximum dosage of 2 mg naloxone in total. Adverse events mentioned in the local guidelines are abstinence, tachycardia and nausea/vomiting. A note in the guideline describes the following points: Admission to hospital is mandatory if the overdose involves opioids known to have long half-lives (e.g. methadone, OxyContin), if the patient has poor response to treatment, or the patient's general condition or other obvious conditions need medical attention, or EMS staff suspect suicidal attempt. If possible, patients are not to be left alone after treatment, and they are encouraged to be physically active to avoid re-intoxication.

Trondheim(34, 35): (Appendix 13)

The Trondheim guideline follows the ABCDE principles with primary and secondary survey. Diagnosis is made on the basis of reduced or absent respiration, reduced consciousness and miosis. The indication for naloxone is suspicion of opioid overdose and respiratory depression after opioid pain relief administration (iatrogenic). Dosing in community overdoses is recommended for adults and children above 12 years as first 0,4 mg IM followed by 0,4 mg IV, with further titration up to a dose of total 2 mg. In cases of iatrogenic overdose, the recommended dose of naloxone is 0,1 mg IV with titration every third minute.

Naloxone Mylan Intentional LLC product insert(36)

"Opioid Overdose—Known or Suspected: An initial dose of 0.4 mg to 2 mg of naloxone hydrochloride may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions are not obtained, it may be repeated at 2-3 minutes intervals."

5.4 Pre-Clinical & Clinical Experience with Investigational Medicinal Product (IMP)

For this section please also refer to our Investigators Brochure (IB) and Investigational Medicinal Product Dossier (IMPD) for nasal naloxone for updated and more extensive information.

There are some studies in IN naloxone in the pre- hospital setting. In Australia the Ambulance Service in Victoria have conducted two open label RCTs comparing IN and IM naloxone. Kelly 2005 (6) compared 2 mg naloxone (5 ml 0,4 mg/ml solution divided in both nostrils) to 2 mg naloxone IM. Kerr in 2009 (5) compared 2 mg naloxone in 1 ml solution IN with 2 mg naloxone IM. A WHO meta- analysis of these studies indicates no difference between the IN and IM administrations with regards to clinical efficacy (8).The Australian group showed good response when comparing IN naloxone (initial dose 2 mg in 1 ml) vs. IM 2 mg naloxone. The IN group required rescue naloxone 13% more than the IM group. An Iranian study (7) compared 0,4 mg naloxone diluted to 2 ml divided in both nostrils to 0,4 mg naloxone IV and found the two routes of administration to be comparable when measuring GCS.

The bioavailability may be a challenge when administrating naloxone IN. One study found the IN bioavailability to be as low as 4% when giving 2 ml naloxone 0,4 mg/ml IN divided in both nostrils (37).

Previous studies of IN administration reported by the WHO (8, 38-40) reminds us that due to the small surface, the nasal mucosa has limited ability to absorb liquid, a concentrated drug formulation is preferred. The maximum volume should not be higher than 0,2 ml per nostril. This is especially relevant for naloxone as minimal effect can be expected from the overflow from the nostrils that enters the GI-tract as it has extensive first pass metabolism in the liver. This means that the enteral route, e.g. naloxone fluid absorbed orally or in the pharynx, will be metabolised in the liver. The bioavailability via the enteral route, e.g. naloxone fluid absorbed orally, in the pharynx or in the GI tract will be as low as 10% or less.

5.4.1 Results of IMP from NTNU

The research group at NTNU has extensive experience with pharmacological studies on this IN formulation of naloxone. Four clinical trials in healthy volunteers are concluded, and one 4-way cross over is finished with samples in analysis as per October 2016. Results are so far unpublished. Please consult Table 1 for details.
Our IMP does not have a marketing authorisation, but as of March 2017 DnE Pharma sent a file for application for such an authorisation. The present study is not a part of that file.

Naloxone has an excellent safety profile, and has been in widespread clinical use since it was first described in 1963 (41). It has no patent protection and is available as a generic product. A study of adverse events of naloxone in the pre-hospital setting in Oslo also demonstrated its safety (30).

Table 5-1. NTNU clinical trials on naloxone

Study	**Eudra CT**	**n=**	**Dose** IN naloxone	**Spray device**	**Cmax** - ng/ml mean (CI 95%)	**Tmax** - min mean (CI95%)	**Bioavailability** - % mean (CI 95%)
OPI 12-001	2012-004989-18	5	2.0 mg	Aptar bidose	4.24 (1.48-7.00)	16.0 (5.80-26.2)	47.1 (38.4-55.8)
OPI 13-001	2013-000050-22	12	0.8 mg 1.6 mg	Aptar bidose	1.45 (1.07-1.84) 2.57 (1.49-3.66)	17.9 (11.4-24.5) 18.6 (14.4-22.9)	54.0 (44.7-63.4) 52.0 (36.8-67.2)
OPI 14-001	2014-001465-27	12	0.8 mg	Aptar unitdose	1.63 (1.25-2.02)	28.0 (22.0-34.0)	74.7* (62.6-86.8)

* Denotes the relative bioavailability of IN to IM naloxone

Tabell 5-2 DnE clinical trial on naloxone(42)

Study ID: OPI 15-002, (EudraCT 2015-0023355-10)

Study Objective	**Study design**	**Subjects No.(M/F) Type Age: mean (range)**	**Mean paramenters (±SD)**					
			Dose and Administration	**Cmax (ug/L)**	**Tmax (h)**	**AUC0-last (ug/L x h)**	**AUC0-inf (ug/L x h)**	**Relative Bioavailability**
Investigate the systemic exposure and pharmacokinetic profile of naloxone after one dose of IN naloxone 1.4 mg compared to IM naloxone 0.8 mg and IV naloxone 0.4 mg.	Open label, 4-way cross-over	24(13/11) Healthy volunteer 26 y (21-31)	1.4 mg IN naloxone	2.36 ±0.68	0.34 ±0.16	2.44 ±1.45	2.84 ±0.93	0,49 ±0,24
			2 x 1.4 mg IN naloxone	4.18 ±1.53	0.35 ±0.16	4.82 ±1.79	5.47 ±1.90	
			0.8 mg IM naloxone	3.73 ±3.34	0.23 ±0.26	3.00 ±0.64	3.43 ±0.66	
			0.4 mg IV naloxone	7.44 ±9.67	0.058 ±0.065	1.84 ±1.49	2.09 ±1.47	

Our IN formulation show systemic exposure similar to IV and IM naloxone, with plasma concentration versus time curves comparable to IM administration. Detailed plasma concentration-time curves are shown in the IB in chapter 5.
The intranasal dose 0.1 ml naloxone 14 mg/ml is chosen on the basis of the previous studies assessing IN naloxone bioavailability in healthy volunteers both with and without opioid influence and clinical judgment relating to current use of naloxone (OPI 12-001, OPI 13-001 and OPI 14- 001). Different IN doses have also been simulated by semi-parametric Monte Carlo simulations to visualize expected outcomes from studies using different IN dosing (see Table 2). Ten independent simulations of 12 patients were performed to compare the different IN doses as shown in Table 2 (1.0, 1.1, 1.2 and 1.4 mg) with the reference of 0.8 mg IM. From the population model developed using data obtained from the previously performed studies (OPI 12- 001, OPI 13-001 and OPI 14-001) 12 random individuals were drawn for each simulation.

Tabell 5-3 presents the mean (95% CI) absolute difference in $AUC_{0\text{-}inf}$ [µg*h/L] of four IN doses versus 0.8 mg IM dose in each of 10 simulated studies. Semi-parametric Monte Carlo simulations were used to estimate the $AUC_{0\text{-}inf}$ based on 1000 simulation per "study" using the population model mean (SD) and covariate matrix for a 70 kg male.

Study	1.0 mg IN		1.1 mg IN		1.2 mg IN		1.4 mg IN	
	mean	95% CI	mean	95% CI	mean	95% CI	mean	95% CI
1	0.40	0.21 - 0.59	0.80	0.59 - 1.01	1.20	0.96 - 1.44	2.00	1.67 - 2.32
2	0.36	0.19 - 0.53	0.74	0.52 - 0.95	1.11	0.85 - 1.37	1.86	1.50 - 2.22
3	0.64	0.50 - 0.79	1.08	0.89 - 1.27	1.52	1.29 - 1.76	2.40	2.07 - 2.74
4	0.09	-0.31 - 0.49	0.49	0.07 - 0.91	0.89	0.45 - 1.33	1.70	1.19 - 2.20
5	0.17	-0.20 – 0.54	0.60	0.20 - 1.00	1.03	0.60 - 1.47	1.90	1.37 - 2.42
6	0.53	0.25 - 0.81	0.98	0.66 - 1.31	1.43	1.06 - 1.80	2.33	1.87 - 2.79
7	0.33	-0.02 – 0.69	0.74	0.37 - 1.11	1.15	0.76 - 1.53	1.96	1.54 - 2.39
8	0.64	0.45 - 0.84	1.09	0.85 - 1.34	1.54	1.23 - 1.84	2.43	2.01 - 2.86

9	0.53	0.22 - 0.84		0.97	0.60 - 1.34		1.41	0.98 - 1.85		2.30	1.73 - 2.88
10	0.23	-0.32 – 0.79		0.69	0.09 - 1.28		1.14	0.50 - 1.78		2.05	1.30 - 2.79

An IN dose of 1.4 mg assures a systemic exposure with similar absorption pattern as the standard dosing used by EMS personnel today which is 0.4 mg IV or 0.8 mg IM. In clinical practice a significant proportion of opioid overdoses are treated with 0.4 mg IM naloxone as solo therapy.
Choosing a dose of IMP was not based purely on pharmacokinetic calculations of previous results and modelling of data. The clinical rationale is also very important, since naloxone has a wide dosing range in its injected form 0.4- 2.0 mg and titration to clinical response (increased respiratory rate). Our main concern is patient safety. The most commonly used dose of injected naloxone is 0.8 mg IM, with some also receiving 0.4 mg IV additionally, and others only 0.4 mg IM with no IV. This is a clinical judgment in the field by EMS staff based on level of overdose, clinical state and size of the patient. We have therefore chosen 14 mg/ml to make sure we achieve a serum concentration that is not inferior to IM 0.8 mg based on simulations using available pharmacokinetic data. In the setting of acute opioid overdoses in the community the most important aim is to give lifesaving antidote early, and in a reasonably high concentration. 14 mg/ml represent a reasonable dose in this setting- when the indication is acute treatment for respiratory arrest. This will provide a clinically effective dose in the majority of patients and in those not satisfactory treated with this dose it will give enough time to evaluate the effect and administer an additional appropriate dose of naloxone.
Relating to too high doses naloxone there are two concerns. Firstly we are not afraid of toxic effects of naloxone, it is a safe drug, and our dose, even 0.1 ml of the 14 mg/ml given formulation is well below the recommended max dose of 10 mg IM or IV(43)
Secondly there may be concerns regarding precipitating acute opioid withdrawal in patients receiving IN naloxone. Such withdrawal reactions include agitation, nausea, vomiting, piloerection, diarrhoea, lacrimation, yawning, and rhinorrhoea; these are not life threatening. We also believe that these reactions will be reduced by the nasal route of administration, which has a slightly slower onset of action and longer absorption time than IM injection. We believe that our chosen dose is not so high it will precipitate serious withdrawal reactions.
The rationale for a dose of 0,1 ml 14 mg/ml IN naloxone is therefore a result of pharmacokinetic calculations and simulation and relating this to a clinical reality. We have chosen a safe dose that aim to not be inferior to 0,8 mg naloxone IM. The main safety margin in our choice is downwards. Concerns about overdosing of naloxone are not in our dose range. Concerns relating to acute withdrawal are minimised by route of administration and not overshooting 0,8 mg IM too much.
A current study “Bioavailability of nasal naloxone compared to injected naloxone, OPI 15-002 EudraCT no.: 2015-0023355-10” providing data in the naloxone 14 mg/ml formulation is recently completed but no results available as of October 2016.

5.4.2 Experience from use of naloxone in current treatment

Standard treatment today is injected naloxone, mostly IM. The choice between IM or IV are made by EMS and based on clinical state of patient, ability to establish IV access and more. Section 5.3 gives details regarding local guidelines in Norway. An on-going study in Oslo have analysed 1054 overdoses over 2014 and 15. (2) This gives a good overview of the current dosing practice.

Tabell 5-4 Dosing of naloxone in Oslo City Centre 2014- 15

First dose naloxone IV and/or IM		No need for rescue naloxone	Need for rescue naloxone	Total
0.0- 0.3 mg	n=	22 81%	5 19%	27 100%
0.4 mg	n=	292 88%	40 12%	332 100%
0.5-0.7 mg	n=	9 90%	1 10%	10 100%
0.8 mg	n=	540 88%	75 12%	615 100%
0.9-3.0 mg	n=	68 97%	2 3%	70 100%
Total	n=	931 88%	123 12%	1054 100%

Tabell 5-5 Amount of naloxone given as rescue dose

Amount of naloxone (mg) given as second dose	n=	Percent
0.2	5	4.1
0.3	1	0.8
0.4	97	78.9
0.8	20	16.3
Total	123	100

The calculations in table 5-3 are based on 1054 administrations of injected naloxone in the Oslo Ambulance service. The majority of patients receive either 0.4 mg (31,5%) or 0.8 mg (58%). In these calculations we have not differed the route of administrations (IV or IM). The aim is to show that with today´s clinical practice only 12 % receive additional naloxone after the first injection. This forms the basis of our power calculation see section 14.1. Based on the ambulance journals studied 70 (7%) of patients in this time period has received higher than 0.8 mg naloxone as their first dose according to our number. 49 are 1.2 mg and 13 1.6 mg. Based on our experience many of these are likely to be doses of 0.8 + 0.4 mg or 0.8mg x 2 given as separate doses, but wrongly being recorded together in the form. We have chosen to display the data is it is, not second guess this. Table 5-4 show how the majority (79%) of second doses are 0.4 mg naloxone injected.
Please note that local treatment guidelines and the Naloxon B Braun SPC for naloxone stress that dosing always should be titrated to effect. In most local guidelines IM is given at the same time, or even before IV, whereas the SPC maintains that IM only should be used if IV is not possible. Clinical practice involved less IV and more IM administration, based on the clinical state of the patient on presentation to EMS staff. Our choices of IM 0.8 mg represent common dosing in clinical practice, and will in our opinion adequately compare the novel IN formulation with today's treatment.

5.5 Rationale for choice of comparator

We are comparing the novel naloxone formulation with standard injected naloxone.

The dosing of comparator, 0.8 mg IM, is based on the findings from our study of 1054 opioid overdoses (see section 5.4.2) in 465 subjects in Oslo in 2014- 2015. and current treatment guidelines in the Oslo and St Olavs University Hospital ambulance services. 93% of patients in the Oslo study received up to 0.8 mg initial dose of naloxone, of which 88% responded with no need for further treatment. 31% (n=332) received naloxone 0.4 mg as their first dose, and hence, the NINA-1 patients will receive a higher dose of naloxone as study medicine. Although doubling the dose from 0.4 to 0.8 mg, the dose is well within the margin set for naloxone (start dose 0.4- 2.0 mg with a maximum dose of 10 mg). Current clinical experience and past published research show that withdrawal reactions are relatively light at doses of 0.8 mg naloxone and below(30).

The IM comparator will be 2 ml of Naloxone Hydrochloride 0.4 mg/ml, a total dose of 0.8mg. The Naloxone Hydrochloride 4mg/10ml from Mylan Institutional LLC will be used(36).

This will be a study with double dummy design, and the placebo products are:
- The IN placebo is identical to IMP Naloxone nasal DNE 14 mg/ml except that is does not have naloxone added. (see separate IMPD)
- The IM placebo is 2 ml of Sodium Chloride intramuscular injection. Product to be used: Natriumklorid B. Braun 9 mg/ml in 10 ml vials(44).

The choice of comparator is a result of the requirement of the intramuscular comparator and a placebo product to be commercially available. Mylan produces naloxone for injection in 10 mL flip top vials, and B. Braun produces similar vials of sodium chloride 9 mg/ml x 10 ml. They have been chosen for this purpose.

Naloxone in 10 mL vials are not known to Norwegian EMS, as they are not in the market. EMS in Norway normally use 2 mL glass ampoule from either B. Braun (Meslungen, Germany) or from Hameln (Hameln pharma plus gmbh, Hameln, Germany). They are familiar of using flip tops vials of other medication and aspirate 2 mL of such vials. The IM comparator from Mylan has the same strength (0.4 mg/mL) as is normally used in Norway. The IM placebo is a sterile physiologic saline solution for injection that is not expected to have any effect on an opioid overdose. See study section 9.1 for further discussion on the double dummy design.

5.6 Rationale for the Study and Purpose

The rationale for this study is to explore the effect of IN compared to IM naloxone in real life, pre- hospital opioid overdoses. The aim is to provide knowledge to fill current knowledge gap in this important field of emergency medicine. Intranasal naloxone has the potential to change how we treat this serious condition today, and several programmes exist with off-label use of a variety of naloxone formulations. Common to all these programmes is the lack of scientific evidence behind the treatment. Other studies have shown that IN can be as effective as IM and/or IV naloxone (5, 6). No studies have had a large enough number of participants (statistical power), blinded design or used a formulation of naloxone with known pharmacology in humans. There is a current international debate regarding the ethics of wide spread distribution of IN naloxone without proper scientific basis (45).
Opioid overdoses are a worldwide epidemic, affecting both users of illicit drugs and patients taking prescribed opioid painkillers. Worldwide, an estimated number of 69.000 people die annually of opioid overdoses, 250 of them in Norway (3, 8). Particularly the US has seen a sharp rise in the later years, and this is recognised as a public health disaster (46)
The number of non- fatal opioid overdoses are manifold this. In Oslo an estimated 500- 1000 emergency ambulance calls for opioid overdoses are made annually. The majority of these patients live in unsecure and poor conditions are often homeless and have numerous health problems (47).
One of the rationales for this study is to provide a new gold standard, to obtain robust medical research to a group of patients that are often denied the best treatment available. The whole field of emergency, pre- hospital medicine suffers from a lack of high quality clinical research, especially drugs trials. This project aims to in a major way rectify this.

5.7 Systematic Literature Search

We have conducted a systematic literature search as part of the work with this protocol. The following databases were searched:
Embase (OvidSP) 1974 to 2014 November 14

Please note that this search is ongoing and that the IB has been updated with literature until the spring of 2017.

1 *Naloxone*
Naloxone/ or (Naloxone or antioplaz or en1530 or en-1530 or en15304 or en-15304 or en1530 or en-1530 or en15304 or en-15304 or allyl-14-hydroxynordihydromorphinone or maloxone or mapin or dihydro-4-hydroxynormorphinone or allylnoroxymorphone hydrochloride or nalaxone or nalone or nalonee or naloxon or naloxona or naloxone or narcan or narcanti or narcon or narvcam or naxone or zynox).ti,ab.

2 *intranasal*
Intranasal drug administration/ or (nasal or nasally or intranasal*).ti,ab.

3 *studies*
exp controlled study/ or case study/ or exp clinical trial/ or exp "clinical trial (topic)"/ or intervention study/ or exp longitudinal study/ or major clinical study/ or exp postmarketing surveillance/ or prospective study/ or exp comparative study/

1 and 2 and 3 > 67 hitsPubMed Nov 17 2014

1 *Naloxone*
Naloxone[mesh] OR Naloxone[tiab] OR antioplaz[tiab] OR en1530[tiab] OR en-1530[tiab] OR en15304[tiab] OR en-15304[tiab] OR en1530[tiab] OR en-1530[tiab] OR en15304[tiab] OR en-15304[tiab] OR allyl-14-hydroxynordihydromorphinone[tiab] OR maloxone[tiab] OR mapin[tiab] OR dihydro-4-hydroxynormorphinone[tiab] OR “allylnoroxymorphone hydrochloride” [tiab] OR nalaxone[tiab] OR nalone[tiab] OR nalonee[tiab] OR naloxon[tiab] OR naloxona[tiab] OR naloxone[tiab] OR narcan[tiab] OR narcanti[tiab] OR narcon[tiab] OR narvcam[tiab] OR naxone[tiab] OR zynox[tiab]

2 *intranasal*
"Administration, Intranasal"[Mesh] OR nasal[tiab] OR nasally[tiab] OR intranasal*[tiab]

3 *studies*

"Clinical Trial" [pt] OR "Case Reports" [Publication Type] OR "Comparative Study" [Publication Type] OR "Meta-Analysis" [Publication Type] OR systematic[sb] OR review[pt] OR ((random*[ti] OR trial[ti] OR control*[ti] OR study[ti]) NOT MEDLINE[sb])

1 and 2 and 3 > 38

CENTRAL (Cochrane Central Register of Controlled Trials) (Cochrane Library) issue Oct 2014

1 Naloxone
(Naloxone or antioplaz or en1530 or en-1530 or en15304 or en-15304 or en1530 or en-1530 or en15304 or en-15304 or allyl-14-hydroxynordihydromorphinone or maloxone or mapin or dihydro-4-hydroxynormorphinone or allylnoroxymorphone hydrochloride or nalaxone or nalone or nalonee or naloxon or naloxona or naloxone or narcan or narcanti or narcon or narvcam or naxone or zynox):ti,ab,kw

2 intranasal
(Intranasal* or nasal or nasally or nose):ti,ab,kw

1 and 2 > 14 hits

CDSR (Cochrane Database of Systematic Reviews) and DARE (Database of Abstracts of Reviews of Effectiveness) (Cochrane Library) issue Nov 2014

Same search as in CENTRAL > 5 hits (CDSR)

ClinicalTrials.gov Nov 17 2014

naloxone AND (nasal OR nasally OR intranasal OR intranasally) > 8 hits

This yielded only three trials of relevance to this protocol:

1. Kerr D, Kelly AM, Dietze P, Jolley D, Barger B. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. Addiction. 2009;104(12):2067-74.

2. Kelly AM, Kerr D, Dietze P, Patrick I, Walker T, Koutsogiannis Z. Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. Medical Journal of Australia. 2005;182(1):24-7.

3. Sabzghabaee AM, Eizadi-Mood N, Yaraghi A, Zandifar S. Naloxone therapy in opioid overdose patients: Intranasal or intravenous? A randomized clinical trial. Archives of Medical Science. 2014;10(2):309-14.

The WHO conducted a very thorough systematic review in this same field recently screening 5594 studies(8), and they only found the Kerr (2009) and Kelly (2005) studies as they conducted their search prior to the publishing of Sabzghabaee (2014). These three trials are extensively referred to and form much of the scientific basis for this protocol, including the power calculation of the RCT.

6 STUDY OBJECTIVES and related endpoints

The main objective of this study is to measure and evaluate clinical response to nasal naloxone in real opioid overdoses in the pre-hospital environment. By evaluating the core clinical parameter in opioid overdoses; the rate of respiration we want to compare the novel nasal formulation of naloxone with traditional IM treatment.

6.1 Primary Endpoint

- Proportion of patients with return of spontaneous respiration (above or equal to 10 breaths per minute) within 10 minutes of naloxone administration in pre-hospital opioid overdose.

6.2 Secondary Endpoints

- **Changes in Glasgow Coma Scale (GCS) and oxygen saturation (SpO2) in patients treated with study medicine for opioid overdose.**

  These parameters are highly indicative for clinical state, and will add valuable additional information regarding the study medicine. GCS is a very common measurement for EMS, as well and

- **Overdose complications (e.g. aspiration, cardiac arrest, death)**

  Acute complications after overdose will be recorded as EMS judge them at the scene.

- **Time from administration of naloxone to respiration above or equal to 10 breaths per minute.**

  The primary end point is the proportion of patients who respond within 10 minutes, this secondary point measures the time from 0 (study medicine given) to respiration is achieved.

- **Opioid withdrawal reaction to naloxone reversal**

  These are described under section 12 and their presence will be recorded in the CRF

- **Suitability of spray device in pre-hospital setting**

  Study workers will be asked if they are satisfied with the use or experience problems on the CRF. No further data will be recorded in the CRF.

- **Adverse reactions to naloxone formulation**

  Please consult section 12 for details

- **Need for rescue naloxone, dose and route of administration during study visit**

  For those not having achieved adequate consciousness and respiration within 10 minutes the dose and route of naloxone will be recorded.

- **Recurrence of opioid overdose/ need for further pre-hospital naloxone within 12 hours of inclusion**

By looking through AMIS and ambulance records, we will record if included patients have received naloxone by pre- hospital staff within 12 hours of inclusion in this study. The place of overdose, dose naloxone, route of administration and follow up treatment of this event will be recorded.

- **Data regarding reasons not to give rescue naloxone to non-responders**

  If non-responders are not given naloxone, the reasons will be recorded. One instance might be if a participant goes into cardiac arrest after study medicine is given and prior to 10 minutes. This participant will then be treated by standard cardiac arrest guidelines, in which naloxone has no place. EMS may also change the most likely diagnosis during the 10 minutes and continue with other therapeutic measures after.

- **Follow up after care**

  The follow up of patients (left at the scene, taken to OKL, admitted to hospital etc.), and reasons for the various follow up options will be recorded and compared between the groups.

7 Overall STUDY Design

The study is a phase III drugs trial of nasal naloxone.
It is double blinded, double dummy, randomised control trial, multi- centre study, non- inferiority design.

Study Period	Estimated date of first patient enrolled: 1. January 2018 Anticipated recruitment period: 48 months Estimated date of last patient completed: 31. December 2021
Treatment Duration:	Approximately 40 minutes
Follow-up:	**Safety follow up:** Clinical status and adverse events will be recorded as described in the CRF. The duration of treatment is defined later, and the study ends when EMS is no longer in contact with the patient. The patient is therefore censored at this time, which will be recorded. Further treatment in the health service is not recorded, except it will be noted if the patient has received naloxone within 12 hours after inclusion. **Oslo and Trondheim:** The follow up will be identical in that included patients will be searched in AMIS at the local AMK. If they are found to have been in contact with the ambulance service within 24 hours after inclusion, the records of this second contact will be checked. If this includes the administration of naloxone in any form or dose, this will be recorded as described in the CRF. **Other follow up:** Through the user participation board (see section 16) and the information material handed out to participants and by other channels, the study team will be open to be contacted by included patients or other concerned parties. If contact is made regarding a specific study visit/ included patient, this will be recorded in the CRF in a free text field.

8 STUDY POPULATION

8.1 Selection of Study Population

The population are people, above 18 years old, with a suspected opioid overdose as identified by EMS at the scene. This typically includes bystanders alerting AMK 113 (dispatch centre) about unconscious patient / suspected overdose etc. and ambulance being sent. Opioid overdoses are common, over 500-1000 annually in Oslo. Clinically the diagnosis is recognised by miosis, reduced consciousness and reduced or absent respiration. Other clues at the scene, such as drug paraphernalia, bystander information may also point to the diagnosis.

Patients will by definition be unconscious at time of inclusion in this study, and inform consent will not be obtained prior to inclusion. Please consult section 16.3 for a more detailed discussion regarding this. An on-going study of opioid overdoses in Oslo city Centre (2) gives good understanding of the population needing emergency naloxone today. Patients are included without prior consent, but with an opportunity to withdraw from the study. So far only 1- one- out of 1055 cases who met the inclusion criteria have contacted the study team to withdraw from the study.

Table 8-1 Epidemiological data opioid overdoses

	n=	%	**Age**		
Number of overdose cases	1054		Mean (n= 458)	37.1	18-96 years SD: 10.9
Number of individuals	465		Age men (n=362)	37.3	
Number in 2014	508	48.2	Age women (n=96)	36.74	
Number in 2015	546	51.8			
Men	368	79.1			
Women	96	20.6			
Unknown gender	1	0.2			

Tabel 8-2

Number of patients providing EMS with their personnel number. Oslo City Centre (1. June 2014- 31. December 2015, n= 872)		
Full identity provided	N= 761	87.3%
Left scene without providing identity	N= 111	12.7 %

Figure 8-1 Age of individuals treated with pre- hospital naloxone

Y axis= number, X axis= age.

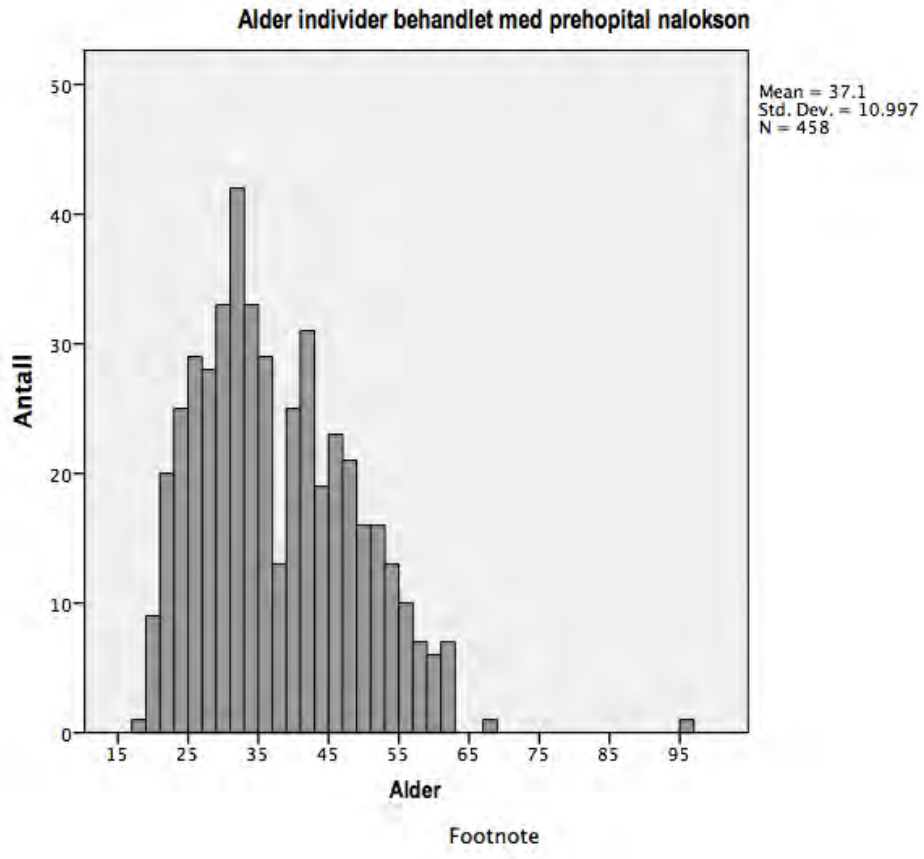


Table 8-3 Place of overdose

	Where do overdoses occur?	Frequency	Percent
	Public place- Outdoors	**361**	**34.3**
	Public place- Indoor e.g. car park	**169**	**16.0**
	Drug Consumption Room, "Sprøyterommet"	**353**	**33.5**
	Shelter, other drug- user facility	**70**	**6.6**
	Health institution, medical office	**8**	**.8**
	Private home	**83**	**7.9**
	Other	**9**	**.9**
	Unknown	**1**	**.1**
	Total	**1054**	**100.0**

Table 8-4 Management after naloxone treatment

Management after administration of pre-hospital naloxone		Frequency	Percent
	Admitted to hospital	**97**	**9.2**
	Admitted to Oslo Kommunale Legevakt	**300**	**28.5**
	Transported elsewhere	**7**	**.7**
	Left by EMS at the scene	**643**	**61.0**
	Dead	**1**	**.1**
	Other	**6**	**.6**
	Total	**1054**	**100.0**

8.2 Number of Patients

200 patients will be included in the RCT. Please consult section 14.1 for details.

8.3 Inclusion Criteria

All of the following conditions must apply to the prospective participant prior to receiving study treatment:

- Suspected opioid overdose clinically diagnosed by EMS based on the following criteria
    1. Reduced (below or equal to 8 breaths per minute) or absent spontaneous respiration
    2. Miosis
    3. Glasgow Coma Scale (GCS) below 12

and

- Palpable carotid or radial arterial pulse

8.4 Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria:

- Cardiac arrest
- Failure to assist ventilation using mask-bag technique
- Facial trauma or epistaxis or visible nasal blockage
- Iatrogenic opioid overdose when opioid is administered in- hospital, or by EMS or other health care workers in the pre- hospital setting
- Suspected participant below 18 years of age
- Suspected or visibly pregnant participant
- Participant that have received naloxone by any route in the current overdose
- Participant in prison or custody by police

- EMS staff without training as study workers
- No study drug available
- Study drug frozen as indicated by Freeze Watch in kit or past its expiry date
- Deemed unfit for inclusion due to any other cause by study personnel at the scene; such as unsafe work environment for EMS.

9 TREATMENT / Investigational medicinal product (IMP)

IMP (IN): For this study nasal naloxone 14 mg/ml is defined as the Investigational Medicinal Product (IMP). This will be administered as 0.1 ml nasal spray using Aptar Unitdose device. Please refer to section 5.4, the IB and IMPD for further details regarding IMP.

Comparator (IM): Comparator is 2 mL Naloxone Hydrochloride 0.4 mg/ml Mylan Institutional LLC, a total dose of 0.8 mg. The IM injection should be given with the syringes provided in the study medicine kit and using 21 G or 23 G hypodermic needle. The choice of needle is made by EMS at the scene and based on the size of the deltoid muscle of the participant. Lean or smaller patients using the 23 G needle.

Placebo IN: The IN comparator is identical to IMP Naloxone nasal DNE 14 mg/ml except that is does not have naloxone added.

Placebo IM: 2 mL Sodium Chloride Injection 9mg/ml, B. Braun as intramuscular injection. The product inserts of these two drugs are attached to this protocol as appendix 3 and 4.

9.1 Double Dummy Design

Blinding refers to the concealment of group allocation in a clinical research study, it is impossible to blind study personnel to whether they give an injection or a nasal spray, and to reduce bias we therefor plan a “double dummy design”. This means that after inclusion patients will be given both a nasal spray and an intramuscular injection at the same time, one of these will hold naloxone and the other an inactive substance. This ensures that all patient receive naloxone- either by IN or the IM route.

The placebo IM and active IM fluid both come in 10 ml glass vials, and will be covered by the labels described under chapter 9.12. They are commercially available products, not specially designed for research, and are therefore not 100 % identical. They differ in the colour of their plastic caps.

The naloxone product form Mylan is not available on the Norwegian market, and is unknown to EMS in Norway. The sodium chloride bottle is available in Norway, but not used in the ambulance service today as they use plastic vials or bottles for their pre- hospital sodium chloride solution.

Unintentional unblinding is unlikely as:
- the vials have their labels covered with the trial labelling described in chapter 9.12.
- the labels used are light impermeable. To un-blind the individual vials study workers need to forcibly remove these labels.
- Study workers have no opportunity to study the vials systematically. They will never see the vials together and directly compare them, neither in training nor during inclusion of participants.
- The study kits will be sealed and should only be opened in the actual treatment situation, which is during emergency treatment for overdose. Kits are to be returned immediately after completion of the study. This means that study workers will be busy treating the patients, including patients in the study and recording data.
- There are an estimated 150 study workers to be recruited and trained in the two study centres, and each study worker is unlikely to include more than a few participants to the trial. The period between each time a study worker includes a patient will in most cases be considerable, thus decreasing the risk of bias by remembering or forming an opinion of the contents in each vial.

- The fact that the EMS are not familiar with these vials on beforehand, and that the existing naloxone and sodium chloride comes in different vials or ampoules.
- Another vial will be used in the training kits, so the study workers will not be exposed to the vials during the training.
- Since both study arms receive active treatment expected to similar clinical effects, unintentional unblinding is unlikely to occur on outcome basis

9.2 Drug Identity, Supply and Storage

The nasal solution is formulated as contractual work by pharmacist Phatsawee Jansook, Pharm D, PhD, Faculty of Pharmacy, Chulalongkorn University, Thailand under the guidance of professor of formulation pharmacy Thorsteinn Loftsson Pharm D, PhD, University of Iceland.

This is a study of the active compound naloxone 14 mg/ml, (±10%). The concentrations are chosen from the observation in our previous studies of the nasal formulation of naloxone. The nasal formulation to be investigated also contains the excipients polyvinyl pyrrolidone, glycerine, sodium edetate, benzalkonium chloride, citric acid monohydrate, sodium citrate dihydrate. Their concentrations are less than 1% (except for glycerine = 1.2%), varying from 0.02 to 0.28 %. The amounts presented to the nasal mucosa in the volume of 100 microL will be small (0.2 to 12 mg (glycerine)), and the amount that may be absorbed to the systemic circulation is probably less.

The IMPs are produced by Sanivo Pharma who also manages the packaging and labelling of the products.
At the study sites, the study drugs will be stored in the drug storage facility already in place at the station, at room temperature and according to local guidelines for drug storage. This storage already holds naloxone and other drugs for clinical use.

There will be no temperature recordings, but all study kits are equipped with an indicator that will tell if the medicine has been exposed to temperatures below 0 degrees centigrade. This is included as an exclusion criterion not to administer study medicine where the indicator is positive. This will form part of training. Please consult appendix 6 for details regarding the study kit.

All ambulances with EMS who have received proper training will have one study kit in the ambulance at all times. The kit will be stored in the ambulance. The exact location within each car will differ somewhat, as the interior varies between ambulance models. Each ambulance and crew will have to decide this locally. This only applies to the kit in the ambulance, the ones in storage at the station will have a predefined space. If unused during one shift, it will be kept in the ambulance for the next shift. It will be recorded in the drug accountability log again when it is either used, damaged (physically or frozen or other) or reaches it date of expiry, there will be no temperature log of this storage in the ambulance.
The supply of study from Sanivo Pharma to the study sites will be described later, but be in accordance with GMP rules. The intramuscular study drugs from Mylan Institutional LLC will be imported by Sanivo Pharma. They are responsible for batch release and that they hold all necessary permissions and licenses to import study drugs for IM administration and release study drugs to sites.

9.3 Double dummy study drugs kit

To blind and randomise between intranasal and intramuscular administration of naloxone, a double dummy design is necessary. This means that participants will receive both an IM injection and an IN spray dosage at the same time. One of these two will contain naloxone and the other sterile physiological saline solution. The contents of the kit will be:

Cardboard box	1
Labels	2
Foam pad to hold equipment safe	1
Stopwatch	1
~~2.0 or~~ 2.5 ml syringe	1
Hypodermic Needle 21G	1

Hypodermic Needle 23G	1
Hypodermic Needle 19G	1
Alcohol Swab	2
Nasal spray marked as described	1
IM vail marked as described	1
Study form with kit number	1
SAE form with kit number ~~in envelope~~	1
Information sheet participant with kit number	1
Information card participant with kit number	1
Freeze indicator	1

A description and illustration of this kit is found in appendix 6. The final design will not be completed until the study is fully approved.

9.4 Dosage and Drug Administration

Half of the subjects will be exposed to the IMP once in the present study. The other half will be exposed to intramuscular naloxone.

The nasal spray will be administered with one puff (100 microL +/- 10%) in one nostril (1.4 mg dose) using the Aptar Unitdose device.

The spray device should be inserted about 1 cm into a nostril, pointing towards the ipsilateral ear and the plunger pushed in a firm and gentle manner for the formulation to be sprayed into the nose. After the plunger is inserted the device is immediately removed from the nose and assisted ventilation continued.
Intramuscular comparator Naloxone Hydrochloride 0.4 mg/ml Mylan Institutional LLC or Sodium Chloride Injection 9mg/ml, B Braun will be administered as a 2 ml IM (0,4 mg/ml) injection in the deltoid muscle, total dose of 0,8 mg naloxone IM if they receive active comparator.

The study treatment will be administered to the subject by authorized personnel only, which in this study are EMS properly trained (see section 10.4) and investigators. They will be trained so that one EMS ventilates the patient, while the other prepare the injection and expose the deltoid muscle. When they are ready, they will fist give the nasal spray, then the IM injection, both within 30 seconds.

9.5 Start of treatment period

Start of treatment period is defined as when study medicine is given: the nasal spray should always be administered first.

9.6 Duration of Therapy

The expected duration of therapy is 10 minutes with a further observation time of up to 30 minutes.
End of protocol therapy is defined when one of the following is achieved:

1: The patient is awake and declines further follow-up from EMS staff, observation time is up to 40 minutes after administration of study drug.

or:

2: The patient is awake and declines further follow-up from EMS staff, but leaves the scene prior to an observation time of 40 minutes despite EMS urging the patient to stay present or be followed up elsewhere.

or:

3: The patient is awake after administration of the study drug and transported to medical follow-up. End time is when EMS hands over treatment responsibility to other health care professionals.

or

4: Patient is not awake after administration of study drug and transported to medical follow-up. End time is when EMS staff hands over treatment responsibility to other health care professionals.

9.7 End of treatment period

End of treatment period is defined as duration of therapy as described in 9.6.

9.8 Premedication and Monitoring

Premedication is not applicable.
Participants are monitored clinically by EMS staff for skin colour, cyanosis, palpable pulse, free airways, effect of mask-bag ventilation. They are continuously assessed based on the ABCDE principles.
Oxygen saturation (SpO2) will be measured from arrival until the patient is awake.
Non-invasive blood pressure and ECG are not routine measurements in pre-hospital treatment of opioid overdoses, and will not be part of the routine monitoring of participants in this study. EMS staff will record these values in the ambulance journal as they deem fit at the scene.

9.9 Concomitant Medication

No concomitant medication will be administered by study personnel as part of this protocol.
After recovery, a focused patient history involving drugs, alcohol and medication used by the patient, both illicit and prescribed medication will be taken and recorded in the patient journal and CRF. Particular care will be taken to record type of opioid and route of administration and type and route of administration for sedatives such as benzodiazepines or alcohol. This information is all routinely gathered by EMS and recorded in the patients' journal today, according to guidelines in Oslo and Trondheim. The ambulance patient journal is part of the source data in this study.
Other drugs:
Rarely EMS administers other drugs than naloxone to opioid overdoses, but if medically indicated such drugs (e.g. nebulizes salbutamol) will be given as per local guidelines. All concomitant drugs administered by the EMS personnel during the treatment period will be recorded in the CRF

9.10 Subject Compliance

Not applicable, study personnel will administer all study drugs in the acute setting.

9.11 Drug Accountability

The responsible site personnel will confirm receipt of study drug and will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution and return of study drugs will be recorded by EMS staff at their local ambulance station on drug accountability logs to be kept locally in ISF and gathered for TMF at the end of the study.
Receipt to ambulance station, return the ambulance station and destruction (if any) of the study drug will be recorded by investigators or by local drug handlers at the ambulance stations in accountability logs to be kept locally in ISF and gathered for TMF at the end of the study. The hospitals pharmacies at each study site will be responsible for study drug destruction, separate agreements will be signed prior to distribution of study drugs to sites.

9.12 Drug Labelling

Labelling is designed according to chapter 4.4. «Merking av utprøvingspreparatet in FOR-2009-10-30-1321 Forskrift om klinisk utprøving av legemidler til mennesker» and «Veiledning til forskrift av 30. oktober 2009 om klinisk utprøving av legemidler til mennesker versjon 2.0./8.-sept-2011». As the regulation requires labels to be in Norwegian, the examples below are written in Norwegian.

17PXXX/17PYYY indicates batch number for Naloxone DnE Nasal Spray and DnE Nasal Spray placebo

ZZZ indicated study number as described in point 9.13

Large label outside box.

NTNU Intranasal Naloxone Trial

Studie: NINA- 1, Eudra CT: 2016-004072-22
Nasjonal utprøver Arne Skulberg. Institutt for sirkulasjon og bildediagnostikk, NTNU, Akutten, Hjerte-lungesenteret, St.Olavs Hospital, Trondheim; Norge. Studietelefon: Oslo AMK: 22932211

Studiemedisin til IN (en spray) og IM (2 mL) administrasjon
Spray inneholder Nalokson 14 mg/ ml eller placebo.
Injeksjonsvæske inneholder Nalokson 0,4 mg/ ml eller placebo.

Etabler frie luftveier og ventiler pasienten hvis pasienten ikke puster tilstrekkelig selv.

Trekk opp IM medikasjon og gjør klar skulderen. Sett først IN og så IM- begge i løpet av 30 sekunder. Start klokka

Batch- Studiekit: 17PXXX/17PYYY-ZZZ
Produksjonsdato: DD.MM.YYYY
Bare for klinisk utprøving, oppbevares utilgjengelig for barn.
Lagres stående ved romtemperatur- brukes ikke om indikator for frost er positiv
Varighet 6 måneder fra produksjonsdato
Utløpsdato: DD.MM.YYYY

NTNU Oslo universitetssykehus ST. OLAVS HOSPITAL UNIVERSITETSSYKEHUSET I TRONDHEIM

Smaller label on nasal spray:

Studiemedisin til IN administrasjon
En spray i ett nesebor før injeksjon
Nalokson 14 mg/ ml eller placebo.
Bare for klinisk utprøving, oppbevares utilgjengelig for barn.
Batch- Studiekit: 17PXXX/17PYYY-ZZZ
Utløpsdato: DD.MM.YYYY
Nasjonal utprøver Arne Skulberg, NTNU

Smaller label on 10 mL vial for injection

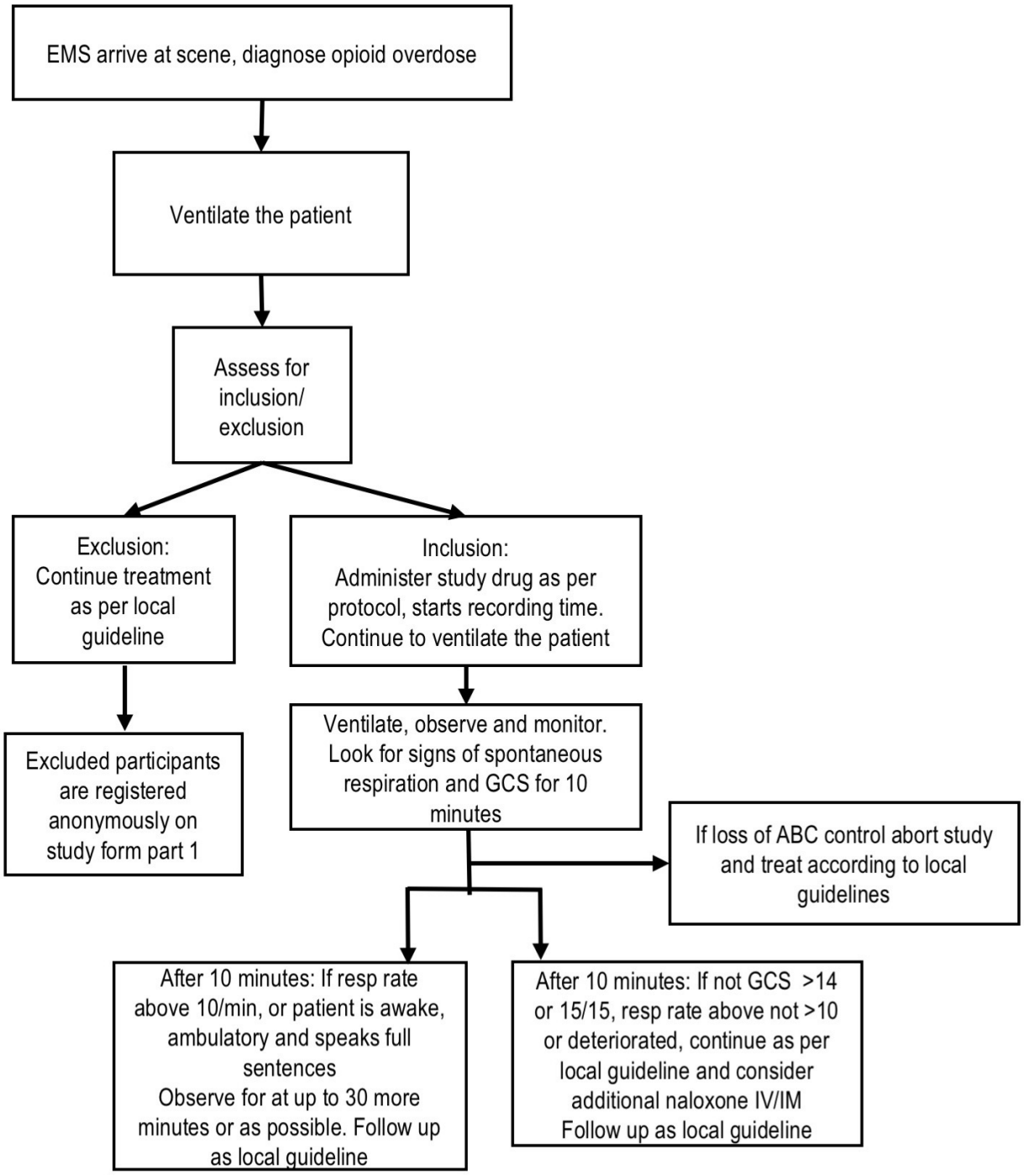
Studiemedisin til IM administrasjon 2 mL til IM injeksjon etter nesespray Nalokson 0,4 mg/ ml eller placebo. Bare for klinisk utprøving, oppbevares utilgjengelig for barn. Batch- Studiekit: 17PXXX/17PYYY-ZZZ Utløpsdato: DD.MM.YYYY Nasjonal utprøver Arne Skulberg, NTNU

9.13 Subject Numbering

Each subject is identified in the study by a unique subject number that is assigned at inclusion. The subject number is identical to the double dummy kit ID number administered. This number will also appear on the information letter given to the patient after inclusion. The numbering will start at 1 and increase in increments of one (2, 3, 4, etc. etc.) The maximum number will depend on the number of study kits produced- this is influenced by inclusion rate, expiry time of kits etc. The maximum number will be recorded, and all numbers accounted for on the study drugs accounting log.
The AMIS number will also follow the study form to ensure traceability with the pre- hospital medical records. Kits will not be used in any particular order, so it will not reflect the number in which participants are included in the study.

10 STUDY procedures

10.1 Flow Chart study visit



10.2 By Visit

This study consists of one study visit only. The information below will be recorded as information is available, which will vary somewhat. Please see CRF for details.

All patients eligible for inclusion shall be assessed. Excluded patients will be recorded at the study form part 1. They will be recorded anonymously, year of birth, gender, date of overdose, place of overdose, follow up (hospital, OKL, left at the scene etc.), reason for exclusion and amount and route of naloxone given will be registered. Excluded patients will not form part of the main database, or be subject to AE, SAE, SUSAR registration as they do not receive IMP. They will not receive an information letter as the information is recorded anonymously from the start. No personal health information is recorded in an identifiable form.

For included patients´ clinical status will be recorded as at several points in time before and after study drug administration by EMS staff. This will include circumstances of the scene of the emergency and reasons for suspecting opioid overdose. Clinical observations such as skin colour, feel of the skin (warm/ cold, dry/clammy), size of the pupils, rate and quality of respiration, rate and quality of pulse. GCS and SpO2 before and after study drug administration will be recorded.

Pulse, ECG and non- invasive blood pressure will be recorded if deemed feasible and necessary by EMS at the scene.
Information from bystanders regarding types, amounts and route of drugs administered, reasons to alert EMS services and call AMK will be recorded if available
Record types, amounts and route of drugs administered, intention of overdose (suicide?), other medical history,
Record follow-up: Left at the scene, transported to health institution, other
Participants will be given information about being included in the study. Study workers shall gather oral consent after the study intervention in as many participants as possible. Participants that cannot consent will receive information orally and in writing by EMS staff. This information contains details about how to withdraw from participation. See section 16.
For study workers, the following template will be used for the execution of a study visit:

Preparation:
All ambulances must have a copy of the study form to fill in part 1 on all patients
Each ambulance with EMS that has received study training must have a study kit available. This kit must be accounted for according to this protocol, be stored correctly and its seal not broken.
Checking the kit should be part of the daily controls performed in the ambulances

On dispatch:
If suspected overdose/ unconsciousness code prepare in the car for possible inclusion in study. The team should talk about the tasks ahead and decide who takes responsibility for airway management and who for inclusion/ study drug administration.
Bring airways/ oxygen bag, emergency drugs, patient monitoring unit and study kit from the ambulance to the patient.

By patient side:
Secure workspace
Quick diagnostic survey: GCS- is the patient awake? Counting respiration- if no spontaneous breaths in the first 6 seconds despite a free airway conclude respiratory rate below 10/minute. Check pupils for miosis.
Start bag mask ventilation- monitor by end tidal CO2 or clinically
If patient has carotid or radial pulse:
Consider inclusion and exclusion:
If NO suspicion of opioid overdose, treat as local protocol→ do not fill inn study form
If YES suspected opioid overdose and a pulse →Inclusion criteria fulfilled
Consider exclusion criteria→ if at least one fulfilled → treat as local protocol and fill in study form part 1
→ if no exclusion criterion fulfilled → include and administer IMP

Treatment of included patients:
EMS no 1 ventilate and monitor, observe for clinical changes, particularly deterioration or loss of airway control. Use positioning of patient, chin lift Guedel airway, end tidal CO2 and other means available for this task.
EMS 2 prepare to administer study medicine:
Open kit, fill syringe with 2 mL from vial and prepare with needle for injection, expose shoulder and deltoid muscle, prepare nasal spray and stop watch.

When all is ready, all within 30 seconds: Insert and deliver nasal spray, swab and inject 2 mL in deltoid muscle, then start the watch.
After this EMS 2 will monitor GCS and respiratory rate. Connect patient to patient monitoring unit, SaO2 is minimum. Consider need for IV-line insertion and blood glucose measuring. If low blood glucose below 4 mmol/L abort study and treat as local protocol for hypoglycaemia.
If patient wakes up within 10 minutes note the number of minutes from administration of study medicine to respiratory rate >10/minute or GCS 14 or 15/15
If the patient does not seem to be waking up use the 9th minute after study drug administration to prepare further treatment. This may include administration of naloxone as per local guideline or other interventions. If in doubt or patient deteriorating call for help: other EMS, air ambulance etc.
When the patient is awake, talk to, comfort and calm the patient. Explain that they have had an overdose and explain follow up options. Inform them that the naloxone they have received is part of a research project comparing naloxone in a nasal spray and as an injection. Gather oral consent after the study intervention in as many participants as possible. If oral consent is not possible, give them the information letter and the business card provided in the kit and explain that they can get more info and with draw online or by telephone.
Participants should be observed particularly for adverse events and for signs of opioid withdrawal. If patient is taken to hospital or deteriorated a serious adverse event must be suspected. All participants that die must be considered a SAE. EMS should stay with the participant for up to 30 minutes after he or she woke up, unless they leave the scene or are handed over to the care of other health personnel.

Completion of the study:
Fill inn study form accurately, fill in ambulance journal accurately. Remember to put study kit number on patient journal. If serious adverse events, fill in SAE form.

Back at ambulance station:
Study forms, journals and SAE forms are left in box/ folder provided.
Study kit (with spray, vial, watch etc.) are put in box provided. Account for the kit used in the log.
The ambulance must have a new kit, take out an unused and account as usual.
If there have been SAEs, serious concerns, problems with study kit or any other reason, please contact the study telephone and ask for a member of the study team.
Any untoward events or problems should also be noted in the patient journal and in the hospital on line system for event reporting.
I Oslo a number of specially trained and experienced EMS operate as single emergency providers, using motorcycles, not car ambulances. They are referred to as “117”. A special “one- man technique” will be described if these are to be recruited as study workers.

10.3 Criteria for Patient Discontinuation

Patients will not be able to discontinue participation as the study only has one visit. They may withdraw from the study contacting the study team as described in section 16.3.5. Participants that withdraw will have their data deleted from the study database.
Participants that withdraw or are withdrawn from the study will be replaced.

10.3.1 Trial Discontinuation

The whole trial may be discontinued at the discretion of the CI or the sponsor in the event of any of the following:

- Occurrence of AEs unknown to date in respect of their nature, severity and duration
- Medical or ethical reasons affecting the continued performance of the trial
- Difficulties in the recruitment of patients
- Changes in funding to research team
- Cancellation of drug development

The sponsor and coordinating investigator will inform all investigators, Data Monitoring and Safety Committee, the relevant Competent Authorities and Ethics Committees of the termination of the trial along with the reasons for such

action. If the study is terminated early on grounds of safety, the Competent Authorities and Ethics Committees will be informed within 15 days.

10.4 Training of study personnel

EMS will have a dual role as health care providers and as study personnel in this study. For individual EMS to include a patient in this study he/she must have undergone a study specific training session according to the training protocol with a study investigator. EMS will be evaluated at the end of a study session. This training will be documented in a training and included in the Invest Site File (ISF) during the study and included in the TMF at the end of the study. EMS are well accustomed to live scenario training using mannequins and role play, this is an integral part of both their pre- and post-graduate training. Our study training will build on these principles. The final version of the training manuals will be completed after the approval of this study protocol. The Norwegian National Advisory Unit on Prehospital Emergency's (NAKOS) web portal will establish an online training module that will include training documentation.

The training will consist of:

- Lecture outlining background of study, primary and secondary outcomes and design
- Familiarising participants with double dummy naloxone kit, study form etc.
- The use of a mannequin to play out a study scenario
- Practice of recording variables and points in time, fill in study forms
- Practice in documenting drugs accountability form at ambulance station
- Lecture focusing on AE, SAE, SUSARs and procedures in case of emergency- study emergency telephone and criteria for code break.
- Standardising counting of respiration rate
- Training in evaluating which participants are eligible to give oral consent
- Talk focusing on patient information, consent and about withdrawal from participation

Please refer to Appendix 7

10.4.1 Documentation of study personnel

Individual EMS that complete training and pass the test at the end of the training session will be certified as study workers. This will involve that they are delegated the tasks to:
IMP preparation, IMP administration, IMP dispensation, collection & accountability, evaluate inclusion & exclusion criteria, record medical history, record & evaluate AE, record concomitant medication, record vital signs, treatment allocation/randomization and perform physical examination.

These tasks will be delegated by the investigator who performs the training and evaluation. All this is delegated from CI. A record of personal details, identification of EMS, completed training and proof of delegation will be filled inn. See appendix 7 page 19. This will be stored in the ISF and filed in the TMF at the end of study.

11 Assessments

11.1 Assessment of Response

The following parameters will be recorded before administration of study drug (time =0) and at least once before or at 10 minutes. If the patient is an obvious responder to the primary target of respiratory rate above 10 and/ or GCS 14 or 15/15 before 10 minutes the time from t=0 to achieving the target shall be noted. After that, record as clinically appropriate. See CRF and ambulance record for details.

- Respiratory rate will be counted at inclusion when holding free airways and stimulating the patient. If no spontaneous breath within 8 seconds, it will be assessed as "a rate below 8/min"

- Patients who can walk with no support and speak in full sentences will be recorded as having a respiratory rate above 10/ minute, and hence be classified as responders.
- Oxygen saturation (SpO2)
- Glasgow Coma Score
- Other parameters of clinical state

11.2 Safety and Tolerability Assessments

Safety will be monitored by the assessments described above as well as the collection of AEs.

11.3 Other Assessments

Time data from the AMIS data system, ambulance journal and CRF will be used to assess time and resource use by ambulance from initial contact with AMK to end of treatment period.
Temporal data on the time of day, weekday, month season etc. of the overdose and the response
Data regarding type of venue e.g.: Sprøyterommet (SIF), public place outdoor, public place indoor such as parking house / hotel, hostel, private home or other venue used by drug users
Data regarding other drugs or substances used in relation to overdose
Age, sex will also be recorded.

12 Safety Monitoring and reporting

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE). Each patient will be informed in the study information leaflet to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.
EMS/ Study workers are well trained and experienced professionals, and know this group of patients well. The observation and description of untoward events are part of their daily job and part of the specific study training. Included participants will be observed until end of treatment period. During this period, EMS will take a detailed patient history, and response to naloxone treatment (here under AEs) is a part of this. This gives participant's ample opportunity to describe possible AEs that will be directly recorded on the study form. Participants may contact the study team at any time, but events after end of treatment period will not be recorded as AE, SAE or SUSAR.

In this study participants that withdraw from the study will have all information collected deleted from the database. This is unusual in clinical drugs trials. But this study is unusual in that it is a drug trial without informed consent prior to inclusion in the study. This may introduce bias in the AE/ SAE/ SUSAR reporting. However, based on the ongoing registration of opioid overdoses in Oslo only one out of 1055 included overdose cases have asked to be withdrawn. This study has a similar consent process to the one outlined in this protocol. Based on this we expect the risk for bias to be very small. In weighing the risk between biased reporting and giving participants a chance to actually withdraw data we see no alternative to letting patients delete all gathered information. Their study number will appear on their ambulance records. These records do not form a part of the study archive, may not be deleted, and patients has full access to these records under Norwegian law.

The methods for collection of safety data are described below.
All non-conformances and serious adverse events that refer to incidents in relation to the research participants or deviations from the approvals that are granted in this protocol must be reported in the hospitals own systems for such reporting. In Oslo this is "Achilles" and in Trondheim "EQS"

12.1 Definitions

12.1.1 Adverse Event (AE)

Is defined as" Any *untoward medical occurrence in a subject administered the study medicine and which does not necessarily have a causal relationship with this treatment'.*
Study workers are trained EMS and very familiar with the clinical response to naloxone. The study form will have a separate AE section, and investigators will fill inn AE forms based on clinical data from study form and ambulance journal.

12.1.2 Serious Adverse Event (SAE)

SAE is defined as *"Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect or is considered medically significant by the investigator".*

We do not have a design that can identify congenital anomalies or birth defects, visibly pregnant women are excluded. No system is in place to detect pregnant women or any follow up of pregnancy/ new born.

A significant amount our patients will warrant hospitalisation, regardless of type of naloxone administered. As shown in section 8.1 38.3 % of patients are today admitted to a health care institution. In the Trondheim study centre this is even higher, 60% are admitted to the hospital and another 10% goes to the Trondheim Municipality Accident and Emergency Clinic. The aim of the health authorities is that this number should be even higher. According to national guidelines, all patients shall be offered follow up at a municipality accident and emergency clinic or at the hospital (48). On this background, we will not report all hospital admissions as SAE. Most of these admissions are administrative admissions, to ensure contact with rehabilitation services/ social care etc. or admissions due to pre-existing disease/ other drug use. Non-responders admitted to hospital will not be recorded as SAE.
EMS will judge if hospitalisation is warranted due to conditions presiding the administration of IMP in time, or for administrative reasons. In such case, the event will not be considered a SAE.

In this study, the following are examples of SAE

1) Death

   Hospitalisation due to:

2) Pulmonary oedema, defined as one or more of the following clinical features lasting more than ten minutes after naloxone reversal: Extreme shortness of breath, wheezing or gasping for breath, a cough that produces frothy sputum that may be tinged with blood, SpO2 <90% without oxygen, or <94% with >2l/min oxygen delivered by mask or by nasal catheter or pulmonary crepitation.

3) Seizures: Any visible convulsions will be recorded as an SAE.

4) Cardiovascular collapse: Hypotension (systolic blood pressure <80 mmHg), bradycardia (heart rate <40 beats per minute) or severe tachycardia (heart rate >140 beats per minute) evident more than ten minutes after reversal with naloxone.

5) Cardiac arrest: The start of cardio-pulmonary resuscitation by EMS with return of spontaneous circulation.

6) Allergic reaction:
   The acute onset of a reaction with involvement of the skin (redness, rash, swelling, itch), mucosal tissue or both and at least one of the following: respiratory compromise; or reduced blood pressure.

7) Epistaxis: Nose bleed that do not resolve spontaneously while EMS is at the scene

8) Other: Any other event EMS consider serious and that lead to hospitalisation for other reasons than standard follow up after overdoses, and that is deemed not to have been present prior to start of treatment period.

Medical and scientific judgment is to be exercised in deciding on the seriousness of a case. Important medical events may not be immediately life-threatening or result in death or hospitalisation, but may jeopardize the subject or may require intervention to prevent one of the listed outcomes in the definitions above. In such situations, or in doubtful cases, the case should be considered as serious. Hospitalisation for administrative reason (for observation or social

reasons) is allowed at the investigator's discretion and will not qualify as serious unless there is an associated adverse event warranting hospitalisation.

12.1.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Adverse Reaction: all untoward and unintended responses to an investigational medicinal product related to any dose administered;

Unexpected Adverse Reaction: an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

Suspected Unexpected Serious Adverse Reaction: SAE that is unexpected as defined and possibly related to the investigational medicinal product.

This protocol has included a range of symptoms both of known naloxone AEs and expected symptoms of acute opioid withdrawal. Any event mentioned as this and considered a SAE will not be defined as a SUSAR.

12.2 Expected Adverse Events

Please see current version of INVESTIGATOR'S BROCHURE for this study for details regarding AEs.

Due to the nature of this study, where naloxone is studied in participants that have necessarily taken opioids and likely other drugs, naloxone is likely to precipitate a certain degree of acute withdrawal symptoms from opioids. Naloxone may also unmask symptoms of other drugs taken.

Tabell 12-1 Features of acute opioid withdrawal

Features of acute opioid withdrawal (49)	
Physical symptoms and signs	Piloerection, nausea, vomiting, diarrhoea, lacrimation, yawning, rhinorrhoea, tachycardia, dilated pupils
Neuropsychiatric symptoms	Agitation, restlessness and anxiety

Mylan Institutional LLC also describes opioid withdrawal in the product insert of the naloxone formulation used as IMP in this study:

"The signs and symptoms of opioid withdrawal in a patient physically dependent on opioids may include, but are not limited to, the following: body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure..."(36)

Naloxone already have a number of known AEs in its injectable form already known.

Tabell 12-2 Adverse events of injected naloxone

Adverse events described in Naloxone Hydrochloride 4 mg/10ml, Mylan Institutional LLC(36) Adverse events associated with the postoperative use of naloxone hydrochloride injection are listed by organ system and in decreasing order of frequency as follows:	
Cardiac Disorders:	pulmonary edema, cardiac arrest or failure, tachycardia, ventricular fibrillation, and ventricular tachycardia. Death, coma, and encephalopathy have been reported as sequelae of these events.

Gastrointestinal Disorders:	vomiting, nausea
Nervous System Disorders	convulsions, paraesthesia, grand mal convulsion
Psychiatric Disorders:	agitation, hallucination, tremulousness
Respiratory, Thoracic, and Mediastinal Disorders:	dyspnea, respiratory depression, hypoxia
Skin and Subcutaneous Tissue Disorders:	nonspecific injection site reactions, sweating
Vascular Disorders:	hypertension, hypotension, hot flashes, or flushing

Pulmonary oedema has been reported as a rare complication to naloxone, but mainly in the post- operative setting (50, 51).

Symptoms and events that are normal consequences of the opioid toxicity, or inevitably follow the reversal of the toxicity with naloxone independently of the route of administration, will be recorded as AE. As Naloxone Hydrochloride 4mg/10ml, Mylan Institutional LLC is IM active comparator this prescribing information is set as reference safety information (RSI).

12.3 Overdose recurrence

In this study an overdose recurrence is defined as:*" The administration of pre- hospital naloxone by EMS to a patient within 12 hours after administration of IMP."*
Naloxone has a half- life of about 90 minutes, shorter than heroin and many of the other opioids seen in overdoses. There has long been a fear that patients treated with naloxone in the field and not under clinical observation after treatment runs the risk of a recurrence of opioid overdose symptoms when the effect of the naloxone wears off, and the serum concentration of opioid has not fallen below a level giving respiratory depression.
This is the main reason EMS and the authorities urge everyone treated with naloxone to be transferred to further observation and follow up, and the reason they are not left alone (but in the company of others) by EMS staff today.
In our study it is important that IMP does not have more cases of recurrence than traditional injected naloxone, and this is added as a secondary end point. It is however difficult sometimes to assess whether a second case of overdose within 12 hours is a genuine recurrence, or a new overdose due to repeated administration of opioids or other sedating drugs. We will reduce the chances of recurrence by admitting as many of the included patients to further services, either health services like OKL, St. Olav's Hospital or with service providers such as the SIF/Sprøyterommet. Treatments of any recurrence will not differ from normal treatment of overdoses. There is today no tradition, legally or medically, to section and/ or force such patient into treatment or observation.

By looking up included patients in AMIS we will be able to record any use of pre-hospital naloxone within 12 hours after inclusion, and compare this between the groups. There may be a considerable time lag (days or weeks) between an actual occurrence of a recurrence and this coming to the attention of the study team. Recurrence is not defined as an Adverse Event of IMP. Its occurrence is after end of treatment period. It is the only information that will be recorded after the end of treatment period.

Information recorded will be:
Participant details. Time and place of recurrence, dose and form of naloxone given, clinical response to naloxone (respiratory rate and GCS) and follow up.

As this information is recorded after end of treatment period it will not be recorded in the eCRF and VieDoc™ database, but a separate data sheet stored at each participating department. The data will be de-identified and linked to the code list at each study site. This storage will comply with local regulations for storage of sensitive patient information.

12.4 Time Period for Reporting AE and SAE

For each patient, the standard time period for collecting and recording AE and SAEs will begin at administration of IMP and will continue until the end of treatment as defined in point 9.6. Any post-treatment events that comes to the attention

of the study team, through any channel, shall be treated as study reports and follow this protocol in terms of reporting and causality assessment.

12.5 Recording of Adverse Events

If the patient has experienced adverse event(s), the investigator will record the following information in the CRF:

- The nature of the event(s) will be described by the EMS in language normally used in pre- hospital medical records.
- The duration of the event will be described in terms of being present or not within the short time the study lasts. Event onset date and time and event ended date and time will be recorded if possible within the time frame of the study. For AE/ SAE that resolve within the duration of treatment this will be recorded. In case the patient decides to leave the scene before the resolution of the AE/SAE this will be recorded. Patients who leave the scene by their own free will, will not be actively followed up, but are free to contact the study team through the channels described. If care is handed over to other health services with an on-going SAE this should be recorded in the CRF and SAE form filled out as described. The study team will seek access to patient records relating to the suspected SAE from the institution that takes over care. Investigators will use these patient records to decide causality and time frame to resolved, chronic or stable.
- The intensity of the adverse event: will be described in in language normally used in pre-hospital medical records. Investigators will later attempt to describe event using the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) system MedDRA (52).
- The Causal relationship of the event to the study medication will be assessed later by the use of the WHO-UMC system for standardised case causality assessment (53). The medically qualified investigators are responsible for evaluating the causal relationship.

Causality term	**Assessment criteria***
Certain	• Event with plausible time relationship to drug intake • Cannot be explained by disease or other drugs (illicit, narcotic, prescription or OTC or alcohol) • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e.an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs (illicit, narcotic, prescription or OTC or alcohol) • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event with reason able time relationship to drug intake

	Could also be explained by disease or other drugs (illicit, narcotic, prescription or OTC or alcohol) • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

*All points should be reasonably complied with

- Action taken

  EMS will record the actions taken as per local protocols for documenting their medical work at their respective local documentation systems. EMS documentation ends at the time as described in point 9.4

12.6 Reporting Procedure

12.6.1 AEs and SAEs

All adverse events and serious adverse events that should be reported as defined in will be recorded in the patient's CRF.
SAEs must be reported by the study personnel to the investigator at investigator/ study telephone via Oslo AMK or email within 24 hours after the personnel has gained knowledge of the SAE. The investigator shall notify to the sponsor and CI within 24 hours after the investigator has gained knowledge of the SAE.
Every SAE must be documented by the investigator on the SAE pages the investigator site file. The Serious Adverse Event Report Form must be completed, signed and sent to CI and to sponsor. The SAE form will be included in the study kit, part 1 is filled in by EMS staff/ Study workers and part 2 by an investigator, the investigator shall also notify the DMSC. The initial report shall promptly be followed by detailed, written reports if necessary. The initial and follow-up reports shall identify the study subjects by unique code numbers assigned to the latter.

Address to Sponsor: Øystein Risa, Department of Circulation and Medical Imaging, ISB, NTNU
Box 8905 MTFS 7491 Trondheim, Norway Tel: (+47) 92613734 E-mail: oystein.risa@ntnu.no

Email to DMSC: nalokson_sikkerhet@medisin.ntnu.no
The sponsor keeps detailed records of all SAEs reported by the investigators and performs an evaluation with respect to seriousness, causality and expectedness.

12.6.2 SUSARs

SUSARs will be reported to the Competent Authority and Ethics Committee according to national regulation. The following timelines should be followed:
The sponsor will ensure that all relevant information about suspected serious unexpected adverse reactions (SUSAR) that are fatal or life-threatening is recorded and reported as soon as possible to the Competent Authority, the DMSC and Ethics Committee in any case no later than seven (7) days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight (8) days.

All other suspected serious unexpected adverse reactions will be reported to the Competent Authority concerned and to the Ethics Committee concerned as soon as possible but within a maximum of fifteen (15) days of first knowledge by the sponsor.
SUSARs will be reported using the CIOMS form. The reporting to the Norwegian Medicines Agency will be done by Department of clinical research support (CRS), Oslo University Hospital by a person not directly involved in the study. As SUSARs will be un-blinded this information will not be shared with sponsor, anyone in the study team, data handlers or monitors. The person at OUS CRS responsible is Martha Colban (email: marcol@ous-hf.no).

12.6.3 Annual Safety Report

Once a year throughout the clinical trial, the sponsor will provide the Competent Authority with an annual safety report. The format will comply with national requirements.

12.6.4 Clinical Study Report

The adverse events and serious adverse events occurring during the study will be discussed in the safety evaluation part of the Clinical Study Report.

12.7 Procedures in Case of Emergency

Participants will be included at a 24 hour a day basis, and EMS/ study workers will be able to contact the study team throughout the day and night in case of SAE/ SUSAR or concerns regarding safety. By order of an investigator unblinding of individual study kits are also available 24 hours a day. The code on an individual participant will be broken only if it's needed to provide the best health care for patients.
The PI on each site is responsible for assuring that there are procedures and expertise available to cope with emergencies during the study. Please note that the Oslo AMK will act as emergency centre for both study centres for study specific handling/ code break. The Oslo AMK 24- hour number is: 22932211. This number will be printed on the study medicine and study forms and be part of the training of study workers.
The study team will provide 24- hour on call by an investigator. The investigator will not be contacted by study workers directly, but via Oslo AMK. At AMK a list will be kept updated about which investigator is on call, and if contacted by concerned study workers for SAE/ SUSAR, need to un-blind or other grave concerns. At the end of the study the on-call list will be filed in the TMF.

12.7.1 Medical emergencies

These will be handled by EMS as per local protocol/ guidelines. This involves alerting local medical/ emergency/ other agencies such as local Air Ambulance doctor/ other EMS/ police etc.
If a suspected SAE/ SUSAR occur EMS shall notify the study team via email or Oslo AMK within 24 hours.

12.7.2 Provide information regarding code break:

Envelopes with codes to un-blind individual study kits will be stored at the Oslo AMK. This has 24-hour coverage by telephone, and the AMK coordinator will be available for investigators, study personnel or others. The decision to un-blind lies with a member of the study team, but Oslo AMK will do actual opening of the envelope. Envelopes must be returned opened or unopened to the study team and accounted for in the TMF.
The Oslo AMK will able to contact CI, PIs or investigators at all times based on a rota system where someone from the study team will be available 24 hrs. The list will be updated continuously, and who is "on- call" will call Oslo AMK and report that they for the time being is the person to be contacted. A log noting date and time will be kept at the Oslo AMK. This system of "on- call" via the Oslo AMK is an established system today for example for medical doctors/ directors. The system has proved safe for many years, and all AMK operators are familiar with this system.

12.8 Data Monitoring and Safety Committee (DMSC)

A DMSC is recruited for this study. They have experience in emergency medicine, research methods and statistics and medical ethics.

They will be independent, and any competing interests towards the sponsor or Den Norske Eterfabrikk and/or NTNU will be declared in the ICMJE (International Committee of Medical Journal Editors) Form for Disclosure of Potential Conflicts of Interest. This form will be kept in the TMF.
Details regarding this work and responsibilities, access to data, open and closed meeting, whistle- blower function etc. will be provided in its own charter, see appendix 14.

12.9 Safety reporting from participants with withdrawn consent

Patients who withdraw or refuse to participate in the treatment situation should not be registered in the regular study database (practice up untill protocol version 3.1)

To ensure that potentially important safety information about the drug is not lost, a separate part of the database containing anonymized data only.

- Neither name, date of birth, temporal data of overdose, ambulance technical data, ambulance chart/ AMIS number or other identifiable information are recorded.
- Does not record effect data (primary endpoint)
- No identifiable code list is established
- Records kit / randomization number to check the route of administration of active medicine is recorded
- Records adverse events similar excisting protcol, including MeDRA classification.
- Reports need for additional naloxone ("rescue naloxone") as this is a safety endpoint (secondary)
- Reports from this database are included in the analyzes "Safety Set", ie the study population that received study medicine.
- We will not measure repeated overdose over the next 12 hours (recurrence) as such measurement is inconsistent with anonymized data.

13 Data management and monitoring

13.1 Case Report Forms (CRFs)

The designated investigator staff will enter the data required by the protocol into the eCase report forms (eCRF). The Investigator is responsible for assuring that data entered into the eCRF is complete, accurate, and that entry is performed in a timely manner.

The signature of the investigator will attest the accuracy of the data on each eCRF. If any assessments are omitted, the reason for such omissions will be noted on the eCRFs. Corrections, with the reason for the corrections will also be recorded. The electronic data management system (eDMC) used in this study is Viedoc™. The setup of the study specific eCRF will be performed by Department of clinical research support (CRS), Oslo University Hospital.

After database lock, the investigator will receive a CD-ROM with PDF copies of the subject data including audit trail for archiving at the investigational site. After database lock, the investigator will receive a data file of the subject data for archiving at NTNU. This archiving will comply with local guidelines for storage of such data.

13.2 Source Data

The following data are source data in our study:

1. Study form
2. Copy of the ambulance journal for the call out where study medicine is used
3. AMIS transcript for the dispatch of case included in study
4. AMIS records/ ambulance journal where pre-hospital naloxone on the person involved within 12 hours after inclusion.
5. Voice recording of AMK call and ambulance dispatch where study medicine has been given.
6. Interview with EMS personnel involved by investigator. Record will be kept on paper and signed by EMS and investigator.

Please note regarding AMIS form: They include telephone number and details regarding the caller to AMK 113 (e.g. John Doe called 113 from telephone 22119690). This data will not form source data in this study and will be blacked out and anonymised in the study archive.

Study form will include:

1. Confirmation that the patient is participating in the study, by including the study kit number and the AMIS number.
2. Results of all assessments confirming a patient's eligibility for the study;
3. Results of assessments performed during the study;
4. Information that study personnel can contact study team is a SAE or SUSAR is suspected.

This study will not have access to participant's medical records outside of the Ambulance Service.

13.3 Study Monitoring

A monitoring agreement will be established and signed, and a monitoring plan made prior to start of the study.
The investigator will be visited on a regular basis by the Clinical Study Monitor, who will check the following:

- Reporting of adverse events and all other safety data
- Ensure that oral consents are confirmed by the signature of the two study workers.
- Ensure that participants that wish to withdraw are withdrawn from database
- Adherence to protocol
- Maintenance of required regulatory documents
- Study drug accountability
- Facilities and equipment: Drug storage at Ambulance station.
- Data completion on the CRFs including source data verification (SDV).

The monitor will review the relevant CRFs for accuracy and completeness and will ask the site staff to adjust any discrepancies as required.
Sponsor's representatives (e.g. monitors, auditors) and/or competent authorities will be allowed access to source data for source data verification. The AMIS transcript and pre- hospital patient record is the only patient record in this study, and will be made available.

13.4 Confidentiality

The investigator shall arrange for the secure retention of the patient identification and the code list. CI shall ensure that such storage (analogue and digital) are reported to, and in accordance with the local Data Protection Officer (Personvernombudet) at Oslo University Hospital and St. Olav's Hospital. The study documentation (eCRFs, Site File etc.) shall be retained and stored during the study and for 15 years after study closure according to guidelines at NTNU. All Information concerning the study will be stored in a safe and secure place inaccessible to unauthorized personnel.

13.5 Database management

The Department of clinical research support, OUS, will perform data management in accordance with ICH guidelines, CRS SOPs and described in the study specific Data Handling Plan.
The plan will describe the processes and documentation related to data capture and data quality control. The data will be captured in an electronic CRF (eCRF).
The eCRF will ensure security (to prevent unauthorized access to, or loss of data) and storage during trial. After database lock, the study data will be archived by sponsor and removed from the eCRF.

14 Statistical methods and data analysis

14.1 Determination of Sample Size

The primary endpoint is the proportion of participants with return of spontaneous respiration (≥10 breaths per minute) within 10 minutes of naloxone administration. The aim is to demonstrate that intranasal administration of naloxone is not clinically inferior to intramuscular administration. It is expected that 88% of the patients on IM treatment (standard treatment) will be responders according to this criterion (p_{rim}=0.88), and an equivalent dose intranasal administration is expected to result in a similar responder rate. The non-inferiority margin is set at Δ=0.15.

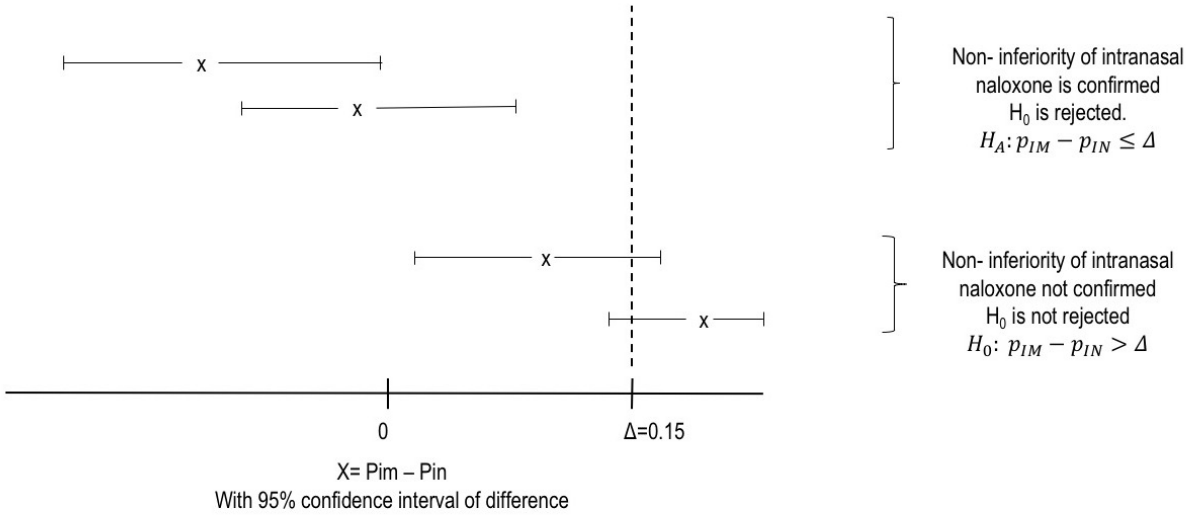
The null hypothesis is that the proportion of responders given intranasal naloxone is smaller than given intramuscular naloxone

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

and the alternative hypothesis is that intranasal naloxone is non-inferior to intramuscular naloxone

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

From this it follows that the upper bound of the 95% confidence interval of the difference between the groups shall not exceed 0.15 in order to reject H0 and confirm Ha



A total of 200 patients are needed to demonstrate that intranasal naloxone is not inferior to intramuscular administration, assuming a two-sided significance level of 5% and a power of 90%.

There is no pre- set target for how many patients each centre will include, but we expect the Oslo Centre to include the majority of cases.

Please refer to chapter 16 (Ethics) regarding further discussions on setting the NI margin Δ to 0.15.

14.2 Randomisation and blinding

14.2.1 Allocation- sequence generation

Computer generated block randomization with random block sizes stratified by centre will be provided by department of clinical research support (CRS), Oslo University Hospital. This list will be provided to Sanivo Pharma for the kit production.

14.2.2 Allocation- procedure to randomize a participant

Included patients will be treated with the study drug available in the ambulance at the scene. This kit is numbered and randomised as described. The kit number will become the participant study number. Thus at the scene there will be no randomisation or opening of sealed envelopes or other techniques to randomise the patient.
The allocation to treatment will happen at the scene, and be determined by which kit is in the ambulance at the time. Ambulances are required to have only one kit at the time, and will refill at the station once a kit is used.

14.2.3 Blinding and emergency un-blinding

The whole study team, including the statistician, will be blinded until after database lock and the primary analysis are done.
The allocation list will be stored by Sanivo Pharma. For each double dummy kit, an envelope with information of the randomisation of that particular kit will be stored at the EMS alarm central (AMK) for quick retrieval of information in case of any case where the study team need un-blinding to safe guard any participants further treatment or follow up. There will not be automatic unblinding of SAEs. Study personnel do not have any access to the allocation list. In case of emergency un-blinding of individual cases investigators can contact AMK Oslo (see point 12.6).
SUSARs will be unblinded and reported on CIOMS form by someone not part of the study group. See 12.6.2

14.2.4 Missing data

Missing data will not be imputed

14.3 Population for Analysis

The primary statistical analyses will be based on patients meeting the definition of the per protocol population according to inclusion and exclusion criteria. Secondary analyses will include all patients receiving study treatment.

By the nature of the randomisation and allocation procedure, no participants will be un- blinded. If information of allocation is exposed post treatment, this will not by any chance happen within the time-frame of the primary end-point. Individuals excluded will be analysed for demographic variables to compare to the group of included participants. Individuals exclude will also be analysed based on the administration and dose of naloxone, time and place of overdose and follow up.

14.4 Planned analyses

The main statistical analysis is performed when all patients are included and after database lock.
A feasibility analysis will be performed after 20 included participants. The results of this will be made available to the DMSC.
No interim analysis is planned, and stopping guidelines are described in the DMSC charter (appendix 14)

Deviation from the original statistical plan will be described and justified in the Clinical Study Report. Amendments to plan can be done until day of database lock.

After 100 patient the DMSC will meet and the folling analysis will be made:

- Summary of patient enrolment (number per site, age, gender and follow-up)
- Safety profile: adverse events, serious adverse events (SAE) and SUSAR reported
- Interventions: The use of recue naloxone
- Follow up: The follow up after study treatment (Hospitalisation, Left at the scene etc)
- Recurrence: The number of participants with recurring overdose within 12 hours after inclusion.
- Mortality: Any deaths by a trial participant during the duration of study time will be reported to by Coordinating investigator the DMSC within 7 days.

No interim analysis of the primary end-point will be performed.

14.5 Statistical analyses

The proportion of responders will be compared between treatment groups. A two sided 95% confidence interval for the difference between proportions will be estimated of which the upper bound shall not cross the chosen non- inferiority margin to reject H0

	IM	IN
With response	a	b
Without response	c	d

P_{IM}= a/ (a+c) P_{IN}= b/ (b+d)

Patients in need of rescue medication (additional naloxone) before 10 minutes will be classified as non-responders in the primary analysis. Additional sensitivity analyses excluding patients given rescue medication before 10 minutes will also be performed.

All categorical variables will be compared between treatment groups by the chi-square test, and the difference between proportions of responders with a corresponding 95% confidence interval will be estimated. Non-inferiority will be considered confirmed if the upper limit of the 95% confidence interval is not larger than the specified non-inferiority margin Δ=0.15.

Continuous variables will be compared between treatment groups by the two-sample t-test, and the mean difference will be estimated together with a 95% confidence interval. Should the distribution of a variable deviate substantially from the normal distribution, transformation will be done as is appropriate alternatively compare the groups with a non- parametric test.

Time to spontaneous respiration will be compared between treatment groups by Kaplan Meier estimates and log rank test. (This analysis will only be performed if measurements are considered to be valid and reasonably robust.) The main analysis will treat patients in need of rescue medication before 10 minutes as censored at the time of administration of additional naloxone. A sensitivity analyses will include censoring patients receiving rescue medication before 10 minutes at 10 minutes rather than at the actual time of administration.

The clinical study report will contain the following:
Baseline demographic variables of included and excluded participants
Baseline ambulance data such as dispatch times, duration of call, other temporal data etc.
Demographic Data Summary figures and table
Efficacy Data Summary figures and tables.

Safety Data Summary figures and tables.
Displays of Adverse Events
Listings of Deaths and Serious Adverse Events
Narratives of Deaths and other Serious Adverse Events

14.5.1 Analysis of secondary endpoints and sub- groups

Pre-specified sub groups that will be analysed both on the primary endpoint and secondary end points:

- Place of treatment (differences between Sprøyterommet, public places indoor and outdoor, private homes and treatment facilities)
- Different follow up: The various follow up after treatment will be compared between the groups
- Time of treatment (times during the day, day of the week and month/ season)
- Gender
- Age
- Divided into those experiencing recurrence and those who do not experience recurrence
- Type of opioid consumed based on available information
- If treated with take-home naloxone prior to arrival of EMS
- Individuals included more than once during the study period if any
- Differences between study centres.

15 STUDY MANAGEMENT

15.1 Investigator Delegation Procedure

The Coordinating investigator (CI) is responsible for making and updating a “delegation of tasks” listing all investigators and monitors and their role in the project. The CI will not personally delegate to all EMS staff; this responsibility is delegated to the investigators who train EMS staff. He/ she will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

EMS that complete the training described will administer study drug, and fill in study forms. Their individual Curriculum Vitaes will not be kept in the TMF. Their full name, employee number in ambulance service date of birth, address and telephone number will be logged in a training log kept in the ISF and transferred to the TMF at the completion of the study.

15.2 Protocol Adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations.
All significant protocol deviations will be recorded and reported in the Clinical Study Report (CSR), kept in the TMF. Significant protocol breeches will be reported to the DMSC within seven days. If a breech is significant will be decided by the CI and the PI of the centre in which the breech happened.

15.3 Study Amendments

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) will be notified to and approved by Norwegian Medicines Agency and the Regional Committees for Medical and Health Research Ethics (REC).

15.4 Audit and Inspections

Authorised representatives of the Data Monitoring and Safety Committee described in this protocol, the Norwegian Medicines Agency and the Regional Committees for Medical and Health Research Ethics (REC) may visit any study centre to perform inspections, including source data verification. Like- wise the representatives from sponsor may visit the centre to perform an audit. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (ICH GCP), and any applicable

regulatory requirements. The coordinating investigator will ensure that the inspectors and auditors will be provided with access to source data/documents.

15.5 Deviations from GCP

Due to the arbitrary and sometimes chaotic pre- hospital environment, and the fact that study personnel are EMS staff on call, some deviations from the GCP principles are pre-specified. These include:

- TMF will not include CV from all EMS staff
- Screening- log: There will be no log of patients screened for eligibility and found not to meet the criteria for inclusion. Anonymous data regarding excluded participants will be recorded.

16 Ethical and regulatory requirements

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki (54) and are consistent with ICH/Good Clinical Practice (55) and applicable regulatory requirements. A wide body of literature exist on this field, some of the articles we have used as a support in our discussion are referenced (56). Registration of patient data will be carried out in accordance with national personal data laws and Data Protection Official for Research at St Olav's Hospital and Oslo University Hospital.

16.1 Ethics Committee Approval

The study protocol, including the patient information leaflet to be used, must be approved by the Regional Committee of Health Research Ethics before enrolment of any patients into the study.
The investigator is responsible for informing the ethics committee of any serious and unexpected adverse events and/or major amendments to the protocol as per national requirements.

16.2 User- participation board

A user participation board has been established. The board has consisted of former and current drug users, representatives from the main drug users organisations and representative from the largest drug- user family organisations. It has met three times during the writing of this protocol and prior to the submission of this protocol to the Norwegian Medicines Agency and Ethics Committee. Representatives from the board also had a field day talking to active drug users in Oslo presenting the study and testing the information leaflet.

The objective of this board is to involve drug users and their families in the project from the planning stage, throughout the study period and in the dissemination of the results. As we conduct research on a group of people in many ways regarded as vulnerable, and on individuals with reduced or absent ability to give informed consent this board is particularly important. The board will act to as consultation to the study team on opinions regarding the project as a whole, particularly matters regarding safety.

The board has been in direct cooperation with the study team for the job of developing the information system used (internet + Facebook) to inform users about their inclusion in the study. This means that any information leaflet that we seek approved by REC will be developed in direct cooperation with members of this board. The aim of this cooperation is to ensure a clear, and for the users understandable, system of informing about inclusion, consent, opportunity to withdraw from the study, what to do for more information etc. The user board will also be given information details to the DMSC if they have serious concerns regarding the conduct of this study.

The user board's activity, proceedings and minutes of meetings and people in attendance will be kept in the TMF.
A separate declaration from the user participation board, and a presentation of its members will be submitted with the REC application and kept in the TMF.

16.3 Ethical considerations:

This study involves research on humans, which is strictly governed by both Norwegian law and international regulations. We hope the next chapter, and the REC applications can show our thinking on this matter.

This chapter has been updated after the decision to approve the study was made by NEM ((2017/44).

The use of nasal naloxone has been discussed and promoted by drug users, their families and politicians the last 10 years. The University of Oslo (SERAF) currently has a project sponsored by The Directorate of Health to hand out nasal naloxone to users in Oslo and Bergen. The program has recently been expanded. The naloxone handed out has a concentration of 1 mg/ml and holds a Marketing Authorisation for drugs for human consumption as an intramuscular injection in the UK, thus no authorisation for intranasal use. The concentration of study drug in our study is 14 mg/ml. The SERAF project has previously been considered by REC, who found this intervention not to warrant REC approval (REC 2014/850). Internationally studies on the efficacy and safety of an intranasal naloxone formulation in pre- hospital opioid overdoses are widely called for. The WHO report from 2014 on community management of overdoses raises several research questions this study hope to answer (8). Questions regarding Overdose morbidity (prolonged adverse outcome of opioid overdose), Opioid withdrawal reaction to naloxone, Time to administer naloxone, Time to opioid overdose reversal and Ease of administration are all classified as critical by the WHO.

There is an international debate is regarding the wide spread use of off- label, poorly researched and dilute naloxone formulations. It has been argued that drug users are offered IN naloxone to treat a life treating condition that does not meet the standards of safe and effective other patients take for granted (45, 57).

Opioid overdoses are increasing. It is impossible to conduct a scientific study of naloxone to treat heroin overdoses in a more controlled environment. Pharmacological studies on healthy human volunteers, such as the ones we have conducted at NTNU (REC 2012/1970, 2013/1519, 2014/740, 2014/2194 and 2015/1285) can only partly answer the important question: Is this drug safe and effective in treating real life opioid overdoses? An overdose of heroin and other opioids are a function of many factors: The type and strength of opioid taken, other sedative drugs and alcohol consumed at the same time, the persons´ tolerance to opioids that day and other physical conditions the person may suffer from. It is impossible to create this condition in a research facility. Indeed, exposing volunteers to highly addictive and unsafe drugs such as street heroin would be unethical.
This study if IN naloxone will be conducted on the patients IN naloxone meant to treat, in the environment in which it is supposed to be used, and by the EMS- the health professionals- that may use it in the future.

16.3.1 Regarding study design, non- inferiority margin and power calculation

Study design

Randomised control trials remain the gold standard to ensure the safety and efficacy of medical interventions. No other design can reduce bias to the same degree. Our study is randomised as described between nasal naloxone and intramuscular injection (comparator). To further reduce bias, we have a “double dummy” design, i.e. both EMS (Study workers) and investigators are blind to which participant received which treatment both at the scene of the overdose and throughout. Our hypothesis is not that the IN naloxone is better than IM, the advantage for nasal administration lies in ease of administration and reduction of blood exposure risk, we have therefor designed a non- inferiority trial. This has implications both for the power calculations and statistical analysis.
A non-inferiority trial seeks to determine whether a new treatment is not worse than a reference treatment by more than an acceptable and pre specified margin. Because proof of exact equivalence is impossible, a pre- stated margin of non-inferiority (Δ) for the treatment effect in a primary patient outcome is defined. Non- inferiority of the new treatment with respect to the reference treatment is of interest on the premise that the new treatment has some other advantage, such as greater availability, reduced cost or less invasiveness. On our case IN naloxone can reduce the risk of blood exposure, it can easily be administered by lay people and it may reduce acute withdrawal symptoms.

Non Inferiority margin

The non- inferiority margin (Δ) is set to 0.15. This means that we allow the 95 % confidence interval of the difference between the groups to be 15 percent points lower than the IM response rate of 88%. This is a relatively wide margin, and is a result of wide discussion within the research group at NTNU and colleagues in the field and based on our epidemiological studies and clinical experience. There is no way to calculate this mathematically, it is always a clinical decision based on the evidence and experience available.

The reasoning behind this is the nature of naloxone administration. The immediate life- saving intervention in an opioid overdose is to free the airways and support ventilation, not only to give the antidote naloxone. Naloxone is only part of the therapy and always in combination with ventilation.

Naloxone is meant to be given in small doses and titrated to clinical effect. In the SPC for our comparator the dosing interval for injected naloxone is between 0.4 and 2.0 mg naloxone. The reason to start low and titrate upwards is to find the point where we reverse the overdose without precipitate an acute opioid withdrawal reaction. As shown earlier we have an 88% response on doses between 0,4 and 0.8 mg injected naloxone. The fact that the standard dose for comparator is not a fixed point also makes a wide non- inferiority margin important, we are in- fact comparing to a movable target.

If IN naloxone 14 mg/ml should come to the market clinicians can titrate based on the knowledge on how one dose compares to IM naloxone. For peer administration IN naloxone will be recue medication as lay people wait for EMS to arrive to provide expert medical treatment, and more naloxone if needed. The administration of naloxone, in any formulation, is aptly described as walking the tight rope between adequate response and life- saving restoration of respiration on one side and precipitating acute withdrawal on the other (51).

In this setting we deem 0,15 (Δ) to be an acceptable difference to claim non- inferiority of IN versus IM naloxone.

NOR- Switch, a recent large Norwegian study designed to assess the safety and efficacy of switching from Remicade to the biosimilar treatment Remsima in patients with auto immune disease used the same non- inferiority design and the same non- inferiority margin (Δ) at 0.15. (58)

Power calculation

The power calculation is more closely explained in 14.1 but we aim for 90% power and two- sided 5% confidence intervals, common values in such studies.

16.3.2 Regarding choice of comparator

We are comparing the novel naloxone formulation with standard injected naloxone.
The dosing of comparator, 0.8 mg IM, is a result of our study of 1054 opioid overdoses in 465 subjects in Oslo in 2014-2015 and current guidelines in the Oslo and Trondheim Ambulance services. Details of this study is given in 5.4.2. 93% of patients in the Oslo study had 0.8 mg or less as their initial dose of naloxone, of which 88% responded with no need for further treatment.
31% (n=332) received naloxone 0.4 mg as their first dose. In this study these patients will receive a higher dose of naloxone as study medicine. Although doubling the dose from 0.4 to 0.8 mg it is still well within the margin set for naloxone (start dose 0.4- 2.0 mg with a maximum dose of 10 mg). Current clinical experience and past published research (30) show that withdrawal reactions are relatively light at doses of 0.8 mg naloxone and below.

16.3.3 Regarding data collected and method of analysis

The data collected will not vary from the data that should be collected by EMS today. Clinical findings at arrival on the scene, diagnosis and response to treatment, as well as personal details and a history of concurrent disease and drug use all is standard of what is registered in patient journals today.
Identifying information; name, date of birth, personnel number etc. will be stored according to regulations of the hospital and not as part of the database, which will have a subject study number linking the CRF to a code list,
The method of analysis for is described in section 14.

16.3.4 Regarding patient population, research on vulnerable groups

To adequately evaluate an antidote, it must be studied in the setting of an intoxication. Research in healthy volunteers can give important information regarding the pharmacology of the substance, but clinical response must be studied in the field. The current nasal naloxone had been studied in healthy human volunteers, some of whom have received an opiate (see section 5.4.1). This forms the scientific basis of the current protocol. Each overdose differs, and to model or replicate heroin overdoses is impossible. Upon presentation to the emergency services the amount and type of opioid is unknown, the amount and type of possible other drugs used are unknown, the individual´s tolerance to opioids is unknown and any systemic illness is unknown. Opioid overdoses in- hospital (iatrogenic) are completely different in all

these regards. This is recognised in the dosing of naloxone in the in- hospital setting starts at 0.1- 0.2 mg (20). The patient population of choice is the opioid overdoses presenting to the ambulance service.
We have studied this population in detail for the years 2014 and 2015, some results are presented in section 8. Opioid users are often considered a vulnerable group in society. The risk of overdose is particularly high for people injecting opioids (heroin), and our inclusion criteria selects out participants with high risk drug use. Many live in poverty, often with no fixed abode, on social benefit and with high crime rates. Many have multiple health problems and difficult access to social and health services. Limited medical research is ever conducted on this group.

Article 20 of the Helsinki Declaration describes research on vulnerable participants. It states *that "Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non- vulnerable group".* Nasal naloxone is a drug designed especially for the group at risk of opioid overdoses, as emergency treatment of a life threatening condition. Further the declaration states *"In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research".* We believe that both conditions of article 20 are met in this study. The condition of article 19 *"All vulnerable groups and individuals should receive specifically considered protection"* is provided throughout the protocol in the safety of the participants and the design of the study.

Too often vulnerable groups are not included in research, leaving them behind the medical advances or worse: exposing them to sub-standard treatments. The current widespread use of unlicensed nasal naloxone formulation in Norway and internationally is an example of this (45).

The Helsinki declaration article 30 regulates the situation of unconscious patients with no legal representative present within the time period research must happen. *"Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group".* Our inclusion criteria describe exactly such a group- where unconsciousness (low GCS) is an inclusion criterion. Reversal of reduced consciousness is a secondary endpoint in the study.

16.3.5 Regarding consent and withdrawal from the study

We will include patients in this study without prior informed, written consent. As a reduced consciousness and respiratory depression/ arrest are inclusion criteria it is impossible to achieve the normal standards regarding informed consent prior to inclusion.

We have applied to the ethics committee for approval of this study under "Act on medical and health research" § 19 (59) regarding consent and medical emergencies. This states:
"In clinical emergencies where the patient is not capable of giving their consent and it is impossible to obtain consent from the person's next-of-kin, research may only take place if the following conditions are satisfied:
a) the potential risks or disadvantages for the person are insignificant,
b) the individual involved is not averse to it and there is no reason for researchers or other personnel to believe that the person concerned would have been averse to participating in the research project if they had had the capacity to give their consent,
c) it is only possible to carry out the research in clinical emergency situations, and
d) the research is justified beyond any doubt on grounds of the prospect of results with major preventive, diagnostic or therapeutic value."
We believe letters a), c) and d) to be well described and fulfilled elsewhere in this protocol. Letter b) is thoroughly discussed with our user- participation board and throughout our information work prior to submission of this protocol. The advice from this board is clear: there is no aversion to participate in a study like this, on the contrary. The experience from the Oslo study in 2014 and 2015 is that only 1- one- out of 1055 cases has withdrawn from registration of opioid overdoses after inclusion.
Both §19 of the Norwegian Health Research Act and article 30 of the Helsinki declaration has a condition that people included without prior consent should have an opportunity to be informed and to consent to further research. Our study has one study visit only, and no further information gathering will be collected after this visit, except for recurrence of overdose within 12 hours (ref section 12.3). Therefore, such consent does not apply in our design.

NEM has approved this protocol with the following 5 conditions (our translation)

1: Study workers shall gather oral consent after the study intervention in as many participants as possible. This consent will be collected by EMS, and both witness and document the consent given in words. The study workers will at the time be able to appraise which participants are not able to consent.

2: Patients that are deemed able consent, and who object to further participation in this trail shall not be included in the study.

3: Written information about the study shall be given to all included patients when they leave *(or is left; NTNU clarification)* the care provided by EMS. REC has had two information letters submitted in the original application. In the opinion of NEM these letter form a good starting point to inform included patients about the possibility to withdraw from the study after the overdose treatment. It is a presumption that final information letter is produced and in approved by REC.

4: To ensure all included is given a real chance to opt out of the study, and that gathered data are not used further in the study, the information measures described, in addition to written information, be carried out.

5: The storage of health information beyond the project period is only allowed to satisfy those requirement set for clinical drugs trials, and for subsequent verification of results in the trial. New or changed use of health information specific to this study require the collection of consent in keeping with the main rule of the Health Research Act.

Procedure for withdrawal from the study (all participants)
All included patients can withdraw from the study at any time. They will be given both oral and written information after inclusion. They will be informed of the treatment given, their number of inclusion/ kit number used and date included. The information will describe how to get in touch with the study team for further information and how to withdraw from the study, either by telephone or online.

The web page in use is www.nalokson.no . We will also establish an open Facebook group that can direct people to the web page and serve as an open contact point to the study team. Facebook cannot be used to send personal data or withdraw. This procedure makes us available 24 hrs a day on a website designed both for laptops and for smartphones. By clicking "I want to withdraw" button participants can fill in a simple form and an email will be generated and sent to the study team. For participants not online they can call the switchboard of Oslo AMK during working hours and inform the secretary there that they want to withdraw. The user board has confirmed that most participants are highly likely to have good access to internet services either at their smart phones, home or shelter or other providers such as The Church City Mission cafés.

This website and email system is not secure to send sensitive data. Therefor participants only have to fill in initials of given- and family- names, year of birth, date of inclusion and their unique study number to be identified. If they do not recall all this information they can include as much as they can and contact details. The same applies to the information to be left at the telephone switchboard. When a participant the form online an email is generated that is sent to the address nalokson@medisin.ntnu.no. The study team has access to this account. For the purpose of monitoring a copy of the form will be sent to monitors at the email oushfpbnina@ous-hf.no. This ensures that an independent body controls that those who wish to withdraw are actually withdrawn.

All contact with the study team will be documented and filed in the TMF. Proof of withdrawal from the study will be supplied monitor who will confirm that data is deleted from analysis.
Participants can withdraw at any time and have their data deleted as stipulated in the Health Research Act §16. After database lock however this will be impossible. Database lock will happen minimum 14 days after last patient is included.

Procedure for oral consent.

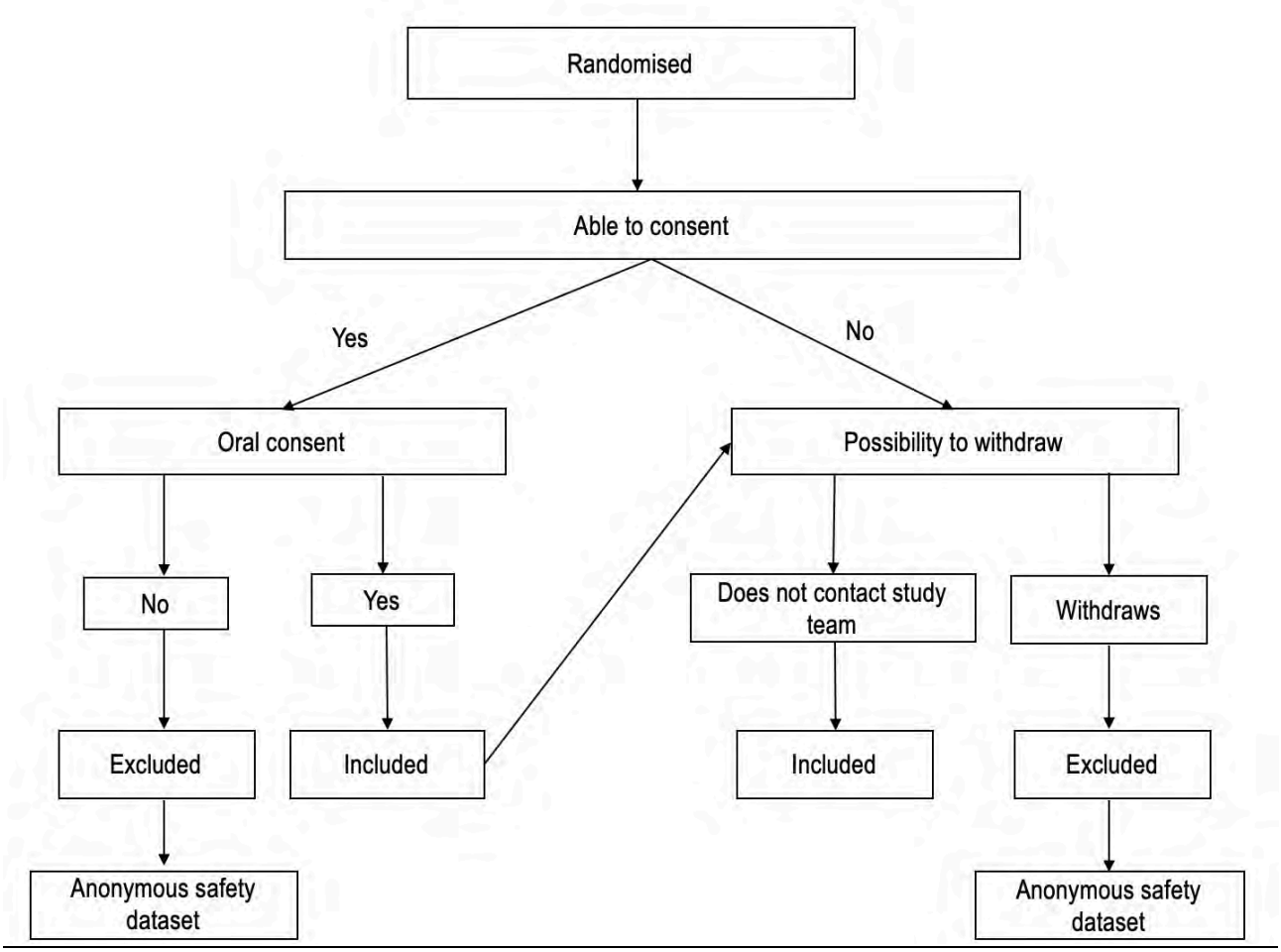
This procedure is added to the protocol after NEM approval. It differentiates between participants and allows a certain number to give oral consent to EMS/ study workers after inclusion. The discretion to decide which participants are eligible to give oral consent lie with EMS/ study workers at the scene. EMS' already makes these decisions outside of this trial in all patients, not at least patients after having suffered an opioid overdose. The following criteria will guide EMS:

1: Participants need to be awake and able to explain the situation they are in (an overdose emergency).

2: Participants must be able to receive information about the study, their inclusion and the risks and reason about study risks and their attitudes concerning consent.
3: If included patients are not willing to discuss the study or receive oral information they shall only be given the written information enclosed in the study kit.

The study form will have a separate section regarding oral informed consent. For a consent to be valid two trained study personnel must document the answer given with two signatures/ personnel numbers.

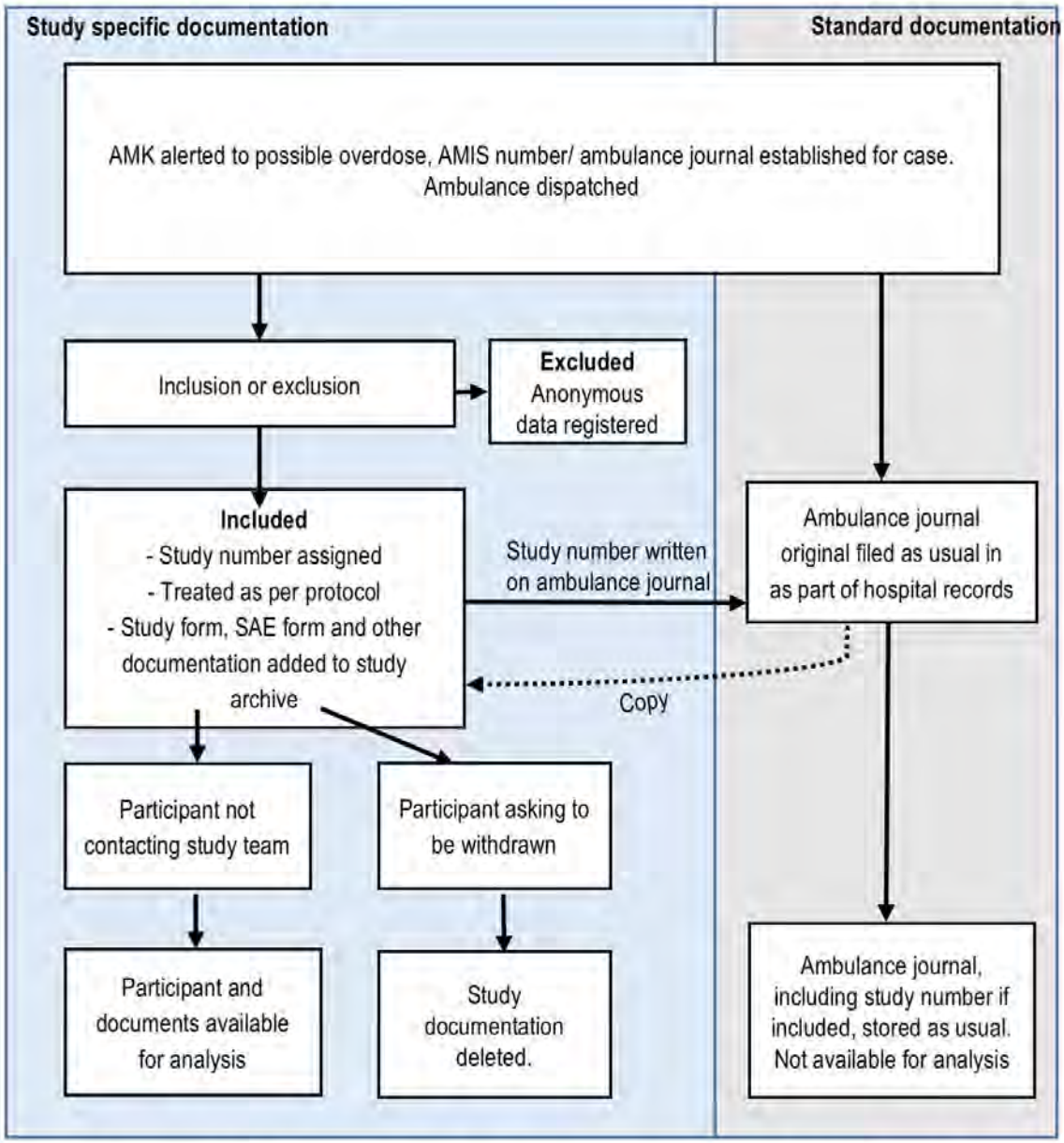
Tabell 16-1 Flow chart consent procedure



Consequence of withdrawal:
The ambulance journal is kept and stored as usual as part of the EMS patient journal system. The participant will have access to their own journal as stipulated by Health & Rights Act (Pasientrettighetsloven) § 5 and Health Personnel Act (Helsepersonellloven) chapter 8. The patient journal will contain inclusion number, and proof that the patient was included in a study and which study medicine he/ she received. This is important if safety concerns arise, and gives the Ambulance service a chance to fulfil their duty of care to the patients. The patient will not be registered in the ordinary database, but anonymous information, as specified in section 12.9, will be registered in a safety database.

Example of information letter is given to the patient and the text online are displayed in appendix 11
Example webpage www.nalokson.no
Example Facebook group: https://www.facebook.com/groups/1331916596853204/ or search for “NTNU nalokson nesespray” on Facebook
Telephone number (open mon- fri 08.30- 16.00) 23 01 53 00

Tabell 16-2 Flowchart of participant Information



A journal is established for all patients treated by the ambulance service. If the patient is included, the inclusion number will be added to the original journal. A copy of the ambulance journal will be added to the study archive, while the original will be archived as a part of the hospital records. If the patient is not included anonymous data will be registered before the journal is archived.

If a participant later wishes to withdraw from the study, all the documentation in the study archive is deleted, however the inclusion information is available on the ambulance journal. If there is any question about safety for the participants, the ambulance service can retrieve this information manually, but the study team does not have access to this information.

16.3.6 Regarding participant safety

Participant safety is the most important aspect of this protocol, and has been ensured in a number of ways. First of all, with the scientific work on the nasal naloxone formulation by previous studies on healthy volunteers. It has been found to be safe and with no serious adverse events. Naloxone itself is a very safe drug with an excellent safety profile, and our formulation had not deviated from that. The formulation consists of excipients that are well known in human nasal pharmacy. The dose chosen is based on previous studies, and is currently undergoing final trials for pharmacokinetic comparison to injected naloxone. The comparator is the standard treatment for opioid overdoses today. The study workers are EMS that are all trained in treating opioid overdoses prior to this study commencing. The emergency treatment of overdose is first and foremost airway control and assisted breathing- this is not changed in this protocol. The study only differs from standard treatment in that study medicine is given, and not additional naloxone for 10 minutes. In normal circumstances, a second dose of naloxone would most often be given at a shorter interval. This deviation does not represent any hazard to study subjects, as ventilatory control is a prerequisite.
To include a patient in the study not only must an opioid overdose be suspected, the patient must not be in cardiac arrest. Ventilation must be maintained, failure to secure this will lead to either exclusion or abortion of the study and return to normal treatment guidelines. At the scene of the study will be a normal ambulance with all the medicines, knowledge and equipment that is normally provided to these patients. No treatment options are withdrawn for included or excluded patients.

Even though a patient has been included and withdraws from the study the ambulance journal will be filed as normal for all patients in the Ambulance Service. The original form will be filed and this will include information regarding inclusion of the patient and which inclusion number. A copy of this form will be filed in the study archive and used as source data for our study. If the patient withdraws the study part of the file will be deleted and the ambulance service file remain.

16.3.7 Regarding risk of including pregnant participants

Fertile women will be included in this study, and there is no chance to conduct a pregnancy test prior to inclusion. A visible or suspected pregnancy is set as an exclusion criterion. Suspected pregnancy will for example be bystander information. Naloxone is a well-known substance, and is today used on pregnant women suffering an overdose. Its teratogenic potential is small, and naloxone is today used in pregnant patients. Previous research show that although naloxone crosses the placenta the serum concentrations in the foetus are lower than those of the mother(60).

16.3.8 Regarding the risk of including participants below 18 years of age

Children suffering an overdose are according to local guidelines treated with particular concern, and EMS are required to immediately contact child protection services if a minor is treated for an overdose. In the 1054 overdoses studied no cases of patients under 18 years of age were reported. We believe this to be a very small problem. However, if a patient appears to be below 18 years of age he or she should not be included in the study. If a minor accidently is exposed to study medicine the data will not be entered into the database.

16.3.9 Regarding the risk of including legally incapable participants above 18 years of age

Only legally competent persons can give consent. The Study Workers in our study will not be able to determine if persons are not legally capable and under guardianship. However, there are no other services in the drug users environment, such as SIF/Sprøyterommet, that has regulations where guardianship has been raised as a possible concern(61).

16.3.10 Regarding risk/ benefit balance of the project

To balance these two concepts, we have 1) identified the risks and minimised them and 2) described potential benefits to individual subjects, groups of patients and society and attempted to enhance them.

Risks:
Opioid overdose is a life threatening condition, this is recognised by the ambulance service today. Any call with opioid overdose as a suspected diagnose will receive immediate dispatch of qualified personnel with appropriate training, medical equipment and naloxone to deal with the situation. Emergency treatment of any unconscious patient; first with airway control and ventilation, is at the core of EMS training. The diagnosis of suspected opioid overdose is based on

clinical signs and naloxone is administered today as an injection. The major risk we identify to included participants are that the IN naloxone should work significantly worse than IM/IV naloxone and not wake the patient up or that the IN naloxone formulation should have adverse events similar to injected naloxone, but to a higher degree or adverse events so far unknown in naloxone.

Efforts to minimise the risks include:

- No change to the core response to unconscious/ suspected overdose treatment: The ambulance/ EMS dispatched have the same training, equipment and medicine as is "the gold standard" today. The first and most important life- saving intervention: free airways and ventilation support are not changed. Patients are treated after the same local guidelines, and all are offered the same follow up- no treatment/ follow up options are denied patients whether they are included or not.
- The dose of IM naloxone is chosen on the basis of local and international guidelines and confirmed in our Oslo epidemiological study. This makes the control arm unchanged from today´s gold normal treatment.
- The dose if IN naloxone (study treatment) is choses on the basis of three phase I pharmacokinetic studies at NTNU, modelling and discussions with the Norwegian Medicines agency.
- Naloxone is a well- known drug with an excellent safety profile. The adverse events are well known- and must be described as mild/ few. Naloxone is now available without a prescription in several countries such as Australia and Canada and many US states (62, 63). Our IN formulation contains naloxone well below the 10 mg maximum dose. The excipients and other substances are also well known in the use in nasal sprays. The formulation and sprayers are produced by Sanivo Pharma conforming to all the rules and regulations in the field of medicines for human use.
- The IN formulation has been tested for pharmacologic properties in healthy volunteers by our study group with no serious adverse events recorded, the most common response from participants was a metallic taste to the back of the mouth.

Efforts to maximise benefit

- Individual participants: Each participant will not benefit from being included at the time of the study visit. However we know that many people suffer multiple non- fatal heroin overdoses, some over many years of drug use. By developing an IN naloxone formulation that is thoroughly tested on the real patient population some patients may themselves benefit from the treatment in the future.
- User participation board: Close cooperation with a wide range of drug users and drug user family's organisations we maximise the benefit to this group of patients. It includes voices that are traditionally not heard in drug development research and simultaneously provide a channel for information and perspectives into the research project. It will also be a channel to disseminate information prior to, during and after the study to stakeholders and other that may traditionally not inform themselves on research in this field.
- Society at large: The opioid overdose epidemic that has riddled Norway for many years, and are on the rise in the US and Europe sets up new research questions that needs urgent answers. The wide spread use of off-label IN naloxone in Norway and other counties are controversial (45). This protocol describes a project that will answer many of the questions asked by the WHO in their seminal report from 2014 highlighting critical outcome measures that needs quality research in this field (8).
- Openness/ Sharing of data: This trial is registered in Eudra CT and www.clinicaltrials.gov prior to inclusion of first participant. The data sharing plan will meet the regulation set by these registries. This open data policy is important in all clinical research, particularly when a vulnerable population are studied, so that other researchers can both scrutinise and benefit from the data. Summary-level results of clinical trials (including adverse event summaries) should be made publicly available no later than 12 months after study completion.

The risk/ benefit balance is the representation of the principles of non- maleficence (first: do not harm) and beneficence (act to the benefit of others). It cannot be calculated from a mathematical formula, but we believe this study is designed in favour of beneficence.

16.3.11 Regarding patients not giving their personal details

An unusual problem we face in this situation where some included participants does not provide their full name or date of birth after they are included and treated with naloxone. Table 8-2 shows that in the epidemiological study 12.7 % (n= 872) of included patients have not provided EMS with their full name. The reasons for this is manifold, but reflects the state of temporal agitation/ confusion many patients find themselves in after the overdose. EMS ask all patients to give their name, but are in no position to demand or force people to identify themselves. These participants well be provided with the exact same study information as everyone else. Their ambulance journal and study form will be marked with name: N. N. (nomen nesico. Unknown name), date of birth: unknown. The AMIS number, study number, gender, time and place will serve as identifiers. In this way, all included patients can contact the study team online and by telephone. There will not be that many patients included at the same time and place. Therefore, study number should be enough to identify who to withdraw for those who withdraw without first giving EMS their personal details.
As the inclusion of the patient and intervention (administration of the study drug) is all- ready done, and there are enough information present for patient to be able to withdraw we find it unethical not to include patients who have not given their full identity to the EMS in the final analysis. If they fulfil the criteria in section 16.3.5, they will be given opportunity to consent, without giving personal details.

16.3.12 Regarding cooperation with pharmaceutical industry

This study is sponsored by NTNU, the Norwegian University for Science and Technology. NTNU will own all data and results generated by this study. The IMP used in the study is owned by NTNU. NTNU has signed a cooperation agreement with DnE Pharma AS regulating the commercialization of the IN naloxone spray used in this study. NTNU´s subsidiary, Technology Transfer Office (TTO) and OD have signed a license agreement with DnE Pharma AS transferring an exclusive, sub licensable, perpetual and worldwide license to use the Intellectual Property Rights and Know-how within the Field utilized in the Product, and whether subject to industrial protection (e.g., patents) or not, for the purpose of enabling DNE Pharma AS to obtaining Marketing Authorizations and Commercialize the Product. Potential royalties from a time-limited future sale of the drug will be shared equally between TTO, NTNU and OD.

Ola Dale and Arne Skulberg has also signed agreements with Sanivo Pharma, please see the TMF for International Committee of Medical Journal Editors (ICMJE) Form for Disclosure of Potential Conflicts of Interest for the signatories to this trial. An agreement between NTNU and Sanivo Pharma in this trial protocol specifically has been signed. This stipulated the rights and responsibilities of the parties and recognizes Sanivo Pharma´s contribution in the production of study medicine, the production and assembly of study kits and the distribution and destruction of such kits throughout the study. Sanivo Pharma re planning to apply for marketing authorization for the IN naloxone formulation, but this trail is not designed to be a part of that application. Sanivo Pharma does not hold ownership of results or data in this trial, and have no right to withhold data or publication. As an academic institution NTNU is in no position to produce study medicine in accordance with the quality regulations required for drugs for human use. Academic initiative for clinical drugs trials are rare in Norway, the industry is the main driver for the few drugs trials we see in Norway, this makes our study special in that all data are secured to remain in public ownership.

16.4 Other Regulatory Approvals and registrations

The protocol will be registered in European Clinical Trials Database (EudraCT) prior to submission to the Norwegian Medicines Agency.
The protocol will be submitted and approved by Norwegian Medicines Agency before commencement of the study.
The protocol will be registered in www.clinicaltrials.gov before inclusion of the first patient.

16.5 Subject Identification

The investigator is responsible for keeping a list of all patients who have received study including patient's date of birth and personal number and full name.
The patients will be identified in the CRFs by naloxone kit number, AMIS number and subject number (as described in 9.11)
In our population we risk that some individuals are not willing to provide this identification information. As shown in table 8-2 87.3 % of patients provide this information today.
If an included patient prove unwilling to give the details he or she will receive the study information and be able to consent if fulfilling the criteria from section 16.3.5, or receive information regarding withdrawal from the study. The CRF will include AMIS number and subject number, and could be identified by time, place and gender. The lack of this information will not lead to a patient being excluded from analysis.

17 Trial sponsorship and financing

This study is financed by:

- Liaison Committee between the St. Olav Hospital and the Norwegian University of Science and Technology (Samarbeidsutvalget NTNU- St. Olav)
- Joint Research Council between St. Olav University Hospital and the Faculty of Medicine, NTNU. Felles forskningsutvalg (FFU) St. Olav's –DMF
- DnE Pharma will pay for the production of the medication kits.

18 Trial insurance

Sponsor will insure all participants in Legemiddelansvarsforeningen, and ensure membership in Drug Liability Association. Coordination Investigator will ensure the right number of participants are insured at any one time.

19 Publication policy

Upon study completion and finalisation of the study report the results of this study will either be submitted for publication and/or posted in a publicly assessable database of clinical study results. It can be published in scientific journals, professional meetings and conferences, non-academic articles and the like.

The results of this study will also be submitted to the Competent Authority and the Ethics Committee according to EU and national regulations.

This protocol itself may be published either in part or in full and/ or be the basis for an article for a peer reviewed journal.

The authorship of this publication will include at least the coordinating investigator, the principal investigators, and the signatories to this protocol and be specified between the parties. Arne Kristian Skulberg and Ida Tylleskar are planned as joint first authors of the main scientific article produced on the basis of this protocol.

The published international guidelines for authorship (International Committee of Medical Journal Editors, 1997) will be adhered to; i.e. 'All persons designed as authors should qualify for authorship. Each author should have participated sufficiently in the work to take public responsibility for the content.'

Authorship credit will therefore be based only on substantial contributions to 1) conception and design, or analysis and interpretation of data; and to 2) drafting the article or revising it critically for important intellectual content; and on 3) final approval of the version to be published. Conditions 1), 2) and 3) must all be met. Participation solely in acquisition of funding or the collation of data does not justify authorship. General supervision of the research group is not sufficient for authorship. It is intended that information on what each author has contributed will be published. It is emphasised however, that only those who entirely meet the above mentioned criteria will be listed as authors.

NTNU "Publishing Policy 2014–2020" document will be used as guidance in all issues regarding publication that may arise.

The sponsor has the right to share de-identified individual-patient data (IPD) underlying the results presented in the article (including tables, figures, and appendices or supplementary material) should any journal or editor require this. The data underlying the results are defined as the IPD required to reproduce the article's findings, including necessary metadata (64).

20 Conflict of interests

All signatories to this trial and members of the DMSC will have to fill in International Committee of Medical Journal Editors (ICMJE) Form for Disclosure of Potential Conflicts of Interest. In particular, they must declare any interest

concerning the following firms: Farma Investment AS (registration number 997 099 276), Sanivo Pharma AS (registration number 991 392 696), DnE pharma as (previously AS Den Norske Eterfabrikk) (registration number 991 741 208) or any other entity that concerns itself with naloxone and/or nasal spray for opioid overdose. The forms will be archived in the TMF.

Norwegian University of Science and Technology (NTNU) and its subsidiary Technology Transfer Office (TTO) have a licensing agreement with Den norske Eterfabrikk (DnE) regarding the naloxone formulation studied. DnE has sent an application for marketing authorization for a drug for human consumption. NTNU, TTO and Ola Dale (OD) have financial benefit from these contracts, sharing the income in equal thirds. OD has been engaged by DnE as Principle Investigator in a pharmacokinetic study of naloxone (EudraCT 2015-0023355-10) for which OD receives no personal honorarium. DnE has compensated OD for two travels from Trondheim to Oslo.

Arne Kristian Skulberg (AKS) does not longer have a “non-compete” contract with DNE, or bindings to DNE/ Farma Holding/ Sanivo Pharma or any other company. Other members of the study team declare they have no conflicts of interest.

21 List of appendices (Please note some documents are updated, consult TMF and ISF for latest versions)

1) **Investigational Medicinal Product Dossier (IMPD) Nalokson Dne Nasal Spray 14 Mg/Ml, Version 3, 30.04.2107**
2) **Investigational medicinal product dossier (IMPD) Placebo Nasal Spray, version 2, 30.04.2017**
3) **Product Insert Naloxone Hydrochloride Injection 4 mg/10ml Mylan Institutional LLC.**
4) **Product Insert Natriumklorid B. Braun 9 mg/ml x 10 ml, B. Braun. (Sodium Chloride injection)**
5) **Investigators Brochure (IB) VERSION 7.0 DATE: 06.03.2020**
6) **Double Dummy Kit example**
7) **Training of EMS to study personnel plan (in Norwegian)**
8) **Study Form**
9) **Ambulance journal Oslo**
10) **Ambulance journal Trondheim**
11) **Participant Information Sheet and text for internet page**
12) **MOM- Guideline Opioid overdose treatment Oslo Ambulance Service**
13) **Guideline opioid overdose treatment Trondheim Ambulance Service**

14) Charter for data monitoring and Safety committee

15) Validation report Eudra CT registration, signature and EudraCT form

16) Membership Legemiddelandsvarsforeningen 2016 and annual updates

22 References:

1. Thim T, Krarup NH, Grove EL, Rohde CV, Lofgren B. Initial assessment and treatment with the Airway, Breathing, Circulation, Disability, Exposure (ABCDE) approach. Int J Gen Med. 2012;5:117-21.
2. Skulberg AK, Madah Amiri D, Lobmaier PP, Heyerdahl F. Surveying opioid overdoses in Oslo City Centre 2014-2015. Unpublished 2016.
3. EMCDDA. European Monitoring Centre for Drugs and Drug Addiction, Annual report: The drug situation in Norway 2012 2012 [cited 2014 31. 03]. Available from: http://www.sirus.no/wp-content/uploads/2014/12/Drug_Situation_Norway_2011.pdf.
4. Helsedirektoratet. «Ja visst kan du bli rusfri – men først må du overleve» [updated April 2014. Available from: http://helsedirektoratet.no/publikasjoner/nasjonal-overdosestrategi-20142017/.
5. Kerr D, Kelly AM, Dietze P, Jolley D, Barger B. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. Addiction. 2009;104(12):2067-74.
6. Kelly AM, Kerr D, Dietze P, Patrick I, Walker T, Koutsogiannis Z. Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. Med J Aust. 2005;182(1):24-7.
7. Sabzghabaee AM, Eizadi-Mood N, Yaraghi A, Zandifar S. Naloxone therapy in opioid overdose patients: intranasal or intravenous? A randomized clinical trial. Arch Med Sci. 2014;10(2):309-14.
8. World Health Organization. Community management of opioid overdose. Geneva: World Health Organization,; 2014. Available from: http://www.ncbi.nlm.nih.gov/books/NBK264311/.
9. Loimer N, Hofmann P, Chaudhry HR. Nasal Administration of Naloxone Is as Effective as the Intravenous Route in Opiate Addicts. Int J Addict. 1994;29(6):819-27.
10. Kaufman RD, Gabathuler ML, Bellville JW. Potency, duration of action and pA2 in man of intravenous naloxone measured by reversal of morphine-depressed respiration. J Pharmacol Exp Ther. 1981;219(1):156-62.
11. Ngai SH, Berkowitz BA, Yang JC, Hempstead J, Spector S. Pharmacokinetics of naloxone in rats and in man: basis for its potency and short duration of action. Anesthesiology. 1976;44(5):398-401.
12. Kerr D, Dietze P, Kelly AM. Intranasal naloxone for the treatment of suspected heroin overdose. Addiction. 2008;103(3):379-86.
13. McDermott C, Collins NC. Prehospital medication administration: a randomised study comparing intranasal and intravenous routes. Emerg Med Int. 2012;2012:476161.
14. Ashton H, Hassan Z. Best evidence topic report. Intranasal naloxone in suspected opioid overdose. Emerg Med J. 2006;23(3):221-3.
15. Doe-Simkins M, Walley AY, Epstein A, Moyer P. Saved by the nose: bystander-administered intranasal naloxone hydrochloride for opioid overdose. Am J Public Health. 2009;99(5):788-91.
16. US Food and Drug Administration. FDA moves quickly to approve easy-to-use nasal spray to treat opioid overdose: U.S. Food and Drug Administration; 2015 [updated 18. Nov 2015. Available from: http://www.webcitation.org/6g1W28jYq
17. Adapt Pharma Inc. Highlights of prescribinginformation NARCAN® NASAL SPRAY. FDA2015 [updated 11/2015. Available from: http://www.webcitation.org/6g1Upt7eu.
18. Vanden Hoek TL, Morrison LJ, Shuster M, Donnino M, Sinz E, Lavonas EJ, et al. Part 12: cardiac arrest in special situations: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010;122(18 Suppl 3):S829-61.
19. Bailey PL, Clark NJ, Pace NL, Stanley TH, East KA, van Vreeswijk H, et al. Antagonism of postoperative opioid-induced respiratory depression: nalbuphine versus naloxone. Anesth Analg. 1987;66(11):1109-14.

20. B. Braun Melsungen AG. Naloxon B. Braun 0,4 mg/ml: Norwegian Medicines Agency; [updated 20.04.2012; cited 2015 12. March]. Summary of Product Characteristics]. Available from: http://slv.no/_layouts/Preparatomtaler/Spc/06-4660.pdf.
21. Dale O, Hoffer C, Sheffels P, Kharasch ED. Disposition of nasal, intravenous, and oral methadone in healthy volunteers. Clin Pharmacol Ther. 2002;72(5):536-45.
22. Dale O, Nilsen T, Loftsson T, Hjorth Tonnesen H, Klepstad P, Kaasa S, et al. Intranasal midazolam: a comparison of two delivery devices in human volunteers. J Pharm Pharmacol. 2006;58(10):1311-8.
23. Moksnes K, Fredheim OM, Klepstad P, Kaasa S, Angelsen A, Nilsen T, et al. Early pharmacokinetics of nasal fentanyl: is there a significant arterio-venous difference? Eur J Clin Pharmacol. 2008;64(5):497-502.
24. Loftsson T, Gudmundsdottir H, Sigurjonsdottir JF, Sigurdsson HH, Sigfusson SD, Masson M, et al. Cyclodextrin solubilization of benzodiazepines: formulation of midazolam nasal spray. Int J Pharm. 2001;212(1):29-40.
25. Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins: basic science and product development. J Pharm Pharmacol. 2010;62(11):1607-21.
26. Gudmundsdottir H, Sigurjonsdottir JF, Masson M, Fjalldal O, Stefansson E, Loftsson T. Intranasal administration of midazolam in a cyclodextrin based formulation: bioavailability and clinical evaluation in humans. Pharmazie. 2001;56(12):963-6.
27. Heyerdahl F, Hovda KE, Bjornaas MA, Nore AK, Figueiredo JC, Ekeberg O, et al. Pre-hospital treatment of acute poisonings in Oslo. BMC Emerg Med. 2008;8:15.
28. Heyerdahl F, Bjornas MA, Hovda KE, Skog K, Opdahl A, Wium C, et al. Acute poisonings treated in hospitals in Oslo: a one-year prospective study (II): clinical outcome. Clin Toxicol (Phila). 2008;46(1):42-9.
29. Heyerdahl F, Bjornaas MA, Dahl R, Hovda KE, Nore AK, Ekeberg O, et al. Repetition of acute poisoning in Oslo: 1-year prospective study. Br J Psychiatry. 2009;194(1):73-9.
30. Buajordet I, Naess AC, Jacobsen D, Brors O. Adverse events after naloxone treatment of episodes of suspected acute opioid overdose. Eur J Emerg Med. 2004;11(1):19-23.
31. Olasveengen TM, Sunde K, Brunborg C, Thowsen J, Steen PA, Wik L. Intravenous drug administration during out-of-hospital cardiac arrest: a randomized trial. JAMA. 2009;302(20):2222-9.
32. Wik L, Kramer-Johansen J, Myklebust H, Sorebo H, Svensson L, Fellows B, et al. Quality of cardiopulmonary resuscitation during out-of-hospital cardiac arrest. JAMA. 2005;293(3):299-304.
33. Karr B BA. Medisinsk Operativ Manual. Versjon 7 ed: Oslo Universitetssykehus HF; 2012.
34. Bakkelund K, Juvkam PC. Opioider- Felles Retningslinjer Ambulansetjenesten i Midt-Norge 2015 [Available from: http://www.webcitation.org/6hlaSg5go
35. Bakkelund K, Moen S, Juvkam PC. Naloxone- Felles Retningslinjer Ambulansetjenesten i Midt-Norge 2014 [Available from: http://www.webcitation.org/6hlasl3lp
36. Mylan Institutional LLC. Prescribing information NALOXONE HYDROCHLORIDE. 2016.
37. Dowling J, Isbister GK, Kirkpatrick CM, Naidoo D, Graudins A. Population pharmacokinetics of intravenous, intramuscular, and intranasal naloxone in human volunteers. Ther Drug Monit. 2008;30(4):490-6.
38. Wermeling DP. Opioid harm reduction strategies: focus on expanded access to intranasal naloxone. Pharmacotherapy. 2010;30(7):627-31.
39. Dale O, Hjortkjaer R, Kharasch ED. Nasal administration of opioids for pain management in adults. Acta Anaesthesiol Scand. 2002;46(7):759-70.
40. Dale O. Nesen – mer enn til å snyte seg i! Tidsskr Nor Legeforen. 2010;13(130).
41. Foldes FF, Lunn JN, Moore J, Brown IM. N-Allylnoroxy-morphone: a new potent narcotic antagonist. Am J Med Sci. 1963;245:23-30.
42. Skulberg AK, Asberg A, Khiabani HZ, Rostad H, Tylleskar I, Dale O. Pharmacokinetics of a novel, approved, 1.4-mg intranasal naloxone formulation for reversal of opioid overdose-a randomized controlled trial. Addiction. 2019.
43. Health Products Regulatory Authority Ireland. Summary of Product Characteristics Naloxone B Braun [cited 2016 17 March]. Available from: http://www.webcitation.org/6g4edopWl
44. B. Braun Melsungen AG. Natriumklorid B. Braun 9 mg/ml oppløsningsvæske til parenteral bruk. Preparatomtale.
45. Strang J, McDonald R, Tas B, Day E. Clinical provision of improvised nasal naloxone without experimental testing and without regulatory approval: imaginative shortcut or dangerous bypass of essential safety procedures? Addiction. 2016;111(4):574-82.
46. Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in Drug and Opioid Overdose Deaths - United States, 2000-2014. MMWR Morb Mortal Wkly Rep. 2016;64(50-51):1378-82.
47. Akopian M, Vallersnes OM, Jacobsen D, Ekeberg O, Brekke M. Living conditions in the districts of Oslo and poisonings by substances of abuse treated at casualty clinic level. Tidsskr Nor Laegeforen. 2015;135(21):1943-8.

48. Helsedirektoratet. Nasjonal faglig retningslinje for avrusning fra rusmidler og vanedannende legemidler 2016 [Available from: http://www.webcitation.org/6hNYJP0vN
49. Latt N. Addiction medicine. Oxford ; New York: Oxford University Press; 2009. xxxi, 459 p. p.
50. Wride SR, Smith RE, Courtney PG. A fatal case of pulmonary oedema in a healthy young male following naloxone administration. Anaesth Intensive Care. 1989;17(3):374-7.
51. Clarke SF, Dargan PI, Jones AL. Naloxone in opioid poisoning: walking the tightrope. Emerg Med J. 2005;22(9):612-6.
52. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Introductory Guide MedDRA Version 19.1 2016 [Available from: http://www.webcitation.org/6kYo5Ypyz.
53. Uppsala Monitoring Centre. The use of the WHO-UMC system for standardised case causality assessment [cited 2016 16th September]. Available from: http://www.webcitation.org/6kYn8ezcY
54. World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-4.
55. International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human u. ICH harmonized tripartite guideline: Guideline for Good Clinical Practice. J Postgrad Med. 2001;47(1):45-50.
56. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? JAMA. 2000;283(20):2701-11.
57. Dale O. Ethical issues and stakeholders matter. Addiction. 2016;111(4):587-9.
58. Jørgensen. K ea. 'LB15 - Biosimilar infliximab (CT-P13) is not inferior to originator infliximab: results from the 52-week randomized NOR-SWITCH trial.'. United European Gastroenterology (UEG) Week meeting 2016, 15-19 October; Vienna, Austria.
59. Act on medical and health research (the Health Research Act), ACT 2008-06-20 no. 44 (2008).
60. Hibbard BM, Rosen M, Davies D. Placental transfer of naloxone. Br J Anaesth. 1986;58(1):45-8.
61. Forskrift om ordning med lokaler for injeksjon av narkotika (sprøyteromsforskriften), FOR-2004-12-17-1661.
62. Lenton SR, Dietze PM, Jauncey M. Australia reschedules naloxone for opioid overdose. Med J Aust. 2016;204(4):146-7.
63. Health Canada. Notice: Prescription Drug List (PDL): Naloxone 2016 [updated 22. MArch 2016. Available from: http://www.webcitation.org/6joB4rJSq
64. Taichman DB, Backus J, Baethge C, Bauchner H, de Leeuw PW, Drazen JM, et al. Sharing Clinical Trial Data--A Proposal from the International Committee of Medical Journal Editors. N Engl J Med. 2016;374(4):384-6.

NTNU
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DATA MONITORING AND SAFETY COMMITTEE CHARTER

NTNU INTRANASAL NALOXONE TRIAL
Double blinded, double dummy, randomised controlled trial of intranasal naloxone for pre- hospital use

Protocol Identification Number: NINA- 1
EudraCT Number: 2016-004072-22

SPONSOR:	Øystein Risa, Head of Department Department of Circulation and Medical Imaging, Norwegian University of Science and Technology (ISB, NTNU) Box 8905 MTFS 7491 Trondheim, Norway Tel: (+47) 92613734 E-mail: oystein.risa@ntnu.no
COORDINATION INVESTIGATOR (CI):	Ola Dale, professor Department of Circulation and Medical Imaging, Norwegian University of Science and Technology (ISB, NTNU) Box 8905 MTFS 7491 Trondheim, Norway Tel: (+47) 91199255 E-mail: ola.dale@ntnu.no

VERSION NO. 2.0 - 04.05.2018

1 Signature Page

Title	NTNU Intranasal Naloxone Trial Double blinded, double dummy, randomised controlled trial of intranasal naloxone for pre hospital use
Protocol ID no:	NINA-1
EudraCT no:	2016-004072-22
Protocol date:	PROTOCOL VERSION NO. 3.0 Date: 9th January 2018

I hereby declare that I will conduct my work in the DMSC in compliance with this charter, the Protocol, ICH GCP and the applicable regulatory requirements:

Name	Title	Signature	Date
Per Farup Member DMSC	MD, PhD Professor		
Øyvind Thomassen Member DMSC	MD, PhD		
Jørgen Dahlberg Member DMSC	MD, PhD		
Ola Dale Coordinating investigator	MD, PhD Professor		
Øystein Risa Sponsor	Director		
Marissa LeBlanc DMSC Statistician			

2 INTRODUCTION

This charter describes the roles and responsibilities of the independent DMSC for the NTNU Intranasal Naloxone Trial, including the timing of meetings, methods of providing information to and from the DMSC, frequency and format of meetings and statistical issues.

3 RESPONSIBILITIES

1. The DMSC will review recruitment, data quality, protocol deviations, safety and adverse events by perform the following tasks:

- Overall conduct of study based on monitoring reports and deviations in Viedoc.
- Monitor safety based on AE, SAE, the use of rescue naloxone, the recurrence of overdoses within 12 hours after inclusion, other medical interventions during the study period. Annual Safety Report to the Norwegian Medicines Agency will also be provided.
- Suggest additional data analyses
- Monitor compliance with previous DMC recommendations

2. Alert SPONSOR if they receive information from a study worker acting as a whistle-blower

The DMSC will make recommendations to the Sponsor regarding study modification, continuation or termination.

The recommendations of the DMSC are advisory and SPONSOR may decide to proceed with the trial.

DMSC members will be reimbursed for travel and accommodation.

4 PROCESS

4.1 Data Review

For all meetings, the DMSC will be provided with reports showing the following data to assess the safety. During closed sessions safety data by treatment group will be reviewed.

- Summary of patient enrolment (number per site, age, gender and follow-up)
- Safety profile: adverse events, serious adverse events (SAE) and SUSAR reported
- Interventions: The use of recue naloxone
- Follow up: The follow up after study treatment (Hospitalisation, Left at the scene etc)
- Recurrence: The number of participants with recurring overdose within 12 hours after inclusion.
- Mortality: Any deaths by a trial participant during the duration of study time will be reported to by Coordinating investigator the DMSC within 7 days.

The datapoints described above will be descriptively tabulated by treatment group. The study statistician will be responsible for preparing the statistical programming underlying the tables, while it is the DMCS statistician's responsibility to merge in the assigned allocation and run the program. The resulting tables will be presented by the DMSC statistician to the rest of the DMSC members. There will be no formal statistical analyses, rules or guidelines respecified for the DMSC meetings. Any statistical analyses requested by the clinical DMSC members will be ad hoc, and will only be used to support decisions on safety issues. In case statistical analyses are performed, the DMSC statistician must be involved in interpreting the results.

4.2 Decision making

The DMSC will recommend stopping a trial if:

- There is a safety concern which warrants stopping the trial

The DMSC will make recommendations which could include:

- No action needed, trial continues as planned
- Early stopping due to harm of a treatment or external evidence.
- Proposing protocol changes

The DMSC will make every effort to reach a unanimous decision. If the DMSC cannot achieve this, a vote may be taken.

5 AUTONOMY

- The DMSC is a standing and independent committee of the NTNU Intranasal Naloxone Trial and shall remain independent in the conduct of its operation and the formulation of its recommendations.

6 CONFIDENTIALITY

- The DMSC may hold Open Sessions with the SPONSOR or representatives to discuss generic safety data concerns.
- Any safety data analysed will be reviewed during Closed Sessions of the DMSC.
- It is the duty of each member of the DMSC to protect the confidentiality of the trial and the results of monitoring.
- The members of the DMSC acknowledge that the data emerging from this trial is the collective property of the Sponsor.
- No member of the DMSC shall have the right to present the data or information derived from this trial at or in in scientific journals, professional meetings and conferences, non-academic articles and the like without the explicit and written permission of SPONSOR.

7 MEETING ORGANISATION

All meetings of the DMSC will be closed, but may be combined with open sessions inviting SPONSOR or other members of the study team. The first meeting will be face-to-face to facilitate full discussion. All subsequent meetings should be face-to-face if possible, but teleconference will be used as appropriate.

Planned meeting will be held after the inclusion of 20 and 100 trial participants, and at the end of the trial.

The DMSC may also at any time announce a meeting and demand access to data. Such unscheduled meetings must be notified to SPONSOR

The NINA-1 DMSC also acts as a whistle- blower reporting mechanism, where the DMSC members can receive emails sent to nalokson_sikkerhet@mh.ntnu.no. This line of information bypass SPONSOR or ant of its representatives.

Upon receiving information through this channel the DMSC must themselves decide the need for meetings, access to data further information, involvement of SPONSOR or others.

The DMSC can organize additional meetings at any time of they see fit.

The Chair of the DMSC will introduce each meeting and define the scope and any constraints and will close each meeting with a summary of the conclusions and recommendations if any. The Chair will appoint a suitable person as a minute taker.

8 REPORTING

- The DMSC will provide written reports to SPONSOR. See appendix 2
- If accepted by the SPONSOR, SPONSOR will circulate the DMSC's recommendations to the study team.
- As such, in the event of a DMSC recommendation to continue the trial, no other information shall be provided to SPONSOR.
- In the event of a DMSC recommendation to terminate the trial in its entirety, the DMSC will provide a full report to the Coordinating Investigator and Sponsor including rationale for study termination.
- Copies of both the Open and Closed Session Minutes of the DMSC will be provided to SPONSOR at the completion of the trial.
- In the event of an unresolved conflict between the SPONSOR and the DMSC, the DMSC may contact the appropriate Research Ethics Committees and Medical Agencies, or Helsetilsynet directly to elaborate on concerns and make recommendations.

9 DMSC RECOMMENDATIONS

- Should the DMSC wish to provide a recommendation to SPONSOR for protocol modification(s) or early termination of the trial for patient safety the Chair of the DMSC must do so in writing and in a timely manner.
- Upon receipt of a DMSC recommendation to modify or terminate the trial, SPONSOR will call an urgent meeting of Coordinating and principal investigators to review the recommendations.
- If in agreement with the recommendations of the DMSC, it is the responsibility of the SPONSOR to determine the appropriate course of actions.
- It is also the responsibility of the ~~chair of~~ SPONSOR to inform the appropriate Research Ethics Board and Medical Agencies of any decision to modify or terminate the trial.

10 CONFLICT OF INTEREST

Individuals who are invited to serve on a DMSC are responsible for disclosing:

1. those significant financial interests that would reasonably appear to be affected by or to affect their research or educational activities, and
2. any significant financial interests in entities whose financial interests would reasonably appear to be affected by or to affect the person's performance of his or her Hospital/University duties, including participation in a DMSC.

DMSC members will in many cases know the members of the SPONSOR and must consider this relationship to ensure they perform their duties with the highest integrity in this context.

- Decisions concerning whether an individual with a conflict of interest or the appearance of conflicts of interest may participate on the DMSC will be made at the discretion of the DMSC Chair.
- Conflict of interest towards the Sponsor or Den Norske Eterfabrikk/ Farmaholding/ Sanivo Pharma will be declared in appendix 3.

11 APPENDIX 1 Study Protocol

12 APPENDIX 2 Template for the DMSC to utilize for reporting to the chair of SPONSOR

Data and Safety Monitoring Meeting

Date: _____

NTNU Intranasal Naloxone Trial
Double blinded, double dummy, randomised controlled trial of intranasal naloxone for pre- hospital use

NINA-1
Eudra CT: 2016-004072-22

Coordinating investigator: Ola Dale

Recommendations:

- □ Continue the trial without modification
- □ Recommend study is amended/changed
- □ Termination of trial
- □ Other

Signature/Chair Data Safety Monitoring Committee:

_____

13 APPENDIX 3 Disclosure Form

Disclosure Form
Data Monitoring Committee members for

Protocol	NTNU Intranasal Naloxone Trial
Sponsor	NTNU, v/ ISB. Øystein Risa

The avoidance of any perception that members of a DMSC may be biased in some fashion is important for the credibility of the decisions made by the DMSC and for the integrity of the trial.

Possible competing interest should be disclosed via the trials office. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) DMSC member should remove the conflict or stop participating in the DMSC.

Potential competing interests include but are not limited to the following:

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the Sponsor
- Frequent speaking engagements on behalf of the intervention
- Career tied up in a product or technique assessed by trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Intellectual conflict e.g. strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) in competing products
- Involvement in the publication

☐ I have no competing interests to declare
☐ I have competing interests to declare (please detail below)

Please provide details of any competing interests:

Name:

Signature

Date (dd mmm yyyy)

STUDIESKJEMA NINA-1

Kit-Nr: ☐☐☐ Studietelefon: **22 93 22 11**

DD MM ÅÅÅÅ

AMIS Nr: ☐☐☐☐☐☐☐-☐ **Dato:** ☐☐.☐☐-☐☐☐☐

INKLUSJON Mistenkt opioidoverdose	JA	NEI
Respirasjonsfrekvens under 8		
GCS under 12		
Miose (små pupiller)		
Palpabel puls (hals eller håndledd)		

JA PÅ ALLE

EKSKLUSJON	JA	NEI
Hjertestans		
Klarer ikke få frie luftveier/assistere ventilasjon		
Ansiktstraume, neseblødning, synlig neseblokkering		
Overdose på opioider gitt av helsepersonell		
Synlig eller kjent graviditet		
Mistenker at deltaker er under 18 år		
Pasienten har fått nalokson før vår ankomst		
Pasient er fengslet eller i arrest		
Personale er ikke opplært i studien		
Studiemedisin er/har vært frosset eller utgått på dato		
Studiemedisin er ikke tilgjengelig		
Ekskludert av andre grunner – oppgi grunnen		

EKSKLUDERT –
TA KOPI AV JOURNAL. ARKIVER SAMMEN MED DETTE SKJEMAET

Årsak til at pasienten er ekskludert? .....

.....

.....

.....

.....

NEI PÅ ALLE

VENTILER PASIENTEN
- Forbered studiemedisin
- Innstikksted
- Stoppeklokke

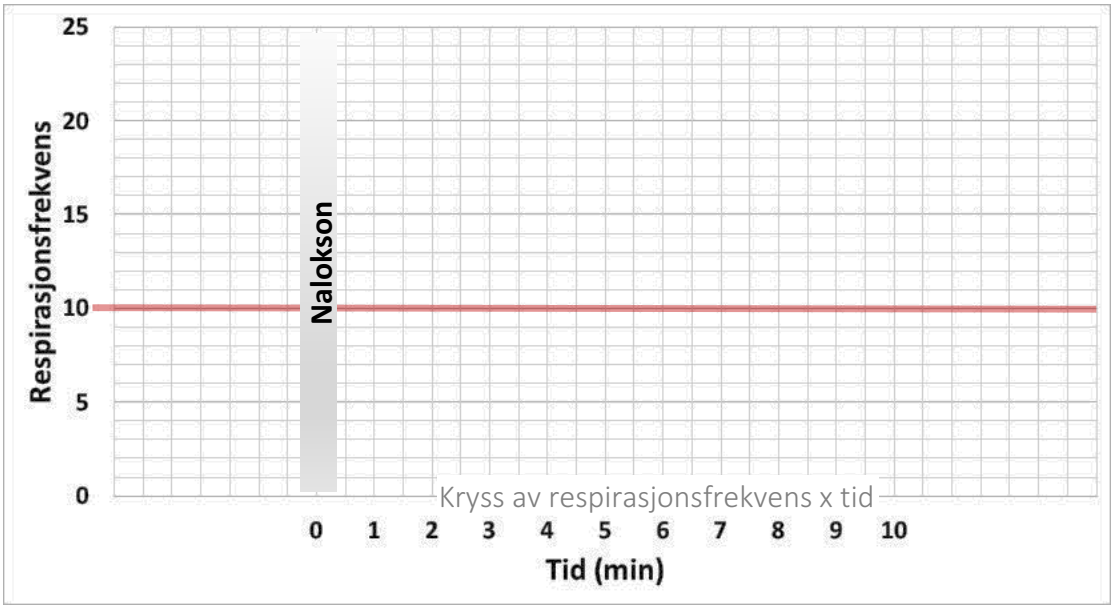
16.1.2 Sample case report form

DEL 2 - BEHANDLINGSFORLØP

Angi på figuren under:

1. Respirasjonsfrekvens og GCS før nalokson
2. Minutter på stoppeklokka når pas. puster mer en 10/ minutt, er våken, snakker eller er oppegående
3. Respirasjonsfrekvens og GCS 10 minutter etter nalokson

   Du kan forløpende angi RF i kurven



Før nalokson	Min. og sek. ved RF over 10 pr min.	10 min.
RF: / min.	:	**RF:** / min.
GCS:		**GCS:**

Er *nesespray* gitt som planlagt **Ja ☐ Nei ☐**

Er *injeksjon* gitt som planlagt **Ja ☐ Nei ☐**

Kommentarer: .....

.....

HVIS PASIENTEN IKKE VÅKNER INNEN 10 minutter på stoppeklokka:

Fortsett behandling etter vanlig prosedyre, noter alle medisiner og tiltak i journalen

Er det gitt ekstra nalokson i tillegg til studiemedisinen? **Ja ☐ Nei ☐**

DEL 3 – BIVIRKNINGER/ OPPFØLGNING/ GJENNOMFØRING

Beskriv bivirkningene: Alvorlighet, varighet og tiltak Rød rute? fyll ut bivirkningsskjema

BIVIRKNINGER

Kvalme	Ja ☐ Nei ☐	Lungeødem	Ja ☐ Nei ☐
Oppkast	Ja ☐ Nei ☐	Kramper	Ja ☐ Nei ☐
Uro/ Rastløshet	Ja ☐ Nei ☐	Alvorlig sirkulasjonssvikt	Ja ☐ Nei ☐
Aggresjon	Ja ☐ Nei ☐	Hjertestans	Ja ☐ Nei ☐
Aspirasjon	Ja ☐ Nei ☐	Allergisk reaksjon	Ja ☐ Nei ☐
Abstinens	Ja ☐ Nei ☐	Neseblødning	Ja ☐ Nei ☐
Hypotermi	Ja ☐ Nei ☐	Død	Ja ☐ Nei ☐
		Andre komplikasjoner	Ja ☐ Nei ☐
		Beskriv:	

GJENNOMFØRING

Var det noe praktisk problem knyttet til bruken av nesesprayen? **Ja ☐ Nei ☐**

Om JA, beskriv:

.....

.....

.....

Ble studien gjennomført som beskrevet i protokollen
og i henhold til den opplæringen som er blitt gitt? **Ja ☐ Nei ☐**

Om NEI, beskriv:

.....

.....

.....

SYKEHUSOPPFØLGING
(gjelder ikke pasienter som transporteres til legevakt eller rusakutt)

Tas pasienten med til sykehus? **Ja ☐ Nei ☐**

Om Ja:
Innleggelsen er relatert til studiegjennomføringen, eller som følge av bivirkninger
av studiemedisinen? **Ja ☐ Nei ☐**

**Hvis Ja
Fyll ut
bivirkningsskjema**

DEL 4 – SAMTYKKE

Pasienten vurderes som samtykkekompetent **Ja ☐ Nei ☐**

Mulighet for kommentar:

.....

.....

.....

.....

Hvis **NEI** - IKKE KOMPETENT

- SAMTYKKE SKAL IKKE INNHENTES!
- Sørg for at pasienten får info-ark og visittkort
- Pasienten skal inkluderes som normalt

Hvis JA:

Har pasienten samtykket til at data som er samlet inn kan brukes i studien?

Ja ☐ Nei ☐

Tjenestenummer: Hvis aktuelt

Navn: ..... Blokkbokstaver

Signatur: .....

Tjenestenummer: Hvis aktuelt

Navn: ..... Blokkbokstaver

Signatur: .....

Samtykke må bekreftes minimum to studiearbeidere

NTNU

Melding om mulig alvorlig bivirkning

Serious Adverse Event Form

OBS: Dette skal kun fylles ut dersom pasienten dør, blir tatt med til sykehus på grunn av lungeødem, kramper, kardiovaskulær kollaps, hjertestans, alvorlig allergisk reaksjon, neseblødning eller forverres klinisk OG den tilstanden kan skyldes studiemedisin. Årsaker til sykehusinnleggelse som skyldes andre tilstander, tilstede før studiemedisin ble gitt skal ikke meldes.

Vurder å ringe nødtelefonen på 22932251, for å få kontakt med studieteamet 24 timer.

DEL 1 – Fylles ut av ambulansepersonell

Studienummer: _____

Inklusjonsdato: __ __. __ __ . __ __ __ __

AMIS nummer: _____

1. Pasienten er: ☐ Mann ☐ Kvinne Alder: _____

2. Dato start hendelse: __ __. __ __ . __ __ __ __ Dato slutt hendelse: __ __. __ __ . __ __ __ __

3. Hvor oppstod hendelsen: _____

4. Beskriv hendelsen:

start, symptomer, alvorlighetsgrad, varighet, tiltak, virkning av disse

NTNU

3. Beskriv alle relevante undersøkelser og opplysninger fra sykehistorien som kan være relevant

4. Medisiner gitt: _____

_____

5. Andre intervensjoner gjort: _____

_____

6. Ble studien avbrutt som følge av hendelsen? ☐ Ja ☐ Nei

7. Hendelsen førte til:
☐ Sykehus opphold, eller forlenging av sykehusopphold
☐ Uførhet
☐ Livstruende tilstand
☐ Død dato: __ __. __ __ . __ __ __ __

NTNU

DEL 2 – Fylles ut av studiepersonell

1. Was interview with study personell conducted? ☐ Yes ☐ No

2. Complementary information achieved regarding the event, treatment or interventions:

3. Complementary information achieved regarding treatment or interventions:

4. Complementary information achieved regarding any relevant tests, examinations, interventions, history, including preexisting medical conditions that may relate:

NTNU

Classification

5. SAE confirmed ☐ Yes ☐ No

If no, why not an SAE? _____

6. Category of serious adverse event:

☐ death – date ____/_____/_____(dd/mm/yyyy)

☐ life-threatening

☐ hospitalization-initial or prolonged

☐ disability / incapacity

☐ other:_____

7. Relationship of event to intervention (see protocol for definitions of WHO-UMC system):

☐ Certain

☐ Probable/ Likely

☐ Possible

☐ Unlikely

☐ Conditional/ Unclassifiable

☐ Unassessable/Unclassifiable

NTNU

8. Was study intervention discontinued due to event? ☐ Yes ☐ No

9. Was this an unexpected adverse event? ☐ Yes ☐ No If yes, contact Martha Colban (OUS) for CIOMS form and unblinding

10. Type of report:

☐ Initial

☐ Follow-up

☐ Final

Signature of Principal Investigator: _____ Date: _____

1.1 Signature page

Title	NTNU Intranasal Naloxone Trial Double blinded, double dummy, randomised controlled trial of intranasal naloxone for pre-hospital use
Protocol ID no:	NINA-1
EudraCT no:	2016-004072-22
Protocol version and date:	No 3.3, 6Th March 2020

I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements:

Name	Title	Role	Signature	Date
Øystein Risa	Director	Sponsor		6/3-2020
Arne Kristian Skulberg	MD, PhD	Coordinating Investigator (CI)		06.03.2020
Anne Cathrine Braarud	MD, PhD	Principal Investigator (PI) Oslo		
Jostein Dale	MD, Head of Department	Principal Investigator (PI) Trondheim		6 march 2020
Ola Dale	Professor, MD, PhD	Investigator		
Ida Tylleskar	MD	Investigator		6 March 2020
Fridtjof Heyerdahl	MD, PhD	Investigator		
Morten Valberg	PhD	Statistician		

16.1.7 Randomisation scheme and codes (patient identification and treatment assigned)

randListOslo

id	stratum	block.id	block.size	treatment	nasal_adm	IM_adm
100	Oslo	1	4	Active	Naloxone	Placebo
101	Oslo	1	4	Active	Naloxone	Placebo
102	Oslo	1	4	Control	Placebo	Naloxone
103	Oslo	1	4	Control	Placebo	Naloxone
104	Oslo	2	6	Active	Naloxone	Placebo
105	Oslo	2	6	Active	Naloxone	Placebo
106	Oslo	2	6	Active	Naloxone	Placebo
107	Oslo	2	6	Control	Placebo	Naloxone
108	Oslo	2	6	Control	Placebo	Naloxone
109	Oslo	2	6	Control	Placebo	Naloxone
110	Oslo	3	6	Active	Naloxone	Placebo
111	Oslo	3	6	Control	Placebo	Naloxone
112	Oslo	3	6	Control	Placebo	Naloxone
113	Oslo	3	6	Active	Naloxone	Placebo
114	Oslo	3	6	Active	Naloxone	Placebo
115	Oslo	3	6	Control	Placebo	Naloxone
116	Oslo	4	4	Control	Placebo	Naloxone
117	Oslo	4	4	Active	Naloxone	Placebo
118	Oslo	4	4	Control	Placebo	Naloxone
119	Oslo	4	4	Active	Naloxone	Placebo
120	Oslo	5	8	Control	Placebo	Naloxone
121	Oslo	5	8	Active	Naloxone	Placebo
122	Oslo	5	8	Control	Placebo	Naloxone
123	Oslo	5	8	Control	Placebo	Naloxone
124	Oslo	5	8	Active	Naloxone	Placebo
125	Oslo	5	8	Active	Naloxone	Placebo
126	Oslo	5	8	Active	Naloxone	Placebo
127	Oslo	5	8	Control	Placebo	Naloxone
128	Oslo	6	4	Active	Naloxone	Placebo
129	Oslo	6	4	Control	Placebo	Naloxone
130	Oslo	6	4	Control	Placebo	Naloxone
131	Oslo	6	4	Active	Naloxone	Placebo

132	Oslo	7	6	Active	Naloxone	Placebo
133	Oslo	7	6	Control	Placebo	Naloxone
134	Oslo	7	6	Active	Naloxone	Placebo
135	Oslo	7	6	Control	Placebo	Naloxone
136	Oslo	7	6	Active	Naloxone	Placebo
137	Oslo	7	6	Control	Placebo	Naloxone
138	Oslo	8	6	Control	Placebo	Naloxone
139	Oslo	8	6	Active	Naloxone	Placebo
140	Oslo	8	6	Active	Naloxone	Placebo
141	Oslo	8	6	Control	Placebo	Naloxone
142	Oslo	8	6	Active	Naloxone	Placebo
143	Oslo	8	6	Control	Placebo	Naloxone
144	Oslo	9	8	Control	Placebo	Naloxone
145	Oslo	9	8	Active	Naloxone	Placebo
146	Oslo	9	8	Control	Placebo	Naloxone
147	Oslo	9	8	Active	Naloxone	Placebo
148	Oslo	9	8	Active	Naloxone	Placebo
149	Oslo	9	8	Control	Placebo	Naloxone
150	Oslo	9	8	Active	Naloxone	Placebo
151	Oslo	9	8	Control	Placebo	Naloxone
152	Oslo	10	8	Active	Naloxone	Placebo
153	Oslo	10	8	Control	Placebo	Naloxone
154	Oslo	10	8	Control	Placebo	Naloxone
155	Oslo	10	8	Active	Naloxone	Placebo
156	Oslo	10	8	Control	Placebo	Naloxone
157	Oslo	10	8	Active	Naloxone	Placebo
158	Oslo	10	8	Control	Placebo	Naloxone
159	Oslo	10	8	Active	Naloxone	Placebo
160	Oslo	11	4	Control	Placebo	Naloxone
161	Oslo	11	4	Active	Naloxone	Placebo
162	Oslo	11	4	Control	Placebo	Naloxone
163	Oslo	11	4	Active	Naloxone	Placebo
164	Oslo	12	6	Control	Placebo	Naloxone
165	Oslo	12	6	Control	Placebo	Naloxone

166	Oslo	12	6	Control	Placebo	Naloxone
167	Oslo	12	6	Active	Naloxone	Placebo
168	Oslo	12	6	Active	Naloxone	Placebo
169	Oslo	12	6	Active	Naloxone	Placebo
170	Oslo	13	6	Control	Placebo	Naloxone
171	Oslo	13	6	Control	Placebo	Naloxone
172	Oslo	13	6	Active	Naloxone	Placebo
173	Oslo	13	6	Control	Placebo	Naloxone
174	Oslo	13	6	Active	Naloxone	Placebo
175	Oslo	13	6	Active	Naloxone	Placebo
176	Oslo	14	8	Control	Placebo	Naloxone
177	Oslo	14	8	Control	Placebo	Naloxone
178	Oslo	14	8	Active	Naloxone	Placebo
179	Oslo	14	8	Control	Placebo	Naloxone
180	Oslo	14	8	Active	Naloxone	Placebo
181	Oslo	14	8	Active	Naloxone	Placebo
182	Oslo	14	8	Active	Naloxone	Placebo
183	Oslo	14	8	Control	Placebo	Naloxone
184	Oslo	15	4	Control	Placebo	Naloxone
185	Oslo	15	4	Active	Naloxone	Placebo
186	Oslo	15	4	Control	Placebo	Naloxone
187	Oslo	15	4	Active	Naloxone	Placebo
188	Oslo	16	2	Control	Placebo	Naloxone
189	Oslo	16	2	Active	Naloxone	Placebo
190	Oslo	17	2	Active	Naloxone	Placebo
191	Oslo	17	2	Control	Placebo	Naloxone
192	Oslo	18	2	Control	Placebo	Naloxone
193	Oslo	18	2	Active	Naloxone	Placebo
194	Oslo	19	8	Control	Placebo	Naloxone
195	Oslo	19	8	Control	Placebo	Naloxone
196	Oslo	19	8	Control	Placebo	Naloxone
197	Oslo	19	8	Control	Placebo	Naloxone
198	Oslo	19	8	Active	Naloxone	Placebo
199	Oslo	19	8	Active	Naloxone	Placebo

200	Oslo	19	8	Active	Naloxone	Placebo
201	Oslo	19	8	Active	Naloxone	Placebo
202	Oslo	20	2	Active	Naloxone	Placebo
203	Oslo	20	2	Control	Placebo	Naloxone
204	Oslo	21	4	Control	Placebo	Naloxone
205	Oslo	21	4	Active	Naloxone	Placebo
206	Oslo	21	4	Control	Placebo	Naloxone
207	Oslo	21	4	Active	Naloxone	Placebo
208	Oslo	22	6	Control	Placebo	Naloxone
209	Oslo	22	6	Control	Placebo	Naloxone
210	Oslo	22	6	Active	Naloxone	Placebo
211	Oslo	22	6	Active	Naloxone	Placebo
212	Oslo	22	6	Control	Placebo	Naloxone
213	Oslo	22	6	Active	Naloxone	Placebo
214	Oslo	23	8	Active	Naloxone	Placebo
215	Oslo	23	8	Active	Naloxone	Placebo
216	Oslo	23	8	Control	Placebo	Naloxone
217	Oslo	23	8	Control	Placebo	Naloxone
218	Oslo	23	8	Active	Naloxone	Placebo
219	Oslo	23	8	Control	Placebo	Naloxone
220	Oslo	23	8	Active	Naloxone	Placebo
221	Oslo	23	8	Control	Placebo	Naloxone
222	Oslo	24	6	Control	Placebo	Naloxone
223	Oslo	24	6	Control	Placebo	Naloxone
224	Oslo	24	6	Active	Naloxone	Placebo
225	Oslo	24	6	Control	Placebo	Naloxone
226	Oslo	24	6	Active	Naloxone	Placebo
227	Oslo	24	6	Active	Naloxone	Placebo
228	Oslo	25	2	Control	Placebo	Naloxone
229	Oslo	25	2	Active	Naloxone	Placebo
230	Oslo	26	8	Active	Naloxone	Placebo
231	Oslo	26	8	Control	Placebo	Naloxone
232	Oslo	26	8	Control	Placebo	Naloxone
233	Oslo	26	8	Control	Placebo	Naloxone

234	Oslo	26	8	Active	Naloxone	Placebo
235	Oslo	26	8	Active	Naloxone	Placebo
236	Oslo	26	8	Control	Placebo	Naloxone
237	Oslo	26	8	Active	Naloxone	Placebo
238	Oslo	27	4	Control	Placebo	Naloxone
239	Oslo	27	4	Control	Placebo	Naloxone
240	Oslo	27	4	Active	Naloxone	Placebo
241	Oslo	27	4	Active	Naloxone	Placebo
242	Oslo	28	2	Active	Naloxone	Placebo
243	Oslo	28	2	Control	Placebo	Naloxone
244	Oslo	29	4	Control	Placebo	Naloxone
245	Oslo	29	4	Active	Naloxone	Placebo
246	Oslo	29	4	Active	Naloxone	Placebo
247	Oslo	29	4	Control	Placebo	Naloxone
248	Oslo	30	6	Control	Placebo	Naloxone
249	Oslo	30	6	Control	Placebo	Naloxone
250	Oslo	30	6	Active	Naloxone	Placebo
251	Oslo	30	6	Control	Placebo	Naloxone
252	Oslo	30	6	Active	Naloxone	Placebo
253	Oslo	30	6	Active	Naloxone	Placebo
254	Oslo	31	8	Active	Naloxone	Placebo
255	Oslo	31	8	Control	Placebo	Naloxone
256	Oslo	31	8	Control	Placebo	Naloxone
257	Oslo	31	8	Active	Naloxone	Placebo
258	Oslo	31	8	Control	Placebo	Naloxone
259	Oslo	31	8	Active	Naloxone	Placebo
260	Oslo	31	8	Active	Naloxone	Placebo
261	Oslo	31	8	Control	Placebo	Naloxone
262	Oslo	32	2	Control	Placebo	Naloxone
263	Oslo	32	2	Active	Naloxone	Placebo
264	Oslo	33	4	Control	Placebo	Naloxone
265	Oslo	33	4	Active	Naloxone	Placebo
266	Oslo	33	4	Active	Naloxone	Placebo
267	Oslo	33	4	Control	Placebo	Naloxone

268	Oslo	34	8	Control	Placebo	Naloxone
269	Oslo	34	8	Active	Naloxone	Placebo
270	Oslo	34	8	Active	Naloxone	Placebo
271	Oslo	34	8	Control	Placebo	Naloxone
272	Oslo	34	8	Control	Placebo	Naloxone
273	Oslo	34	8	Active	Naloxone	Placebo
274	Oslo	34	8	Control	Placebo	Naloxone
275	Oslo	34	8	Active	Naloxone	Placebo
276	Oslo	35	8	Active	Naloxone	Placebo
277	Oslo	35	8	Control	Placebo	Naloxone
278	Oslo	35	8	Active	Naloxone	Placebo
279	Oslo	35	8	Active	Naloxone	Placebo
280	Oslo	35	8	Control	Placebo	Naloxone
281	Oslo	35	8	Active	Naloxone	Placebo
282	Oslo	35	8	Control	Placebo	Naloxone
283	Oslo	35	8	Control	Placebo	Naloxone
284	Oslo	36	2	Active	Naloxone	Placebo
285	Oslo	36	2	Control	Placebo	Naloxone
286	Oslo	37	6	Control	Placebo	Naloxone
287	Oslo	37	6	Active	Naloxone	Placebo
288	Oslo	37	6	Control	Placebo	Naloxone
289	Oslo	37	6	Active	Naloxone	Placebo
290	Oslo	37	6	Control	Placebo	Naloxone
291	Oslo	37	6	Active	Naloxone	Placebo
292	Oslo	38	6	Control	Placebo	Naloxone
293	Oslo	38	6	Active	Naloxone	Placebo
294	Oslo	38	6	Control	Placebo	Naloxone
295	Oslo	38	6	Control	Placebo	Naloxone
296	Oslo	38	6	Active	Naloxone	Placebo
297	Oslo	38	6	Active	Naloxone	Placebo
298	Oslo	39	6	Active	Naloxone	Placebo
299	Oslo	39	6	Active	Naloxone	Placebo
300	Oslo	39	6	Control	Placebo	Naloxone
301	Oslo	39	6	Active	Naloxone	Placebo

302	Oslo	39	6	Control	Placebo	Naloxone
303	Oslo	39	6	Control	Placebo	Naloxone
304	Oslo	40	6	Control	Placebo	Naloxone
305	Oslo	40	6	Control	Placebo	Naloxone
306	Oslo	40	6	Active	Naloxone	Placebo
307	Oslo	40	6	Active	Naloxone	Placebo
308	Oslo	40	6	Control	Placebo	Naloxone
309	Oslo	40	6	Active	Naloxone	Placebo
310	Oslo	41	8	Control	Placebo	Naloxone
311	Oslo	41	8	Control	Placebo	Naloxone
312	Oslo	41	8	Control	Placebo	Naloxone
313	Oslo	41	8	Active	Naloxone	Placebo
314	Oslo	41	8	Control	Placebo	Naloxone
315	Oslo	41	8	Active	Naloxone	Placebo
316	Oslo	41	8	Active	Naloxone	Placebo
317	Oslo	41	8	Active	Naloxone	Placebo
318	Oslo	42	6	Control	Placebo	Naloxone
319	Oslo	42	6	Active	Naloxone	Placebo
320	Oslo	42	6	Control	Placebo	Naloxone
321	Oslo	42	6	Active	Naloxone	Placebo
322	Oslo	42	6	Control	Placebo	Naloxone
323	Oslo	42	6	Active	Naloxone	Placebo
324	Oslo	43	4	Active	Naloxone	Placebo
325	Oslo	43	4	Active	Naloxone	Placebo
326	Oslo	43	4	Control	Placebo	Naloxone
327	Oslo	43	4	Control	Placebo	Naloxone
328	Oslo	44	8	Control	Placebo	Naloxone
329	Oslo	44	8	Active	Naloxone	Placebo
330	Oslo	44	8	Control	Placebo	Naloxone
331	Oslo	44	8	Active	Naloxone	Placebo
332	Oslo	44	8	Control	Placebo	Naloxone
333	Oslo	44	8	Control	Placebo	Naloxone
334	Oslo	44	8	Active	Naloxone	Placebo
335	Oslo	44	8	Active	Naloxone	Placebo

336	Oslo	45	6	Control	Placebo	Naloxone
337	Oslo	45	6	Control	Placebo	Naloxone
338	Oslo	45	6	Active	Naloxone	Placebo
339	Oslo	45	6	Active	Naloxone	Placebo
340	Oslo	45	6	Control	Placebo	Naloxone
341	Oslo	45	6	Active	Naloxone	Placebo
342	Oslo	46	4	Control	Placebo	Naloxone
343	Oslo	46	4	Active	Naloxone	Placebo
344	Oslo	46	4	Active	Naloxone	Placebo
345	Oslo	46	4	Control	Placebo	Naloxone
346	Oslo	47	8	Active	Naloxone	Placebo
347	Oslo	47	8	Control	Placebo	Naloxone
348	Oslo	47	8	Control	Placebo	Naloxone
349	Oslo	47	8	Active	Naloxone	Placebo
350	Oslo	47	8	Control	Placebo	Naloxone
351	Oslo	47	8	Active	Naloxone	Placebo
352	Oslo	47	8	Control	Placebo	Naloxone
353	Oslo	47	8	Active	Naloxone	Placebo
354	Oslo	48	2	Active	Naloxone	Placebo
355	Oslo	48	2	Control	Placebo	Naloxone
356	Oslo	49	2	Control	Placebo	Naloxone
357	Oslo	49	2	Active	Naloxone	Placebo
358	Oslo	50	4	Active	Naloxone	Placebo
359	Oslo	50	4	Control	Placebo	Naloxone
360	Oslo	50	4	Active	Naloxone	Placebo
361	Oslo	50	4	Control	Placebo	Naloxone
362	Oslo	51	8	Active	Naloxone	Placebo
363	Oslo	51	8	Control	Placebo	Naloxone
364	Oslo	51	8	Control	Placebo	Naloxone
365	Oslo	51	8	Active	Naloxone	Placebo
366	Oslo	51	8	Control	Placebo	Naloxone
367	Oslo	51	8	Active	Naloxone	Placebo
368	Oslo	51	8	Control	Placebo	Naloxone
369	Oslo	51	8	Active	Naloxone	Placebo

370	Oslo	52	2	Control	Placebo	Naloxone
371	Oslo	52	2	Active	Naloxone	Placebo
372	Oslo	53	8	Active	Naloxone	Placebo
373	Oslo	53	8	Control	Placebo	Naloxone
374	Oslo	53	8	Active	Naloxone	Placebo
375	Oslo	53	8	Active	Naloxone	Placebo
376	Oslo	53	8	Control	Placebo	Naloxone
377	Oslo	53	8	Active	Naloxone	Placebo
378	Oslo	53	8	Control	Placebo	Naloxone
379	Oslo	53	8	Control	Placebo	Naloxone
380	Oslo	54	4	Active	Naloxone	Placebo
381	Oslo	54	4	Active	Naloxone	Placebo
382	Oslo	54	4	Control	Placebo	Naloxone
383	Oslo	54	4	Control	Placebo	Naloxone
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385	Oslo	55	8	Active	Naloxone	Placebo
386	Oslo	55	8	Control	Placebo	Naloxone
387	Oslo	55	8	Control	Placebo	Naloxone
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389	Oslo	55	8	Active	Naloxone	Placebo
390	Oslo	55	8	Control	Placebo	Naloxone
391	Oslo	55	8	Control	Placebo	Naloxone
392	Oslo	56	6	Active	Naloxone	Placebo
393	Oslo	56	6	Active	Naloxone	Placebo
394	Oslo	56	6	Control	Placebo	Naloxone
395	Oslo	56	6	Control	Placebo	Naloxone
396	Oslo	56	6	Control	Placebo	Naloxone
397	Oslo	56	6	Active	Naloxone	Placebo
398	Oslo	57	8	Active	Naloxone	Placebo
399	Oslo	57	8	Control	Placebo	Naloxone
400	Oslo	57	8	Control	Placebo	Naloxone
401	Oslo	57	8	Active	Naloxone	Placebo
402	Oslo	57	8	Control	Placebo	Naloxone
403	Oslo	57	8	Active	Naloxone	Placebo

404	Oslo	57	8	Active	Naloxone	Placebo
405	Oslo	57	8	Control	Placebo	Naloxone

randListOslo_extra_numbers

id	stratum	block.id	block.size	treatment	nasal_adm	IM_adm
1406	Oslo	1	2	Active	Naloxone	Placebo
1407	Oslo	1	2	Control	Placebo	Naloxone
1408	Oslo	2	4	Control	Placebo	Naloxone
1409	Oslo	2	4	Active	Naloxone	Placebo
1410	Oslo	2	4	Active	Naloxone	Placebo
1411	Oslo	2	4	Control	Placebo	Naloxone
1412	Oslo	3	8	Control	Placebo	Naloxone
1413	Oslo	3	8	Control	Placebo	Naloxone
1414	Oslo	3	8	Control	Placebo	Naloxone
1415	Oslo	3	8	Active	Naloxone	Placebo
1416	Oslo	3	8	Control	Placebo	Naloxone
1417	Oslo	3	8	Active	Naloxone	Placebo
1418	Oslo	3	8	Active	Naloxone	Placebo
1419	Oslo	3	8	Active	Naloxone	Placebo
1420	Oslo	4	2	Active	Naloxone	Placebo
1421	Oslo	4	2	Control	Placebo	Naloxone
1422	Oslo	5	8	Control	Placebo	Naloxone
1423	Oslo	5	8	Active	Naloxone	Placebo
1424	Oslo	5	8	Active	Naloxone	Placebo
1425	Oslo	5	8	Control	Placebo	Naloxone
1426	Oslo	5	8	Control	Placebo	Naloxone
1427	Oslo	5	8	Active	Naloxone	Placebo
1428	Oslo	5	8	Control	Placebo	Naloxone
1429	Oslo	5	8	Active	Naloxone	Placebo
1430	Oslo	6	4	Active	Naloxone	Placebo
1431	Oslo	6	4	Active	Naloxone	Placebo
1432	Oslo	6	4	Control	Placebo	Naloxone
1433	Oslo	6	4	Control	Placebo	Naloxone
1434	Oslo	7	8	Active	Naloxone	Placebo
1435	Oslo	7	8	Control	Placebo	Naloxone
1436	Oslo	7	8	Active	Naloxone	Placebo
1437	Oslo	7	8	Control	Placebo	Naloxone

1438	Oslo	7	8	Active	Naloxone	Placebo
1439	Oslo	7	8	Active	Naloxone	Placebo
1440	Oslo	7	8	Control	Placebo	Naloxone
1441	Oslo	7	8	Control	Placebo	Naloxone
1442	Oslo	8	6	Control	Placebo	Naloxone
1443	Oslo	8	6	Active	Naloxone	Placebo
1444	Oslo	8	6	Active	Naloxone	Placebo
1445	Oslo	8	6	Control	Placebo	Naloxone
1446	Oslo	8	6	Active	Naloxone	Placebo
1447	Oslo	8	6	Control	Placebo	Naloxone
1448	Oslo	9	4	Control	Placebo	Naloxone
1449	Oslo	9	4	Active	Naloxone	Placebo
1450	Oslo	9	4	Active	Naloxone	Placebo
1451	Oslo	9	4	Control	Placebo	Naloxone
1452	Oslo	10	4	Control	Placebo	Naloxone
1453	Oslo	10	4	Active	Naloxone	Placebo
1454	Oslo	10	4	Control	Placebo	Naloxone
1455	Oslo	10	4	Active	Naloxone	Placebo
1456	Oslo	11	8	Control	Placebo	Naloxone
1457	Oslo	11	8	Control	Placebo	Naloxone
1458	Oslo	11	8	Active	Naloxone	Placebo
1459	Oslo	11	8	Active	Naloxone	Placebo
1460	Oslo	11	8	Control	Placebo	Naloxone
1461	Oslo	11	8	Control	Placebo	Naloxone
1462	Oslo	11	8	Active	Naloxone	Placebo
1463	Oslo	11	8	Active	Naloxone	Placebo
1464	Oslo	12	4	Control	Placebo	Naloxone
1465	Oslo	12	4	Control	Placebo	Naloxone
1466	Oslo	12	4	Active	Naloxone	Placebo
1467	Oslo	12	4	Active	Naloxone	Placebo
1468	Oslo	13	6	Active	Naloxone	Placebo
1469	Oslo	13	6	Control	Placebo	Naloxone
1470	Oslo	13	6	Active	Naloxone	Placebo
1471	Oslo	13	6	Control	Placebo	Naloxone

1472	Oslo	13	6	Active	Naloxone	Placebo
1473	Oslo	13	6	Control	Placebo	Naloxone
1474	Oslo	14	6	Active	Naloxone	Placebo
1475	Oslo	14	6	Control	Placebo	Naloxone
1476	Oslo	14	6	Control	Placebo	Naloxone
1477	Oslo	14	6	Active	Naloxone	Placebo
1478	Oslo	14	6	Active	Naloxone	Placebo
1479	Oslo	14	6	Control	Placebo	Naloxone
1480	Oslo	15	8	Active	Naloxone	Placebo
1481	Oslo	15	8	Control	Placebo	Naloxone
1482	Oslo	15	8	Active	Naloxone	Placebo
1483	Oslo	15	8	Control	Placebo	Naloxone
1484	Oslo	15	8	Control	Placebo	Naloxone
1485	Oslo	15	8	Control	Placebo	Naloxone
1486	Oslo	15	8	Active	Naloxone	Placebo
1487	Oslo	15	8	Active	Naloxone	Placebo
1488	Oslo	16	8	Control	Placebo	Naloxone
1489	Oslo	16	8	Control	Placebo	Naloxone
1490	Oslo	16	8	Active	Naloxone	Placebo
1491	Oslo	16	8	Active	Naloxone	Placebo
1492	Oslo	16	8	Control	Placebo	Naloxone
1493	Oslo	16	8	Active	Naloxone	Placebo
1494	Oslo	16	8	Active	Naloxone	Placebo
1495	Oslo	16	8	Control	Placebo	Naloxone
1496	Oslo	17	8	Active	Naloxone	Placebo
1497	Oslo	17	8	Control	Placebo	Naloxone
1498	Oslo	17	8	Control	Placebo	Naloxone
1499	Oslo	17	8	Active	Naloxone	Placebo
1500	Oslo	17	8	Control	Placebo	Naloxone
1501	Oslo	17	8	Active	Naloxone	Placebo
1502	Oslo	17	8	Control	Placebo	Naloxone
1503	Oslo	17	8	Active	Naloxone	Placebo
1504	Oslo	18	6	Active	Naloxone	Placebo
1505	Oslo	18	6	Active	Naloxone	Placebo

1506	Oslo	18	6	Active	Naloxone	Placebo
1507	Oslo	18	6	Control	Placebo	Naloxone
1508	Oslo	18	6	Control	Placebo	Naloxone
1509	Oslo	18	6	Control	Placebo	Naloxone
1510	Oslo	19	8	Active	Naloxone	Placebo
1511	Oslo	19	8	Control	Placebo	Naloxone
1512	Oslo	19	8	Control	Placebo	Naloxone
1513	Oslo	19	8	Control	Placebo	Naloxone
1514	Oslo	19	8	Active	Naloxone	Placebo
1515	Oslo	19	8	Control	Placebo	Naloxone
1516	Oslo	19	8	Active	Naloxone	Placebo
1517	Oslo	19	8	Active	Naloxone	Placebo
1518	Oslo	20	4	Control	Placebo	Naloxone
1519	Oslo	20	4	Active	Naloxone	Placebo
1520	Oslo	20	4	Control	Placebo	Naloxone
1521	Oslo	20	4	Active	Naloxone	Placebo
1522	Oslo	21	2	Control	Placebo	Naloxone
1523	Oslo	21	2	Active	Naloxone	Placebo
1524	Oslo	22	2	Control	Placebo	Naloxone
1525	Oslo	22	2	Active	Naloxone	Placebo
1526	Oslo	23	6	Active	Naloxone	Placebo
1527	Oslo	23	6	Control	Placebo	Naloxone
1528	Oslo	23	6	Active	Naloxone	Placebo
1529	Oslo	23	6	Active	Naloxone	Placebo
1530	Oslo	23	6	Control	Placebo	Naloxone
1531	Oslo	23	6	Control	Placebo	Naloxone
1532	Oslo	24	4	Control	Placebo	Naloxone
1533	Oslo	24	4	Control	Placebo	Naloxone
1534	Oslo	24	4	Active	Naloxone	Placebo
1535	Oslo	24	4	Active	Naloxone	Placebo
1536	Oslo	25	4	Active	Naloxone	Placebo
1537	Oslo	25	4	Control	Placebo	Naloxone
1538	Oslo	25	4	Control	Placebo	Naloxone
1539	Oslo	25	4	Active	Naloxone	Placebo

1540	Oslo	26	4	Active	Naloxone	Placebo
1541	Oslo	26	4	Control	Placebo	Naloxone
1542	Oslo	26	4	Control	Placebo	Naloxone
1543	Oslo	26	4	Active	Naloxone	Placebo
1544	Oslo	27	6	Active	Naloxone	Placebo
1545	Oslo	27	6	Control	Placebo	Naloxone
1546	Oslo	27	6	Active	Naloxone	Placebo
1547	Oslo	27	6	Control	Placebo	Naloxone
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1549	Oslo	27	6	Control	Placebo	Naloxone
1550	Oslo	28	4	Active	Naloxone	Placebo
1551	Oslo	28	4	Control	Placebo	Naloxone
1552	Oslo	28	4	Active	Naloxone	Placebo
1553	Oslo	28	4	Control	Placebo	Naloxone
1554	Oslo	29	2	Active	Naloxone	Placebo
1555	Oslo	29	2	Control	Placebo	Naloxone
1556	Oslo	30	6	Control	Placebo	Naloxone
1557	Oslo	30	6	Control	Placebo	Naloxone
1558	Oslo	30	6	Control	Placebo	Naloxone
1559	Oslo	30	6	Active	Naloxone	Placebo
1560	Oslo	30	6	Active	Naloxone	Placebo
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1562	Oslo	31	8	Control	Placebo	Naloxone
1563	Oslo	31	8	Control	Placebo	Naloxone
1564	Oslo	31	8	Control	Placebo	Naloxone
1565	Oslo	31	8	Active	Naloxone	Placebo
1566	Oslo	31	8	Active	Naloxone	Placebo
1567	Oslo	31	8	Active	Naloxone	Placebo
1568	Oslo	31	8	Control	Placebo	Naloxone
1569	Oslo	31	8	Active	Naloxone	Placebo
1570	Oslo	32	2	Control	Placebo	Naloxone
1571	Oslo	32	2	Active	Naloxone	Placebo
1572	Oslo	33	8	Active	Naloxone	Placebo
1573	Oslo	33	8	Control	Placebo	Naloxone

1574	Oslo	33	8	Active	Naloxone	Placebo
1575	Oslo	33	8	Control	Placebo	Naloxone
1576	Oslo	33	8	Control	Placebo	Naloxone
1577	Oslo	33	8	Active	Naloxone	Placebo
1578	Oslo	33	8	Control	Placebo	Naloxone
1579	Oslo	33	8	Active	Naloxone	Placebo
1580	Oslo	34	6	Active	Naloxone	Placebo
1581	Oslo	34	6	Control	Placebo	Naloxone
1582	Oslo	34	6	Active	Naloxone	Placebo
1583	Oslo	34	6	Control	Placebo	Naloxone
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1585	Oslo	34	6	Control	Placebo	Naloxone
1586	Oslo	35	4	Active	Naloxone	Placebo
1587	Oslo	35	4	Control	Placebo	Naloxone
1588	Oslo	35	4	Control	Placebo	Naloxone
1589	Oslo	35	4	Active	Naloxone	Placebo
1590	Oslo	36	6	Active	Naloxone	Placebo
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1599	Oslo	37	6	Control	Placebo	Naloxone
1600	Oslo	37	6	Active	Naloxone	Placebo
1601	Oslo	37	6	Control	Placebo	Naloxone
1602	Oslo	38	4	Active	Naloxone	Placebo
1603	Oslo	38	4	Control	Placebo	Naloxone
1604	Oslo	38	4	Active	Naloxone	Placebo
1605	Oslo	38	4	Control	Placebo	Naloxone
1606	Oslo	39	2	Control	Placebo	Naloxone
1607	Oslo	39	2	Active	Naloxone	Placebo

1608	Oslo	40	4	Control	Placebo	Naloxone
1609	Oslo	40	4	Control	Placebo	Naloxone
1610	Oslo	40	4	Active	Naloxone	Placebo
1611	Oslo	40	4	Active	Naloxone	Placebo
1612	Oslo	41	4	Control	Placebo	Naloxone
1613	Oslo	41	4	Active	Naloxone	Placebo
1614	Oslo	41	4	Active	Naloxone	Placebo
1615	Oslo	41	4	Control	Placebo	Naloxone
1616	Oslo	42	2	Active	Naloxone	Placebo
1617	Oslo	42	2	Control	Placebo	Naloxone
1618	Oslo	43	6	Control	Placebo	Naloxone
1619	Oslo	43	6	Control	Placebo	Naloxone
1620	Oslo	43	6	Active	Naloxone	Placebo
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1622	Oslo	43	6	Active	Naloxone	Placebo
1623	Oslo	43	6	Control	Placebo	Naloxone
1624	Oslo	44	2	Active	Naloxone	Placebo
1625	Oslo	44	2	Control	Placebo	Naloxone
1626	Oslo	45	2	Control	Placebo	Naloxone
1627	Oslo	45	2	Active	Naloxone	Placebo
1628	Oslo	46	6	Control	Placebo	Naloxone
1629	Oslo	46	6	Active	Naloxone	Placebo
1630	Oslo	46	6	Control	Placebo	Naloxone
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1632	Oslo	46	6	Control	Placebo	Naloxone
1633	Oslo	46	6	Active	Naloxone	Placebo
1634	Oslo	47	2	Control	Placebo	Naloxone
1635	Oslo	47	2	Active	Naloxone	Placebo
1636	Oslo	48	2	Active	Naloxone	Placebo
1637	Oslo	48	2	Control	Placebo	Naloxone
1638	Oslo	49	2	Active	Naloxone	Placebo
1639	Oslo	49	2	Control	Placebo	Naloxone
1640	Oslo	50	2	Control	Placebo	Naloxone
1641	Oslo	50	2	Active	Naloxone	Placebo

1642	Oslo	51	2	Control	Placebo	Naloxone
1643	Oslo	51	2	Active	Naloxone	Placebo
1644	Oslo	52	4	Control	Placebo	Naloxone
1645	Oslo	52	4	Active	Naloxone	Placebo
1646	Oslo	52	4	Control	Placebo	Naloxone
1647	Oslo	52	4	Active	Naloxone	Placebo
1648	Oslo	53	4	Active	Naloxone	Placebo
1649	Oslo	53	4	Control	Placebo	Naloxone
1650	Oslo	53	4	Control	Placebo	Naloxone
1651	Oslo	53	4	Active	Naloxone	Placebo
1652	Oslo	54	6	Active	Naloxone	Placebo
1653	Oslo	54	6	Active	Naloxone	Placebo
1654	Oslo	54	6	Control	Placebo	Naloxone
1655	Oslo	54	6	Control	Placebo	Naloxone
1656	Oslo	54	6	Active	Naloxone	Placebo
1657	Oslo	54	6	Control	Placebo	Naloxone
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1659	Oslo	55	6	Active	Naloxone	Placebo
1660	Oslo	55	6	Control	Placebo	Naloxone
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1662	Oslo	55	6	Control	Placebo	Naloxone
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1664	Oslo	56	4	Active	Naloxone	Placebo
1665	Oslo	56	4	Active	Naloxone	Placebo
1666	Oslo	56	4	Control	Placebo	Naloxone
1667	Oslo	56	4	Control	Placebo	Naloxone
1668	Oslo	57	8	Control	Placebo	Naloxone
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1670	Oslo	57	8	Control	Placebo	Naloxone
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1672	Oslo	57	8	Control	Placebo	Naloxone
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1674	Oslo	57	8	Active	Naloxone	Placebo
1675	Oslo	57	8	Control	Placebo	Naloxone

1676	Oslo	58	6	Control	Placebo	Naloxone
1677	Oslo	58	6	Control	Placebo	Naloxone
1678	Oslo	58	6	Control	Placebo	Naloxone
1679	Oslo	58	6	Active	Naloxone	Placebo
1680	Oslo	58	6	Active	Naloxone	Placebo
1681	Oslo	58	6	Active	Naloxone	Placebo
1682	Oslo	59	2	Active	Naloxone	Placebo
1683	Oslo	59	2	Control	Placebo	Naloxone
1684	Oslo	60	2	Control	Placebo	Naloxone
1685	Oslo	60	2	Active	Naloxone	Placebo
1686	Oslo	61	6	Active	Naloxone	Placebo
1687	Oslo	61	6	Control	Placebo	Naloxone
1688	Oslo	61	6	Control	Placebo	Naloxone
1689	Oslo	61	6	Active	Naloxone	Placebo
1690	Oslo	61	6	Active	Naloxone	Placebo
1691	Oslo	61	6	Control	Placebo	Naloxone
1692	Oslo	62	2	Control	Placebo	Naloxone
1693	Oslo	62	2	Active	Naloxone	Placebo
1694	Oslo	63	8	Control	Placebo	Naloxone
1695	Oslo	63	8	Active	Naloxone	Placebo
1696	Oslo	63	8	Control	Placebo	Naloxone
1697	Oslo	63	8	Active	Naloxone	Placebo
1698	Oslo	63	8	Active	Naloxone	Placebo
1699	Oslo	63	8	Control	Placebo	Naloxone
1700	Oslo	63	8	Control	Placebo	Naloxone
1701	Oslo	63	8	Active	Naloxone	Placebo
1702	Oslo	64	8	Control	Placebo	Naloxone
1703	Oslo	64	8	Control	Placebo	Naloxone
1704	Oslo	64	8	Active	Naloxone	Placebo
1705	Oslo	64	8	Active	Naloxone	Placebo
1706	Oslo	64	8	Active	Naloxone	Placebo
1707	Oslo	64	8	Active	Naloxone	Placebo
1708	Oslo	64	8	Control	Placebo	Naloxone
1709	Oslo	64	8	Control	Placebo	Naloxone

randListTrondheim

id	stratum	block.id	block.size	treatment	nasal_adm	IM_adm
500	Trondheim	1	4	Control	Placebo	Naloxone
501	Trondheim	1	4	Active	Naloxone	Placebo
502	Trondheim	1	4	Control	Placebo	Naloxone
503	Trondheim	1	4	Active	Naloxone	Placebo
504	Trondheim	2	6	Active	Naloxone	Placebo
505	Trondheim	2	6	Control	Placebo	Naloxone
506	Trondheim	2	6	Control	Placebo	Naloxone
507	Trondheim	2	6	Active	Naloxone	Placebo
508	Trondheim	2	6	Active	Naloxone	Placebo
509	Trondheim	2	6	Control	Placebo	Naloxone
510	Trondheim	3	8	Control	Placebo	Naloxone
511	Trondheim	3	8	Control	Placebo	Naloxone
512	Trondheim	3	8	Control	Placebo	Naloxone
513	Trondheim	3	8	Active	Naloxone	Placebo
514	Trondheim	3	8	Active	Naloxone	Placebo
515	Trondheim	3	8	Control	Placebo	Naloxone
516	Trondheim	3	8	Active	Naloxone	Placebo
517	Trondheim	3	8	Active	Naloxone	Placebo
518	Trondheim	4	4	Control	Placebo	Naloxone
519	Trondheim	4	4	Control	Placebo	Naloxone
520	Trondheim	4	4	Active	Naloxone	Placebo
521	Trondheim	4	4	Active	Naloxone	Placebo
522	Trondheim	5	2	Control	Placebo	Naloxone
523	Trondheim	5	2	Active	Naloxone	Placebo
524	Trondheim	6	2	Active	Naloxone	Placebo
525	Trondheim	6	2	Control	Placebo	Naloxone
526	Trondheim	7	2	Control	Placebo	Naloxone
527	Trondheim	7	2	Active	Naloxone	Placebo
528	Trondheim	8	2	Active	Naloxone	Placebo
529	Trondheim	8	2	Control	Placebo	Naloxone
530	Trondheim	9	6	Control	Placebo	Naloxone
531	Trondheim	9	6	Control	Placebo	Naloxone

532	Trondheim	9	6	Active	Naloxone	Placebo
533	Trondheim	9	6	Active	Naloxone	Placebo
534	Trondheim	9	6	Active	Naloxone	Placebo
535	Trondheim	9	6	Control	Placebo	Naloxone
536	Trondheim	10	4	Active	Naloxone	Placebo
537	Trondheim	10	4	Control	Placebo	Naloxone
538	Trondheim	10	4	Active	Naloxone	Placebo
539	Trondheim	10	4	Control	Placebo	Naloxone
540	Trondheim	11	6	Active	Naloxone	Placebo
541	Trondheim	11	6	Active	Naloxone	Placebo
542	Trondheim	11	6	Control	Placebo	Naloxone
543	Trondheim	11	6	Control	Placebo	Naloxone
544	Trondheim	11	6	Active	Naloxone	Placebo
545	Trondheim	11	6	Control	Placebo	Naloxone
546	Trondheim	12	2	Control	Placebo	Naloxone
547	Trondheim	12	2	Active	Naloxone	Placebo
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549	Trondheim	13	6	Control	Placebo	Naloxone
550	Trondheim	13	6	Active	Naloxone	Placebo
551	Trondheim	13	6	Active	Naloxone	Placebo
552	Trondheim	13	6	Control	Placebo	Naloxone
553	Trondheim	13	6	Control	Placebo	Naloxone
554	Trondheim	14	4	Active	Naloxone	Placebo
555	Trondheim	14	4	Active	Naloxone	Placebo
556	Trondheim	14	4	Control	Placebo	Naloxone
557	Trondheim	14	4	Control	Placebo	Naloxone
558	Trondheim	15	4	Active	Naloxone	Placebo
559	Trondheim	15	4	Active	Naloxone	Placebo
560	Trondheim	15	4	Control	Placebo	Naloxone
561	Trondheim	15	4	Control	Placebo	Naloxone
562	Trondheim	16	4	Control	Placebo	Naloxone
563	Trondheim	16	4	Control	Placebo	Naloxone
564	Trondheim	16	4	Active	Naloxone	Placebo
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566	Trondheim	17	4	Active	Naloxone	Placebo
567	Trondheim	17	4	Control	Placebo	Naloxone
568	Trondheim	17	4	Control	Placebo	Naloxone
569	Trondheim	17	4	Active	Naloxone	Placebo
570	Trondheim	18	2	Active	Naloxone	Placebo
571	Trondheim	18	2	Control	Placebo	Naloxone
572	Trondheim	19	4	Control	Placebo	Naloxone
573	Trondheim	19	4	Active	Naloxone	Placebo
574	Trondheim	19	4	Active	Naloxone	Placebo
575	Trondheim	19	4	Control	Placebo	Naloxone
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578	Trondheim	21	2	Active	Naloxone	Placebo
579	Trondheim	21	2	Control	Placebo	Naloxone
580	Trondheim	22	6	Active	Naloxone	Placebo
581	Trondheim	22	6	Control	Placebo	Naloxone
582	Trondheim	22	6	Control	Placebo	Naloxone
583	Trondheim	22	6	Active	Naloxone	Placebo
584	Trondheim	22	6	Control	Placebo	Naloxone
585	Trondheim	22	6	Active	Naloxone	Placebo
586	Trondheim	23	2	Control	Placebo	Naloxone
587	Trondheim	23	2	Active	Naloxone	Placebo
588	Trondheim	24	2	Active	Naloxone	Placebo
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592	Trondheim	25	4	Active	Naloxone	Placebo
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594	Trondheim	26	4	Active	Naloxone	Placebo
595	Trondheim	26	4	Control	Placebo	Naloxone
596	Trondheim	26	4	Control	Placebo	Naloxone
597	Trondheim	26	4	Active	Naloxone	Placebo
598	Trondheim	27	6	Control	Placebo	Naloxone
599	Trondheim	27	6	Control	Placebo	Naloxone

600	Trondheim	27	6	Active	Naloxone	Placebo
601	Trondheim	27	6	Active	Naloxone	Placebo
602	Trondheim	27	6	Control	Placebo	Naloxone
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604	Trondheim	28	4	Active	Naloxone	Placebo
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622	Trondheim	31	6	Active	Naloxone	Placebo
623	Trondheim	31	6	Control	Placebo	Naloxone
624	Trondheim	31	6	Active	Naloxone	Placebo
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632	Trondheim	33	8	Active	Naloxone	Placebo
633	Trondheim	33	8	Active	Naloxone	Placebo

634	Trondheim	33	8	Control	Placebo	Naloxone
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636	Trondheim	33	8	Control	Placebo	Naloxone
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646	Trondheim	36	4	Active	Naloxone	Placebo
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665	Trondheim	40	4	Control	Placebo	Naloxone
666	Trondheim	40	4	Control	Placebo	Naloxone
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668	Trondheim	41	4	Active	Naloxone	Placebo
669	Trondheim	41	4	Active	Naloxone	Placebo
670	Trondheim	41	4	Control	Placebo	Naloxone
671	Trondheim	41	4	Control	Placebo	Naloxone
672	Trondheim	42	2	Control	Placebo	Naloxone
673	Trondheim	42	2	Active	Naloxone	Placebo
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675	Trondheim	43	8	Active	Naloxone	Placebo
676	Trondheim	43	8	Active	Naloxone	Placebo
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678	Trondheim	43	8	Control	Placebo	Naloxone
679	Trondheim	43	8	Control	Placebo	Naloxone
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681	Trondheim	43	8	Control	Placebo	Naloxone
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683	Trondheim	44	6	Active	Naloxone	Placebo
684	Trondheim	44	6	Control	Placebo	Naloxone
685	Trondheim	44	6	Control	Placebo	Naloxone
686	Trondheim	44	6	Active	Naloxone	Placebo
687	Trondheim	44	6	Active	Naloxone	Placebo
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689	Trondheim	45	6	Control	Placebo	Naloxone
690	Trondheim	45	6	Active	Naloxone	Placebo
691	Trondheim	45	6	Control	Placebo	Naloxone
692	Trondheim	45	6	Active	Naloxone	Placebo
693	Trondheim	45	6	Control	Placebo	Naloxone
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695	Trondheim	46	2	Control	Placebo	Naloxone
696	Trondheim	47	8	Control	Placebo	Naloxone
697	Trondheim	47	8	Control	Placebo	Naloxone
698	Trondheim	47	8	Control	Placebo	Naloxone
699	Trondheim	47	8	Active	Naloxone	Placebo
700	Trondheim	47	8	Control	Placebo	Naloxone
701	Trondheim	47	8	Active	Naloxone	Placebo

702	Trondheim	47	8	Active	Naloxone	Placebo
703	Trondheim	47	8	Active	Naloxone	Placebo
704	Trondheim	48	2	Control	Placebo	Naloxone
705	Trondheim	48	2	Active	Naloxone	Placebo
706	Trondheim	49	8	Active	Naloxone	Placebo
707	Trondheim	49	8	Active	Naloxone	Placebo
708	Trondheim	49	8	Control	Placebo	Naloxone
709	Trondheim	49	8	Control	Placebo	Naloxone
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713	Trondheim	49	8	Control	Placebo	Naloxone
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715	Trondheim	50	8	Control	Placebo	Naloxone
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718	Trondheim	50	8	Active	Naloxone	Placebo
719	Trondheim	50	8	Control	Placebo	Naloxone
720	Trondheim	50	8	Control	Placebo	Naloxone
721	Trondheim	50	8	Active	Naloxone	Placebo
722	Trondheim	51	6	Control	Placebo	Naloxone
723	Trondheim	51	6	Active	Naloxone	Placebo
724	Trondheim	51	6	Control	Placebo	Naloxone
725	Trondheim	51	6	Active	Naloxone	Placebo
726	Trondheim	51	6	Active	Naloxone	Placebo
727	Trondheim	51	6	Control	Placebo	Naloxone
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731	Trondheim	52	6	Control	Placebo	Naloxone
732	Trondheim	52	6	Control	Placebo	Naloxone
733	Trondheim	52	6	Active	Naloxone	Placebo
734	Trondheim	53	6	Control	Placebo	Naloxone
735	Trondheim	53	6	Active	Naloxone	Placebo

736	Trondheim	53	6	Active	Naloxone	Placebo
737	Trondheim	53	6	Active	Naloxone	Placebo
738	Trondheim	53	6	Control	Placebo	Naloxone
739	Trondheim	53	6	Control	Placebo	Naloxone
740	Trondheim	54	4	Control	Placebo	Naloxone
741	Trondheim	54	4	Control	Placebo	Naloxone
742	Trondheim	54	4	Active	Naloxone	Placebo
743	Trondheim	54	4	Active	Naloxone	Placebo
744	Trondheim	55	8	Active	Naloxone	Placebo
745	Trondheim	55	8	Control	Placebo	Naloxone
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747	Trondheim	55	8	Control	Placebo	Naloxone
748	Trondheim	55	8	Control	Placebo	Naloxone
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750	Trondheim	55	8	Control	Placebo	Naloxone
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761	Trondheim	58	4	Active	Naloxone	Placebo
762	Trondheim	58	4	Control	Placebo	Naloxone
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768	Trondheim	59	6	Control	Placebo	Naloxone
769	Trondheim	59	6	Active	Naloxone	Placebo

770	Trondheim	60	2	Active	Naloxone	Placebo
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772	Trondheim	61	6	Active	Naloxone	Placebo
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774	Trondheim	61	6	Control	Placebo	Naloxone
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776	Trondheim	61	6	Active	Naloxone	Placebo
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778	Trondheim	62	2	Active	Naloxone	Placebo
779	Trondheim	62	2	Control	Placebo	Naloxone
780	Trondheim	63	4	Control	Placebo	Naloxone
781	Trondheim	63	4	Active	Naloxone	Placebo
782	Trondheim	63	4	Active	Naloxone	Placebo
783	Trondheim	63	4	Control	Placebo	Naloxone
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796	Trondheim	67	8	Active	Naloxone	Placebo
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798	Trondheim	67	8	Control	Placebo	Naloxone
799	Trondheim	67	8	Control	Placebo	Naloxone
800	Trondheim	67	8	Control	Placebo	Naloxone
801	Trondheim	67	8	Active	Naloxone	Placebo
802	Trondheim	67	8	Control	Placebo	Naloxone
803	Trondheim	67	8	Active	Naloxone	Placebo

16.1.8 Audit certificates

Monitoring plan NINA-1

Abbreviation or special term	Explanation
AE	Adverse Event
CRF	Case Report Form
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product
ISF	Investigator's Site File
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

16.1.8 Audit certificates

1. Protocol title

NTNU INTRANASAL NALOXONE TRIAL
Double blinded, double dummy, randomized controlled trial of intranasal naloxone for pre hospital use

Short title: NINA-1

EudraCT number: 2016-004072-22

2. Monitoring conditions

The monitoring plan is based on NorCRIN's SOPs and risk assessment version 2.0.
The monitoring plan has been written in cooperation with the national coordinating investigator, who is responsible for the plan.

This monitoring plan describes the extent of the monitoring activities that will be performed by monitors.

On-site monitoring visits will be documented in NorCRIN monitoring reports adapted to the different types of visits (initiation, monitoring, and close-out). Norwegian templates will be used.

Patient specific issues found by monitoring (based on review of eCRF data or worksheets) will be documented by queries in the eCRF, and in the monitoring report.

3. Monitoring activities

3.1. Initiation

An initiation visit should take place at each site before the enrolment of trial subjects. When all requirements at a site are met, the sponsor will be notified that the site is ready to start the inclusion (via the initiation monitoring report or other applicable documentation).

Monitor will check that the study documents are stored in a restricted access area, and that there is a training log for the study workers.

Monitor will check storage location of the medical kits that they are stored in a cabinet containing the "Email for whistle- blowers" clearly visible.
This will be made a note of in the initiation report.
Monitor will also check that there is an established place for return of medical kits.

3.2. During the study

The first monitoring visit will be scheduled after inclusion of three trial subjects, at each participating study centre. The study centre will inform their monitor when three trial subjects are included.

A minimum of 1 visit per year to each site is required so long as the site has included new trial subjects during this year. The monitoring frequency may increase in case of high trial subject recruitment, poor quality of data or other risk factors. Any increase of the monitoring frequency will be discussed with the national coordinating investigator.

Monitoring should take into account the DMSC feasibility analysis:
After 100 included study subjects.

3.3. Close-out visit

After the last study subject is included and all eCRFs are completed, a close-out monitoring visit should take place at each site. The close-out visit may be combined with the last regular monitoring visit if applicable.

4. Monitoring of general protocol compliance and data quality

The monitor will verify the compliance to study protocol and study specific procedures.

Adherence to protocol
The first patient included at each site, as well as one randomly selected patient per site per year, will be fully monitored. Randomization will be performed online at www.random.org.

Further SDV will be specified under section 5.

5. Description of monitoring activities related to a risk based assessment

5.1. Training

Monitor will check:

- That the investigators in the study have completed GCP training and that they have received adequate training in allocated study specific tasks and procedures.
- That the study workers' service number is listed as "completed" in the NAKOs training database.

5.2. Trial subject's rights and safety

For all included study subjects, monitor will check:

- That the information noted regarding informed consent matches the information on the study form, and that the study workers' service number is listed on the training log.
- That each study subject has a folder containing
  - Ambulance journal
  - Study form (4 pages)
  - AE form
  - AMIS-report
- If a patient has withdrawn from the study, the monitor will check that all data registered in Viedoc has been deleted.

5.3. Data

SDV will be performed for all patients for the following:

- The patient's return of spontaneous respiration
- That the kit number entered in Viedoc is in accordance with the number written on all study documents
- That end of treatment matches what is listed in the ambulance journal and AMIS-report
- If rescue medication is given and registered correctly

The data management plan will specify further edit checks included in the database.

5.4. Protocol procedures

Not applicable.

5.5. Study drug/IMP

Monitor will check:

- That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.
- That the use and return of the investigational products at the trial sites are controlled and documented adequately.
- That compliance data entered in the eCRF are consistent with the drug accountability log.
- That the disposing of unused investigational products at the trial sites complies with the protocol.

5.6. Safety management

Monitor will check:

- Registration and reporting of SAEs according to the protocol with SDV for all trial subjects.
- That all SAE reports are consistent with the source documents and are reported to the sponsor in a timely manner.
- At sponsor site, that SUSARs have been reported and that annual safety reports are sent to the authority as required.

5.7. Organisation of trial

The ISF/TMF will be checked for completeness during the initiation visit and the close out visit. During regular monitoring visits monitor will check:

- the inclusion and exclusion log
- drug accountability log
- the NAKOs training log

6. Other monitoring related activities

Not applicable.

7. Monitoring of national and site specific conditions

Not applicable.

8. Evaluation of the monitoring plan

The monitor will assess whether the monitoring plan is appropriate for each specific site after each monitoring visit. The assessment will be included in the monitoring report. The national coordinating investigator must then evaluate the need for an update of the monitoring plan.

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9. Reports

The report is a summary of all relevant findings and will specify issues to be resolved by the site. Finalized reports will be sent to specify to whom and when to send the reports, e.g. sponsor, investigator or data manager:

- Local PI
- National coordinating investigator

All findings must be resolved within two months after receiving the monitoring report.

If findings are not closed and there is no plan for closing, the issue management procedure, "Lukking av avvik" (www.norcrin.no) will be followed.

10. Signatures

The following monitoring plan is approved by both parties and will apply until amended.

22/5-18 _____
Date National coordinating investigator (sponsor)

22 MAY 2018 _____
Date National monitor

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11. Monitoring plan appendixes

11.1. Monitoring plan summary

Norwegian NorCRIN templates for initiation, monitoring and close-out visits will be used for the monitoring of NINA-1

initiation:
Storage of documents:

- Restricted access area
- Training log for study workers exist
- Initial storage location of study drug kits
- Easily accessible email for whistleblowers
- Established place for returning study medication kits
- TMF/ISF

First monitoring visit:
Will take place after the inclusion of the 3rd study subject

- First patient at each study site will be fully monitored

Following monitoring visits:
At minimum once a year as long as the site is recruiting, also taking into account the DMSC feasibility analyses after 100 inclusions.

- Fully monitor one study subject, randomly chosen using www.random.org
- Registration and reporting of SAEs according to the protocol with SDV for all trial subjects.
- That all SAE reports are consistent with the source documents and are reported to the sponsor in a timely manner.
- At sponsor site, that SUSARs have been reported and that annual safety reports are sent to the authority as required.
- That the information noted regarding informed consent matches the information on the study form, and that the study workers' service number is listed on the training log.
- That each study subject has a folder containing
  - Ambulance journal
  - Study form (4 pages)
  - AE form
  - AMIS-report
- If a patient has withdrawn from the study, the monitor will check that all data registered in Viedoc has been deleted.
- The patient's return of spontaneous respiration
- That the kit number entered in Viedoc is in accordance with the number written on all study documents
- That end of treatment matches what is listed in the ambulance journal and AMIS-report
- If rescue medication is given and registered correctly

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Study drugs:

- That storage times and conditions for study drugs are acceptable, and that supplies are sufficient throughout the trial.
- That the use and return of the investigational products at the trial sites are controlled and documented adequately.
- That compliance data entered in the CRF are consistent with the drug accountability log.
- That the disposing of unused investigational products at the trial sites complies with the protocol.

TMF/ISF:

- Study workers have completed the NAKOs training database
- the inclusion and exclusion log
- drug accountability log
- the NAKOs training log

Close Out-visit:

When inclusion is completed.
TMF/ISF will be checked for completeness.

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INITIERINGSRAPPORT MONITORERING

Protokoll	**NINA-1**	**Dato for besøk**	**01.06 2018**
Studiesenter	**Ullevål & legevakt**	**EudraCT nr.**	**2016-004072-22**
Hovedutprøver	**Anne-Cathrine Braarud/Arne Skulberg**	**Rapport nr.**	**1, initiering**

	Navn				**Rolle**
Studiepersonell til stede	Arne Skulberg Anne-Cathrine Braarud Tore Skålhegg				Utprøver Hovedutprøver Koordinator
Monitorering	**På studiesenter**	**X**	**Per telefon**		
Monitor(er)	Mariann Friis-Ottessen				

1. Essensielle dokumenter		**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
1.1	Er protokoll og ev. protokolltillegg signert og datert av sponsor og hovedutprøver?	X			
1.2	Er en Investigator Site File (ISF) eller en Trial Master File (TMF), etablert og oppdatert?	X			

2. Godkjenninger		**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
2.1	• Interne godkjenninger	X			
	• REK	X			
	• SLV	X			
	• Andre (f. eks. Hdir)	X			
2.2	Er dette senteret omfattet av godkjenningene?	X			

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INITIERINGSRAPPORT MONITORERING

3. Versjonsoversikt

3.1 REKs godkjenning:

Protokoll og protokollendringer (versjon og dato)	Versjon 3.0 09.01 2018		
Godkjent dato (dato-måned-år)	05.02 2018		
Informasjonsskriv/samtykke (versjon og dato)	Ingen samtykke i studien		
Godkjent dato (dato-måned-år)			

3.2 SLVs godkjenning:

Protokoll og protokollendringer (versjon og dato)	Versjon 3.0 09.01 2018		
Godkjent dato (dato-måned-år)	12.01 2018		

Protokoll:
Versjon 3.0 er den første godkjente protokollen i studien.

Samtykke:
Det er ikke informasjonsskriv og samtykkeskjema i studien
Deltakere blir inkludert, og kan aktivt trekke samtykket.
Det er opprettet nettside og telefonnummer for dette, og monitor får epost dersom noen skulle trekke samtykke

4. Ekstern registrering		Ja	Nei	Ikke relevant	Ikke sjekket
4.1	Hos sponsor, er prosjektet registrert i ClinicalTrials.gov eller lignende?	X			
4.2	Hos nasjonal koordinerende utprøver (NKU) er prosjektet registrert på kliniskestudier.HelseNorge.no?		X		

4.1: Oppdatert til aktiv rekruttering ved begge studiesites
4.2: Studien er forsøkt registrert i helsenorge, men utprøver får ikke gjennomslag for dette ved OUS da sponsor er ved St.Olav. dokumentasjon foreligger.

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INITIERINGSRAPPORT MONITORERING

5. Studiepersonell		Ja	Nei	Ikke relevant	Ikke sjekket
5.1	Er delegeringslogg fylt ut og signert?	X			
5.2	Foreligger signert og datert CV fra sentrale medarbeidere?	X			
5.3	Har sentrale medarbeidere dokumenterte ICH-GCP-kunnskaper?	X			
5.4	Har studiepersonellet fått opplæring i protokoll, føring av CRF og gjennomføring av studien?	X			

5.1-5.2: Delegeringslogg og treningslogg for ambulansepersonell er opprettet, fylt ut og signert,
5.3: Ambulansepersonell skal ikke ha CV i studieperm. Det finnes CV for andre studiedeltakere
5.4: Sertifisering av ambulansepersonell skal dokumenteres i en treningsdatabase (NAKO?) og i en papir-logg
Det er også laget en mulighet til å registrere om en studiemedarbeider mister delegering

6. Ressurser		Ja	Nei	Ikke relevant	Ikke sjekket
6.1	Har avdelingen(e) de nødvendige ressurser for gjennomføring av studien?	X			

7. Avtaler		Ja	Nei	Ikke relevant	Ikke sjekket
7.1	Foreligger det avtaler mellom sykehus og sponsor, og/eller andre?	X			
7.2	Er det inngått avtale med et laboratorium?			X	
7.3	Er det inngått avtale med et apotek?	X			
7.4	Er det inngått avtale med et legemiddelfirma?	X			
7.5	Er forsikring (via Legemiddelansvarsforeningen, LAF) tegnet?	X			

7.5: LAF 2018
Det finnes avtale mellom sponsor og AMK, angående studietelefon (24timers bemanning)

8. Fasiliteter og utstyr (ekskl. laboratoriet)		Ja	Nei	Ikke relevant	Ikke sjekket
8.1	Er fasiliteter/utstyr på avdelingen(e) hensiktsmessige for gjennomføringen av studien?	X			
8.2	Er det utarbeidet retningslinjer for bruk, ev. vedlikeholdsavtaler?	X			
8.3	Er utstyret oppdatert og kalibrert/validert?	X			
8.4	Er forskningsbiobanker forsvarlig oppbevart?			X	

8.1-8.3: sykehusavdeling med full daglig drift, og underlagt sykehusets avtaler om vedlikehold og drift.

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INITIERINGSRAPPORT MONITORERING

9. Laboratorieprøver		Ja	Nei	Ikke relevant	Ikke sjekket
9.1	Er nødvendig lab. utstyr, personell og fasiliteter på plass?	X			
9.2	Er prosedyrer for håndtering, oppbevaring og ev. forsendelse av laboratorieprøver etablert?			X	
9.3	Finnes det akkreditering/ekstern kvalitetskontroll for aktuelle analyser?			X	
9.4	Finnes det referanseverdier for relevante undersøkelser?			X	
9.5	Skal laboratorieprøver sendes til andre laboratorier?		X		

10. Forsøkspersonene		Ja	Nei	Ikke relevant	Ikke sjekket
10.1	Er forsøkspersonene pasienter med egen journal?	X			
10.2	Vil journalnotat skrives for hvert studiebesøk?	X			
10.3	Er screeningliste opprettet?	X			
10.4	Er deltakerliste opprettet?	X			
10.5	Er studiepersonell informert om at forsøkspersonene skal ha kopi av hele informasjonsskjemaet med underskrevet samtykkeerklæring, og at originalen skal lagres i ISF?			X	
10.6	Er studiepersonell informert om at ingen studiespesifikke prosedyrer kan gjennomføres før samtykkeerklæring er innhentet?			X	

10.1-10.2: Det føres opplysninger er ambulansejournal og AMIS-rapporter
10.3-10.4: Det finnes en inklusjonslogg og en eksklusjonslogg for studien, ikke screeninglogg
10.5-10.6: Det er ikke informasjonsskriv og signert samtykke for studien.
Det vil deles ut en enkel informasjon (1side) til alle som inkluderes i studien, med adresse/telefonnummer for aktiv utmeldelse.
Muntlig samtykke skal dokumenteres av to studiemedarbeidere

11. Utprøvingspreparat(er)		Ja	Nei	Ikke relevant	Ikke sjekket
11.1	Foreligger nyeste utgave av IB eller SmPC?	X			
11.2	Er randomiseringen beskrevet?	X			
11.3	Er avblindingsprosedyre beskrevet?	X			
11.4	Finnes prosedyrer for mottakelse, håndtering, oppbevaring og destruksjon av utprøvingspreparat(ene)?	X			
11.5	Oppbevares utprøvingspreparat(er) korrekt iht. merking/pakningsvedlegg?	X			
11.6	Føres temperaturlogg?	X			
11.7	Er prosedyrer for legemiddelregnskap etablert for hver forsøksperson og samlet for hvert studiesenter?	X			
11.8	Oppbevares utprøvingspreparat(er) på avdelingen?	X			
11.9	Foreligger et eksempel på merking av utprøvingspreparat(er)?	X			

11.1: IB for Naloxon nesespray, og SmPC for intramuskulær komparator, og en IMPD for spray uten aktiv substans
11.4-11.5: Det er laget studiespesifikke prosedyrer og SOP-er
11.6: Alle studiemedisin-kit er utstyrt med frost-indikator, beskrevet i protokoll, godkjent av SLV

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11.8: Det er opprettet eget medisinskap ved ambulansesentral, der studiemedisin oppbevares før det tas med i studie-aktiv ambulanse. Det er også opprettet system for retur av studiemedisin
Det er opprettet legemiddelregnskap for mottak av studiemedisiner fra Trondheim til hovedlager i Oslo, eget til utlevert til ambulansesentral, og videre til aktiv studie-ambulanse. Eget regnskap for retur.

12. CRF		Ja	Nei	Ikke relevant	Ikke sjekket
12.1	Er utfyllbare CRF-er tilgjengelige? Ev. spesifiser versjon.	X			
12.2	Ligger en kopi av CRF-en i Investigator Site File/Trial Master File?		X		
12.3	Oppbevares aktive CRF-er på et sted med begrenset tilgang?	X			
12.4	Er studiepersonell informert om prosedyre for innsendelse av CRF?			X	

12.1: Studien bruker Viedoc, med datahåndterer ved CTU
12.2: Datahåndterer sender en PDF-versjon av annotert eCRF

13. Kildedokumentasjon		Ja	Nei	Ikke relevant	Ikke sjekket
13.1	Er kildedataoversikt laget?	X			

Noen punkter i kildedataliste har dobbeltkryss. Dette beskrives i kommentarfelt, slik at det alltid er mulig å identifisere kilde

14. Håndtering av alvorlige hendelser SAE/SUSAR		Ja	Nei	Ikke relevant	Ikke sjekket
14.1	Er studiepersonell informert om SAE-registrering og rapportering til sponsor?	X			
14.2	Er senteret (sponsor) informert om sikkerhetsrapportering (SUSAR og årsrapport) til SLV?	X			

14.2: Husk at årsrapport til SLV skal sendes 1 år etter dato for første godkjenning av studie.

15. Arkivering		Ja	Nei	Ikke relevant	Ikke sjekket
15.1	Er plan for arkivering og lagring av studiedokumenter, inkludert deltakerliste beskrevet?				

Langtidslagring etter studieslutt: Følger OUS-prosedyrer
Lagring igjennom studiens forløp: studien har eget arkivskap med nøkkel og kodelås.

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INITIERINGSRAPPORT MONITORERING

16. Monitorering		Ja	Nei	Ikke relevant	Ikke sjekket
16.1	Foreligger avtale om monitorering av studien?	X			
16.2	Foreligger monitoreringsplan?	X			

17. Status		Ja	Nei	Ikke relevant	Ikke sjekket
17.1	Kan inklusjon av forsøkspersoner starte?	X			

Alle studiens godkjenninger, logger og lister er på plass.
Studiesenter klareres for inklusjon muntlig ved initieringsbesøket.
Inklusjon av første pasient kan skje før initieringsrapporten er sendt og signert.

18. Oppgaver til oppfølging

Dato	Oppgave	Tidsfrist	Ansvar	Utført

Kommentar:

19. Underskrifter

Rapporten er skrevet av:

Mariann Friis-Olsen — Monitor

1/6 -18 — Dato

Som hovedutprøver har jeg lest rapporten og tar ansvar for å følge opp mangler.

Anne-Cathrine Braarud — Hovedutprøver

1/6-18 — Dato

Sponsor / nasjonal koordinerende utprøver — Dato

Et signert eksemplar skal arkiveres i ISF, et signert eksemplar oppbevares hos til sponsor, et signert eksemplar oppbevares av monitor.

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MONITORERINGSRAPPORT

Protokoll	**NINA-1**	**Dato for besøk**	**02.07 2018**
Studiesenter	**OUS**	**EudraCT nr.**	**2016-004072-22**
Hovedutprøver	**Anne-Cathrine Braarud / Arne Skulberg**	**Rapport nr.**	**2**

	Navn				**Rolle**
Studiepersonell til stede	Arne Skulberg Tore Skålhegg				Utprøver Koordinator
Monitorering utført (kryss av)	**På studiesenter**	X	**Per telefon**		
Monitor	Mariann Friis-Ottessen / Kristina Schee				

1. Forsøksperson status	**Siden oppstart**	**Siden siste besøk**		**Siden oppstart**	**Siden siste besøk**
Planlagt inkludert:	200		Pågående:	-	
Screenet:	58		Utgått etter inklusjon/ randomisering:	3	
Inkludert/randomisert til nå:	14		Fullført:	11	
Utgått før inklusjon/ randomisering	58-14	-			

Ingen pasienter er pågående i studien. Det er kun ett besøk.

2. Monitoreringsplan		**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
2.1	Er monitoreringsplanen til studien fulgt ved dette monitoreringsbesøket?	X			
2.2	Er alle avvik fra forrige monitoreringsbesøk rettet opp?			X	
2.3	Bør monitoreringsplanen revideres for dette senteret?		X		

Monitor har ikke besøkt medisinregnskap. Det holdes løpende kontakt med studiegruppen, og dersom det anses som nødvendig vil monitor se på regnskapet i forkant av feasibility-analysen planlagt etter 20 inkluderte pasienter. Om ikke, blir regnskapet sjekket ved neste monitoreringsbesøk.

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MONITORERINGSRAPPORT

3. Versjonsoversikt

3.1 REKs godkjenning:

Protokoll og protokollendringer (versjon og dato)	Versjon 3.0 09.01 2018		
Godkjent dato (dato-måned-år)	05.02 2018		
Pasientinformasjon/samtykke (versjon og dato)	Ingen samtykke i studien		
Godkjent dato (dato-måned-år)			

3.2 SLVs godkjenning:

Protokoll og protokollendringer (versjon og dato)	Versjon 3.0 09.01 2018		
Godkjent dato (dato-måned-år)	12.01 2018		

Informasjonsarket deltakere får med seg etter studiemedisin er gitt er oversatt til polsk, rumensk, somali og engelsk.
Det skrives endringsmelding, og protokollen vil oppdateres.

4. Pasientinformasjon og samtykkeerklæring		**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
4.1	Finnes det en korrekt signert og datert samtykkeerklæring for hver av de gjennomgåtte forsøkspersonene?			X	
4.2	Er ICH-GCP fulgt ved innhenting av samtykkeerklæring?		X		

4.2: studiedeltaker 01-047 er feil-inkludert: vedkommende var samtykkekompetent, og hadde sagt nei. Ytterligere to samtykkekompetente personer har ikke samtykket. Ved disse tilfellene er det korrekt registrert i database at vedkommende sa nei til deltakelse.

Studiemedarbeidere vil kurses ekstra i hvordan håndtere samtykkeprosedyrer

5. Protokollavvik, avvik fra ICH-GCP		**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
5.1	Er protokollavvik/avvik fra ICH-GCP avdekket?	X			
5.2	Er protokollavvik dokumentert og, om nødvendig, forklart?	X			
5.3	Ved protokollavvik, er avvikene rettet opp og er det innført forebyggende tiltak?	X			

5.1: En pasient er inkludert med respirasjonsfrekvens = 8, og GCS = 12.
5.3: Det er allerede satt i gang tiltak for å unngå at dette skjer igjen.
Avviksmelding var sendt i forkant av monitors besøk på senter.

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6. Uønskede hendelser		Ja	Nei	Ikke relevant	Ikke sjekket
6.1	Er alle relevante hendelser (AE) registrert og fulgt opp?	X			
6.2	Er alle SAEer rapportert til sponsor og fulgt opp på senteret?			X	
6.3	Ved besøk hos sponsor, har sponsor rapportert ev. SUSAR(er) til SLV?			X	
6.4	Har sponsor sendt inn årsrapport(er) til SLV?			X	

6.4: HU er klar over årsrapport som skal sendes innen 7. januar (+60 dager)

7. CRF og kildedata		Ja	Nei	Ikke relevant	Ikke sjekket
7.1	Oppbevares alle kildedata som avtalt?	X			
7.2	Er alle inkluderte forsøkspersoner inkludert iht. protokollen?		X		
7.3	Er det avdekket avvik mellom CRF og kildedata på dette besøket?	X			
7.4	Er CRF signert, datert og tilfredsstillende utfylt?	X			
7.5	Inneholder CRF forsøkspersonenes fulle navn og/eller fødselsnummer?		X		

7.1: Det er tilnærmet umulig å ha kun 1 kryss på datapunkt på kildedatalisten i denne studien. Det foreslås at kilden for datapunkter nummereres i stedet for krysses, og at det lages en tekst som forklarer nummerering
7.2: Se kommentar på punkt 4.2 og 5.1
7.3: Mindre avvik fra kildedata er markert direkte i eCRF med queries
Det ble funnet at kildedata manglet i noen tilfeller, da studiepersonell ikke hadde laget komplette journalnotater etter hva som skal føres i eCRF.

8. Utprøvingspreparat(er)		Ja	Nei	Ikke relevant	Ikke sjekket
8.1	Gjennomføres randomiseringsprosedyrene som avtalt?	X			
8.2	Er ev. blinding av studien ivaretatt?	X			
8.3	Er ev. avblinding av forsøkspersoner utført i henhold til prosedyre?			X	
8.4	Er legemiddelhåndteringen i henhold til bestemt prosedyre?	X			
8.5	Oppbevares utprøvingspreparat(ene) i henhold til merking/ pakningsvedlegget (f.eks. temperatur, sollys osv.)?	X			
8.6	Foreligger/følges prosedyre vedrørende merking av utprøvingspreparat(ene)?	X			
8.7	Er forsyning og holdbarhet av utprøvingspreparat(ene) tilstrekkelig?	X			
8.8	Oppbevares rekvisisjon til/fra apoteket?	X			
8.9	Har forsøkspersonene fått informasjon om bruk, oppbevaring og retur av utprøvingspreparat(er)?			X	
8.10	Ved besøk hos sponsor, er årlig gjennomgang/fornyelse av IB/SmPC gjennomført?			X	

Det ble oppdaget av studiegruppen at kit-forseglingen kunne brytes i transport fra Trondheimapotekene til studiesite i Oslo. Dette ble meldt i elektronisk avvikssystem (i Viedoc), og løst ved at kit foreløpig pakkes i zip-lock poser før forsending. Det er anmodet fra site at apotek bruker en kraftigere tape til forsegling ved neste forsendelse.

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MONITORERINGSRAPPORT

Monitor anser saken som avsluttet og gjør ingenting med denne.

9. Medisinsk utstyr, forskningsbiobanker m.m. tilknyttet studien		Ja	Nei	Ikke relevant	Ikke sjekket
9.1	Er det vilkår/forhold som bør diskuteres med involverte avdelinger?		X		
9.2	Er referanseområdene fortsatt de samme?			X	
9.3	Er forskningsbiobanker forsvarlig oppbevart?			X	
9.4	Er instrumenter og utstyr vedlikeholdt og kalibrert iht. rutinene?	X			
9.5	Er instrumenter eller utstyr erstattet?		X		

9.4-9.5: Det er ingen forskjell i utstyr og vedlikehold fra notat i initieringsrapporten

10. Studiesenter		Ja	Nei	Ikke relevant	Ikke sjekket
10.1	Har det vært endringer i studiepersonell?	X			
10.2	Er delegeringsloggen i ISF/TMF fylt ut og oppdatert?	X			
10.3	Er det tilstrekkelig ressurser på avdelingen for å gjennomføre studien?	X			
10.4	Er studiepersonell gjort kjent med vesentlige endringer i studien?			X	
10.5	Hvis studien er lukket for inklusjon av forsøkspersoner, har nasjonal koordinerende utprøver (NKU) oppdatert informasjonen i HelseNorge.no?			X	
10.6	Hos sponsor, er ClinicalTrials.gov oppdatert i løpet av de siste 6 månedene?			X	

10.1: Det er kontinuerlig opplæring nye studiemedarbeidere. Dette loggføres i opplæringslogg.

Det er særdeles viktig med oppfriskning av kursmateriale for allerede godkjente studiemedarbeidere i denne studien. Det må legges vekt på samarbeid mellom den som noterer i journal og den som noterer på studieark, slik at det ikke er tvil om kilden for data. Det er også viktig at alle datapunkter som skal samles inn har en kilde.

11. Investigator Site File (ISF) / Trial Master File (TMF)		Ja	Nei	Ikke relevant	Ikke sjekket
11.1	Er alle nye forsøkspersoner ført på deltakerliste?	X			
11.2	Er monitors besøkslogg oppdatert?	X			
11.3	Er ISF/TMF sjekket ved dette monitoreringsbesøket?		X		
11.4	Er noen av studiens essensielle dokumenter endret siden sist?		X		
11.5	Hvis ja, er dokumentene sendt til myndighetenes godkjenning?			X	
11.6	Oppdateres og vedlikeholdes alle essensielle dokumenter?	X			
11.7	Oppbevares alle essensielle dokumenter i TMF/ISF som avtalt?	X			

11.3: Studiepermen ble ikke gjennomgått ved besøket. Monitor sjekket inklusjon- og eksklusjonslogger, samt delegeringslogg og opplæringslogg for studiemedarbeidere.
Fra initiering er det notert at alle godkjenninger, avtaler og prosedyrer er på plass. Protokoll er signert.
Initiering ble gjort 1ste juni, og det er ikke skjedd større endringer som fordret at permen måtte gjennomgås på nytt.

11.6: IB skal oppdateres etter ny mal fra SLV. Dette informerte HU om, monitor ser at dette er under kontroll.

16.1.8 Audit certificates

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MONITORERINGSRAPPORT

11.7: Det er opprettet egne permer for opplæringslogger og inklusjon/eksklusjonslogg.

12. Oppgaver til oppfølging*

Dato	Oppgave	Tidsfrist	Ansvar	Utført
10.07 2018	Adressere queries i eCRF (pkt 7.3)	2 mnd.	Studiegruppe	
10.07 2018	Dokumentere at rutiner er styrket i forbindelse med samtykke/samtykke kompetente deltakere (pkt 4.2)	2 mnd.	Studiegruppe	
10.07 2018	Oppdatere kildedataliste (pkt 7.1)	2 mnd.	Studiegruppe	
10.07 2018	Dokumentere at rutiner rundt innsamling av studiedata styrkes (pkt 7.3)	2 mnd.	Studiegruppe	

13. Underskrifter

Rapporten er skrevet av:

Maryam Fridi-Aksseim — Monitor

10.07 2018 — Dato

Som hovedutprøver har jeg lest rapporten og tar ansvar for å følge opp mangler.

Anne-Cathrine Braarud — Hovedutprøver

6/8-18 — Dato

Sponsor/nasjonal koordinerende utprøver

Dato

Et signert eksemplar skal arkiveres i ISF, et signert eksemplar oppbevares av sponsor, et signert eksemplar oppbevares av monitor.

16.1.8 Audit certificates

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MONITORERINGSRAPPORT

Protokoll	**NINA-1**	**Dato for besøk**	**06.08 2018**
Studiesenter	**OUS**	**EudraCT nr.**	**2016-004072-22**
Hovedutprøver	**Anne-Cathrine Braarud / Arne Skulberg**	**Rapport nr.**	**3**

	Navn				**Rolle**
Studiepersonell til stede	Arne Skulberg				Utprøver
Monitorering utført (kryss av)	**På studiesenter**	X	**Per telefon**		
Monitor	Mariann Friis-Ottessen				

1. Forsøksperson status	**Siden oppstart**	**Siden siste besøk**		**Siden oppstart**	**Siden siste besøk**
Planlagt inkludert:	200		Pågående:	-	
Screenet:	104		Utgått etter inklusjon/ randomisering:	5	
Inkludert/randomisert til nå:	26		Fullført:	21	
Utgått før inklusjon/ randomisering	78				

26 har egentlig fullført studien, da denne er på 1 besøk uten aktivt samtykke.
5 har sagt nei til bruk av data, og dermed er det, pr 6/8 -18, data på 21 av dem som har som har fullført studien.
Det er også en mulighet for å trekke seg fra studien i etterhånd, men dette er ikke benyttet pr monitorering 6.8 -18

2. Monitoreringsplan		**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
2.1	Er monitoreringsplanen til studien fulgt ved dette monitoreringsbesøket?	X			
2.2	Er alle avvik fra forrige monitoreringsbesøk rettet opp?		X		
2.3	Bør monitoreringsplanen revideres for dette senteret?		X		

2.2: Kildedatalisten er ikke enda oppdatert.
Dette monitoreringsbesøket kommer innenfor 2mnd-vindu for løsning av oppgaver, og det er avtalt at studiegruppen og monitor utformer kildedataliste slik at den gir best mulig kildehenvisning.

16.1.8 Audit certificates

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MONITORERINGSRAPPORT

3. Versjonsoversikt

3.1 REKs godkjenning:

Protokoll og protokollendringer (versjon og dato)	Versjon 3.0 09.01 2018		
Godkjent dato (dato-måned-år)	05.02 2018		
Pasientinformasjon/samtykke (versjon og dato)	Ingen samtykke i studien		
Godkjent dato (dato-måned-år)			

3.2 SLVs godkjenning:

Protokoll og protokollendringer (versjon og dato)	Versjon 3.0 09.01 2018		
Godkjent dato (dato-måned-år)	12.01 2018		

Det er ikke endringer i studiedokumenter fra monitorering i juli.

4. Pasientinformasjon og samtykkeerklæring		**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
4.1	Finnes det en korrekt signert og datert samtykkeerklæring for hver av de gjennomgåtte forsøkspersonene?			X	
4.2	Er ICH-GCP fulgt ved innhenting av samtykkeerklæring?	X			

5 studiedeltakere har aktivt ikke samtykket til bruk av data i studie. Alle er korrekt registrert i database, data er trukket og det er registrert at kandidaten aktivt sa nei.
Kandidater som ikke møter seleksjonskriterier får ikke studiemedisin, og registreres anonymt i database.

Ordningen med to studiemedarbeidere som samarbeider i prosessen med samtykke og studieforløp fungerer nå veldig fint.

Ingen har foreløpig benyttet epostadressen for å trekke seg fra studien i etterkant.

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MONITORERINGSRAPPORT

5. Protokollavvik, avvik fra ICH-GCP		Ja	Nei	Ikke relevant	Ikke sjekket
5.1	Er protokollavvik/avvik fra ICH-GCP avdekket?	X			
5.2	Er protokollavvik dokumentert og, om nødvendig, forklart?	X			
5.3	Ved protokollavvik, er avvikene rettet opp og er det innført forebyggende tiltak?	X			

5.1: 01-068 fikk studiemedisin gitt i feil rekkefølge.

Ved et tilfelle ble IM studiemedisin benyttet, men spray ble ikke brukt. Det ble, ved en misforståelse, ikke bedt om samtykke i etterkant, og data kan ikke benyttes.

Begge tilfeller var oppdaget i forkant av monitoreringsbesøk, rapportert og løst av studiegruppen med Note to File og medfølgende CAPA

6. Uønskede hendelser		Ja	Nei	Ikke relevant	Ikke sjekket
6.1	Er alle relevante hendelser (AE) registrert og fulgt opp?				X
6.2	Er alle SAE-er rapportert til sponsor og fulgt opp på senteret?			X	
6.3	Ved besøk hos sponsor, har sponsor rapportert ev. SUSAR(er) til SLV?			X	
6.4	Har sponsor sendt inn årsrapport(er) til SLV?			X	

6.1: Monitor skal ikke sjekke AE i denne studien
6.2: Ingen SAE var rapportert siden forrige monitorering.

7. CRF og kildedata		Ja	Nei	Ikke relevant	Ikke sjekket
7.1	Oppbevares alle kildedata som avtalt?	X			
7.2	Er alle inkluderte forsøkspersoner inkludert iht. protokollen?	X			
7.3	Er det avdekket avvik mellom CRF og kildedata på dette besøket?	X			
7.4	Er CRF signert, datert og tilfredsstillende utfylt?	X			
7.5	Inneholder CRF forsøkspersonenes fulle navn og/eller fødselsnummer?		X		

7.3: Mindre avvik fra kildedata er markert direkte i eCRF med queries. Disse besvares fortløpende.

Inkluderte studiedeltakere t.o.m. 01-071 er monitorert.
01-052 (random.org) ble fullmonitorert

16.1.8 Audit certificates

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MONITORERINGSRAPPORT

8. Utprøvingspreparat(er)		Ja	Nei	Ikke relevant	Ikke sjekket
8.1	Gjennomføres randomiseringsprosedyrene som avtalt?	X			
8.2	Er ev. blinding av studien ivaretatt?	X			
8.3	Er ev. avblinding av forsøkspersoner utført i henhold til prosedyre?			X	
8.4	Er legemiddelhåndteringen i henhold til bestemt prosedyre?	X			
8.5	Oppbevares utprøvingspreparat(ene) i henhold til merking/ pakningsvedlegget (f.eks. temperatur, sollys osv.)?	X			
8.6	Foreligger/følges prosedyre vedrørende merking av utprøvingspreparat(ene)?	X			
8.7	Er forsyning og holdbarhet av utprøvingspreparat(ene) tilstrekkelig?	X			
8.8	Oppbevares rekvisisjon til/fra apoteket?	X			
8.9	Har forsøkspersonene fått informasjon om bruk, oppbevaring og retur av utprøvingspreparat(er)?			X	
8.10	Ved besøk hos sponsor, er årlig gjennomgang/fornyelse av IB/SmPC gjennomført?			X	

Monitor har sjekket legemiddelregnskap etter monitoreringsplanen.

Studiegruppen har låsbart skap for oppbevaring av studiemedisin, det føres fortløpende regnskap på hvor studiekit er til enhver tid. Regnskapet stemmer med det som er rapportert i studiedatabasen.

Ved avslutningsbesøk vil det gjøres en total-monitorering av hele legemiddelregnskapet, med telling av hva som er levert til destruksjon. Monitoreringsbesøk i løpet av studien vil sjekke rapportert legemiddelregnskap.

9. Medisinsk utstyr, forskningsbiobanker m.m. tilknyttet studien		Ja	Nei	Ikke relevant	Ikke sjekket
9.1	Er det vilkår/forhold som bør diskuteres med involverte avdelinger?		X		
9.2	Er referanseområdene fortsatt de samme?			X	
9.3	Er forskningsbiobanker forsvarlig oppbevart?			X	
9.4	Er instrumenter og utstyr vedlikeholdt og kalibrert iht. rutinene?	X			
9.5	Er instrumenter eller utstyr erstattet?		X		

9.4-9.5: Det er ingen forskjell i utstyr og vedlikehold fra forrige monitoreringsbesøk

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MONITORERINGSRAPPORT

10. Studiesenter		Ja	Nei	Ikke relevant	Ikke sjekket
10.1	Har det vært endringer i studiepersonell?	X			
10.2	Er delegeringsloggen i ISF/TMF fylt ut og oppdatert?	X			
10.3	Er det tilstrekkelig ressurser på avdelingen for å gjennomføre studien?	X			
10.4	Er studiepersonell gjort kjent med vesentlige endringer i studien?			X	
10.5	Hvis studien er lukket for inklusjon av forsøkspersoner, har nasjonal koordinerende utprøver (NKU) oppdatert informasjonen i HelseNorge.no?			X	
10.6	Hos sponsor, er ClinicalTrials.gov oppdatert i løpet av de siste 6 månedene?			X	

10.1: Det er kontinuerlig opplæring nye studiemedarbeidere. Dette loggføres i opplæringslogg.

Opplæring ble diskutert ved forrige monitoreringsbesøk, og det er gjort tiltak på dette. Rutiner og studienotater er blitt merkbart forbedret.

11. Investigator Site File (ISF) / Trial Master File (TMF)		Ja	Nei	Ikke relevant	Ikke sjekket
11.1	Er alle nye forsøkspersoner ført på deltakerliste?	X			
11.2	Er monitors besøkslogg oppdatert?	X			
11.3	Er ISF/TMF sjekket ved dette monitoreringsbesøket?	X			
11.4	Er noen av studiens essensielle dokumenter endret siden sist?		X		
11.5	Hvis ja, er dokumentene sendt til myndighetenes godkjenning?			X	
11.6	Oppdateres og vedlikeholdes alle essensielle dokumenter?	X			
11.7	Oppbevares alle essensielle dokumenter i TMF/ISF som avtalt?	X			

11.3: I henhold til monitoreringsplan blir kun noen av dokumentene i studiepermen sjekket.

16.1.8 Audit certificates

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MONITORERINGSRAPPORT

12. Oppgaver til oppfølging*

Dato	Oppgave	Tidsfrist	Ansvar	Utført
08.08 2018	Følge opp queries i Viedoc	2 mnd.	Studiegruppe	
08.08 2018	Ferdigstille kildedataliste	2 mnd.	Studiegruppe	

13. Underskrifter

Rapporten er skrevet av:

Mariann Friis-Ottessen — Monitor

8.8 -18 — Dato

Som hovedutprøver har jeg lest rapporten og tar ansvar for å følge opp mangler.

Hovedutprøver — Dato

Sponsor/nasjonal koordinerende utprøver — Dato

Et signert eksemplar skal arkiveres i ISF, et signert eksemplar oppbevares av sponsor, et signert eksemplar oppbevares av monitor.

16.1.8 Audit certificates

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MONITORERINGSRAPPORT

Protokoll	**NINA-1**	**Dato for besøk**	**25/26.02 2019**
Studiesenter	**OUS**	**EudraCT nr.**	**2016-004072-22**
Hovedutprøver	**Anne-Cathrine Braarud / Arne Skulberg**	**Rapport nr.**	**4**

	Navn				**Rolle**
Studiepersonell til stede	Arne Skulberg Anne-Cathrine Braarud Tore Skålhegg				Utprøver Hovedutprøver Koordinator
Monitorering utført (kryss av)	**På studiesenter**	X	**Per telefon**		
Monitor	Mariann Friis-Ottessen				

1. Forsøksperson status	**Siden oppstart**	**Siden siste besøk**		**Siden oppstart**	**Siden siste besøk**
Planlagt inkludert:	200		Pågående:	-	-
Screenet:	303	199	Utgått etter inklusjon/ randomisering:	27	22
Inkludert/randomisert til nå:	99	73	Fullført:	72	51
Utgått før inklusjon/ randomisering	204	126			

72 er inkludert per protokoll, og har fullført studien
Totalt er 99 kit åpnet

De resterende 27 inkluderer ITT (intention to treat) populasjon:
- både feil inklusjoner og åpnede kit som ikke ble administrert
samt 2 som har trukket seg i etterkant via telefon, eller epost

2. Monitoreringsplan		**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
2.1	Er monitoreringsplanen til studien fulgt ved dette monitoreringsbesøket?	X			
2.2	Er alle avvik fra forrige monitoreringsbesøk rettet opp?	X			
2.3	Bør monitoreringsplanen revideres for dette senteret?		X		

16.1.8 Audit certificates

MONITORERINGSRAPPORT

3. Versjonsoversikt

3.1 REKs godkjenning:

Protokoll og protokollendringer (versjon og dato)	Versjon 3.0 09.01 2018		
Godkjent dato (dato-måned-år)	05.02 2018		
Pasientinformasjon/samtykke (versjon og dato)	Ingen samtykke i studien		
Godkjent dato (dato-måned-år)			

3.2 SLVs godkjenning:

Protokoll og protokollendringer (versjon og dato)	Versjon 3.0 09.01 2018		
Godkjent dato (dato-måned-år)	12.01 2018		

Det er ikke endringer i studiedokumenter siden forrige monitoreringsbesøk

4. Pasientinformasjon og samtykkeerklæring		Ja	Nei	Ikke relevant	Ikke sjekket
4.1	Finnes det en korrekt signert og datert samtykkeerklæring for hver av de gjennomgåtte forsøkspersonene?			X	
4.2	Er ICH-GCP fulgt ved innhenting av samtykkeerklæring?	X			

Samtykkeløsningen/inklusjonsprosedyren er beskrevet i tidligere monitoreringsrapporter

5. Protokollavvik, avvik fra ICH-GCP		Ja	Nei	Ikke relevant	Ikke sjekket
5.1	Er protokollavvik/avvik fra ICH-GCP avdekket?	X			
5.2	Er protokollavvik dokumentert og, om nødvendig, forklart?	X			
5.3	Ved protokollavvik, er avvikene rettet opp og er det innført forebyggende tiltak?	X			

Ved et tilfelle ble studiemedisin administrert på tross av at frostindikator i kit viste at det hadde vært frosset. Dette er allerede fanget opp av studiegruppen, og det er laget Note to File med CAPA. Dette vil ikke følges videre opp av monitor

Ett tilfelle av at studiemedisin ble administrert IV i stedet for IM. Dette er ikke farlig for pasienten, uavhengig av om det er aktiv substans eller placebo, da begge er godkjent for både IM og IV administrasjon.
Det er likevel et protokollbrudd, og det vil igjen lages en Note to File med CAPA, og studieledelse har hatt samtale med involvert personell. Det vil ikke følges opp videre av monitor

Pasienter inkluderes med pustefrekvens 8, mot protokoll statuerer «under 8» som inklusjonskriterium.
Dette forklares med at det ikke er mulig å fastslå pustefrekvens nøyaktig: det er et estimat.

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MONITORERINGSRAPPORT

6. Uønskede hendelser		Ja	Nei	Ikke relevant	Ikke sjekket
6.1	Er alle relevante hendelser (AE) registrert og fulgt opp?				X
6.2	Er alle SAE-er rapportert til sponsor og fulgt opp på senteret?			X	
6.3	Ved besøk hos sponsor, har sponsor rapportert ev. SUSAR(er) til SLV?			X	
6.4	Har sponsor sendt inn årsrapport(er) til SLV?			X	

6.2: Det har ikke forekommet noen SAE i studien
6.4: Årsrapport er sendt til SLV, denne blir arkivert i studieperm

7. CRF og kildedata		Ja	Nei	Ikke relevant	Ikke sjekket
7.1	Oppbevares alle kildedata som avtalt?	X			
7.2	Er alle inkluderte forsøkspersoner inkludert iht. protokollen?		X		
7.3	Er det avdekket avvik mellom CRF og kildedata på dette besøket?	X			
7.4	Er CRF signert, datert og tilfredsstillende utfylt?	X			
7.5	Inneholder CRF forsøkspersonenes fulle navn og/eller fødselsnummer?		X		

7.2: I tilfellet med aktivert frostindikator i kit ble pasient spurt om samtykke og inkludert i studien.
Dette er en feilinklusjon, da frosset kit er et eksklusjonskriterium. Dette er allerede håndtert av studiegruppen
7.3: Mindre avvik fra kildedata er markert direkte i eCRF med queries. Disse besvares fortløpende.

Inkluderte studiedeltakere t.o.m. 01-266 er monitorert, ingen er fullmonitorert ved dette besøket

8. Utprøvingspreparat(er)		Ja	Nei	Ikke relevant	Ikke sjekket
8.1	Gjennomføres randomiseringsprosedyrene som avtalt?	X			
8.2	Er ev. blinding av studien ivaretatt?	X			
8.3	Er ev. avblinding av forsøkspersoner utført i henhold til prosedyre?			X	
8.4	Er legemiddelhåndteringen i henhold til bestemt prosedyre?	X			
8.5	Oppbevares utprøvingspreparat(ene) i henhold til merking/ pakningsvedlegget (f.eks. temperatur, sollys osv.)?	X			
8.6	Foreligger/følges prosedyre vedrørende merking av utprøvingspreparat(ene)?	X			
8.7	Er forsyning og holdbarhet av utprøvingspreparat(ene) tilstrekkelig?	X			
8.8	Oppbevares rekvisisjon til/fra apoteket?	X			
8.9	Har forsøkspersonene fått informasjon om bruk, oppbevaring og retur av utprøvingspreparat(er)?			X	
8.10	Ved besøk hos sponsor, er årlig gjennomgang/fornyelse av IB/SmPC gjennomført?			X	

Det er kommet ny batch med studiemedisiner
Regnskap for første batch er sendt til Trondheim
Destruksjonsbekreftelse kommer, og lagres i studieperm

16.1.8 Audit certificates

MONITORERINGSRAPPORT

9. Medisinsk utstyr, forskningsbiobanker m.m. tilknyttet studien		Ja	Nei	Ikke relevant	Ikke sjekket
9.1	Er det vilkår/forhold som bør diskuteres med involverte avdelinger?		X		
9.2	Er referanseområdene fortsatt de samme?			X	
9.3	Er forskningsbiobanker forsvarlig oppbevart?			X	
9.4	Er instrumenter og utstyr vedlikeholdt og kalibrert iht. rutinene?	X			
9.5	Er instrumenter eller utstyr erstattet?		X		

9.4-9.5: Det er ingen forskjell i utstyr og vedlikehold fra forrige monitoreringsbesøk

10. Studiesenter		Ja	Nei	Ikke relevant	Ikke sjekket
10.1	Har det vært endringer i studiepersonell?	X			
10.2	Er delegeringsloggen i ISF/TMF fylt ut og oppdatert?	X			
10.3	Er det tilstrekkelig ressurser på avdelingen for å gjennomføre studien?	X			
10.4	Er studiepersonell gjort kjent med vesentlige endringer i studien?			X	
10.5	Hvis studien er lukket for inklusjon av forsøkspersoner, har nasjonal koordinerende utprøver (NKU) oppdatert informasjonen i HelseNorge.no?			X	
10.6	Hos sponsor, er ClinicalTrials.gov oppdatert i løpet av de siste 6 månedene?			X	

Treningsdatabasen NAKOS treningslogg holdes oppdatert, og det kan lett sjekkes hvem som er opplært til studien. Det er planlagt ny runde med opplæring av 30 nye medarbeidere, og også oppfriskning for dem som allerede er opplært

Det er generelt veldig gode notater i ambulansejournaler og høy compliance blant studiemedarbeidere.
Tidvis mangler kit-nummer i journal, men det er notert deltakelse i studie og ofte navn på studien.
Det noteres også ofte i journalnotater at pasienten er fornøyd med å få delta i en studie.

11. Investigator Site File (ISF) / Trial Master File (TMF)		Ja	Nei	Ikke relevant	Ikke sjekket
11.1	Er alle nye forsøkspersoner ført på deltakerliste?	X			
11.2	Er monitors besøkslogg oppdatert?	X			
11.3	Er ISF/TMF sjekket ved dette monitoreringsbesøket?	X			
11.4	Er noen av studiens essensielle dokumenter endret siden sist?	X			
11.5	Hvis ja, er dokumentene sendt til myndighetenes godkjenning?	X			
11.6	Oppdateres og vedlikeholdes alle essensielle dokumenter?	X			
11.7	Oppbevares alle essensielle dokumenter i TMF/ISF som avtalt?	X			

Det er laget ny IB for Nalokson-spray, i samarbeid med SLV.
Den er godkjent av SLV, og blir signert av hovedutprøver på monitoreringsmøte 26/2.
IB er lagret i studiepermen.

16.1.8 Audit certificates

MONITORERINGSRAPPORT

12. Oppgaver til oppfølging*

Dato	Oppgave	Tidsfrist	Ansvar	Utført
26.02 2019	Følge opp queries i Viedoc	2 mnd.	Studiegruppe	25/5 - 20 cd
26.02 2019	Informere om/repetere at KIT-nummer skal noteres i pasientens journal i tillegg til på studiearket.	Fortløpende, og på kurs	Studiegruppe	25/5 - 20 cd
26.02 2019	Oppdatere studieperm med manglende dokumenter (årsrapport og, når den er klar, destruksjonsbekreftelse)	2 mnd.	Studiegruppe	25/5 - 20 cd

13. Underskrifter

Rapporten er skrevet av:

Maurum Friis-Aksen — Monitor

8/3 - 19 — Dato

Som hovedutprøver har jeg lest rapporten og tar ansvar for å følge opp mangler.

Anne-Kath. Braarud — Hovedutprøver

12/3-19 — Dato

Sponsor/nasjonal koordinerende utprøver

12/3-19 — Dato

Et signert eksemplar skal arkiveres i ISF, et signert eksemplar oppbevares av sponsor, et signert eksemplar oppbevares av monitor.

16.1.8 Audit certificates

16.1.8 Audit certificates

MONITORERINGSRAPPORT
NINA-1

		Rapport nr.	**5**
Protokoll	**NTNU INTRANASAL NALOXONE TRIAL Double blinded, double dummy, randomised controlled trial of intranasal naloxone for pre-hospital use**	**Dato for besøk**	**Februar/mars 2020**
Studiesenter	**OUS**	**EudraCT nr.**	**2016-004072-22**
Hovedutprøver	**Arne Skulberg / Anne-Cathrine Braarud**	**Sponsor**	**NTNU**

	Navn	**Rolle**
Studiepersonell til stede	Arne Skulberg Anne-Cathrine Braarud Tore Skålhegg	Koordinerende utprøver Hovedutprøver ved senter Koordinator
Monitorering utført (kryss av)	**På studiesenter** X **Fjernmonitorering**	
Monitor(er)	Mariann Friis-Ottessen	
Monitoreringsplan	Versjonsnummer: 3.0, 14.05 2018	

1. Status	**Siden oppstart**		**Siden oppstart**
Planlagt inkludert på studiesenter:	200 (PP*)	Pågående:	Ingen
Screenet:	775	Utgått etter inklusjon:	15
Randomisert til nå:	240	Fullførte:	157 (PP)
Randomisert, men utgått før inklusjon:	43	Ikke samtykket/trukket samtykke:	25

*PP = per protokoll

240 randomisert inkluderer alle åpnede studiekit.
Fra disse er 43 kit åpnet, men ikke administrert til noen kandidat
25 personer har ikke samtykket/trukket samtykke i etterkant
15 feilinklusjoner, eller feil ved administrert studiemedisin

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MONITORERINGSRAPPORT
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2. Versjonsoversikt – kun gjeldende versjoner

2.1 REKs godkjenning:

Protokoll og protokollendringer (versjon og dato)	Versjon 3.2 02.09 19
Godkjent dato (dato-måned-år)	15.11 19
Pasientinformasjon/samtykke (versjon og dato)	-
Godkjent dato (dato-måned-år)	-

2.2 SLVs godkjenning:

Protokoll og protokollendringer (versjon og dato)	Versjon 3.2 02.09 19
Godkjent dato (dato-måned-år)	30 dager

Gruppen har oppdatert protokollen 2 ganger siden forrige monitoreringsbesøk.
Det er god orden med føring av endringslogg for protokoll.

Informasjonsbrevet og -kortet som deltakere får etter inklusjon er begge oppdatert i forbindelse med protokollendringer, men det er ikke ansett som vesentlige endringer som krever innsendelse til myndigheter

3. Studiesenter		**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
3.1	Har det vært endringer i studiepersonell?	X			
3.2	Er det tilstrekkelig ressurser på avdelingen for å gjennomføre studien?	X			
3.3	Er studiepersonell gjort kjent med vesentlige endringer i studien?			X	

Studien har stadig opplæring av nytt ambulansepersonell, og også repetisjonskurs.
Dette er dokumentert i NAKOS (www.nakos.no), der det finnes et eget kurs for studien. Dette gjennomføres i tillegg til en gjennomgang av studien med sentralt studiepersonell, før en deltaker er sertifisert som studiemedarbeider. Kursvarighet er 4+4 timer.

Monitor får utskrift av tjenestenummer registrert i databasen, og kan med dette sjekke at de som inkluderer i studien har gjennomført opplæring.

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MONITORERINGSRAPPORT
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4. Pasientinformasjon og samtykkeerklæring		Ja	Nei	Ikke relevant	Ikke sjekket
4.1	Finnes det en korrekt signert og datert samtykkeerklæring for hver av de gjennomgåtte forsøkspersonene?		X		
4.2	Er ICH-GCP fulgt ved innhenting av samtykkeerklæring?		X		

Studien har dispensasjon fra de generelle samtykkeprosedyrene, og det deles ut informasjon i etterkant av administrert studiemedisin. Prosedyrene er godt dokumentert, og fungerer godt.

Det er god kontroll på prosedyrer for å trekke seg fra studien, og det dokumenterer at deltakere får med seg informasjonsskriv.

5. CRF og kildedata		Ja	Nei	Ikke relevant	Ikke sjekket
5.1	Finnes det en kildedataliste i ISF?	X			
5.2	Oppbevares alle kildedata i henhold til kildedataliste?	X			
5.3	Er forsøkspersonene inkludert iht. protokoll?		X		
5.4	Er det avdekket avvik mellom CRF og kildedata på dette besøket?	X			
5.5	Er CRF signert, datert og tilfredsstillende utfylt?	X			
5.6	Inneholder CRF forsøkspersonenes fulle navn og/eller fødselsnummer?		X		

6 deltakere er inkludert med respirasjonsrate på 8/minutt. Dette er i følge protokoll feil, da det skal inkluderes med respirasjonsrate under 8/minutt. Disse 6 er per i dag inkludert i studiens Intention To Treat (ITT)-populasjon, og ikke i Per-Protokoll (PP)-populasjon

Det vurderes å oppdatere protokoll for å kunne inkludere med denne respirasjonsfrekvensen, og det vil da også argumenteres for å flytte de 6 registrerte fra ITT til PP, i etterkant. Dette blir i så tilfelle dokumentert i studiens avviksdatabase.

I ITT-populasjonen er det også pasienter som har fått studiemedisin på tross av at frost-indikatoren i kit er utløst, og pasienter som ikke har fått korrekt dose studiemedisin, enten fra spray, eller injeksjon.
For pasienter i ITT registreres kit-nummer, og eventuelle sikkerhets-data.

Det noteres som note to file i Viedoc i de tilfellene en deltaker har fått avvikende mengde studiemedisin.

Ved besøket ble alle inkluderte pasienter monitorert etter planen, frem til 01-672
Det finnes noen små avvik, som er notert som queries i Viedoc.
Det er sjekket at alle som har trukket samtykke er registrert på korrekt måte i Viedoc.

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MONITORERINGSRAPPORT
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6. Uønskede hendelser		Ja	Nei	Ikke relevant	Ikke sjekket
6.1	For hendelser sjekket iht. monitoreringsplan; er alle AEer registrert og fulgt opp?	X			
6.2	For hendelser sjekket iht. monitoreringsplan; er alle SAEer rapportert til sponsor og fulgt opp på senteret?	X			
6.3	Ved besøk hos sponsor, har sponsor rapportert ev. SUSARer til SLV?			X	
6.4	Har sponsor sendt årsrapport til SLV innen tidsfristen?	x			

AE-er logges fortløpende, og alle sjekkes av medical monitor.

Det er rapportert en SAE i studien, og denne skal tas opp i studiens administrasjonsgruppe, for å avgjøre om det faktisk er en SAE, eller om den kan nedskaleres til en AE.
Dersom det justeres vil det lages et notat på det, som bekrefter og begrunner avgjørelsen.

Årsrapport ble sendt til SLV i desember 2019

7. Utprøvingspreparat(er)		Ja	Nei	Ikke relevant	Ikke sjekket
7.1	Foreligger nyeste utgave av IB eller SmPC?	X			
7.2	Gjennomføres randomiseringsprosedyren som beskrevet?	X			
7.3	Er ev. blinding av studien ivaretatt?	X			
7.4	Er ev. avblinding av forsøkspersoner utført i henhold til prosedyre?	X			
7.5	Er forsyning og holdbarhet av utprøvingspreparat(ene) tilstrekkelig?	X			
7.6	Oppbevares utprøvingspreparat(ene) i henhold til merking/ pakningsvedlegget?	X			
7.7	Føres temperaturlogg?	X			
7.8	Dersom det foreligger prosedyre(r) for mottak, håndtering, merking, oppbevaring og/eller destruksjon av utprøvingspreparat(ene), blir denne fulgt?	X			
7.9	Er prosedyrer for legemiddelregnskap etablert for hver forsøksperson og samlet for hvert studiesenter?	X			
7.10	Oppbevares rekvisisjon til/fra apoteket?	X			
7.11	Har forsøkspersonene fått informasjon om bruk, oppbevaring og retur av utprøvingspreparat(er)?			X	

Foreløpig foreligger versjon 5 av IB.
Denne skal oppdateres og også publiseres.

Det vil komme en ny omgang med studiekit, og studiegruppen har kontroll på dette.

Siden det neste besøket er monitorering ved lukking av database ble medisinregnskapet ikke sjekket.

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MONITORERINGSRAPPORT
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8. Fasiliteter, lab og utstyr		**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
8.1	Er det vilkår/forhold som bør diskuteres med involverte avdelinger?		X		
8.2	Er referanseområdene fortsatt de samme?			X	
8.3	Er forskningsbiobanker forsvarlig oppbevart?			X	
8.4	Foreligger dokumentasjon på at utstyr som skal monitoreres er vedlikeholdt/kalibrert/validert?			X	
8.5	Er noe av utstyret fra pkt. 8.4 erstattet?			X	

Vedlikehold og utbytting av utstyr foregår etter plan ved avdeling
Utstyr benyttet i studien er ambulanser. Sjekk av disse inngår ikke i monitoreringsplanen.

9. Investigator Site File (ISF) / Trial Master File (TMF)		**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
9.1	Er alle nye forsøkspersoner ført på deltakerliste?	X			
9.2	Er ISF/TMF sjekket ved dette monitoreringsbesøket?		X		
9.3	Er noen av studiens essensielle dokumenter endret siden sist?	X			
9.4	Hvis ja, er dokumentene sendt til myndighetenes godkjenning?	X			
9.5	Oppbevares alle essensielle dokumenter i ISF/TMF?	X			

Deltakerlisten er todelt. Den er omtalt i en tidligere rapport.
Denne ble ikke sjekket fysisk ved dette besøket, men på spørsmål blir det opplyst at lister føres kontinuerlig.
TMF/ISF ble ikke sjekket ved dette besøket, da neste besøk er ved lukking av database, og det er naturlig å sjekke permen da.

Protokoll og samtykkeinformasjon er oppdatert, det er omtalt ved punkt 2 i denne rapporten

Det er lagt til et datapunkt i Viedoc, som gjør at «repeaters» kan identifiseres. Dette er kandidater som har flere, uavhengige besøk i databasen; og ikke det samme som «recurrence», som er kandidater med gjentatte besøk i studien innenfor 12 timer.

10. Avvik		**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
10.1	Er det oppdaget avvik på dette besøket som ikke er beskrevet over?		X		
10.2	Er samtlige avvik dokumentert iht. sponsors plan for håndtering av avvik i studien?	X			

Dette er et studiesenter med særdeles god oversikt over studieprosedyrer, -papirer og data.
Det er også dokumentert, og meget god, kontakt mellom studieledelse og studiemedarbeidere.

16.1.8 Audit certificates

MONITORERINGSRAPPORT
NINA-1

11. Monitoreringsplan		**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
11.1	Er monitoreringsplanen til studien fulgt ved dette monitoreringsbesøket?	X			
11.2	Er alle avvik fra forrige monitoreringsbesøk rettet opp?	X			
11.3	Bør monitoreringsplanen revideres for dette senteret?			X	

Monitoreringsplanen ble fulgt med tanke på alle pasienter. Det som ikke ble fulgt i planen er notert under individuelle punkter.

Alle oppgaver fra forrige besøk var utført.

Grunnet Covid-19 ble rapport ikke ferdigstilt før mai 2020.
Tall og opplysninger nevnt i rapporten var korrekte etter monitorering i februar/mars 2020

12. Underskrifter

Rapporten er skrevet av:

Maryam Friis-Ottessen
Monitor

20.05.20
Dato

A. Skulberg
Sponsor/nasjonal koordinerende utprøver

25/5-20
Dato

Et signert eksemplar arkiveres i Trial Master File hos sponsor og et signert eksemplar sendes monitor.

16.1.8 Audit certificates

MONITORERINGSRAPPORT
NINA-1

VEDLEGG 1

OPPGAVER TIL OPPFØLGING ETTER MONITORERINGSBESØK

Protokoll	Hele studiens navn	**Dato for besøk**	
Studiesenter		**EudraCT nr.**	
Hovedutprøver		**Rapport nr.**	

13. Oppgaver til oppfølging	**Ingen ☒**		
Oppgave	**Tidsfrist**	**Utført av**	**Dato**
Kommentar:			

14. Underskrifter

Det bekreftes at punktene til oppfølging er utført.

Navn	Rolle i studien	Dato

Et signert eksemplar arkiveres i Investigator Site File hos hovedutprøver og et signert eksemplar sendes monitor.

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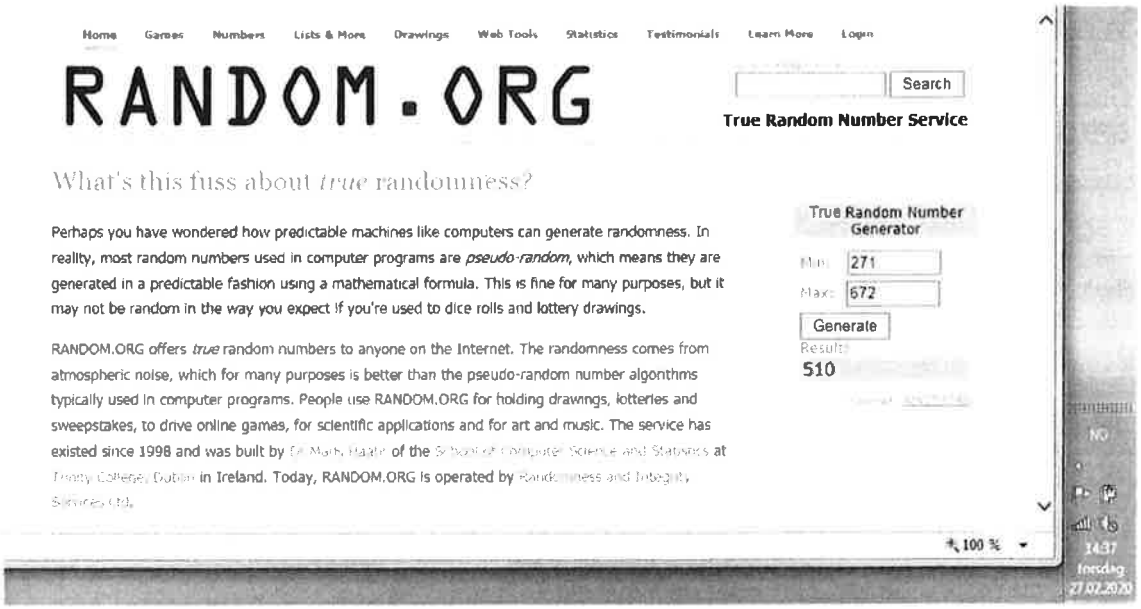
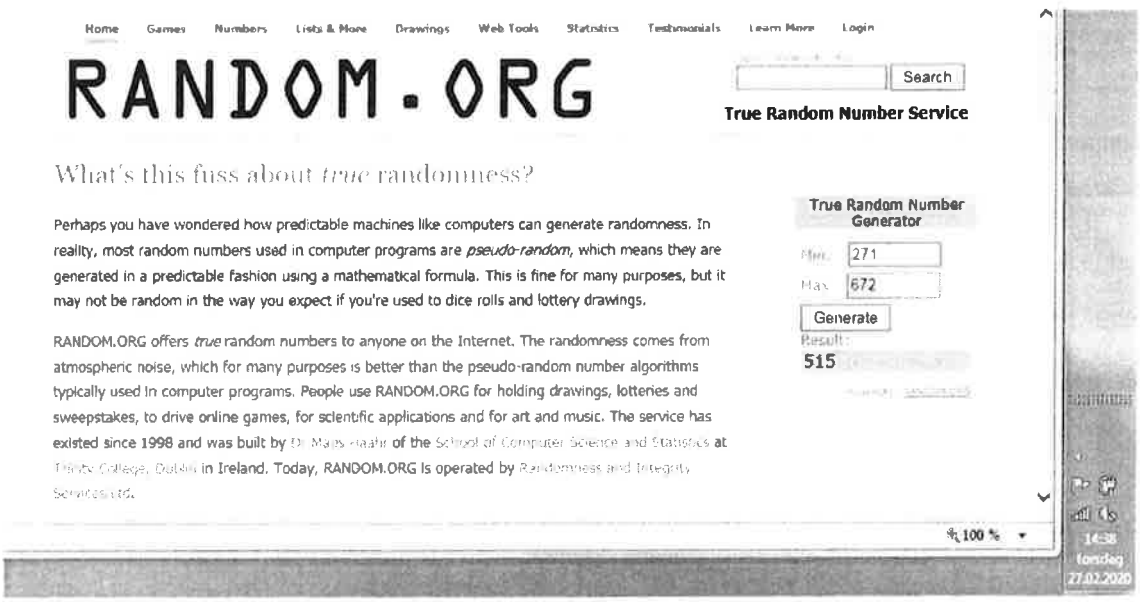
Pasienter til fullmonitorering 27.02 2020, NINA-1 studie

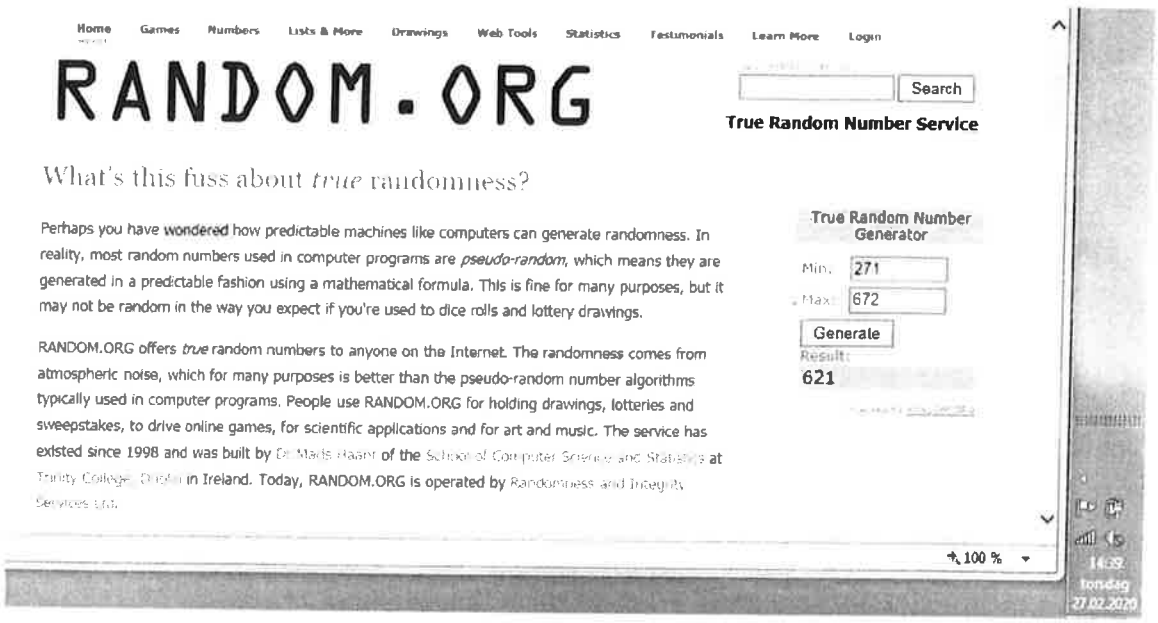


Ok: inkludert pasient

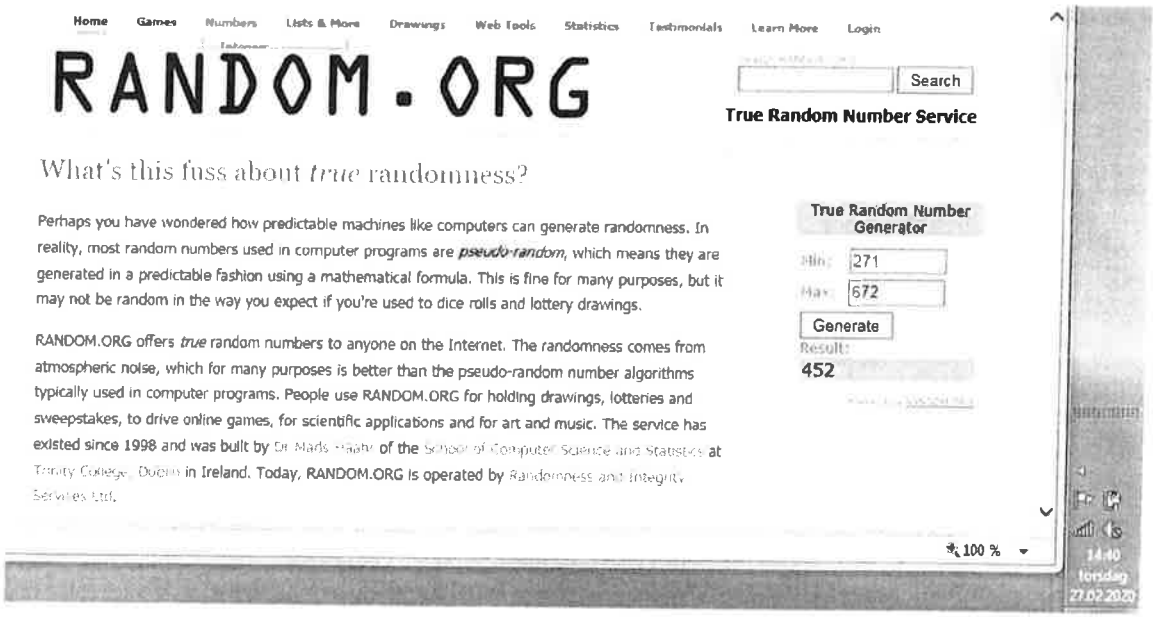


Ikke en inkludert pasient

16.1.8 Audit certificates



Ikke inkludert pasient



Ok: inkludert pasient

16.1.8 Audit certificates

16.1.8 Audit certificates

MONITORERINGSRAPPORT
NINA-1

		Rapport nr.	**6**
Protokoll	**NTNU INTRANASAL NALOXONE TRIAL Double blinded, double dummy, randomised controlled trial of intranasal naloxone for pre-hospital use**	**Dato for besøk**	**7-8 september 2020**
Studiesenter	**OUS**	**EudraCT nr.**	**2016-004072-22**
Hovedutprøver	**Arne Skulberg / Anne-Cathrine Braarud**	**Sponsor**	**NTNU**

	Navn	**Rolle**
Studiepersonell til stede	**Arne Skulberg**	**Koordinerende utprøver**
Monitorering utført	**På studiesenter**	
Monitor(er)	**Mariann Friis-Ottessen**	
Monitoreringsplan	**Versjonsnummer: 3.0, 14.05 2018**	

1. Status	**Siden oppstart**		**Siden oppstart**
Planlagt inkludert på studiesenter:	200 (PP*)	Pågående:	Ingen
Screenet:	843	Utgått etter inklusjon:	8
Randomisert til nå:	266	Fullførte:	186 (PP)
Randomisert, men utgått før inklusjon:	46	Ikke samtykket/trukket samtykke:	27

*PP = per protokoll

Tall kommer i avslutningsrapport, når legemiddelregnskap er gjort opp

16.1.8 Audit certificates

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MONITORERINGSRAPPORT
NINA-1

2. Versjonsoversikt – kun gjeldende versjoner

2.1 REKs godkjenning:

Protokoll og protokollendringer (versjon og dato)	Versjon 3.3 06.03 2020
Godkjent dato (dato-måned-år)	03.04 2020
Pasientinformasjon/samtykke (versjon og dato)	-
Godkjent dato (dato-måned-år)	-

2.2 SLVs godkjenning:

Protokoll og protokollendringer (versjon og dato)	Versjon 3.3 06.03 2020
Godkjent dato (dato-måned-år)	08.04 2020

Det er kommet en ny protokollversjon, som er godkjent av både REK og SLV

Informasjonsbrevet og -kortet som deltakere får etter inklusjon er ikke endret fra forrige monitoreringsbesøk

3. Studiesenter		Ja	Nei	Ikke relevant	Ikke sjekket
3.1	Har det vært endringer i studiepersonell?	X			
3.2	Er det tilstrekkelig ressurser på avdelingen for å gjennomføre studien?	X			
3.3	Er studiepersonell gjort kjent med vesentlige endringer i studien?	X			

Studien har stadig opplæring av nytt ambulansepersonell, og også repetisjonskurs.
Dette er dokumentert i NAKOS (www.nakos.no), der det finnes et eget kurs for studien. Dette gjennomføres i tillegg til en gjennomgang av studien med sentralt studiepersonell, før en deltaker er sertifisert som studiemedarbeider. Kursvarighet er 4+4 timer.

Monitor får utskrift av tjenestenummer registrert i databasen, og kan med dette sjekke at de som inkluderer i studien har gjennomført opplæring.

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4. Pasientinformasjon og samtykkeerklæring		Ja	Nei	Ikke relevant	Ikke sjekket
4.1	Finnes det en korrekt signert og datert samtykkeerklæring for hver av de gjennomgåtte forsøkspersonene?		X		
4.2	Er ICH-GCP fulgt ved innhenting av samtykkeerklæring?		X		

Studien har dispensasjon fra de generelle samtykkeprosedyrene, og det deles ut informasjon i etterkant av administrert studiemedisin.

Det er god oversikt over deltakere som ikke ønsker å være med i studien, også dem som trekker samtykket i etterkant.

5. CRF og kildedata		Ja	Nei	Ikke relevant	Ikke sjekket
5.1	Finnes det en kildedataliste i ISF?	X			
5.2	Oppbevares alle kildedata i henhold til kildedataliste?	X			
5.3	Er forsøkspersonene inkludert iht. protokoll?		X		
5.4	Er det avdekket avvik mellom CRF og kildedata på dette besøket?	X			
5.5	Er CRF signert, datert og tilfredsstillende utfylt?	X			
5.6	Inneholder CRF forsøkspersonenes fulle navn og/eller fødselsnummer?		X		

Dette var det siste monitoreringsbesøk for studien. Alle pasienter er monitorert etter monitoreringsplanen. Noen mindre avvik ble notert som queries i Viedoc, og løses fortløpende av studiegruppen.

Pasient 01-703 ble fullmonitorert.

6. Uønskede hendelser		Ja	Nei	Ikke relevant	Ikke sjekket
6.1	For hendelser sjekket iht. monitoreringsplan; er alle AEer registrert og fulgt opp?	X			
6.2	For hendelser sjekket iht. monitoreringsplan; er alle SAEer rapportert til sponsor og fulgt opp på senteret?	X			
6.3	Ved besøk hos sponsor, har sponsor rapportert ev. SUSARer til SLV?			X	
6.4	Har sponsor sendt årsrapport til SLV innen tidsfristen?			X	

Ingen nye SAE-er siden forrige monitoreringsbesøk.

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MONITORERINGSRAPPORT
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7. Utprøvingspreparat(er)		Ja	Nei	Ikke relevant	Ikke sjekket
7.1	Foreligger nyeste utgave av IB eller SmPC?	X			
7.2	Gjennomføres randomiseringsprosedyren som beskrevet?	X			
7.3	Er ev. blinding av studien ivaretatt?	X			
7.4	Er ev. avblinding av forsøkspersoner utført i henhold til prosedyre?	X			
7.5	Er forsyning og holdbarhet av utprøvingspreparat(ene) tilstrekkelig?	X			
7.6	Oppbevares utprøvingspreparat(ene) i henhold til merking/ pakningsvedlegget?	X			
7.7	Føres temperaturlogg?	X			
7.8	Dersom det foreligger prosedyre(r) for mottak, håndtering, merking, oppbevaring og/eller destruksjon av utprøvingspreparat(ene), blir denne fulgt?	X			
7.9	Er prosedyrer for legemiddelregnskap etablert for hver forsøksperson og samlet for hvert studiesenter?	X			
7.10	Oppbevares rekvisisjon til/fra apoteket?	X			
7.11	Har forsøkspersonene fått informasjon om bruk, oppbevaring og retur av utprøvingspreparat(er)?			X	

Foreløpig foreligger versjon 7 av IB. 06.03 2020

Legemiddelregnskapet blir sjekket i forbindelse med avsluttende monitoreringsrapport, etter avtale med studiegruppen.

8. Fasiliteter, lab og utstyr		Ja	Nei	Ikke relevant	Ikke sjekket
8.1	Er det vilkår/forhold som bør diskuteres med involverte avdelinger?		X		
8.2	Er referanseområdene fortsatt de samme?			X	
8.3	Er forskningsbiobanker forsvarlig oppbevart?			X	
8.4	Foreligger dokumentasjon på at utstyr som skal monitoreres er vedlikeholdt/kalibrert/validert?			X	
8.5	Er noe av utstyret fra pkt. 8.4 erstattet?			X	

Vedlikehold og utbytting av utstyr foregår etter plan ved avdeling
Utstyr benyttet i studien er ambulanser. Sjekk av disse inngår ikke i monitoreringsplanen.

16.1.8 Audit certificates

MONITORERINGSRAPPORT
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9. Investigator Site File (ISF) / Trial Master File (TMF)		Ja	Nei	Ikke relevant	Ikke sjekket
9.1	Er alle nye forsøkspersoner ført på deltakerliste?	X			
9.2	Er ISF/TMF sjekket ved dette monitoreringsbesøket?		X		
9.3	Er noen av studiens essensielle dokumenter endret siden sist?	X			
9.4	Hvis ja, er dokumentene sendt til myndighetenes godkjenning?	X			
9.5	Oppbevares alle essensielle dokumenter i ISF/TMF?	X			

Protokoll er oppdatert, det er omtalt ved punkt 2 i denne rapporten

ISF blir gjennomgått sammen med studiegruppen i forbindelse med lagring av studiemateriale og sending av aktuelle dokumenter til TMF ved St.Olav. Det vil dokumenteres i en avsluttende monitoreringsrapport.

10. Avvik		Ja	Nei	Ikke relevant	Ikke sjekket
10.1	Er det oppdaget avvik på dette besøket som ikke er beskrevet over?		X		
10.2	Er samtlige avvik dokumentert iht. sponsors plan for håndtering av avvik i studien?	X			

Senteret har hatt veldig høy compliance gjennom hele studieforløpet.

11. Monitoreringsplan		Ja	Nei	Ikke relevant	Ikke sjekket
11.1	Er monitoreringsplanen til studien fulgt ved dette monitoreringsbesøket?	X			
11.2	Er alle avvik fra forrige monitoreringsbesøk rettet opp?	X			
11.3	Bør monitoreringsplanen revideres for dette senteret?			X	

16.1.8 Audit certificates

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MONITORERINGSRAPPORT
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12. Underskrifter

Rapporten er skrevet av:

Marianne Friis-Ottesen — 11/9-20
Monitor — Dato

[signature] CI — 11/09/20
Sponsor/nasjonal koordinerende utprøver — Dato

Et signert eksemplar arkiveres i Trial Master File hos sponsor og et signert eksemplar sendes monitor.

16.1.8 Audit certificates

16.1.8 Audit certificates

MONITORERINGSRAPPORT
NINA-1

VEDLEGG 1

OPPGAVER TIL OPPFØLGING ETTER MONITORERINGSBESØK

Protokoll	Hele studiens navn NTNU Inflammed Melanom TNM	**Dato for besøk**	7-8/9 - 20
Studiesenter	Oslo	**EudraCT nr.**	2016-004022-27
Hovedutprøver	A.C. Braarud / A. Blomberg	**Rapport nr.**	

13. Oppgaver til oppfølging	**Ingen ☒**		
Oppgave	**Tidsfrist**	**Utført av**	**Dato**
Kommentar:			

14. Underskrifter

Det bekreftes at punktene til oppfølging er utført.

Anne-Cathrine Braarud	PI - Oslo	11/9-20
Navn	Rolle i studien	Dato

Et signert eksemplar arkiveres i Investigator Site File hos hovedutprøver og et signert eksemplar sendes monitor.

16.1.8 Audit certificates

16.1.8 Audit certificates

INITIERINGSRAPPORT MONITORERING

Protokoll	NTNU, Intranasal Naloxone trial, NINA-1 studien	**Dato for besøk**	01.06.18
Studiesenter	Klinikk for akutt og mottaksmedisin,St. Olavs Hospital	**EudraCT nr.**	2016-004072-22
Hovedutprøver	Sindre Mellesmo	**Rapport nr.**	

	Navn				**Rolle**
Studiepersonell til stede	Jan Barstein Ida Tylleskär				Studie koordinator Utprøver
Monitorering utført (kryss av)	**På studiesenter**	**x**	**Per telefon**		
Monitor(er)	Harriet Selle				

Markeringer i grå bokser skal kommenteres

1. Essensielle dokumenter		**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
1.1	Er protokoll og ev. protokolltillegg signert og datert av sponsor og hovedutprøver?	x			
1.2	Er en Investigator Site File (ISF) eller en Trial Master File (TMF), etablert og oppdatert? (*Benytt mal*)	x			
Kommentar:					

2. Godkjenninger		**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
2.1	• Interne godkjenninger	x			
	• REK	x			
	• SLV	x			
	• Andre (f. eks. Hdir)	x			
2.2	Er dette senteret omfattet av godkjenningene?	x			
Kommentar:					

16.1.8 Audit certificates

INITIERINGSRAPPORT MONITORERING

3. Versjonsoversikt

3.1 REKs godkjenning:

Protokoll og protokollendringer (versjon og dato)	NINA-1 Versjon 3.0 09.01.18		
Godkjent dato (dato-måned-år)	05.02.18		
Informasjonsskriv/samtykke (versjon og dato)	Egen prosedyre for hvordan dette avklares		
Godkjent dato (dato-måned-år)			

3.2 SLVs godkjenning:

Protokoll og protokollendringer (versjon og dato)	NINA-1 Versjon 3.0 09.01.18		
Godkjent dato (dato-måned-år)	12.01.18		

Kommentar:

4. Ekstern registrering		**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
4.1	Hos sponsor, er prosjektet registrert i ClinicalTrials.gov eller lignende?	X			
4.2	Hos nasjonal koordinerende utprøver (NKU) er prosjektet registrert på kliniskestudier.HelseNorge.no?		X		

Kommentar:

5. Studiepersonell		**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
5.1	Er delegeringslogg fylt ut og signert?	X			
5.2	Foreligger signert og datert CV fra sentrale medarbeidere?	X			
5.3	Har sentrale medarbeidere dokumenterte ICH-GCP-kunnskaper?	X			
5.4	Har studiepersonellet fått opplæring i protokoll, føring av CRF og gjennomføring av studien?	X			

Kommentar:Pkt 5.1 to personer fra apoteket har ikke signert delegeringslogg. Pkt 5.3 mangler GCP dokumentasjon på hovedutprøver

16.1.8 Audit certificates

INITIERINGSRAPPORT MONITORERING

6. Ressurser		Ja	Nei	Ikke relevant	Ikke sjekket
6.1	Har avdelingen(e) de nødvendige ressurser for gjennomføring av studien?	x			
Kommentar:					

7. Avtaler		Ja	Nei	Ikke relevant	Ikke sjekket
7.1	Foreligger det avtaler mellom sykehus og sponsor, og/eller andre?	x			
7.2	Er det inngått avtale med et laboratorium?			x	
7.3	Er det inngått avtale med et apotek?	x			
7.4	Er det inngått avtale med et legemiddelfirma?	x			
7.5	Er forsikring (via Legemiddelansvarsforeningen, LAF) tegnet?	x			
Kommentar:					

8. Fasiliteter og utstyr (ekskl. laboratoriet)		Ja	Nei	Ikke relevant	Ikke sjekket
8.1	Er fasiliteter/utstyr på avdelingen(e) hensiktsmessige for gjennomføringen av studien?	x			
8.2	Er det utarbeidet retningslinjer for bruk, ev. vedlikeholdsavtaler?	x			
8.3	Er utstyret oppdatert og kalibrert/validert? Spesifiser utstyr:	x			
8.4	Er forskningsbiobanker forsvarlig oppbevart? (spesifiser lagringssted) *(Hvis sjekking av forskningsbiobank er en del av monitoreringsplanen, bruk mal Monitorering av forskningsbiobank.)*			x	
Kommentar:					

9. Laboratorieprøver		Ja	Nei	Ikke relevant	Ikke sjekket
9.1	Er nødvendig lab. utstyr, personell og fasiliteter på plass?	x			
9.2	Er prosedyrer for håndtering, oppbevaring og ev. forsendelse av laboratorieprøver etablert?			x	
9.3	Finnes det akkreditering/ekstern kvalitetskontroll for aktuelle analyser?			x	
9.4	Finnes det referanseverdier for relevante undersøkelser?			x	
9.5	Skal laboratorieprøver sendes til andre laboratorier?		x		
Kommentar:					

10. Forsøkspersonene		Ja	Nei	Ikke relevant	Ikke sjekket
10.1	Er forsøkspersonene pasienter med egen journal?	x			
10.2	Vil journalnotat skrives for hvert studiebesøk?	x			
10.3	Er screeningliste opprettet?	x			
10.4	Er deltakerliste opprettet?	x			

16.1.8 Audit certificates

INITIERINGSRAPPORT MONITORERING

10.5	Er studiepersonell informert om at forsøkspersonene skal ha kopi av hele informasjonsskjemaet med underskrevet samtykkeerklæring, og at originalen skal lagres i ISF?			x	
10.6	Er studiepersonell informert om at ingen studiespesifikke prosedyrer kan gjennomføres før samtykkeerklæring er innhentet?			x	
Kommentar:					

11. Utprøvingspreparat(er)		Ja	Nei	Ikke relevant	Ikke sjekket
11.1	Foreligger nyeste utgave av IB eller SmPC?	x			
11.2	Er randomiseringen beskrevet?	x			
11.3	Er avblindingsprosedyre beskrevet?	x			
11.4	Finnes prosedyrer for mottakelse, håndtering, oppbevaring og destruksjon av utprøvingspreparat(ene)?	x			
11.5	Oppbevares utprøvingspreparat(er) korrekt iht. merking/pakningsvedlegg?	x			
11.6	Føres temperaturlogg?	x			
11.7	Er prosedyrer for legemiddelregnskap etablert for hver forsøksperson og samlet for hvert studiesenter?	x			
11.8	Oppbevares utprøvingspreparat(er) på avdelingen?	x			
11.9	Foreligger et eksempel på merking av utprøvingspreparat(er)? (*F.eks. i protokoll*)?	x			
Kommentar:					

12. CRF		Ja	Nei	Ikke relevant	Ikke sjekket
12.1	Er utfyllbare CRF-er tilgjengelige? Ev. spesifiser versjon.	x			
12.2	Ligger en kopi av CRF-en i Investigator Site File/Trial Master File?		x		
12.3	Oppbevares aktive CRF-er på et sted med begrenset tilgang?	x			
12.4	Er studiepersonell informert om prosedyre for innsendelse av CRF?			x	
Kommentar: Pkt.12.2 får tilsendt kopi av e-CRF når Viedoc er ferdigstilt, som så legges i ISF					

13. Kildedokumentasjon		Ja	Nei	Ikke relevant	Ikke sjekket
13.1	Er kildedataoversikt laget?	x			
Kommentar:					

14. Håndtering av alvorlige hendelser SAE/SUSAR		Ja	Nei	Ikke relevant	Ikke sjekket
14.1	Er studiepersonell informert om SAE-registrering og rapportering til sponsor?	x			
14.2	Er senteret (sponsor) informert om sikkerhetsrapportering (SUSAR og årsrapport) til SLV?	x			
Kommentar:					

16.1.8 Audit certificates

INITIERINGSRAPPORT MONITORERING

15. Arkivering		Ja	Nei	Ikke relevant	Ikke sjekket
15.1	Er plan for arkivering og lagring av studiedokumenter, inkludert deltakerliste beskrevet?	X			
Kommentar:					

16. Monitorering		Ja	Nei	Ikke relevant	Ikke sjekket
16.1	Foreligger avtale om monitorering av studien?	X			
16.2	Foreligger monitoreringsplan?	X			
Kommentar: Monitoreringsavtale for AKF, NTNU signeres 04.06.18					

17. Status		Ja	Nei	Ikke relevant	Ikke sjekket
17.1	Kan inklusjon av forsøkspersoner starte?	X			
Kommentar:					

18. Oppgaver til oppfølging

Dato	Oppgave	Tidsfrist	Ansvar	Utført
01.06.18	Delegeringslogg mangler to signaturer fra apoteket	snarest	Ida Tylleskär	
01.06.18	GCP dokumentasjon mangler hos hovedutprøver	snarest	Ola Dale	
01.06.18	Tilsendt kopi av e-CRF når den er ferdigstilt	snarest	Arne Skulberg	
Kommentar:				

16.1.8 Audit certificates

INITIERINGSRAPPORT MONITORERING

19. Underskrifter

Rapporten er skrevet av:

Harriet Selle _____ 04.06.18

Monitor Dato

Som hovedutprøver har jeg lest rapporten og tar ansvar for å følge opp mangler.

_____ 13/6-2018

Hovedutprøver Dato

Sindre Mellesmo
Klinikksjef
Hpr nr: 2129221
Klinikk for akutt- og mottaksmedisin
St. Olavs Hospital HF

_____ 6/6-2018

Sponsor / nasjonal koordinerende utprøver Dato

Et signert eksemplar skal arkiveres i ISF, et signert eksemplar oppbevares hos til sponsor, et signert eksemplar oppbevares av monitor.

16.1.8 Audit certificates

MONITORERINGSRAPPORT

Protokoll	NTNU, Intranasal Naloxone Trial, NINA-1 studien	**Dato for besøk**	13.08.18
Studiesenter	Klinikk for akutt og mottaksmedisin, St. Olavs Hospital	**EudraCT nr.**	2016-004072-22
Hovedutprøver	Sindre Mellesmo	**Rapport nr.**	1

	Navn				**Rolle**
Studiepersonell til stede	Ida Tylleskär Jostein Dale				**Utprøver** **PI assistent**
Monitorering utført (kryss av)	**På studiesenter**	x	**Per telefon**		
Monitor(er)	Harriet Selle				

Markeringer i grå bokser skal kommenteres

1. Forsøksperson status	**Siden oppstart**	**Siden siste besøk**		**Siden oppstart**	**Siden siste besøk**
Planlagt inkludert:			Pågående:		
Screenet:	17		Utgått etter inklusjon/ randomisering:	1	
Inkludert/randomisert til nå:	4		Fullført:		
Utgått før inklusjon/ randomisering					
Kommentar:					

2. Monitoreringsplan		**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
2.1	Er monitoreringsplanen til studien fulgt ved dette monitoreringsbesøket?	x			
2.2	Er alle avvik fra forrige monitoreringsbesøk rettet opp?	x			
2.3	Bør monitoreringsplanen revideres for dette senteret? *(Besvares når monitoreringsoppgavene er utført)*		x		
Kommentar:					

MONITORERINGSRAPPORT

3. Versjonsoversikt			
3.1 REKs godkjenning:			
Protokoll og protokollendringer (versjon og dato)	NINA-1 Versjon 3.0 09.01.18		
Godkjent dato (dato-måned-år)	05.02.18		
Pasientinformasjon/samtykke (versjon og dato)	Egen prosedyre for hvordan dette avklares		
Godkjent dato (dato-måned-år)	05.02.18		
3.2 SLVs godkjenning:			
Protokoll og protokollendringer (versjon og dato)	NINA-1 Versjon 3 09.01.18		
Godkjent dato (dato-måned-år)	12.01.18		
Kommentar:			

4. Pasientinformasjon og samtykkeerklæring		**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
4.1	Finnes det en korrekt signert og datert samtykkeerklæring for hver av de gjennomgåtte forsøkspersonene? *Bruk kommentarfeltet nedenfor til å angi hvilke nr. som ble gjennomgått på monitoreringen denne gang*				
4.2	Er ICH-GCP fulgt ved innhenting av samtykkeerklæring?				
Kommentar: Punkt 4: Egen prosedyre for hvordan samtykke innhentes i denne studien					

5. Protokollavvik, avvik fra ICH-GCP		**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
5.1	Er protokollavvik/avvik fra ICH-GCP avdekket?		x		
5.2	Er protokollavvik dokumentert og, om nødvendig, forklart?			x	
5.3	Ved protokollavvik, er avvikene rettet opp og er det innført forebyggende tiltak?			x	
Kommentar:					

6. Uønskede hendelser		**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
6.1	Er alle relevante hendelser (AE) registrert og fulgt opp?			x	
6.2	Er alle SAEer rapportert til sponsor og fulgt opp på senteret?			x	
6.3	Ved besøk hos sponsor, har sponsor rapportert ev. SUSAR(er) til SLV?			x	
6.4	Har sponsor sendt inn årsrapport(er) til SLV?			x	

MONITORERINGSRAPPORT

Kommentar:

7. CRF og kildedata		Ja	Nei	Ikke relevant	Ikke sjekket
7.1	Oppbevares alle kildedata som avtalt?	x			
7.2	Er alle inkluderte forsøkspersoner inkludert iht. protokollen?	x			
7.3	Er det avdekket avvik mellom CRF og kildedata på dette besøket? *Bruk kommentarfeltet nedenfor til å angi hvilke nr. som ble gjennomgått på monitoreringen denne gang.*		x		
7.4	Er CRF signert, datert og tilfredsstillende utfylt?	x			
7.5	Inneholder CRF forsøkspersonenes fulle navn og/eller fødselsnummer?		x		
Kommentar:					

8. Utprøvingspreparat(er)		Ja	Nei	Ikke relevant	Ikke sjekket
8.1	Gjennomføres randomiseringsprosedyrene som avtalt?	x			
8.2	Er ev. blinding av studien ivaretatt?	x			
8.3	Er ev. avblinding av forsøkspersoner utført i henhold til prosedyre?			x	
8.4	Er legemiddelhåndteringen i henhold til bestemt prosedyre?	x			
8.5	Oppbevares utprøvingspreparat(ene) i henhold til merking/ pakningsvedlegget (f.eks. temperatur, sollys osv.)?	x			
8.6	Foreligger/følges prosedyre vedrørende merking av utprøvingspreparat(ene)?	x			
8.7	Er forsyning og holdbarhet av utprøvingspreparat(ene) tilstrekkelig?	x			
8.8	Oppbevares rekvisisjon til/fra apoteket?	x			
8.9	Har forsøkspersonene fått informasjon om bruk, oppbevaring og retur av utprøvingspreparat(er)?			x	
8.10	Ved besøk hos sponsor, er årlig gjennomgang/fornyelse av IB/SmPC gjennomført?	x			
Kommentar:					

9. Medisinsk utstyr, forskningsbiobanker m.m. tilknyttet studien		Ja	Nei	Ikke relevant	Ikke sjekket
9.1	Er det vilkår/forhold som bør diskuteres med involverte avdelinger?		x		
9.2	Er referanseområdene fortsatt de samme? *(Hvis ikke, informer datahåndterer hvis aktuelt)*			x	
9.3	Er forskningsbiobanker forsvarlig oppbevart? (*Hvis sjekking av forskningsbiobank er en del av monitoreringsplanen, bruk mal Monitorering av forskningsbiobank.*).			x	
9.4	Er instrumenter og utstyr vedlikeholdt og kalibrert iht. rutinene?	x			
9.5	Er instrumenter eller utstyr erstattet?		x		
Kommentar:					

16.1.8 Audit certificates

MONITORERINGSRAPPORT

10. Studiesenter		**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
10.1	Har det vært endringer i studiepersonell?		x		
10.2	Er delegeringsloggen i ISF/TMF fylt ut og oppdatert?	x			
10.3	Er det tilstrekkelig ressurser på avdelingen for å gjennomføre studien?	x			
10.4	Er studiepersonell gjort kjent med vesentlige endringer i studien (protokollen, IB/SmPC, pasientinformasjon)?	x			
10.5	Hvis studien er lukket for inklusjon av forsøkspersoner, har nasjonal koordinerende utprøver (NKU) oppdatert informasjonen i HelseNorge.no? *Gjelder også ved endring i deltakende sentra, ny hovedutprøver, endring av kontaktinformasjon o.l..*			x	
10.6	Hos sponsor, er ClinicalTrials.gov oppdatert i løpet av de siste 6 månedene?	x			
Kommentar:					

11. Investigator Site File (ISF) / Trial Master File (TMF)		**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
11.1	Er alle nye forsøkspersoner ført på deltakerliste?	x			
11.2	Er monitors besøkslogg oppdatert?	x			
11.3	Er ISF/TMF sjekket ved dette monitoreringsbesøket? Spesifiser mangler.	x			
11.4	Er noen av studiens essensielle dokumenter endret siden sist?		x		
11.5	Hvis ja, er dokumentene sendt til myndighetenes godkjenning?			x	
11.6	Oppdateres og vedlikeholdes alle essensielle dokumenter?	x			
11.7	Oppbevares alle essensielle dokumenter i TMF/ISF som avtalt?	x			
Kommentar:					

12. Oppgaver til oppfølging*				
Dato	**Oppgave**	**Tidsfrist**	**Ansvar**	**Utført**
13.08.18	Ingen oppgaver til oppfølging			

13. Underskrifter

Rapporten er skrevet av:

_____ _____

Monitor Dato

Som hovedutprøver har jeg lest rapporten og tar ansvar for å følge opp mangler.

_____ _____

Hovedutprøver Dato

_____ _____

Sponsor/nasjonal koordinerende utprøver Dato

Et signert eksemplar skal arkiveres i ISF, et signert eksemplar oppbevares av sponsor, et signert eksemplar oppbevares av monitor.

16.1.8 Audit certificates

AVSLUTNINGSRAPPORT
NINA-1

Protokoll	NTNU Intranasal Naloxone Trial		**Dato for besøk**	27.08.2020
Studiesenter	St. Olavs hospital, ~~Prehospital division~~ Klin akuttmottaksmed	**EudraCT nr.**	2016-004072-22	
Hovedutprøver	Jostein Dale, ~~NTNU~~ St. Olav	**Sponsor**	Øystein Risa, NTNU	

Studiepersonell til stede	Arne Skulberg Jostein Dale,		NCI PI, St. Olavs Hospital	
Monitorering utført	**På studiesenter**	X	**Fjernmonitorering**	
Monitor(er)	Inger Storaker og Sigve Nyvik Aas			
Monitoreringsplan	**Versjonsnummer:** Versjon 3.0, datert 09.01.2018			

1. Status	**Siden oppstart**		**Siden oppstart**
Screenet:	126	Utgåtte etter inklusjon/ randomisering:	3
Inkludert/randomisert til nå:	18	Fullførte:	15
Utgått før inklusjon/randomisering:	108		

Kommentar:
125 card i Viedoc på St. Olav, databasenummer 02-087 mangler i Viedoc men ligger i eksklusjonslog.

Pasientene som er monitorert er:
02-061
02-085
02-088
02-094
02-095
02-096
02-107
02-111
02-113

16.1.8 Audit certificates

AVSLUTNINGSRAPPORT
NINA-1

Markeringer i grå bokser skal kommenteres

2. Versjonsoversikt – kun gjeldende versjoner

2.1 REKs godkjenning:

Protokoll og protokollendringer (versjon og dato)	NINA-1 Versjon 3.3, 06.03.20
Godkjent dato (dato-måned-år)	03.04.20
Pasientinformasjon/samtykke (versjon og dato)	Versjon 5, 02.05.19
Godkjent dato (dato-måned-år)	15.11.19

2.2 SLVs godkjenning:

Protokoll og protokollendringer (versjon og dato)	NINA-1 Versjon 3.3, 06.03.20
Godkjent dato (dato-måned-år)	31.03.20

Kommentar:

3. Studiesenter (St. Olavs)	**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
3.1 Har det vært endringer i studiepersonell?	X			

Kommentar:
Arne Skulberg har overtatt NCI rolle for Ola Dale, korriger delegeringslog i TMF / ISF.

4. Avsluttende studiestatus	**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
4.1 Er studien avsluttet i henhold til planen?	X			
4.2 Ble studien avbrutt av sikkerhetsgrunner?		X		
4.3 Hvis ja på spørsmål 4.2; er dette meldt myndighetene innen 15 dager?			X	

Kommentar:

16.1.8 Audit certificates

AVSLUTNINGSRAPPORT
NINA-1

5. CRF og kildedata		Ja	Nei	Ikke relevant	Ikke sjekket
5.1	Er alle oppgaver fra tidligere monitoreringsbesøk ved St. Olavs fulgt opp?	X			
5.2	Finnes det en kildedataliste i ISF?	X			
5.3	Oppbevares alle kildedata i henhold til kildedataliste?	X			
5.4	Er forsøkspersonene inkludert iht. protokoll?	X			
5.5	Er det avdekket avvik mellom CRF og kildedata på dette besøket?		X		
5.6	Er CRF signert, datert og tilfredsstillende utfylt?	X			
5.7	Inneholder CRF forsøkspersonenes fulle navn og/eller fødselsnummer?		X		
5.8	Er CRF for hver forsøksdeltaker tilfredsstillende fylt ut og endelig godkjent (undertegnet) av en utprøver?	X			
Kommentar: 5.7: Studiemappene må ryddes for sensitive opplysninger som oppbevares andre steder, for eksempel ambulansejournal.					

6. Uønskede hendelser		Ja	Nei	Ikke relevant	Ikke sjekket
6.1	For hendelser sjekket iht. monitoreringsplan; er alle AEer registrert og fulgt opp?	X			
6.2	For hendelser sjekket iht. monitoreringsplan; er alle SAEer rapportert til sponsor og fulgt opp på senteret?	X			
6.3	Ved besøk hos sponsor, har sponsor rapportert ev. SUSARer til SLV?			X	
6.4	Har sponsor sendt årsrapport til SLV innen tidsfristen?	X			
Kommentar: 6.2 Ingen SAE i studien ved St. Olav, 1 SAE ved OUS.					

7. Utprøvingspreparat		Ja	Nei	Ikke relevant	Ikke sjekket
7.1	Er ev. blinding av studien ivaretatt?	X			
7.2	Er ev. avblinding av forsøkspersoner utført i henhold til prosedyre?	X			
7.3 denne	Dersom det foreligger prosedyre(r) for mottak, håndtering, merking, oppbevaring og/eller destruksjon av utprøvingspreparat(ene), blir fulgt?	X			
7.4 og	Er prosedyrer for legemiddelregnskap etablert for hver forsøksperson samlet for hvert studiesenter?	X			
7.5	Oppbevares rekvisisjon til/fra apoteket?	X			
7.6 dersom	Foreligger dokumentasjon på destruksjon av utprøvingspreparat det ikke er spesifisert i protokoll eller avtale at utprøvingspreparat destrueres iht. sykehusets eller apoteks rutiner?	X			
7.7	Er avsluttende legemiddelregnskap gjort opp?		X		
Kommentar: 7.7 Totalregnskap for studiemedisin fullføres etter data lock.					

16.1.8 Audit certificates

AVSLUTNINGSRAPPORT
NINA-1

8. Investigator's Site File (ISF)/Trial Master File (TMF)		Ja	Nei	Ikke relevant	Ikke sjekket
8.1	Er ISF/TMF oppdatert og komplett ved avslutning og klar til arkivering?		X		
8.2	For ISF i multisenterstudie: Har utprøver sendt kopi til sponsor av dokumenter som skal arkiveres i TMF?	X			
8.3	For TMF i multisenterstudie: Foreligger det fra alle sentrene kopier av dokumenter som skal arkiveres i TMF?	X			
Kommentar: 8.1: Det aller meste er på plass, oppdater permer i henhold til øvrige punkt i rapporten samt etter sluttmonitorering ved OUS.					

9. Avvik		Ja	Nei	Ikke relevant	Ikke sjekket
9.1	Er det oppdaget avvik på dette besøket som ikke er beskrevet over?		X		
9.2	Er samtlige avvik dokumentert iht. sponsors plan for håndtering av avvik i studien?			X	
9.3	Er tidligere avvik blitt korrekt fulgt opp av studiepersonalet?	X			
9.4	Er dokumentasjon på protokollavvik og tilhørende CAPAs arkivert på senteret?	X			
Kommentar:					

10. Arkivering		Ja	Nei	Ikke relevant	Ikke sjekket
10.1	Er det en plan for langtidsarkivering av ISF/TMF?	X			
10.2	Oppbevares identifikasjonslisten og samtykkene adskilt fra CRFen?	X			
10.3	Sikres det at kildedata eksisterer i hele arkiveringsperioden?	X			
Kommentar:					

11. Registrerings- og rapporteringsplikt		Ja	Nei	Ikke relevant	Ikke sjekket
11.1	Er studien meldt avsluttet i henhold til interne retningslinjer der det finnes slike?				X
11.2	Har sponsor meldt studien avsluttet til SLV innen fristen?				X
11.3	Har sponsor sendt sluttrapport for studien til SLV innen fristen?				X
11.4	Har sponsor sendt sluttmelding til REK?				X
11.5	Har resultatene blitt lagt inn i EudraCT?				X

16.1.8 Audit certificates

AVSLUTNINGSRAPPORT
NINA-1

11.6	Har NKU oppdatert informasjonen på spesialisthelsetjenestens hjemmesider?				X
11.7	Har sponsor oppdatert informasjonen i ClinicalTrials.gov?				X

Kommentar:
11.1 Please report the study as completed according to the hospital's internal guidelines.
11.2 Please report the study as completed to competent authority within 90 days after the study is completed.
11.3 Please send a final report for the study to the competent authority within 12 months after the study is completed.
11.4 Please send a final report for the study to the ethics committee as soon as possible after the study is completed.
11.5 Please updated EudraCT with the results of the study within 12 months after the study is completed.
11.6 Please update study information on the hospital's web pages as soon as possible after the study is completed.
11.7 Please update study information on ClinicalTrials.gov within 30 days after the study is completed.

12. Status for samarbeid med monitor		**Ja**	**Nei**	**Ikke relevant**	**Ikke sjekket**
12.1	Har prosjektet blitt monitorert i henhold til monitoreringsplanen?	X			
12.2	Er monitoreringen å betrakte som avsluttet fra monitors side?	X			

Kommentar:

13. Underskrifter

Rapporten er skrevet av:

Signe Myrdal Aas Inge Stavik — 28/8-20

Monitor — Dato

— 28/8/20

Sponsor/nasjonal koordinerende utprøver — Dato

p.v.c. Josbein Dale, PI St. Olavs hospital

Et signert eksemplar arkiveres i Trial Master File hos sponsor og et signert eksemplar sendes monitor.

16.1.8 Audit certificates

RANDOM.ORG

True Random Number Service

Do you own an iOS or Android device? Check out our app!

What's this fuss about *true* randomness?

Perhaps you have wondered how predictable machines like computers can generate randomness. In reality, most random numbers used in computer programs are *pseudo-random*, which means they are generated in a predictable fashion using a mathematical formula. This is fine for many purposes, but it may not be random in the way you expect if you're used to dice rolls and lottery drawings.

RANDOM.ORG offers *true* random numbers to anyone on the Internet. The randomness comes from atmospheric noise, which for many purposes is better than the pseudo-random number algorithms typically used in computer programs. People use RANDOM.ORG for holding drawings, lotteries and sweepstakes, to drive online games, for scientific applications and for art and music. The service has existed since 1998 and was built by Dr Mads Haahr of the School of Computer Science and Statistics at Trinity College, Dublin in Ireland. Today, RANDOM.ORG is operated by Randomness and Integrity Services Ltd.

True Random Number Generator

Min: 5

Max: 7

Generate

Result:

6

Powered by RANDOM.ORG

Deltaker nummer 6 ble valgt ut for fullmonitorering.
Dette tilsvarer viedoc ID 02-034.

FREE services

Games and Lotteries

Lottery Quick Pick is perhaps the Internet's most popular with over 280 lotteries
Keno Quick Pick for the popular game played in many countries
Coin Flipper will give you heads or tails in many currencies
Dice Roller does exactly what it says on the tin
Playing Card Shuffler will draw cards from multiple shuffled decks
Birdie Fund Generator will create birdie holes for golf courses

PAID service

Random Drawings

Q3.1 in the FAQ explains how to pick a winner for your giveaway for FREE
Third-Party Draw Service is the premier solution to holding random drawings online
Step-by-Step Guide explains how to hold a drawing with the Third-Party Draw Service

SV: eCRF NINA studien

SLETT SVAR SVAR ALLE VIDERESEND •••

Ida Karin Tylleskär

on 05.09.2018 15:38

Marker som ulest

Til: Harriet Selle;

Det var visst en oppgave til oppfølging fra initeringsmonitoreringen den 1/6-18.
Nå er alle punkter til oppfølging fra den rapporten lukket.

Vennlig hilsen
Ida Tylleskär

Fra: Ida Karin Tylleskär
Sendt: 5. september 2018 11:43
Til: Harriet Selle
Emne: eCRF NINA studien

Hei Harriet,
Har notert meg at du ønsker kopi av eCRFen. Her er den
/Ida

16.1.8 Audit certificates

Gmail

Ida Tylleskär <ida.tylleskar@gmail.com>

TMF i NINA-1 studien 04.04.18

Ida Tylleskär <ida.tylleskar@gmail.com> Thu, Sep 6, 2018 at 3:42 PM
To: Harriet Selle <harriet.selle@ntnu.no>
Cc: Ola Dale <ola.dale@ntnu.no>

Hei Harriet,
(og Ola som kopi)

Jeg glemte svare ut denne mailen.
1. TMFen er blitt utvidet til fem permer, og det er utvidet med flere plastmapper for bedre oversikt. Det er angitt utenpå hvilke kapitler som ligger i hvilken perm.
2. Signaturer på protokoll og fra DMSC er innhentet.
3. Alle IBer er signert.
4. Det er versjonsnummer på samtykkesskjemaene som brukes i studien.
5. Det er opprettet egen prosedyre for AE/SAE rapportering. Den ble sendt til deg på mail 1 juni.
6. Delegasjonslogg er fullstendig utfylt. Oversendt i forbindelse med oppstartsmonitorering.
7. Alle CVer er signert og datert.
8. Monitoreringslogg for Trondheim opprettet her. Monitoreringslogg for Oslo oppbevares i Oslo under studietiden.
9. Monitoreringsavtale og plan foreligger for begge studiesteder. Du skal ha fått disse på mail tidligere.

Vennlig hilsen
Ida Tylleskär
[Quoted text hidden]

16.1.8 Audit certificates

Gmail

Ida Tylleskär <ida.tylleskar@gmail.com>

Lukking av avvik i forbindelse med oppstartsmonitorering av naloksonstudien

7 messages

Ida Tylleskär <ida.tylleskar@gmail.com> Mon, Jun 11, 2018 at 5:08 PM
To: Harriet Selle <harriet.selle@ntnu.no>

Hei Harriet,

- Vedlagt er signert delegasjonslogg.

- Vi har fått bekreftet fra medisinsk teknisk at det gjennomføres årlig vedlikehold av medisinsk teknisk utstyr iht leverandørens anbefalinger. Maskinene var sist inne i september-november 2017, og det er planlagt ny runde denne høsten.

- Det er sendt inn søknad om at dere skal få tilgang til viedoc. Så invitasjon burde ha kommet/kommer når som helst, om det ikke gjør der må du gi beskjed. eCRFen er klar, men vi har foreløpig ikke fått PDF-kopi, men du får den straks vi har den.

- Sindre Mellesmo har dokumentert GCP-kompetanse (du fikk kopi av GCPbevis sist uke).

Konklusjon: Studiested Trondheim er klar for inklusjon, og har idag startet studien med å dele ut legemiddel-kitene.

Hilsen
Ida Tylleskär

11.06.201809-11-02.pdf
1726K

Harriet Selle <harriet.selle@ntnu.no> Tue, Jun 12, 2018 at 6:30 PM
To: Ida Tylleskär <ida.tylleskar@gmail.com>

Hei Ida,

Takk for tilsendt oppdatering. Da trenger jeg bare signatur fra Sindre Mellesmo på sjekkliste for oppstart og initieringsrapport.

Hilsen Harriet

Fra: Ida Tylleskär <ida.tylleskar@gmail.com>
Sendt: 11. juni 2018 17:08
Til: Harriet Selle
Emne: Lukking av avvik i forbindelse med oppstartsmonitorering av naloksonstudien

[Quoted text hidden]

Ida Tylleskär <ida.tylleskar@gmail.com> Wed, Jun 13, 2018 at 2:32 PM
To: Harriet Selle <harriet.selle@ntnu.no>

16.1.8 Audit certificates

Her er møtereferat signert av sponsor og PI og sjekklisten signert av PI.

Sjekklisten som vi signerte på når vi hadde møte ble levert til PI, og han har signert på den og sendt den med internposten. Den har derimot ikke kommet frem på to uker, så jeg vet ikke helt hvor den er blitt av... Derfor har jeg printet en ny sjekkliste som ble signert på idag sammen med referatet, men den er altså ikke signert at oss tre som var på møtet. Men det er vel heller ikke påkrevd, i og med at det ikke er med i malen, så regner med at det er greit.

Hilsen
Ida

[Quoted text hidden]

2 attachments

13.06_1.201814-25-52.pdf
1929K

13.06.201814-25-52.pdf
2534K

Harriet Selle <harriet.selle@ntnu.no> Thu, Jun 14, 2018 at 10:10 AM
To: Ida Tylleskär <ida.tylleskar@gmail.com>

Hei Ida,

Takk for tilsendte papirer!

Lykke til med inkludering av deltakere:)

Hilsen Harriet

Fra: Ida Tylleskär <ida.tylleskar@gmail.com>
Sendt: 13. juni 2018 14:32
Til: Harriet Selle
Emne: Re: Lukking av avvik i forbindelse med oppstartsmonitorering av naloksonstudien

[Quoted text hidden]

Ida Tylleskär <ida.tylleskar@gmail.com> Thu, Jun 14, 2018 at 1:21 PM
To: Harriet Selle <harriet.selle@ntnu.no>

Har du fått tilgang til viedoc?
[Quoted text hidden]

Harriet Selle <harriet.selle@ntnu.no> Thu, Jun 14, 2018 at 1:28 PM
To: Ida Tylleskär <ida.tylleskar@gmail.com>

Hei Ida, ja det er på plass 😊 Harriet

Sendt fra min iPhone
[Quoted text hidden]

Ida Tylleskär <ida.tylleskar@gmail.com> Thu, Jun 14, 2018 at 1:43 PM

To: Harriet Selle <harriet.selle@ntnu.no>

Perfekt!
Første pasient er forresten inkludert.
/Ida
[Quoted text hidden]

NTNU
Norwegian University of Science and Technology

Oslo universitetssykehus

STATISTICAL ANALYSIS PLAN

NTNU Intranasal Naloxone Trial

Double blinded, double dummy, randomised controlled trial of intranasal naloxone for pre- hospital use

Protocol Identification Number: NINA- 1

EudraCT Number: 2016-004072-22

SPONSOR:

Øystein Risa, Head of Department

Department of Circulation and Medical Imaging, Norwegian University of Science and Technology (ISB, NTNU)

Box 8905 MTFS
7491 Trondheim, Norway

Tel: (+47) 92613734

E-mail: oystein.risa@ntnu.no

COORDINATING INVESTIGATOR (CI):

Arne Kristian Skulberg, MD, PhD

Department of Circulation and Medical Imaging, Norwegian University of Science and Technology (ISB, NTNU)

Box 8905 MTFS

7491 Trondheim, Norway

Tel: (+47) 93083544

E-mail: arne.skulberg@ntnu.no

Statistical Analysis Plan version 1.0

Date: 06.10.2020

Administrative information:

Sponsor name	Øystein Risa, Head of Department Department of Circulation and Medical Imaging, Norwegian University of Science and Technology (ISB, NTNU)
Sponsor address	Box 8905 MTFS 7491 Trondheim, Norway Tel: (+47) 92613734 E-mail: oystein.risa@ntnu.no
EudraCT number / REC no	EudraCT Number: 2016-004072-22 REK Sør Øst C: 2016/2000
Trial title	NTNU INTRANASAL NALOXONE TRIAL Double blinded, double dummy, randomised controlled trial of intranasal naloxone for pre- hospital use
Trial ID	NINA- 1
Trial registration number	ClinicalTrials.gov Identifier: NCT03518021

SAP and protocol version:

SAP version and date:	1.0 Date 06.10.2020
Protocol version	PROTOCOL VERSION NO. 3.3 Date: 06.03.2020

SAP revision history:

Protocol version	SAP version	Section number changed	Description and reason for change	Date changed
3.3	1.0	NA	First SAP	

SIGNATURE PAGE

COORDINATING INVESTIGATOR:

Arne Kristian Skulberg, MD, PhD
NTNU

Signature

06/10/2020
Date (dd/mmm/yyyy)

TRIAL STATISTICIAN:

Morten Valberg, PhD
Oslo Centre for Biostatistics and Epidemiology, Oslo University Hospital.

Signature

06/10/2020
Date (dd/mmm/yyyy)

QC STATISTICIAN:

Inge Christoffer Olsen
Oslo Centre for Biostatistics and Epidemiology, Oslo University Hospital.

Signature

07/10/2020
Date (dd/mmm/yyyy)

ABBREVIATIONS

AE	Adverse Event
AMIS	Akuttmedisinsk informasjonssystem (The program for coordination of emergency calls and dispatch used in Norway)
AR	Adverse Reaction
CI	Confidence Interval
DMSC	Data Monitoring and Safety Committee
eCRF	electronic Case Report Form
EMS	Emergency Medical System
FAS	Full Analysis Set
GCS	Glasgow Coma Scale
GEE	Generalized Estimating Equations
IM	Intramuscular
IMP	Investigational Medicinal Product
IN	Intranasal
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per Protocol
RMST	Restricted Mean Survival Time
SAE	Serious Adverse Event
SD	Standard Deviation
TMF	Trial Master File

TABLE OF CONTENTS

1 Introduction

1.1 Background and rationale

Nasal naloxone has been introduced around the world as an alternative to injected antidote for reversal of opioid overdoses. This is a response to the ongoing rise in deaths from opioid overdoses (1). The last few years have shown an increase in the scientific evidence behind this route of administration. Several products with marketing approval from medicinal authorities are now available, however, the approvals are all based on pharmacokinetic studies in healthy human volunteers only. Thus, their efficacy in real life overdose patients have not been proven (2). A few randomised clinical trials have been conducted on nasal naloxone compared to injected, but none of these tested an approved nasal naloxone formulation, only various off-label medicines were studied (3-6). The present investigational medicinal product has received a marketing authorisation. It has undergone several pharmacokinetic and pharmacodynamic studies in human volunteers, all already published. It has a bioavailability of about 50%, far exceeding that of the off-label formulations (7-11).

This Statistical Analysis Plan follows the "Guidelines for the Content of Statistical Analysis Plans in Clinical Trials" published by Gamble et al (12), complying with the ICH E9 guideline.

1.2 Trial Objectives

Measure and evaluate clinical response to nasal naloxone in opioid overdoses treated by ambulance personnel in the pre-hospital environment.

1.2.1 Primary Objective

The primary objective is to assess if treatment with intranasal naloxone is not inferior to intramuscular naloxone on return of spontaneous respiration (above or equal to 10 breaths per minute) within 10 minutes of naloxone administration, in pre-hospital opioid overdoses.

1.2.2 Secondary Objectives

Secondary objectives of this study are to assess if there are differences between the two treatments with regards to:

- Changes in Glasgow Coma Scale (GCS) from baseline to the end of the intervention.
- Changes in oxygen saturation (SpO2) from baseline to the end of the intervention.
- Occurrence of overdose complications (e.g. aspiration, cardiac arrest, death).
- Time from administration of naloxone to respiration above or equal to 10 breaths per minute.
- Occurrence of opioid withdrawal reaction to naloxone reversal.
- Occurrence of adverse reactions to naloxone formulation.
- Occurrence of need for rescue naloxone.
- Recurrence of opioid overdose/need for further pre-hospital naloxone within 12 hours of inclusion.
- Follow up after care: Whether the patient is being left at the scene or transferred care to other tiers of the health service after treatment with study medicine

The remaining secondary objectives "*Suitability of spray device in pre-hospital setting*" and "*Reasons not to give rescue naloxone to non-responders*" as defined in the study protocol will only be reported descriptively, with no formal statistical testing of group differences.

2 Trial Methods

2.1 Trial Design

This is a phase III double-blinded, double-dummy, multi-centre, non-inferiority randomised controlled trial on the use of intranasal versus intramuscular naloxone in subjects treated for opioid overdose outside hospital.

2.2 Randomisation

Included patients will be treated with the study drug available in the ambulance at the scene. The treatment kit contains either a placebo nasal spray and a naloxone containing syringe, or naloxone nasal spray and placebo containing syringe. Each kit is numbered according to a prespecified random allocation list. The kit number will become the participant study number.

The allocation to treatment happens at the scene and is determined by the kit present in the ambulance at the time of inclusion. Ambulances are required to have only one kit at the time. Refill at will take place at the ambulance station.

Eligible patients will be randomized in a 1:1 ratio between the two treatment groups. Block randomization, with varying block sizes will be used, and the randomization will be stratified by study centre (there are two study centres; Oslo University Hospital, Oslo, and St. Olav's Hospital, Trondheim). The randomisation process is described in full in the clinical trial protocol. Details of the randomisation including the final random allocation list are held securely and unavailable to unauthorized trial personnel, making sure statisticians, researchers or study workers have no access.

2.3 Sample size

The aim is to investigate if administration of 1.4 mg intranasal naloxone hydrochloride is non-inferior to intramuscular administration of 0.8 mg naloxone hydrochloride. The primary endpoint is the proportion of participants with return of spontaneous respiration (≥10 breaths per minute) within 10 minutes of naloxone administration. It is expected that 88% of the patients on IM treatment (standard treatment) will be responders according to this criterion, and an equivalent dose intranasal administration is expected to result in a similar responder rate. The non-inferiority margin is set to Δ=15%.

A total of 200 cases are needed to demonstrate that intranasal naloxone is non-inferior to intramuscular administration, assuming a two-sided significance level of 5% and a power of 90%.

Previous protocols has used the word «patients" to explain the power calculation, but as explained further in point 3.3. the analysis is performed on the number of included cases where study medicine is administered, and one individual may present as a patient to the ambulance service several times during the study period.

There is no pre-set target for how many patients each centre will include, but we expect the Oslo Centre to include the majority of cases.

2.4 Statistical Framework

2.4.1 Hypothesis Test

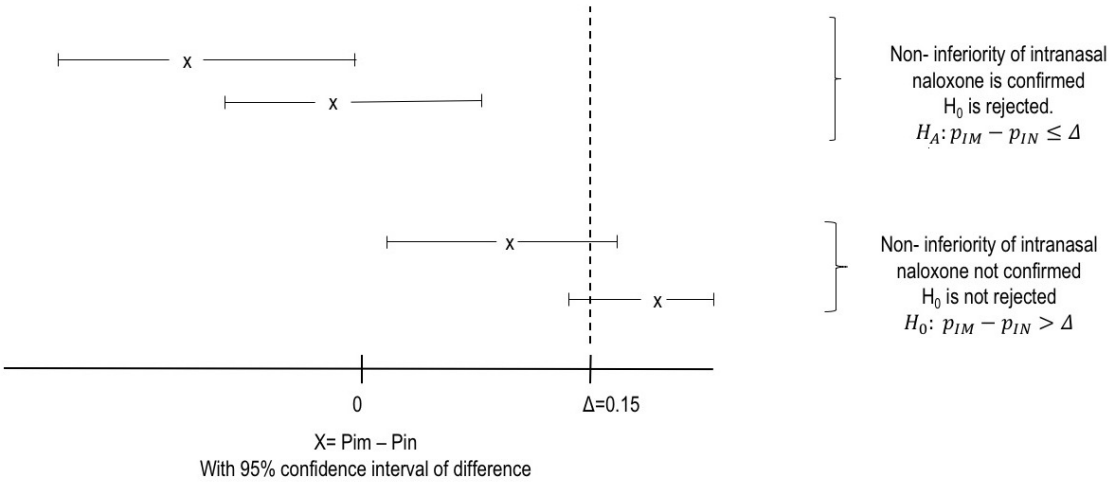
The null hypothesis is that the proportion of responders given intranasal naloxone is smaller by the 0.15 non-inferiority margin than given intramuscular naloxone

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

and the alternative hypothesis is that the proportion of responders given intranasal naloxone is not smaller by the 0.15 non-inferiority margin compared to intramuscular naloxone

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

From this it follows that the upper bound of the 95% confidence interval of the difference between the groups shall not exceed 0.15 in order to reject H0 and confirm Ha



2.4.2 Decision Rule

This trial is designed to address a single primary outcome. Non-inferiority is claimed if the primary null hypothesis is rejected on the significance level (alpha) of 0.025 (one-sided). That is, if the upper limit of the 95% two-sided confidence interval for the treatment difference is less than 15%.

2.5 Statistical Interim Analyses and Stopping Guidance

A feasibility analysis will be performed after 20 included participants. The results of this will be made available to the DMSC. The DMSC will make stopping recommendations if there are safety concerns that warrants this.

Deviation from the original statistical plan will be described and justified in the Clinical Study Report. Amendments to plan can be done until day of database lock.

After 100 patient the DMSC will meet and conduct the following unblinded analysis:

- Summary of patient enrolment (number per site, age, gender and follow-up).
- Safety profile: adverse events, serious adverse events (SAE) and SUSAR reported.
- Interventions: The use of rescue naloxone.
- Follow up: The follow up after study treatment (hospitalisation, left at the scene etc).
- Recurrence: The number of participants with recurring overdose within 12 hours after inclusion.
- Mortality: Any deaths by a trial participant during the duration of study time will be reported to by Coordinating investigator the DMSC within 7 days.

No interim analysis of the primary endpoint will be performed.

2.6 Timing of Final Analysis

The main statistical analysis is performed when all patients are included, entered in the data capture system, monitored, validated and the database has been locked.

2.7 Timing of Outcome Assessments

The trial consists of one study visit only, where primary endpoint is assessed within the duration of this visit.

The primary endpoint will be assessed within 10 minutes after administration of study drug.

The expected duration of therapy is 10 minutes with a further observation time of up to an additional 30 minutes. End of protocol therapy is defined when one of the following is achieved:

1: The patient is awake and declines further follow-up from EMS staff, observation time is up to 40 minutes after administration of study drug.

or:

2: The patient is awake and declines further follow-up from EMS staff, but leaves the scene prior to an observation time of 40 minutes despite EMS urging the patient to stay present or be followed up elsewhere.

or:

3: The patient is awake after administration of the study drug and transported to medical follow-up. End time is when EMS hands over treatment responsibility to other health care professionals.

or

4: Patient is not awake after administration of study drug and transported to medical follow-up. End time is when EMS staff hands over treatment responsibility to other health care professionals.

In addition, all included participants with known national identity number is cross-checked for recurrence of opioid overdoses within 12 hours after inclusion (which is a secondary endpoint) with the Acute Medical Information System (AMIS) at the medical dispatch centre. Recurrence is defined as administration of naloxone as Take Home naloxone known to the ambulance service, or administration of naloxone by the ambulance service itself within 12 hours after inclusion. Other data sources such as the National Cause of Death Registry does not report to the study database, making recurrent fatal overdoses within 12 hours unknown to the study team.

3 Statistical Principles

3.1 Confidence Intervals and p-values

As this is a non-inferiority trial, no p-value will be reported for the test of treatment differences in the primary outcome. Instead, the 95% confidence interval will be reported, and the upper bound will be compared with the non-inferiority margin. As there is only one primary endpoint, there will be no adjustment for multiplicity. Analysis of all subgroups and secondary endpoints will be done on the (two-sided) significance level of 5%. P-values will be avoided, and 95% confidence intervals will be reported for group comparison, unless otherwise explicitly stated in Section 5. There will be no multiplicity adjustments in subgroup analyses or in the analyses of secondary endpoints.

3.2 Adherence and Protocol Deviations

3.2.1 Adherence to Allocated Treatment

Study personnel will administer all study drugs in this trial. There is a possibility of partial or failed administration of the study drugs, or administration not in line with the study protocol. These occurrences will be listed. The cases where such problems have occurred will be part of the full analysis dataset, FAS), but not the per protocol dataset (PPS) (see Section 3.3 for a description of these). Each overdose treatment will be classified to be either of the following:

- Full adherence: The patient received both IMPs according to protocol.
- Partial adherence: The patient has only partially been given one or both of the two investigational medicinal products (IMPs).
- Failed adherence: The patient received neither of the two IMPs.

3.2.2 Protocol Deviations

The following are pre-defined protocol deviations regarded to affect the efficacy of the intervention:

- Entering the trial when the eligibility criteria should have prevented trial entry.
- Patients not giving consent, or who have not been given information and opportunity to consent or withdraw as described in the protocol
- Failed or partial administration of study drug (see Section 3.2.1).

Protocol deviations are classified prior to unblinding of treatment. The number (and percentage) of overdoses with protocol deviations will be summarised by treatment group with details of type of deviation provided. The patients included in the full analysis set (FAS, see below) will be used as the denominator to calculate the percentages. No formal statistical testing will be undertaken.

3.3 Analysis Populations

In this trial an individual may be included several times, a person could be treated for overdoses by the ambulance service several times during the study period (repeaters). In the description of the analysis populations it is the individual treatment occasion, and not the individual patient, that is considered. I.e. a patient with multiple overdoses might contribute overdose events that each are included in different populations. A number of participants will have unknown identity to the researcher. These will be registered as *"Nomen nescio"* abbreviated to N.N. or unnamed person. Any repeaters in this group will be treated as separate individuals.

We define the following patient-overdose populations in this trial.

- All randomized overdose events: All events that have been randomized whether or not the patient received treatment.
- Safety Set: All events where the patient received study medicine (full or partial adherence to allocated treatment) and including anonymous data on from participants who have not consented
- Full analysis set (FAS): All events where the patient received study medicine and where the patient did not refuse or withdrew consent.
- Per protocol set (PPS): All events where the patient received study medicine fully compliant with the study protocol (see Section 3.2.2) and where the patient did not refuse or withdrew consent.

As this is a non-inferiority trial, the PPS will be used for the primary analysis, while the FAS will be used for sensitivity analysis. Safety data will be analysed from the Safety Set.

4 Trial Population

4.1 Screening Data, Eligibility and Recruitment

The total number of screened patients and reasons for not entering the trial will be summarised and tabulated. Patient's age, gender, location of overdose, follow up and details regarding the treatment with non-IMP naloxone will be reported.

A CONSORT flow diagram (appendix A) will be used to summarise the number of overdose events that were:

- assessed for eligibility at screening
- eligible at screening
- ineligible at screening*
- eligible and randomised
- eligible but not randomised*
- received the randomised allocation
- received the randomised allocation, but withdrew consent.
- did not receive the randomised allocation*
- lost to follow-up*
- failed administration of study drugs*
- randomised and included in the primary analysis
- randomised and excluded from the primary analysis*

*reasons will be provided.

4.2 Withdrawal/Follow-up

The status of eligible and randomised patients at trial end will be tabulated by treatment group according to

- withdrew consent.
- death.

4.3 Baseline Characteristics

Baseline characteristics will be presented for each treatment group and overall in both groups combined. The variables to be summarized are:

- Age (in years) of patient.
- Sex of patient.
- Study centre.
- Overdose location.
- Time of year of overdose (four seasons).
- Weekday of overdose (two categories: Monday-Thursday, Friday-Sunday).
- Time of day of overdose (day (07:00-17:59), evening (18:00-23:59), night (00:00-06:56)).
- Baseline Glasgow Coma Scale (GCS) score (two categories: =3/15) or >3/15).
- Baseline respiratory rate (two categories: =0 or >0 breaths per minute).
- Primary suspected drug.
- Route of primary suspected drug.
- Whether benzodiazepine/GHB/alcohol suspected to be one of drugs used by the patient. (yes/ no)
- Whether the national identity number of the patient is known.
- Baseline oxygen saturation (%)
- Ambulance dispatch times (hours, minutes).

Overdose demographics and baseline characteristic will be summarised for each treatment arm, using descriptive statistics (N, mean, standard deviation) for continuous variables, and number and percentages of overdose events for categorical variables. There will be no statistical analysis of treatment differences. Any clinical important imbalance between the treatment groups will be noted.

5 Analysis

5.1 Outcome Definitions

5.1.1 General Definitions and Derived Variables

5.1.1.1 Glasgow Coma Scale (GCS)

Scale assessing the patient's level of consciousness. Ranges from 3 (deep coma) to 15 (conscious) based on response in eyes, verbal response and motor response.

5.1.1.2 Oxygen saturation

SpO_2 = oxygen saturation as measured by light absorptionn through a non-invasive pulse oximeter. It is the fraction of oxygen-saturated haemoglobin relative to total haemoglobin (unsaturated + saturated) in the blood. SpO_2 is given as a percentage.

5.1.1.3 Adverse reaction

An adverse event deemed to have a certain, probable/likely or possible causal relationship to the IMP will be classified as an adverse reaction.

5.1.1.4 Overdose complications

Adverse events that are defined as unlikely relationship to the IMP will be considered possible overdose complications.

5.1.1.5 Opioid withdrawal reaction to naloxone reversal

Adverse reactions defined as opioid withdrawal syndromes (MedDra lowest level term (LLT) 10030882). It includes responses subjectively described as abstinence, agitation or aggression.

5.1.1.6 Follow-up after care

Defined as the level of health care to which the patient is transferred after treatment by ambulance services, or if left at the scene.

The variable contains the following categories:

1. Left at the scene of treatment. This represent patients who are not transported to further care or follow up after treatment with study drug. For ambulance personnel to choose this option patients should be physiologically normal with adequate level of consciousness, respiration and circulation, and to be fully competent to make informed decisions of their own.

2. Handed over to primary care. In Norway defined as general practitioners and Accident and Emergency Outpatient Clinic (Kommunal legevakt). For the sake of level of medical care, it also includes specialized in- patient addiction services that accept patient referred by ambulance personnel, such as Rusakutten-Aker in Oslo. These facilities accept patients without need for advanced emergency medical follow up.
3. Handed over to hospital. Patient is transferred to tertiary care, defined as hospitals with facilities for advanced medical investigations and treatment.
4. Others. Some patients are transferred to places not fitting any of these categories, such as drug-user shelters.

5.1.1.7 Recurrence of opioid overdose

Recurrence is defined as having received naloxone within 12 hours after discharge from study visit. This includes Take Home Naloxone known to EMS, or naloxone administered by the ambulance service. It is assessed by analysing medical records in the Ambulance Service for ambulance callouts to individuals included with known national Identity Number for 12 hours following inclusion in this trial. However, patients who receive Take-Home Naloxone without involving the ambulance service will not be recorded. Patients suffering a fatal overdose in this 12-hour window may not be registered in the trial as the study database will not be linked to the Norwegian National Cause of Death Registry

5.1.1.8 Received rescue naloxone

This is defined as patients treated with non- IMP naloxone in addition to study drug during the study visit, or immediately after transfer to follow up.

Some patients will be in clinical need of further naloxone, but not have this given for various reasons. Such reasons not to give rescue naloxone to non-responders will be recorded and listed.

5.1.2 Primary Outcome Definition

The primary outcome is the return of spontaneous respiration (above or equal to 10 breaths per minute) within 10 minutes of naloxone administration. The primary outcome is dichotomous.

5.1.3 Secondary Outcomes Definitions

5.1.3.1 Changes in Glasgow Coma Scale (GCS)

Two measures of change in GCS will be considered:

- The change in GCS as measured before the intervention (at baseline), to the GCS value measured at the end of the intervention (at 10 minutes). This is a continuous outcome.
- The change in GCS as measured before the intervention (at baseline), to the maximum GCS value measured in the extended follow-up time (up to 40 minutes, see Section 2.7). This is a continuous outcome.

5.1.3.2 Changes in oxygen saturation (SpO2)

Two measures of change in SpO2 will be considered:

- The change in SpO2 as measured before the intervention (at baseline), to the SpO2 value measured at the end of the intervention (at 10 minutes). This is a continuous outcome.

- The change in SpO2 as measured before the intervention (at baseline), to the maximum SpO2 value measured in the extended follow-up time (up to 40 minutes, see Section 2.7). This is a continuous outcome.

5.1.3.3 Adverse reaction

Whether or not the patient has an adverse reaction to the naloxone formulation. This is recorded during the time of protocol therapy (up to 40 minutes, see Section 2.7). This is a dichotomous outcome.

5.1.3.4 Overdose complications

Whether or not the patient has an overdose complication. This is recorded during the time of protocol therapy. This is a dichotomous outcome.

5.1.3.5 Opioid withdrawal reaction to naloxone reversal

Whether or not the patient has an opioid withdrawal reaction to naloxone reversal. This is recorded during the time of protocol therapy (up to 40 minutes, see Section 2.7). This is a dichotomous endpoint.

5.1.3.6 Time from administration of naloxone to respiration above or equal to 10 breaths per minute.

The time from naloxone administration to respiration above or equal to 10 breaths per minute. This is a time to event endpoint.

5.1.3.7 Suitability of spray device in pre-hospital setting

Whether or not there was a practical problem of using the nasal spray device. This is a dichotomous endpoint.

5.1.3.8 Received rescue naloxone

Whether or not the patient was treated with rescue naloxone during the time of protocol therapy (see Section 2.7). This may include additional naloxone administered at hospital during hand over (see Section 2.7 point 4) This is a dichotomous endpoint.

5.1.3.9 Recurrence of opioid overdose/ need for further pre-hospital naloxone within 12 hours of inclusion

Whether or not the patient had a recurrence of opioid overdose within 12 hours of inclusion. This is a dichotomous endpoint.

5.1.3.10 Follow up after care

The following follow-up endpoints are defined:

- Whether or not a patient is followed up at a hospital after care. This is a dichotomous endpoint.

5.1.4 Overview of Outcomes

Level	Outcome	Timeframe	Type
Primary	Return of spontaneous respiration	During visit	Dichotomous
Secondary	Changes in Glasgow Coma Scale (GCS) in patients treated with study medicine for opioid overdose.	During visit	Continuous
	Changes in oxygen saturation (SpO2) in patients treated with study medicine for opioid overdose.	During visit	Continuous
	Adverse reactions to naloxone formulation	During visit	Dichotomous
	Overdose complication	During visit	Dichotomous
	Opioid withdrawal reaction to naloxone reversal	During visit	Dichotomous
	Time from administration of naloxone to respiration above or equal to 10 breaths per minute.	During visit	Time-to-event
	Suitability of spray device in pre-hospital setting	During visit	Dichotomous

	Receiving rescue naloxone	During visit	Dichotomous
	Recurrence of opioid overdose/ need for further pre-hospital naloxone within 12 hours of inclusion	12 hours	Dichotomous
	Follow up after care	During visit	Dichotomous

5.2 Analysis Methods

5.2.1 Primary Outcome

5.2.1.1 Primary Analysis

The event of returning to spontaneous breathing within 10 minutes after study drug administration will be analysed using a logistic regression model. The dichotomous treatment variable will be adjusted by study site (the stratification factor used in the randomisation). To account for the possibility that the same individual may be included several times in the trial (i.e. the same person can have several overdoses), the parameters in the logistic regression model will be estimated by the means of generalized estimating equations (GEE) with exchangeable working correlation. Once the logistic regression model has been fitted to the data, the difference in the marginal predicted probabilities of returning to spontaneous breathing within 10 minutes will be calculated for each group.

The primary analysis will be done in the PPS.

5.2.1.2 Summary Measures

The primary effect estimate will be the difference in the marginal predicted probabilities of returning to spontaneous breathing within 10 minutes between the groups. This adjusted risk difference will be presented as the risk in the control group (intramuscular naloxone) minus the risk in the active group (intranasal naloxone). If the upper bound of the 95% confidence interval of the risk difference is less than 0.15, then non-inferiority of the active treatment (intranasal naloxone) to the control treatment will be claimed.

5.2.1.3 Assumption Checks and Alternative Analyses

As there are no continuous covariates in the logistic regression, there will be no assumption checks performed for the primary analysis.

5.2.1.4 Missing Data

Because of the nature of the trial, we do not expect any missing data for the variables used in the analysis of the primary endpoint. A blinded review of the data prior to database lock revealed that there were no missing values for the variables used in the primary analysis of the primary endpoint.

5.2.1.5 Sensitivity Analyses

A sensitivity analysis for the primary endpoint will be performed by analysing the FAS, rather than the PPS.

5.2.1.6 Subgroup Analyses

Subgroup analyses will be performed by including an interaction term between the variable in question and the dichotomous treatment variable in the model for the primary outcome. Subgroup analyses based on the following variables will be performed.

- Place of treatment.
    - Dichotomous variable: Safe injection facility (Sprøyterommet) or not.
- Sex.
    - Dichotomous variable: Male/Female.
- Age group.
    - Dichotomous variable: Divided into two groups, below and above the mean age.
- Type of opioid consumed
    - Dichotomous variable: Was benzodiazepines/GHB/Alcohol suspected as one of drugs taken by patient (yes/no)
- Baseline GCS
    - Dichotomous variable (≤ 3/15, >3/15)
- Baseline respiratory rate.
    - Dichotomous variable (=0, >0 breaths per minute)

The results from the subgroup analysis will be presented by displaying the confidence intervals of the risk difference (IM minus IN) in a forest plot.

5.2.2 Dichotomous Secondary Outcomes

For one dichotomous secondary outcome, suitability of spray device, there will be no statistical analysis. The remaining dichotomous secondary outcomes will be analysed as the primary outcome.

5.2.2.1 Main Analysis

Same as for the primary outcome.

5.2.2.2 Summary Measures

Same as for the primary outcome.

5.2.2.3 Assumption Checks

Same as for the primary outcome.

5.2.2.4 Missing Data

Same as for the primary outcome.

5.2.2.5 Sensitivity Analyses

Same as for the primary outcome.

5.2.2.6 Subgroup Analyses

No subgroup analyses will be performed for the secondary dichotomous outcomes.

5.2.3 Continuous Secondary Outcomes

There are four continuous secondary outcomes. The changes in GCS and Oxygen saturation, respectively, will be considered

- from before the intervention to end of the intervention (at 10 minutes) and,
- from before the intervention to the maximum measurement in the extended follow-up time (up to 40 minutes, see Section 2.7).

5.2.3.1 Main Analysis

A linear regression model will be fitted to the data, with the change value (for GCS and oxygen saturation, respectively) as the dependent variable. The dichotomous treatment variable will be adjusted for by study site and the initial measurement before the trial. The model parameters will be fitted using GEE with exchangeable working correlation, to account for the clustering of the data (possibly more than one overdose in each individual).

5.2.3.2 Summary Measures

From the fitted linear regression model, the adjusted mean difference will be reported, together with its 95% confidence interval.

5.2.3.3 Assumption Checks

A blinded review of the data revealed no model improvement by using a more general (unstructured) working correlation structure.

If the outcome variable is very skewed, then a Wilcoxon Sum rank test for clustered data will be applied to the raw-data (non-imputed, and unadjusted for study site and baseline measurement) as an additional sensitivity analysis(13).

5.2.3.4 Missing Data

Missing data will be imputed by multiple imputation with chained equations. Each imputed dataset will be analysed as described above (Section 5.2.3.1), and the result will be pooled to produce the final result. Note that the change variables (change in GCS or oxygen saturation, respectively) will be

imputed using passive imputation (the baseline, 10-minute and maximum measurements will be imputed, while the differences will be passively imputed as the change from baseline.

5.2.3.5 Sensitivity Analyses

A sensitivity analysis will be done in the FAS.

5.2.3.6 Subgroup Analyses

No subgroup analyses will be performed for these endpoints.

5.2.4 Time to event secondary outcomes

There is one time to event endpoint, the time to satisfactory breathing (time from naloxone administration to respiration above or equal to 10 breaths per minute).

5.2.4.1 Main Analysis

If, for a given overdose, the patient has not achieved satisfactory breathing within 10 minutes, the time will be censored at 10 minutes.

The difference in the restricted mean survival time (RMST) between the groups will be calculated at each minute of follow-up, from 1 to 10 minutes. That is, the difference in the area under the survival curves in the two groups will be calculated at each of these time points. The treatment variable will be adjusted by study site.

The jack-knife will be used to construct 95% confidence intervals for the RMST differences. In each jack-knife sample, one individual will be left out (rather than one overdose) to account for the clustering in the data.

5.2.4.2 Summary Measures

The RMST difference at each minute of follow-up, from 1 to 10 minutes, will be reported with 95% confidence intervals constructed by using the jack-knife.

5.2.4.3 Assumption Checks

As the RMST is non-parametric, no assumption checks will be done.

5.2.4.4 Missing Data

Patients that has not achieved satisfactory breathing within 10 minutes, will be censored at 10 minutes. Because of the nature of the trial, we do not expect any further missing data for this endpoint.

5.2.4.5 Sensitivity Analyses

The RMST differences without the adjustment for study centre will be calculated as sensitivity analyses.

A sensitivity analyses will also be conducted in the FAS.

5.2.4.6 Subgroup Analyses

No subgroup analyses will be performed for this outcome.

5.2.5 Additional Analyses

Not applicable.

6 Safety Analyses

6.1 Adverse Events

The risk of having at least one adverse reaction (AR) will be compared between the two treatment groups, as described in Sections 5.1.3.3 and 5.2.2.

The risk of having at least one overdose complication will be compared between the two treatment groups, as described in Sections 5.1.3.4 and 5.2.2.

The risk of having an opioid withdrawal reaction to naloxone reversal will be compared between the two treatment groups, as described in Sections 5.1.3.5 and 5.2.2.

The risk of receiving rescue naloxone will be compared between the two treatment groups, as described in Sections 5.1.3.8 and 5.2.2. The reasons for giving rescue naloxone, and the reasons not to give it when it was deemed needed, will be listed.

Each adverse event is coded in MedDRA and assessed for severity, relationship to study intervention, action taken, outcome and expectedness. These will be tabulated based on for each treatment groups based on MedDRA System Organ Class and Preferred Term.

Each Adverse event will be assessed for severity using Common Terminology Criteria for Adverse Events (CTCAE) v5.0 November 27, 2017.

7 Statistical Software

All statistical analyses will be done in R version 3.6.3 (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

8 References

1. World Health Organization. Community management of opioid overdose. Geneva: World Health Organization,; 2014. Available from: http://www.ncbi.nlm.nih.gov/books/NBK264311/.
2. Strang J, McDonald R, Campbell G, Degenhardt L, Nielsen S, Ritter A, et al. Take-Home Naloxone for the Emergency Interim Management of Opioid Overdose: The Public Health Application of an Emergency Medicine. Drugs. 2019;79(13):1395-418.
3. Kelly AM, Kerr D, Dietze P, Patrick I, Walker T, Koutsogiannis Z. Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. Med J Aust. 2005;182(1):24-7.
4. Kerr D, Kelly AM, Dietze P, Jolley D, Barger B. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. Addiction. 2009;104(12):2067-74.
5. Sabzghabaee AM, Eizadi-Mood N, Yaraghi A, Zandifar S. Naloxone therapy in opioid overdose patients: intranasal or intravenous? A randomized clinical trial. Arch Med Sci. 2014;10(2):309-14.

6. Dietze P, Jauncey M, Salmon A, Mohebbi M, Latimer J, van Beek I, et al. Effect of Intranasal vs Intramuscular Naloxone on Opioid Overdose: A Randomized Clinical Trial. JAMA Netw Open. 2019;2(11):e1914977.
7. Skulberg AK, Asberg A, Khiabani HZ, Rostad H, Tylleskar I, Dale O. Pharmacokinetics of a novel, approved, 1.4-mg intranasal naloxone formulation for reversal of opioid overdose-a randomized controlled trial. Addiction. 2019.
8. Skulberg AK. Characteristics of opioid overdoses and Intranasal pharmacology of naloxone. Trondheim, Norway: Norwegian University of Science and Technology; 2019.
9. Tylleskar I, Skulberg AK, Nilsen T, Skarra S, Dale O. Naloxone nasal spray - bioavailability and absorption pattern in a phase 1 study. Tidsskr Nor Laegeforen. 2019;139(13).
10. Skulberg AK, Tylleskar I, Nilsen T, Skarra S, Salvesen O, Sand T, et al. Pharmacokinetics and -dynamics of intramuscular and intranasal naloxone: an explorative study in healthy volunteers. Eur J Clin Pharmacol. 2018;74(7):873-83.
11. Tylleskar I, Skulberg AK, Nilsen T, Skarra S, Jansook P, Dale O. Pharmacokinetics of a new, nasal formulation of naloxone. Eur J Clin Pharmacol. 2017;73(5):555-62.
12. Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Dore C, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017;318(23):2337-43.
13. Datta S, Satten GA. Rank-Sum Tests for Clustered Data. Journal of the American Statistical Association. 2005;100(471):908-15.

8.1 Data Handling Plan

Reference is made to Data Handling Plan (DHP) version 1.0 18APR2018, current at the time of signing this SAP

8.2 Reference to the Trial Master File and Statistical Documentation

Not applicable

8.3 Reference to other Standard Operating Procedures or Documents

Not applicable

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RESEARCH REPORT

ADDICTION SSA

Comparison of intranasal and intramuscular naloxone in opioid overdoses managed by ambulance staff: a double-dummy, randomised, controlled trial

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Abstract

Aims: To measure and evaluate clinical response to nasal naloxone in opioid overdoses in the pre-hospital environment.

Design: Randomised, controlled, double-dummy, blinded, non-inferiority trial, and conducted at two centres.

Setting: Participants were included by ambulance staff in Oslo and Trondheim, Norway, and treated at the place where the overdose occurred.

Participants: Men and women age above 18 years with miosis, rate of respiration ≤8/min, and Glasgow Coma Score <12/15 were included. Informed consent was obtained through a deferred-consent procedure.

Intervention and comparator: A commercially available 1.4 mg/0.1 mL intranasal naloxone was compared with 0.8 mg/2 mL naloxone administered intramuscularly.

Measurements: The primary end-point was restoration of spontaneous respiration of ≥10 breaths/min within 10 minutes. Secondary outcomes included time to restoration of spontaneous respiration, recurrence of overdose within 12 hours and adverse events.

Findings: In total, 201 participants were analysed in the per-protocol population. Heroin was suspected in 196 cases. With 82% of the participants being men, 105 (97.2%) in the intramuscular group and 74 (79.6%) in the intranasal group returned to adequate spontaneous respiration within 10 minutes after one dose. The estimated risk difference was 17.5% (95% CI, 8.9%–26.1%) in favour of the intramuscular group. The risk of receiving additional naloxone was 19.4% (95% CI, 9.0%–29.7%) higher in the intranasal group. Adverse reactions were evenly distributed, except for drug withdrawal reactions, where the estimated risk difference was 6.8% (95% CI, 0.2%–13%) in favour of the intranasal group in a *post hoc* analysis.

Conclusion: Intranasal naloxone (1.4 mg/0.1 mL) was less efficient than 0.8 mg intramuscular naloxone for return to spontaneous breathing within 10 minutes in overdose patients in the pre-hospital environment when compared head-to-head. Intranasal

16.1.11 Publications based on the study

naloxone at 1.4 mg/0.1 mL restored breathing in 80% of participants after one dose and had few mild adverse reactions.

KEYWORDS
Administration, drug overdose, injections, intramuscular, intranasal, naloxone, narcotic antagonists, physiological effects of drugs, substance-related disorders

INTRODUCTION

Opioid overdose remains a global epidemic, with an annual death toll of more than 100 000 [1]. As a response, the main opioid antagonist naloxone has been made available to lay people in Take Home Naloxone (THN) Programmes from the late 1990s. THN was never meant to replace callout to and treatment by emergency medical services. It is a head start at the scene to shorten the time to the administration of the antidote while awaiting the emergency medical services for professional management and post-overdose follow-up.

The route of administration and dosing of naloxone in opioid overdoses in the community are debated, not least in the fentanyl era in North America [2]. Recommendations range from 0.04 to 2.0 mg via the intravenous or intramuscular route and titration to desired effect [3, 4]. The World Health Organisation (WHO) recommends starting at the lower end of that spectrum to avoid eliciting withdrawal [5]. Off-label, unapproved, dilute nasal sprays have been used in THN programs [2, 6]. Nasal administration is preferred by lay people owing to its ease of use [7]. Since 2015, several nasal naloxone products with single doses ranging from 0.9 mg to 8.0 mg have entered the market. These formulations were approved based on phase I pharmacokinetic studies in healthy volunteers alone [8–12]. The lack of clinical trials of these high concentration/low volume sprays and the lack of trials comparing different naloxone regimens, leave an important knowledge gap in best practice for management of opioid overdoses in the community. Previous trials of intranasal (IN) naloxone have shown promise, but were limited in that the formulations investigated were neither specifically designed for IN use nor commercially available. They also lacked systematic information on adverse events and the risk of rebound overdose after initial naloxone revival [13–16].

The nasal spray with 1.4 mg of naloxone hydrochloride dihydrate, equivalent to 1.26 mg naloxone (dne pharma as, Oslo, Norway), has been developed by the Norwegian University of Science and Technology (NTNU). The 1.4 mg/0.1 mL formulation was shown to provide adequate systemic concentrations compared to intramuscular 0.8 mg injection [10], and its absolute bioavailability was ∼50% in healthy volunteers [17, 18]. However, exposure to the opioid remifentanil gives a relative bioavailability as high as 75% [19]. This highlights the need for clinical studies in the target population. Clinicians, lay people responders and policy makers should know precisely how a nasal naloxone spray performs in the field, compared to injectable antidotes. This requires studies that investigate both the effect and harm in the target population, allowing for evidence-based decision-making. The population of interest in this trial corresponds to patients suffering from severe opioid overdose who were treated by ambulance personnel outside the hospital. The intervention was the administration of a single dose of the 1.4 mg/0.1 mL dose naloxone nasal spray compared to 0.8 mg naloxone injected intramuscularly. The primary outcome was the return of spontaneous respiration within 10 minutes of drug administration. The main hypothesis was that, in a head-to-head comparison, the nasal spray would be non-inferior to the injection.

METHODS

Study design

The NTNU Intranasal Naloxone Trial (NINA-1) was a two-centre, randomised, double-dummy blinded, phase III, non-inferiority trial [20]. Participants were recruited through ambulance services at Oslo University Hospital and St. Olav's University Hospital Trondheim, both in Norway. Extensive trial documentation, including information letters for consent and the protocol, is available at the NTNU Open Research Data repository [21].

Participants

Participants treated by ambulance services for suspected opioid overdose, recognised by reduced or absent spontaneous respiration (≤8 breaths/min), Glasgow Coma Score <12/15 and miosis, were included. However, those who had cardiac arrest, suspected pregnancy, age below 18 years or had received naloxone before the arrival of ambulance staff were excluded. A complete list of the inclusion and exclusion criteria and a flowchart of the consent procedure are provided in Supporting information Table S1, Fig. S1.

Naloxone formulation and dosing

The investigational medicinal product (IMP) was a 1.4 mg/0.1 mL naloxone hydrochloride dihydrate (equivalent to 1.26 mg naloxone) nasal spray produced by Sanivo Pharma, Oslo, Norway. The drug was administered as 1.4 mg/0.1 mL nasal spray using an unidose device (Aptar Pharma). The active comparator was a 2 mL intramuscular (IM) injection of 0.4 mg/mL naloxone hydrochloride (naloxone hydrochloride injection USP 4 mg/10 mL; Mylan Institutional). The IN placebo was similar to the IMP, except that it did not contain naloxone. The IM placebo was a 2 mL injection of sterile 9 mg/mL sodium chloride. The vials for injection were similar, blinded, and labelled for clinical trial use.

Randomisation and masking

To ensure blinding, a double-dummy design was used. Active and placebo drugs were kept in a sealed box—a study kit that also contained case report forms, written information for consent and needles and syringes for IM injection. Study drugs were labelled, and kits were randomised, assembled and sealed by the Hospital Pharmacy, St. Olav's Hospital, Trondheim, Norway. Each ambulance only held one kit at a time, the drug contents of which were randomised to the nasal spray or vial for injection contained naloxone or a placebo. Staff were not randomised, but used the kit available in their vehicle. Participants were randomly assigned in a 1:1 ratio to receive either IN or IM naloxone. Randomisation was stratified by study centre, and random block sizes were used. Stratification was done both for practical reasons and to ensure balance of the treatment groups within each centre, because Trondheim does not have a safe injection facility that was a priory considered to be a possible prognostic factor. Computer generated randomisation lists were produced by The Clinical Trial Unit at Oslo University Hospital. The blinding was kept for all until after the database was locked, and only then did we perform the primary analysis. The whole study team, including the statistician, was blinded to the interventions. A procedure for emergency unblinding was in place, but never used.

Procedures

All participants were treated with airway control and ventilation using the bag-mask technique before treatment with the study drug. Participants were treated in situ where the overdose occurred, not evacuated to an ambulance car or an emergency room before the administration of the study drug. Nasal spray and IM injection were administered simultaneously, or within 30 seconds of each other, with nasal spray always given first. Ambulance staff noted the time from the administration of the study drug to when a spontaneous respiration rate of ≥10 breaths/min was observed. The number of breaths per minute was counted manually. If the participant did not respond adequately or did not wake up after 10 minutes, additional intramuscular naloxone (0.4 mg/mL from either Naloxone B, Braun, Melsungen, or from Naloxon Hameln, Hameln, both in Germany) or other treatments were provided as clinically indicated. A 10-minute cut-off for the primary end-point was similar to other trials in the field [14, 16]. After treatment and observation, participants were either left at the scene or transported to other health care sites following the local protocol at each site. Participants with a known national identity number were identified through an ambulance dispatch system for repeated naloxone treatment and for recurrence of opioid overdose within 12 hours after inclusion. A flowchart of the study treatment and a description of the dummy design kit are provided in Supporting information Figs. S2 and S3. To ensure fidelity to the study protocol, each ambulance worker underwent rigorous training that consisted of electronic learning and live scenarios. Re-training and refresher courses were administered at all sites during the study period.

Outcomes

The primary outcome was the return of spontaneous respiration (≥10 breaths/min) within 10 minutes of administering the study drug. Secondary outcomes included the time from administration of naloxone to respiration of ≥10 breaths/min, receiving additional naloxone, and recurrence of opioid overdose within 12 hours of inclusion. Adverse reactions to naloxone formulation were assessed and coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Symptoms of agitation or aggression, or statements from participants that they were in withdrawal, were coded as drug withdrawal syndrome, whereas nausea and vomiting were coded separately. A full list of pre-specified outcomes and subgroups is provided in Supporting information (Table S2, Figure S4) and Study Protocol.

Statistical analysis

We assumed a probability of 88% for return to spontaneous respiration within 10 minutes in both groups and calculated that 200 cases were required to determine with 90% (power) confidence that the upper limit of the two-sided 95% CI would exclude a difference of >15% in favour of the IM group. The non-inferiority margin of 15% and the non-inferiority of IN to IM administration were claimed if the 95% CI of the treatment difference for the primary end-point lay fully within the margin. The 15% margin was not a mathematical calculation, but was based on clinical judgement and experience with naloxone. A similar range has been used to compare efficacy and safety in a biosimilar medication [22]. The primary efficacy analyses were conducted in the per-protocol population, which comprised participants fully compliant with the pre-specified treatment strategy. In non-inferiority trials, analysis of the per-protocol set is regarded as the primary analysis. This is a conservative approach, because a full analysis set (FAS)/intention to treat analysis is generally considered to be biased toward smaller differences between groups [23]. Protocol deviations that led to exclusion from the per-protocol population are presented in Supporting information Table S3. Sensitivity analyses were performed in the FAS, which included all participants who received the study drug and did not withdraw consent. Safety analyses were conducted in all participants who received any study drugs, including those in the FAS as well as those who withdrew consent (safety set).

The primary and secondary dichotomous end-points were analysed using logistic regression, wherein the treatment variable was adjusted for the study centre. To account for clustering in the data (the same individuals may have had several overdose events), generalised estimating equations with an exchangeable working correlation were used to estimate the parameters. The risk difference was calculated from the estimated model using average marginal means and corresponding 95% CIs using the delta method. The time-to-event end-point of time to spontaneous respiration was analysed by calculating the difference in restricted mean survival time between the two treatment groups at each minute of follow-up, adjusted for study centre. The time-to-event data were censored at 10 minutes. The

jack-knife technique was used to calculate the 95% CI, where one individual rather than one overdose event was left out in each jack-knife sample, to account for clustering in the data. A complete overview of all pre-specified end-points and a detailed description of the statistical methods used are given in the Supplementary Statistical Analysis Plan.

Ethics and consent

The study was approved by the Norwegian Medicines Agency (EudraCT number: 2016–004072-22) and Regional Committees for Medical and Health Research Ethics (REC 2016/2000). The trial was performed in accordance with the principles of the Declaration of Helsinki and adhered to the Good Clinical Practice guidelines of the International Council for Harmonisation of Technical Requirements. Participants were insured through the Drug Liability Association, Norway.

Informed consent was obtained through a deferred-consent procedure. That is, participants were informed after regaining consciousness and the ability to consent, and two ambulance workers documented an orally given consent. The information stated that they were included in a clinical drugs trial, describing the intervention and information regarding the withdrawal procedure. Participants who did not respond to naloxone or were unable to give informed consent at the scene were provided written information and an option to withdraw later online or by telephone. In participants who withdrew, data on adverse events and safety end-points were anonymised and retained. For more information, please consult Supporting information Figure S1 and S2.

Public consultation and involvement

A board of drug user representatives and family representatives of participants advised investigators in the study design, protocol, information letter writing and in applying the study for ethics committee approval. This work included assessing the burden of the deferred-consent model for participants, compared to the burden in other consent models such as proxy consent or prior consent. The board actively informed the community throughout the inclusion period about the ongoing trial and will be part of disseminating the results. For details regarding the members, please consult the Supporting information.

RESULTS

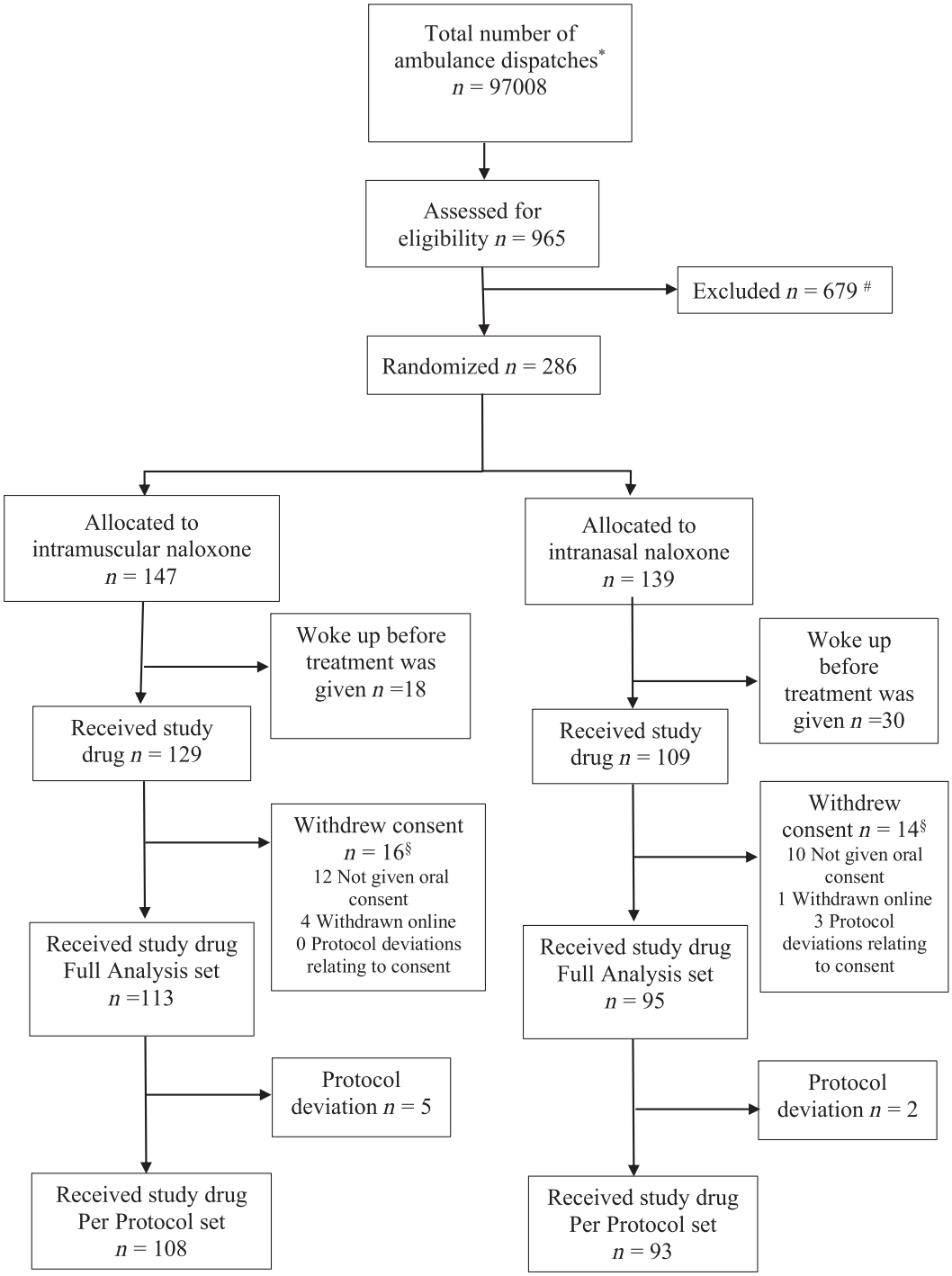
Characteristics of the participants

From June 12, 2018, to August 4, 2020, a total of 147 cases of opioid overdose were randomised to IM naloxone treatment and 139 cases to IN (Figure 1). The per-protocol sample was 108 for IM and 93 for IN. Overall, the groups were balanced in terms of baseline characteristics (Table 1). The overall allocation of treatment is balanced (Table 1). However, there is an unbalance among those individuals included several times in the study toward more often IM treatment (Table 1). Because of the apparently successful blinding procedure, we have no indication that this is anything but a chance occurrence. Characteristics of excluded participants and those in the FAS are available in Supporting information Table S4. Participants were included in both public places and private homes in n = 121/201, (60%), and in the Oslo Safe Injection Facility in n = 80/201 (40%). The dispatch time was 5.5 (SD, 3.5) minutes. Participants left at the scene were treated for 50.4 (SD, 18.0) minutes, whereas participants transferred elsewhere for further care were treated by ambulance staff for 40.0 (SD, 15.9) min. Heroin was suspected in n = 196/201 (98%) cases and concomitant drugs in n = 35/201 (17%) cases. Respiratory arrest was present in n = 56/201 (30%) of cases, they had no spontaneous breaths within 10 seconds despite a free airway. Another n = 82/201 (40%) had a respiratory rate of 4/min or less. The median respiratory rate was 3/min, and n = 157/201 (78%) had a Glasgow Coma Score of 3/15, which was also the median score (Figure 1).

Primary outcome

There were 105 participants (97.2%) in the IM and 74 (79.6%) in the IN group with overdose events who achieved spontaneous breathing within 10 minutes after one dose of the study drug. The estimated risk difference between IM and IN naloxone was 17.5% (95% CI, 9.0%–26.1%) (Table 2, Figure 2). An unadjusted (for centre) *post hoc* robustness analysis gave a risk difference of 17.7% (95% CI, 9.0%, 26.3%). The primary analysis population in this non-inferiority trial was the per-protocol population. These results are consistent in an analysis of the FAS (Table 2). The FAS was the closest to a theoretical ITT population that is possible to get. The FAS did not contain patients that did not receive any treatment or patients that have withdrawn consent (see Figure 1). The results were also consistent across several pre-specified subgroup analyses of possible prognostic factors (Supporting information Figure S4). For the Oslo centre, the estimate and 95% CI was 15.6% (6.9%, 24.4%). For the much smaller Trondheim centre, the estimate and 95% CI was 42.9% (7.1%, 78.6%) Furthermore, results are also consistent in *post hoc* analyses adjusting the treatment variable for each of the baseline variables given in Table 1 (Supporting information Table S5).

Figure 3(a) displays the probability of not breathing 10 spontaneous breaths per minute over time. The IN curve retained its linear shape in the 10-minute observation period. Figure 3(b) displays the average delay in the time to spontaneous breathing in the IN group compared to the IM group quantified by the restricted mean survival time. After 4 minutes, a difference existed between the groups according to the upper 95% CI limit. Within the total follow-up of 10 minutes, participants in the IM group returned to spontaneous respiration at an average of 2.3 (95% CI, 1.6–3.0) minutes earlier than in the IN group.



*: All ambulance callouts in period from first to last patient at both participating sites
#: Reasons for exlusion are provided in Supplement "Table S8: Reasons to exclude participants"
§: Participants who withdrew consent have safety information registered anonymously and combined with the "Full Analysis set" to create "Safety set". There are no estimate on primary end point in this group

FIGURE 1 Flowchart of participants of the trial

Secondary outcomes

In the per-protocol population, additional naloxone was administered in 10 (9.3%) cases in the IM group and 27 (29.0%) in the IN group. The estimated risk difference was −19.4% (95% CI, −29.7% to −9.0%). Similar results were found when repeating the analysis in the FAS and safety set. The mean dose of additional naloxone administered was 0.6 (SD, 0.35) mg.

TABLE 1 Baseline overdose event characteristics of the per-protocol population

	No. of overdose events with data		*Intramuscular (n = 108)*	*Intranasal (n = 93)*	*Overall (n = 201)*
Centre (%)	201	Oslo University Hospital	101 (93.5)	86 (92.5)	187 (93.0)
		St. Olav's Hospital, Trondheim	7 (6.5)	7 (7.5)	14 (7.0)
Sex (%)	201	Female	19 (17.6)	17 (18.3)	36 (17.9)
		Male	88 (81.5)	75 (80.6)	163 (81.1)
		Unknown	1 (0.9)	1 (1.1)	2 (1.0)
Age (mean [SD])	183		37.3 (10.2)	38.5 (10.8)	38.9 (10.5)
Identity known (%)	201	Yes	100 (92.6)	83 (89.2)	183 (91.0)
		No	8 (7.4)	10 (10.8)	18 (9.0)
Baseline respiratory rate in breaths/min (%)	201	0	30 (27.8)	26 (28.0)	56 (27.9)
		1–4	46 (42.6)	36 (38.7)	82 (40.8)
		5–8	32 (29.6)	31 (33.3)	63 (31.3)
Baseline Glasgow Coma Score (%)	201	3/15	86 (79.6)	71 (76.3)	157 (78.1)
		4–11/15	22 (20.4)	22 (23.7)	44 (21.9)
Primary suspected drug (%)	201	Heroin	106 (98.1)	90 (96.8)	196 (97.5)
		Methadone	0 (0.0.)	1 (1.1)	1 (0.5)
		Other opioids	2 (1.9)	2 (2.2)	4 (2.0)
Benzodiazepines, alcohol, gamma hydroxybutyrate, or other drugs suspected (%)	201	Yes	19 (17.6)	16 (17.2)	35 (17.4)
		No	89 (82.4)	77 (82.8)	166 (82.6)
Location of overdose (%)	201	Oslo Safe injection facility	51 (47.2)	29 (31.2)	80 (39.8)
		Private or public	57 (52.8)	64 (68.8)	121 (60.2)
No. of times included (per protocol set)	201	1	68	63	131
		2	18	12	30
		3	9	9	18
		4	3	1	4
		5	8	2	10
		8	7	1	8

TABLE 2 Primary outcome results in both the per-protocol analysis and the full analysis set analysis

Effect estimate	*Analysis population*	*n_IM*	*n_IN*	*Estimate (95% CI)*
Risk difference	Per-protocol population	105/108	74/93	17.5% (9.0%, 26.1%)
Risk difference	Full analysis set	110/113	76/95	17.3% (8.9%, 25.7%)

IM = intramuscular; IN = intranasal.

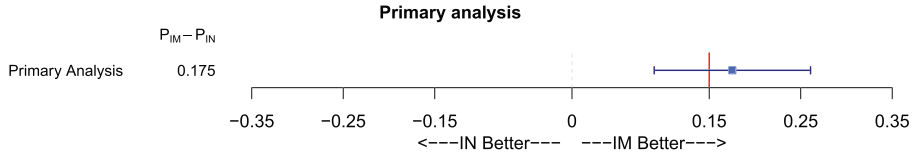


FIGURE 2 Results of primary analysis of the primary end-point in the per-protocol population. The risk difference with 95% CI is displayed. The red vertical line represents the non-inferiority margin of 15%. IN, intranasal; IM, intramuscular

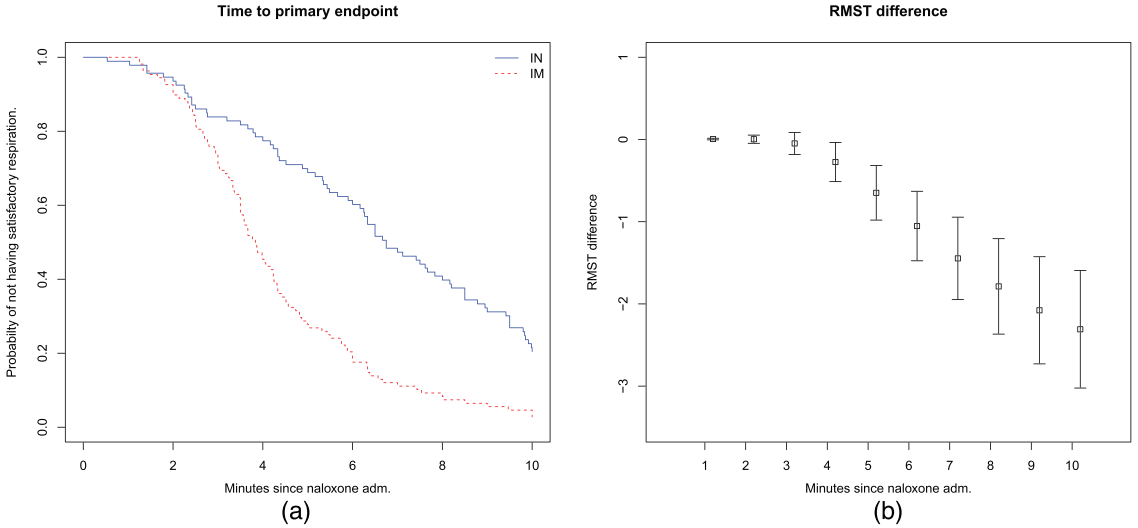


FIGURE 3 Probability of unsatisfactory respiration and average delay in spontaneous breathing. (a) Kaplan–Meier plot (unadjusted for study centre) showing the probability of not having reached satisfactory respiration (10 breaths/minute). (b) Restricted mean survival time (RMST) difference in minutes (intramuscular minus intranasal) at each minute of follow-up time, from 1 to 10 minutes. IM, intramuscular; IN, intranasal

TABLE 3 Number and proportion of cases from the safety set population with adverse reactions classified according to MedDRA

		Treatment group		
System organ class	***Preferred term***	***Intramuscular* (*n* = 129)**	***Intranasal* (*n* = 109)**	***Overall* (*n* = 238)**
Cardiac disorders	Bradycardia (%)	0 (0.0)	1 (0.9)	1 (0.4)
Gastrointestinal disorders	Nausea (%)	5 (3.9)	7 (6.4)	12 (5.0)
	Vomiting (%)	0 (0.0)	2 (1.8)	2 (0.8)
General disorders and administration site conditions	Drug withdrawal syndrome (%)	15 (11.6)	5 (4.6)	20 (8.4)
Nervous system disorders	Dizziness (%)	1 (0.8)	0 (0.0)	1 (0.4)
	Headache (%)	5 (3.9)	4 (3.7)	9 (3.8)

Data on the remaining secondary end-points are presented in Supporting information Table S6, Figure S5. MedDRA, Medical Dictionary for Regulatory Activities.

In the 201 overdose events in the per-protocol population, four (3.7%) in the IM group and four (4.3%) in the IN group received treatment with naloxone by the ambulance service at another callout within 12 hours of inclusion. The estimated risk difference was −0.2% (95% CI, −6.7%, 6.3%). However, only 183 cases had known identities and could be followed up for recurrence.

In the per-protocol population, there were 14 (13.0%) and 14 (15.1%) adverse reactions in the IM and IN groups, respectively. The estimated risk difference was −2.2% (95% CI, −11.5%–7.1%). Table 3 shows an overview of the adverse reactions in the safety set. One serious adverse event (self-limiting bradycardia) was reported in the intranasal group. All participants survived during the treatment period. There were no reports of suspected unexpected serious adverse reactions. In the per-protocol population, there were eight (7.5%) and five (5.4%) occurrences of drug withdrawal syndrome in the IM and IN groups, respectively. The estimated risk difference was 2.0% (95% CI, −4.6%–8.5%). However, in the safety set, a *post hoc* analysis revealed a borderline significant estimated risk difference of 6.8% (95% CI, 0.2%–13%), with a lower risk of withdrawal in the IN group. Among participants in the IM group with adverse events who refused or withdrew consent, six of the eight cases suffered withdrawal syndrome.

DISCUSSION

A single dose of 1.4 mg/0.1 mL IN naloxone was inferior to 0.8 mg IM naloxone in terms of return to spontaneous breathing at 10 minutes after administration. In the IM naloxone group, 97% of cases achieved the primary end-point, which outperformed our expectation of 88%. After a single 1.4 mg/0.1 mL spray, 80% achieved satisfactory respiration within 10 minutes. This likely resulted from an average slower

uptake of naloxone in the IN group. After 3 minutes the stronger effect of IM became evident (Figure 3) and, within the follow-up of 10 minutes, the effect of naloxone was 2.3 minutes slower in the IN group than in the IM group. The nasal effect curve was linear from about 3 minutes until censoring at 10 minutes, where non-responders were administered additional IM naloxone according to protocol. Previous pharmacokinetic studies have shown that IN serum concentration continues to rise after 10 minutes, and measurement beyond 10 minutes would likely show an overall similar potency between IM and IN [10]. Both 0.8 mg IM and 1.4 mg/0.1 mL IN naloxone showed few and mostly mild, adverse reactions. There was no difference in the overall risk of adverse reactions, overdose complications, follow-up after treatment or notable opioid overdose recurrence. However, more drug withdrawal reactions occurred in the IM group in the safety set. This is not a trivial matter, because over-antagonism is associated with physical reactions, aggression, refusal of treatment and premature self-discharge [3, 24].

To avoid over-antagonism and triggering opioid withdrawal, naloxone should be titrated. Our findings that 0.8 mg IM was sufficient for reversal in almost 100% of cases indicate that it was too high as a starting dose and lower doses should be tested. This has also been seen previously in Australia [16]. Pharmacokinetic trials show that dose-corrected concentrations of intravenous naloxone are many times as high as those achieved with IM naloxone [2]. This forms a strong argument for the efficacy and safety of the intramuscular route of administration in contrast to intravenous, which has a high probability of triggering withdrawal.

Role of 1.4 mg/0.1 mL in THN programs

Because the spray is primarily meant for THN distribution, it seems pertinent to discuss our findings in this context. THN aims to provide a head start in opioid reversal and the chain of overdose survival, to restore respiration, to regain consciousness and then to facilitate post-overdose follow-up, including addiction management and prevention of future overdoses. In this perspective, the slower onset of action of the 1.4 mg/0.1 mL IN dose, with an 80% probability of achieving spontaneous breathing within 10 minutes, seems a reasonable starting point for overdose treatment in THN. THN based on dose titration has worked in the past [25].

However, discussion on THN dosing of naloxone should also embrace fentanyl intoxications. Evidence indicating that large naloxone doses are required for fentanyl overdoses is limited and contradictory [2, 26]. The presence of fentanyl overdose deaths in Massachusetts has increased continuously, but the overdose rate has been stable since 2016 [27, 28]. A moderate increase in multiple naloxone dosing in the preceding years in the United States (US) has been reported, whereas the rate of additional nasal naloxone has not changed [29–31]. The amount of naloxone used for reversal has not increased either [32, 33]. However, the introduction of Narcan in 2016 [34] resulted in a dramatic rise of dose levels approaching those associated with serious pulmonary complications [35]. Ultimately, the major challenge with THN in preventing overdose deaths may not be the dose of naloxone, but whether there are bystanders present that carry naloxone [27].

Comparisons to other trials

Four previous trials of nasal naloxone used dilute IN formulations with unknown pharmacokinetic characteristics, making pharmacological assessment of the comparator impossible [13–16]. However, all trials agreed that intranasal naloxone is a feasible and safe alternative to naloxone by the needle in opioid overdose. IM had a faster effect in all with less need for repeat doses. Therefore, the superiority of IM to IN in a bioequivalent head-to-head comparison in opioid exposed participants seemed not to completely overcome the slower action of IN, despite similar pharmacokinetics in healthy volunteers [8–10].

Advantages and limitations

The major advantage of this study was that the performance of a properly characterised and approved nasal naloxone spray was studied in the target population, strengthening the basis of evidence in the field. The inclusion criteria ensured that the overdoses studied were severe, and that the participants were in deep coma with inadequate spontaneous respiration. Compared to those in a non-selected sample in Oslo, the participants had lower median respiratory rates (3 vs 7/min) and Glasgow Coma Score (3 vs 4/15) [36]. The nasal dose was chosen based on several pharmacokinetic studies of volunteers, including a study in which volunteers were exposed to an opioid [10, 17, 19]. The comparator dose exceeded the 0.4 mg IM dose required for regulatory purposes and was chosen based on a field study and recommendations of the WHO [5, 36]. The trial conformed to contemporary standards of clinical trial study design and conductance according to the Good Clinical Practice guidelines, including the registration, classification and publication of adverse events, such as recurrence of overdose in the 12 hours post-inclusion. Our main results were consistent in all the trial populations.

The study is limited in that it only compares two single administrations of naloxone head-to-head and not regimens of titration, which would have been more relevant to the THN scenario. Administering up to two 1.4 sprays in one study arm to incremental doses of 0.4 mg IM naloxone in the other would have increased the value of this trial. The main end-point number of breaths per minute was manually counted, which allowed for mistakes. The study drugs were administered simultaneously when possible and always within 30 seconds of each other, with IN first. Although we selected cases with severe overdoses, the low rate of fentanyl intoxications in this study is also a limitation. Future clinical studies should focus on overdose management, first aid response, the timely administration and titration of naloxone and follow-up beyond the initial treatment. Studies should be conducted in areas with suspected fentanyl as overdose culprits. Policy and practitioners must recognise that opioid overdoses

are a medical emergency that needs urgent first aid and antidote, but also follow-up and prevention of new overdoses. The concept of 'a chain of survival' as seen in cardiac arrest may guide future practise [37]. For this to work, over-antagonism with naloxone must be reduced and post-overdose care must be expanded.

CONCLUSION

In conclusion, this study showed that 1.4 mg/0.1 mL IN naloxone was less efficient, owing to a slower onset, than 0.8 mg IM naloxone in terms of return of spontaneous breathing within 10 minutes in participants with serious opioid overdoses, and that 0.8 mg IM naloxone had an almost 100% success rate. However, notably, 1.4 mg/0.1 mL IN naloxone restored breathing in 80% of participants after one dose and was associated with few and mild adverse reactions, allowing for titration.

DECLARATION OF INTERESTS

A.K.S. spoke at a seminar arranged by dne pharma in Lisbon on October 2019 without an honorarium or other compensation. I.T. has nothing to disclose. M.V. has nothing to disclose. A.C.B. has nothing to disclose. J.D. has nothing to disclose. F.H. reports grants from Norwegian Air Ambulance Foundation during the conduct of the study. T.S. has nothing to disclose. J.B. has nothing to disclose. S.M. has nothing to disclose. O.D. reports grants from Regional Health Trust, Central Norway, grants from St. Olav's University Hospital, Trondheim, NO, grants from The Laerdal Foundation, during the conduct of the study; and NTNU; the Norwegian University of Science and Technology has signed a collaboration and licensing agreement with dne pharma to commercialise the nasal spray. Dne pharma has received marketing authorisation for a naloxone nasal spray (Ventizolve/Respinal) based on this collaboration. The formulation was invented by O.D., and the agreements ensure potential royalties for him through NTNU and NTNU's subsidiary Technology Transfer (TTO). The agreements do not restrict NTNU's opportunity to publish results from its own research on the product. O.D. was principal investigator (no personal honorarium) for dne pharma on a study of naloxone spray in volunteers and has been reimbursed for project related journeys between Oslo and Trondheim. He has received honoraria and travel support from dne pharma for presentations on marketing events.

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AUTHOR CONTRIBUTIONS

A.K.S. and I.T. share first authorship of this manuscript. Together with M.V. and O.D., they prepared the first draft of the manuscript. A.C.B., J.D., J.B., F.H., S.M. and T.S. all revised that draft into its final form. No other writing assistance apart from language editing from Editage has been used on this manuscript. All authors have seen and accepted the version being submitted.

CLINICAL TRIAL REGISTRATION

ClinicalTrials.gov identifier: NCT03518021. EudraCT Number: 2016–004072-22.

DATA SHARING

Trial documents and metadata are openly published in the Norwegian University of Science and Technology Open Repository (doi.org/10.18710/ABRUWW). Summaries of clinical study results will be posted in European Clinical Trials Database with 1 year of completion of the trial. Deidentified individual participant data will be made available on reasonable demand to recipients' conditional of data processor agreement being entered with NTNU.

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REFERENCES

1. Degenhardt L, Grebely J, Stone J, Hickman M, Vickerman P, Marshall BDL, et al. Global patterns of opioid use and dependence: Harms to populations, interventions, and future action. Lancet. 2019;394(10208):1560–79.
2. Strang J, McDonald R, Campbell G, Degenhardt L, Nielsen S, Ritter A, et al. Take-home naloxone for the emergency interim Management of Opioid Overdose: The public health application of an emergency medicine. Drugs. 2019;79(13):1395–418.
3. Kim HK, Nelson LS. Reducing the harm of opioid overdose with the safe use of naloxone: A pharmacologic review. Expert Opin Drug Saf. 2015;14(7):1137–46.

4. Clarke SF, Dargan PI, Jones AL. Naloxone in opioid poisoning: Walking the tightrope. Emerg Med J. 2005;22(9):612–6.
5. World Health Organization. Community management of opioid overdose. Geneva: World Health Organization; 2014 Available from: http://www.ncbi.nlm.nih.gov/books/NBK264311/
6. Strang J, Darke S, Hall W, Farrell M, Ali R. Heroin overdose: The case for take-home naloxone. BMJ. 1996;312(7044):1435–6.
7. Mcdonald R, Breidahl S, Abel-Ollo K, Akhtar S, Clausen T, Day E, et al. Take-home naloxone kits: Attitudes and likelihood-of-use outcomes from a European survey of potential overdose witnesses. Eur Addict Res. 2021.
8. Krieter P, Chiang N, Gyaw S, Skolnick P, Crystal R, Keegan F, et al. Pharmacokinetic properties and human use characteristics of an FDA-approved intranasal naloxone product for the treatment of opioid overdose. J Clin Pharmacol. 2016;56(10):1243–53.
9. McDonald R, Lorch U, Woodward J, Bosse B, Dooner H, Mundin G, et al. Pharmacokinetics of concentrated naloxone nasal spray for opioid overdose reversal: Phase I healthy volunteer study. Addiction. 2018;113(3):484–93.
10. Skulberg AK, Asberg A, Khiabani HZ, Rostad H, Tylleskar I, Dale O. Pharmacokinetics of a novel, approved, 1.4-mg intranasal naloxone formulation for reversal of opioid overdose-a randomized controlled trial. Addiction. 2019;114(5):859–67.
11. Base de Données Publique des Médicaments. NALSCUE 0,9 mg/0,1 ml, Résumé des caractéristiques du produit, 2020 [cited 2020 5. october]. Available from: http://base-donnees-publique.medicaments.gouv.fr/affichageDoc.php?specid=60855566&typedoc=R
12. Knopf A. High-dose naloxone nasal spray approved. Alcohol Drug Abuse Weekly. 2021;33(20):6.
13. Kelly AM, Kerr D, Dietze P, Patrick I, Walker T, Koutsogiannis Z. Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. Med J Aust. 2005;182(1):24–7.
14. Kerr D, Kelly AM, Dietze P, Jolley D, Barger B. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. Addiction. 2009;104(12):2067–74.
15. Sabzghabaee AM, Eizadi-Mood N, Yaraghi A, Zandifar S. Naloxone therapy in opioid overdose patients: Intranasal or intravenous? A randomized clinical trial. Arch Med Sci. 2014;10(2):309–14.
16. Dietze P, Jauncey M, Salmon A, Mohebbi M, Latimer J, van Beek I, et al. Effect of intranasal vs intramuscular naloxone on opioid overdose: A randomized clinical trial. JAMA Netw Open. 2019;2(11):e1914977.
17. Tylleskar I, Skulberg AK, Nilsen T, Skarra S, Jansook P, Dale O. Pharmacokinetics of a new, nasal formulation of naloxone. Eur J Clin Pharmacol. 2017;73(5):555–62.
18. Tylleskar I, Skulberg AK, Nilsen T, Skarra S, Dale O. Naloxone nasal spray - bioavailability and absorption pattern in a phase 1 study. Tidsskr nor Laegeforen. 2019;139(13).
19. Skulberg AK, Tylleskar I, Nilsen T, Skarra S, Salvesen O, Sand T, et al. Pharmacokinetics and -dynamics of intramuscular and intranasal naloxone: An explorative study in healthy volunteers. Eur J Clin Pharmacol. 2018;74(7):873–83.
20. Skulberg AK, Tylleskär I, Braarud A-C, Dale J, Heyerdahl F, Mellesmo S, et al. 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. BMJ Open. 2020;10(11):e041556.
21. Skulberg AK, Dale O. NTNU Intranasal Naloxone Trial (NINA-1) Study documents. DataverseNO; 2020 Available from: https://doi.org/10.18710/ABRUWW
22. Jørgensen. K ea. 'LB15 - Biosimilar infliximab (CT-P13) is not inferior to originator infliximab: results from the 52-week randomized NORSWITCH trial. In: United European Gastroenterology (UEG) Week meeting 2016, 15–19 October; Vienna, Austria.
23. Mauri L, D'Agostino RB Sr. Challenges in the design and interpretation of noninferiority trials. N Engl J Med. 2017;377(14):1357–67.
24. Neale J, Strang J. Naloxone--does over-antagonism matter? Evidence of iatrogenic harm after emergency treatment of heroin/opioid overdose. Addiction. 2015;110(10):1644–52.
25. Madah-Amiri D, Clausen T, Lobmaier P. Rapid widespread distribution of intranasal naloxone for overdose prevention. Drug Alcohol Depend. 2017;173:17–23.
26. Kim HK, Connors NJ, Mazer-Amirshahi ME. The role of take-home naloxone in the epidemic of opioid overdose involving illicitly manufactured fentanyl and its analogs. Expert Opin Drug Saf. 2019;18(6):465–75.
27. Somerville NJ, O'Donnell J, Gladden RM, Zibbell JE, Green TC, Younkin M, et al. Characteristics of fentanyl overdose - Massachusetts, 2014-2016. MMWR Morb Mortal Wkly Rep. 2017;66(14):382–6.
28. Massachusetts Department of Public Health. Data Brief: Opioid-Related Overdose Deaths among Massachusetts Residents 2020 Available from: https://www.mass.gov/doc/opioid-related-overdose-deaths-among-ma-residents-june-2020/download
29. Faul M, Lurie P, Kinsman JM, Dailey MW, Crabaugh C, Sasser SM. Multiple naloxone administrations among emergency medical service providers is increasing. Prehosp Emerg Care. 2017;21(4):411–9.
30. Weiner SG, Mitchell PM, Temin ES, Langlois BK, Dyer KS. Use of intranasal naloxone by basic life support providers. Prehosp Emerg Care. 2017;21(3):322–6.
31. Klebacher R, Harris MI, Ariyaprakai N, Tagore A, Robbins V, Dudley LS, et al. Incidence of naloxone redosing in the age of the new opioid epidemic. Prehosp Emerg Care. 2017;1–6.
32. Bell A, Bennett AS, Jones TS, Doe-Simkins M, Williams LD. Amount of naloxone used to reverse opioid overdoses outside of medical practice in a city with increasing illicitly manufactured fentanyl in illicit drug supply. Subst Abus. 2019;40(1):52–5.
33. Carpenter J, Murray BP, Atti S, Moran TP, Yancey A, Morgan B. Naloxone dosing after opioid overdose in the era of illicitly manufactured fentanyl. J Med Toxicol. 2020;16(1):41–8.
34. Mahonski SG, Leonard JB, Gatz JD, Seung H, Haas EE, Kim HK. Prepacked naloxone administration for suspected opioid overdose in the era of illicitly manufactured fentanyl: A retrospective study of regional poison center data. Clin Toxicol (Phila). 2020;58(2):117–23.
35. Farkas A, Lynch MJ, Westover R, Giles J, Siripong N, Nalatwad A, et al. Pulmonary complications of opioid overdose treated with naloxone. Ann Emerg Med. 2020;75(1):39–48.
36. Tylleskar I, Gjersing L, Bjornsen LP, Braarud AC, Heyerdahl F, Dale O, et al. Prehospital naloxone administration - what influences choice of dose and route of administration? BMC Emerg Med. 2020;20(1):71.
37. Tagami T, Hirata K, Takeshige T, Matsui J, Takinami M, Satake M, et al. Implementation of the fifth link of the chain of survival concept for out-of-hospital cardiac arrest. Circulation. 2012;126(5):589–97.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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16.2.3 Patients excluded from the efficacy analysis

Reasons for participants to be excluded from Per Ptotocol to the Full Analysis Set

Centre	Database number	Description of deviation	Treatment arm
Oslo University Hospital	01-018	1 mL intramuscular, rather than 2 mL administered	Intramuscular naloxone
Oslo University Hospital	01-048	Administered study drug despite Glasgow Coma Score = 12/15	Intranasal naloxone
Oslo University Hospital	01-221	Freeze watch released prior to drug administration. Patient should have been excluded	Intramuscular naloxone
Oslo University Hospital	01-274	1 mL intramuscular, rather than 2 mL administered	Intramuscular naloxone
Oslo University Hospital	01-592	Freeze watch released prior to drug administration. Patient should have been excluded	Intramuscular naloxone
Oslo University Hospital	01-686	Leak between syringe and needle during injection, uncertain amount of study drug administered intramuscularly	Intranasal naloxone
St Olavs, Trondheim University Hospital	02-094	Injection administered 45 seconds after nasal spray, not with protocol specification of as simultaneously as possible, and not above 30 seconds difference	Intramuscular naloxone

16.2.7 Adverse event listings (each patient)

SiteName	SubjectId	EventName	EventDate	Term
Oslo University Hospital	01-021	Adverse Events	2018-06-22	Vomits in ambulance during transport
Oslo University Hospital	01-151	Adverse Events	2018-09-20	Patient described as aggressive and not willing to engage in meaningful discussion regarding consent. Offered follow up declines.
Oslo University Hospital	01-263	Adverse Events	2019-02-28	Nausea
Oslo University Hospital	01-140	Adverse Events	2019-03-01	Nausea
Oslo University Hospital	01-140	Adverse Events	2019-03-01	Vomiting
Oslo University Hospital	01-125	Adverse Events	2019-04-26	Nausea
Oslo University Hospital	01-235	Adverse Events	2019-04-26	EMS marked out nausea as symptom, not described severity, but patient deemed well enough to remain at Sprøyterommet.
Oslo University Hospital	01-253	Adverse Events	2019-04-26	headache, severity not described, but patient deemed fit to remain at the scene without follow up.
Oslo University Hospital	01-287	Adverse Events	2019-04-26	Patient describes light head-ache, EMS not recorded severity, but patient allowed to remain at the scene. Must be considered not serious or require medical attention.
Oslo University Hospital	01-253	Adverse Events	2019-04-26	Dizziness, light-headedness described in chart, severity not described, but patient deemed fit to remain at the scene without follow-up.
St. Olav's University Hospital	02-033	Adverse Events	2019-04-27	Patient expressed nausea during transport, transient and short lasting. Relieved by entering the emergency room. No vomiting. Cannot rule our car-sickness.

16.2.7 Adverse event listings (each patient)

SiteName	SubjectId	EventName	EventDate	Term
Oslo University Hospital	01-122	Adverse Events	2019-03-01	Aggression
St. Olav's University Hospital	02-009	Adverse Events	2018-08-06	hypothermia, cold and shivering, found lying on the floor
Oslo University Hospital	01-388	Adverse Events	2019-06-16	Crossed off for aggression in CRF
Oslo University Hospital	01-389	Adverse Events	2019-06-20	Described as agitated, but not violent by EMS. Does cooperate
Oslo University Hospital	01-395	Adverse Events	2019-08-17	Crossed off for nausea at paper CRF, not described in more detail
Oslo University Hospital	01-417	Adverse Events	2019-11-24	Describes as aggressive, agitated and abstinent by ambulance workers. These three are all expressions of the same clinical syndrome of opioid abstinence, and coded as one AE for this patient
Oslo University Hospital	01-583	Adverse Events	2019-11-24	Nausea, crossed off at paper CRF, not described more closely
Oslo University Hospital	01-402	Adverse Events	2019-11-24	Headache described in paper CRF
Oslo University Hospital	01-411	Adverse Events	2019-11-24	Aspiration. Patient has vomited and aspirated prior to the arrival of ambulance crew
Oslo University Hospital	01-373	Adverse Events	2019-11-24	Headache
Oslo University Hospital	01-373	Adverse Events	2019-11-24	nausea

16.2.7 Adverse event listings (each patient)

SiteName	SubjectId	EventName	EventDate	Term
Oslo University Hospital	01-673	Adverse Events	2020-02-10	Patient shivering and cold, being outside and wet
Oslo University Hospital	01-677	Adverse Events	2020-02-13	Patient included as per protocol. A few minutes into observation period study workers experiences masseter spasm. She had Guedel airway in place at the time, and no ventilation issues occurred. EMS contacted physician backup, administered 0.4 mg IV naloxone and 5 mg diazepam IV as per local protocol. Patient a a few minutes bradycardia 28-40 beats/minute. No sign of hypotension of hypoxia. No skin reaction/ bronchospasm described. Bradycardia self limited. Patient regained spontaneous respiration, bur remained unconscious at GCS =9/15. Admitted to Lovisenberg Hospital. She was administered repeat dose naloxone at hospital with no reaction and observed for 14 hours prior to being discharged to home with no sequelae. As described bradycardia is main reaction. Masseter spasm is more unclear in description and aetiology, and may be seen in relation to Guedel airway
Oslo University Hospital	01-194	Adverse Events	2020-02-26	Chart describe rhinorrea form opposite nostril to IMP administration during inclusion. They speculate if this is stomach content, but not sure. Patient wakes up without signs of aspiration, nausea or vomiting

16.2.7 Adverse event listings (each patient)

SiteName	SubjectId	EventName	EventDate	Term
Oslo University Hospital	01-607	Adverse Events	2020-02-10	Aggressive and agitated.
Oslo University Hospital	01-619	Adverse Events	2020-03-03	Symptoms of abstinence. Allieviated when morfin iv was administered due to pain after bystander CPR
Oslo University Hospital	01-630	Adverse Events	2020-02-26	Study personell crossed off for aggression/agitation and abstinence. Not well described in chart
Oslo University Hospital	01-658	Adverse Events	2020-03-03	Crossed off for abstinence
St. Olav's University Hospital	02-012	Adverse Events	2020-03-03	Aggression. Did not want naloxone. Goes after EMS staff.
St. Olav's University Hospital	02-088	Adverse Events	2020-03-03	Aggression and withdrawal reaction. Wakes up 4 minutes after study drug administration. Upset that he was given naloxone and that the opioid effect was taken from him. Described as "mildt utaggerende" (mildly challenging?), spitting and kicking.
Oslo University Hospital	01-410	Adverse Events	2019-06-16	Headache, not described more closely
Oslo University Hospital	01-235	Adverse Events	2020-02-26	Crossed off as agitated + abstinent after inclusion. Not further described in chart
Oslo University Hospital	01-333	Adverse Events	2020-03-03	Crossed off for aggression in chart.

16.2.7 Adverse event listings (each patient)

SiteName	SubjectId	EventName	EventDate	Term
Oslo University Hospital	01-619	Adverse Events	2020-02-26	Nausea/ vomiting crossed off in CRF
Oslo University Hospital	01-592	Adverse Events	2020-03-30	CRF describes headache. no further information
Oslo University Hospital	01-817	Adverse Events	2020-07-09	Patient found outside, described as cold and hypothermic by crew, no temperature measured
Oslo University Hospital	01-819	Adverse Events	2020-07-09	Described in chart as hypothermic, no temperature measured. Found utside in the street
Oslo University Hospital	01-706	Adverse Events	2020-08-10	Study workers indicated nausea in paper CRF, no more information available
Oslo University Hospital	01-694	Adverse Events	2020-08-10	paper CRF states agitation, but patient calms Down when explained what happens. Explicitly stated in patient chart that he does not seem to suffer from opioid abstinence/ withdrawal
Oslo University Hospital	01-677	Adverse Events	2020-08-10	patient was cold. temprature measured (infrared at tympanic membrane) to 35,1 degrees celcius
Oslo University Hospital	01-796	Adverse Events	2020-08-11	patient found outside, body temprature measured to 34,2 degrees by infrared measurement tympanic membrane
Oslo University Hospital	01-803	Adverse Events	2020-08-11	Staff crossed off for opioid abstinence reaction in CRF, not described more closely
Oslo University Hospital	01-069	Adverse Events	2019-11-24	aggression, agitation. Also previously described in AMK database. known for aggression- jumping angrily around. Not conistent With opioid withdrawal reatcion

16.2.7 Adverse event listings (each patient)

SiteName	SubjectId	EventName	EventDate	Term
Oslo University Hospital	01-140	Adverse Events	2020-02-26	Crossed off for agitated, interpreted as opioid withdrawal
Oslo University Hospital	01-264	Adverse Events	2020-02-10	Aggression, immedeatly injects heroin while EMS still present. Interpreted as opioid withdrawal
Oslo University Hospital	01-329	Adverse Events	2020-02-10	aggressive, interpreted as abstinence
Oslo University Hospital	01-443	Adverse Events	2019-07-18	Aggression, leaves ambulance, interpreted as abstinence
Oslo University Hospital	01-677	Adverse Events	2020-02-13	Masseter spasm is more unclear in description and aetiology, and may be seen in relation to Guedel airway . See AE no 1 for closer description of jaw spasm
St. Olav's University Hospital	02-095	Adverse Events	2020-08-23	Nausea described in chart, no intervention
St. Olav's University Hospital	02-095	Adverse Events	2020-08-23	Study workers describe irrregular pulse while palpating, not ECG changes recorded. Circulatory stable. NO intervention. Not reason for hospital admission
St. Olav's University Hospital	02-094	Adverse Events	2020-08-23	nausea crossed off in chart, not described in more detail. no vomiting, no medical intervention for nausea
St. Olav's University Hospital	02-094	Adverse Events	2020-08-23	crossed of for agitation, not described in detail. interpreted as possible withdrawal.
St. Olav's University Hospital	02-096	Adverse Events	2020-08-23	Freeze and shakes, no intervention except taken into warm ambulance

16.2.7 Adverse event listings (each patient)

SiteName	SubjectId	EventName	EventDate	Term
Oslo University Hospital	01-021	Adverse Events	2018-06-22	Headache
Oslo University Hospital	01-202	Adverse Events	2019-04-26	EMS have crossed out for headache, but not described severity. Patient deemed competent and somatically well enough to be admitted to Rusakutten not Legevakt or Hospital
Oslo University Hospital	01-619	Adverse Events	2020-03-03	Hypothermia. Was cold after lying outside for 30 minutes prior to AMK alerted. It was wintertime. Warmed up when entering ambulance
Oslo University Hospital	01-619	Adverse Events	2020-03-03	Pain in chest after bystander CPR. Relieved by administered morphine (se concomitant medication this patient)
Oslo University Hospital	01-057	Adverse Events	2020-02-10	Angry and verbally abusive, interpreted as abstinence reaction
Oslo University Hospital	01-619	Adverse Events	2020-03-03	Aspiration, described in study chart as crackles at auscultation and respiratory distress. No vomiting and aspiration is described occurring after EMS came to the scene, so presumed happening prior of arrival and prior to administration if IMP
Oslo University Hospital	01-700	Adverse Events	2020-09-11	Headache described in chart, no mention of severity or duration. No medical intervention and left on site
Oslo University Hospital	01-140	Adverse Events	2019-03-01	Patient described as spastic, hypertonic and transported to Diakonhjemmet Hospital. Not described as seizures, and not treated as seizure by EMS. Suspected GHB intoxication.

16.2.7 Adverse event listings (each patient)

SubjectId	DictInstance	soc_code	soc_name	hlgt_code	hlgt_name	hlt_code
01-021	MedDRA, Version 20.1	10017947	Gastrointestinal disorders	10018012	Gastrointestinal signs and symptoms	10028817
01-151	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10062915	Therapeutic and nontherapeutic effects (excl toxicity)	10068756
01-263	MedDRA, Version 20.1	10017947	Gastrointestinal disorders	10018012	Gastrointestinal signs and symptoms	10028817
01-140	MedDRA, Version 20.1	10017947	Gastrointestinal disorders	10018012	Gastrointestinal signs and symptoms	10028817
01-140	MedDRA, Version 20.1	10017947	Gastrointestinal disorders	10018012	Gastrointestinal signs and symptoms	10028817
01-125	MedDRA, Version 20.1	10017947	Gastrointestinal disorders	10018012	Gastrointestinal signs and symptoms	10028817
01-235	MedDRA, Version 20.1	10017947	Gastrointestinal disorders	10018012	Gastrointestinal signs and symptoms	10028817
01-253	MedDRA, Version 20.1	10029205	Nervous system disorders	10019231	Headaches	10019233
01-287	MedDRA, Version 20.1	10029205	Nervous system disorders	10019231	Headaches	10019233
01-253	MedDRA, Version 20.1	10029205	Nervous system disorders	10029305	Neurological disorders NEC	10029306
02-033	MedDRA, Version 20.1	10017947	Gastrointestinal disorders	10018012	Gastrointestinal signs and symptoms	10028817

16.2.7 Adverse event listings (each patient)

SubjectId	DictInstance	soc_code	soc_name	hlgt_code	hlgt_name	hlt_code
01-122	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10062915	Therapeutic and nontherapeutic effects (excl toxicity)	10068756
02-009	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10005908	Body temperature conditions	10005907
01-388	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10062915	Therapeutic and nontherapeutic effects (excl toxicity)	10068756
01-389	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10062915	Therapeutic and nontherapeutic effects (excl toxicity)	10068756
01-395	MedDRA, Version 20.1	10017947	Gastrointestinal disorders	10018012	Gastrointestinal signs and symptoms	10028817
01-417	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10062915	Therapeutic and nontherapeutic effects (excl toxicity)	10068756
01-583	MedDRA, Version 20.1	10017947	Gastrointestinal disorders	10018012	Gastrointestinal signs and symptoms	10028817
01-402	MedDRA, Version 20.1	10029205	Nervous system disorders	10019231	Headaches	10019233
01-411	MedDRA, Version 20.1	10038738	Respiratory, thoracic and mediastinal disorders	10038716	Respiratory disorders NEC	10057184
01-373	MedDRA, Version 20.1	10029205	Nervous system disorders	10019231	Headaches	10019233
01-373	MedDRA, Version 20.1	10017947	Gastrointestinal disorders	10018012	Gastrointestinal signs and symptoms	10028817

16.2.7 Adverse event listings (each patient)

SubjectId	DictInstance	soc_code	soc_name	hlgt_code	hlgt_name	hlt_code
01-673	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10005908	Body temperature conditions	10005907
01-677	MedDRA, Version 20.1	10007541	Cardiac disorders	10007521	Cardiac arrhythmias	10037908
01-194	MedDRA, Version 20.1	10038738	Respiratory, thoracic and mediastinal disorders	10079101	Respiratory tract signs and symptoms	10046313

16.2.7 Adverse event listings (each patient)

SubjectId	DictInstance	soc_code	soc_name	hlgt_code	hlgt_name	hlt_code
01-607	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10062915	Therapeutic and nontherapeutic effects (excl toxicity)	10068756
01-619	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10062915	Therapeutic and nontherapeutic effects (excl toxicity)	10068756
01-630	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10062915	Therapeutic and nontherapeutic effects (excl toxicity)	10068756
01-658	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10062915	Therapeutic and nontherapeutic effects (excl toxicity)	10068756
02-012	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10062915	Therapeutic and nontherapeutic effects (excl toxicity)	10068756
02-088	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10062915	Therapeutic and nontherapeutic effects (excl toxicity)	10068756
01-410	MedDRA, Version 20.1	10029205	Nervous system disorders	10019231	Headaches	10019233
01-235	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10062915	Therapeutic and nontherapeutic effects (excl toxicity)	10068756
01-333	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10062915	Therapeutic and nontherapeutic effects (excl toxicity)	10068756

16.2.7 Adverse event listings (each patient)

SubjectId	DictInstance	soc_code	soc_name	hlgt_code	hlgt_name	hlt_code
01-619	MedDRA, Version 20.1	10017947	Gastrointestinal disorders	10018012	Gastrointestinal signs and symptoms	10028817
01-592	MedDRA, Version 20.1	10029205	Nervous system disorders	10019231	Headaches	10019233
01-817	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10005908	Body temperature conditions	10005907
01-819	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10005908	Body temperature conditions	10005907
01-706	MedDRA, Version 20.1	10017947	Gastrointestinal disorders	10018012	Gastrointestinal signs and symptoms	10028817
01-694	MedDRA, Version 20.1	10037175	Psychiatric disorders	10002861	Anxiety disorders and symptoms	10002869
01-677	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10005908	Body temperature conditions	10005907
01-796	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10005908	Body temperature conditions	10005907
01-803	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10062915	Therapeutic and nontherapeutic effects (excl toxicity)	10068756
01-069	MedDRA, Version 20.1	10037175	Psychiatric disorders	10034726	Personality disorders and disturbances in behaviour	10004209

16.2.7 Adverse event listings (each patient)

SubjectId	DictInstance	soc_code	soc_name	hlgt_code	hlgt_name	hlt_code
01-140	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10062915	Therapeutic and nontherapeutic effects (excl toxicity)	10068756
01-264	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10062915	Therapeutic and nontherapeutic effects (excl toxicity)	10068756
01-329	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10062915	Therapeutic and nontherapeutic effects (excl toxicity)	10068756
01-443	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10062915	Therapeutic and nontherapeutic effects (excl toxicity)	10068756
01-677	MedDRA, Version 20.1	10028395	Musculoskeletal and connective tissue disorders	10028302	Muscle disorders	10028343
02-095	MedDRA, Version 20.1	10017947	Gastrointestinal disorders	10018012	Gastrointestinal signs and symptoms	10028817
02-095	MedDRA, Version 20.1	10007541	Cardiac disorders	10007521	Cardiac arrhythmias	10037908
02-094	MedDRA, Version 20.1	10017947	Gastrointestinal disorders	10018012	Gastrointestinal signs and symptoms	10028817
02-094	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10062915	Therapeutic and nontherapeutic effects (excl toxicity)	10068756
02-096	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10005908	Body temperature conditions	10005907

16.2.7 Adverse event listings (each patient)

SubjectId	DictInstance	soc_code	soc_name	hlgt_code	hlgt_name	hlt_code
01-021	MedDRA, Version 20.1	10029205	Nervous system disorders	10019231	Headaches	10019233
01-202	MedDRA, Version 20.1	10029205	Nervous system disorders	10019231	Headaches	10019233
01-619	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10005908	Body temperature conditions	10005907
01-619	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10018073	General system disorders NEC	10033372
01-057	MedDRA, Version 20.1	10018065	General disorders and administration site conditions	10062915	Therapeutic and nontherapeutic effects (excl toxicity)	10068756
01-619	MedDRA, Version 20.1	10038738	Respiratory, thoracic and mediastinal disorders	10038716	Respiratory disorders NEC	10057184
01-700	MedDRA, Version 20.1	10029205	Nervous system disorders	10019231	Headaches	10019233
01-140	MedDRA, Version 20.1	10029205	Nervous system disorders	10029317	Neuromuscular disorders	10028342

16.2.7 Adverse event listings (each patient)

SubjectId	hlt_name	pt_code	pt_name	pt_soc_code	llt_code	llt_name
01-021	Nausea and vomiting symptoms	10047700	Vomiting	10017947	10047700	Vomiting
01-151	Withdrawal and rebound effects	10013754	Drug withdrawal syndrome	10018065	10030882	Opiate withdrawal symptoms
01-263	Nausea and vomiting symptoms	10028813	Nausea	10017947	10028813	Nausea
01-140	Nausea and vomiting symptoms	10028813	Nausea	10017947	10028813	Nausea
01-140	Nausea and vomiting symptoms	10047700	Vomiting	10017947	10047700	Vomiting
01-125	Nausea and vomiting symptoms	10028813	Nausea	10017947	10028813	Nausea
01-235	Nausea and vomiting symptoms	10028813	Nausea	10017947	10028813	Nausea
01-253	Headaches NEC	10019211	Headache	10029205	10019211	Headache
01-287	Headaches NEC	10019211	Headache	10029205	10019211	Headache
01-253	Neurological signs and symptoms NEC	10013573	Dizziness	10029205	10013573	Dizziness
02-033	Nausea and vomiting symptoms	10028813	Nausea	10017947	10028813	Nausea

16.2.7 Adverse event listings (each patient)

SubjectId	hlt_name	pt_code	pt_name	pt_soc_code	llt_code	llt_name
01-122	Withdrawal and rebound effects	10013754	Drug withdrawal syndrome	10018065	10030882	Opiate withdrawal symptoms
02-009	Body temperature altered	10021113	Hypothermia	10018065	10021113	Hypothermia
01-388	Withdrawal and rebound effects	10013754	Drug withdrawal syndrome	10018065	10030882	Opiate withdrawal symptoms
01-389	Withdrawal and rebound effects	10013754	Drug withdrawal syndrome	10018065	10030882	Opiate withdrawal symptoms
01-395	Nausea and vomiting symptoms	10028813	Nausea	10017947	10028813	Nausea
01-417	Withdrawal and rebound effects	10013754	Drug withdrawal syndrome	10018065	10030882	Opiate withdrawal symptoms
01-583	Nausea and vomiting symptoms	10028813	Nausea	10017947	10028813	Nausea
01-402	Headaches NEC	10019211	Headache	10029205	10019211	Headache
01-411	Respiratory tract disorders NEC	10003504	Aspiration	10038738	10048996	Aspiration of gastrointestinal contents into airways
01-373	Headaches NEC	10019211	Headache	10029205	10019211	Headache
01-373	Nausea and vomiting symptoms	10028813	Nausea	10017947		

16.2.7 Adverse event listings (each patient)

SubjectId	hlt_name	pt_code	pt_name	pt_soc_code	llt_code	llt_name
01-673	Body temperature altered	10021113	Hypothermia	10018065	10021113	Hypothermia
01-677	Rate and rhythm disorders NEC	10006093	Bradycardia	10007541	10006093	Bradycardia
01-194	Upper respiratory tract signs and symptoms	10039101	Rhinorrhoea	10038738	10039100	Rhinorrhea

16.2.7 Adverse event listings (each patient)

SubjectId	hlt_name	pt_code	pt_name	pt_soc_code	llt_code	llt_name
01-607	Withdrawal and rebound effects	10013754	Drug withdrawal syndrome	10018065	10030882	Opiate withdrawal symptoms
01-619	Withdrawal and rebound effects	10013754	Drug withdrawal syndrome	10018065	10030882	Opiate withdrawal symptoms
01-630	Withdrawal and rebound effects	10013754	Drug withdrawal syndrome	10018065	10030882	Opiate withdrawal symptoms
01-658	Withdrawal and rebound effects	10013754	Drug withdrawal syndrome	10018065	10030882	Opiate withdrawal symptoms
02-012	Withdrawal and rebound effects	10013754	Drug withdrawal syndrome	10018065	10030882	Opiate withdrawal symptoms
02-088	Withdrawal and rebound effects	10013754	Drug withdrawal syndrome	10018065	10030882	Opiate withdrawal symptoms
01-410	Headaches NEC	10019211	Headache	10029205	10019211	Headache
01-235	Withdrawal and rebound effects	10013754	Drug withdrawal syndrome	10018065	10030882	Opiate withdrawal symptoms
01-333	Withdrawal and rebound effects	10013754	Drug withdrawal syndrome	10018065	10030882	Opiate withdrawal symptoms

16.2.7 Adverse event listings (each patient)

SubjectId	hlt_name	pt_code	pt_name	pt_soc_code	llt_code	llt_name
01-619	Nausea and vomiting symptoms	10028813	Nausea	10017947	10028813	Nausea
01-592	Headaches NEC	10019211	Headache	10029205	10019211	Headache
01-817	Body temperature altered	10021113	Hypothermia	10018065	10021113	Hypothermia
01-819	Body temperature altered	10021113	Hypothermia	10018065	10021113	Hypothermia
01-706	Nausea and vomiting symptoms	10028813	Nausea	10017947	10028813	Nausea
01-694	Anxiety symptoms	10001497	Agitation	10037175	10001497	Agitation
01-677	Body temperature altered	10021113	Hypothermia	10018065	10021113	Hypothermia
01-796	Body temperature altered	10021113	Hypothermia	10018065	10021113	Hypothermia
01-803	Withdrawal and rebound effects	10013754	Drug withdrawal syndrome	10018065	10030882	Opiate withdrawal symptoms
01-069	Behaviour and socialisation disturbances	10001488	Aggression	10037175	10001488	Aggression

16.2.7 Adverse event listings (each patient)

SubjectId	hlt_name	pt_code	pt_name	pt_soc_code	llt_code	llt_name
01-140	Withdrawal and rebound effects	10013754	Drug withdrawal syndrome	10018065	10030882	Opiate withdrawal symptoms
01-264	Withdrawal and rebound effects	10013754	Drug withdrawal syndrome	10018065	10030882	Opiate withdrawal symptoms
01-329	Withdrawal and rebound effects	10013754	Drug withdrawal syndrome	10018065	10030882	Opiate withdrawal symptoms
01-443	Withdrawal and rebound effects	10013754	Drug withdrawal syndrome	10018065	10030882	Opiate withdrawal symptoms
01-677	Muscle tone abnormalities	10044684	Trismus	10028395	10023158	Jaw spasm
02-095	Nausea and vomiting symptoms	10028813	Nausea	10017947	10028813	Nausea
02-095	Rate and rhythm disorders NEC	10003119	Arrhythmia	10007541	10003120	Arrhythmia (NOS)
02-094	Nausea and vomiting symptoms	10028813	Nausea	10017947	10028813	Nausea
02-094	Withdrawal and rebound effects	10013754	Drug withdrawal syndrome	10018065	10030882	Opiate withdrawal symptoms
02-096	Body temperature altered	10021113	Hypothermia	10018065	10021113	Hypothermia

16.2.7 Adverse event listings (each patient)

SubjectId	hlt_name	pt_code	pt_name	pt_soc_code	llt_code	llt_name
01-021	Headaches NEC	10019211	Headache	10029205	10019211	Headache
01-202	Headaches NEC	10019211	Headache	10029205	10019211	Headache
01-619	Body temperature altered	10021113	Hypothermia	10018065	10021113	Hypothermia
01-619	Pain and discomfort NEC	10062501	Non-cardiac chest pain	10018065	10008480	Chest pain (non-cardiac)
01-057	Withdrawal and rebound effects	10013754	Drug withdrawal syndrome	10018065	10030882	Opiate withdrawal symptoms
01-619	Respiratory tract disorders NEC	10003504	Aspiration	10038738	10048996	Aspiration of gastrointestinal contents into airways
01-700	Headaches NEC	10019211	Headache	10029205	10019211	Headache
01-140	Muscle tone abnormal	10020852	Hypertonia	10029205	10028369	Muscular tonus increased

I want to withdraw from the trial.

Trial of naloxone as a nasal spray

Name of the trial: NTNU Intranasal Naloxone Trial (NINA-1)
Registration number: EudraCT 2016-004072-22

Who is responsible?

Professor Ola Dale of the Norwegian University of Science and Technology (NTNU), Department of Circulation and Medical Imaging (ISB).

The ambulance service in Oslo and Akershus and the ambulance service in Trondheim are the trial locations.

The trial has been approved by the Regional Ethics Committee and the Norwegian Medicines Agency. The trial cooperates with two pharmaceutical companies in Norway named Sanivo Pharma and DnE Farms.

What are we researching?

Naloxone, an antidote for opioids, is primarily administered by syringe at present.

We are researching a new naloxone nasal spray that we feel is simpler and better than the one currently available, and we would like it to be fully approved as a medicine. That is to say that both the efficacy and side effects are well known.

We have been testing the nasal spray on volunteers in Trondheim in 2013 to 2016, and we are now testing the spray on real overdose cases in Oslo and Trondheim.

What have we done to you?

You have joined a trial in which you have either received the ordinary antidote by syringe or the new naloxone nasal spray. The usual treatment with respiratory facilitation has not changed.

When ambulance personnel find a patient with a suspected overdose, the first thing they do is to help the patient breathe with a mask and breathing bag. This has not changed in the trial.

Patients normally receive the antidote directly into a vein or the shoulder muscle. In this trial, the ambulance has a box of medicines that contains a syringe and nasal spray, both of which are administered to the patient. One of them contains active medicine (naloxone) and the other contains water without medicine. All patients receive the antidote in one way or the other.

The syringe contains 0.4 mg/ml of naloxone. The dose is 2 ml intramuscularly = a dose of 0.8 mg naloxone to the participant. The syringe dose is the same that is usually administered by ambulance personnel today.

The nasal spray has a concentration of 14 mg/ml of naloxone, and the dose is 0.1 ml = a dose of 1.4 mg naloxone to the participant. We expect a little over half of the nasal spray to reach your blood.

It is random whether you receive naloxone as a spray or a syringe, and neither the ambulance personnel nor those who analyse the data will know what has been received until the trial is over. This means that our trial is double-blinded and randomised. This is scientifically the best way to determine how the medicine works.

Is this safe?

The safety of the participants has the highest priority in this trial. An overdose is a life-threatening condition, and life-saving first aid and competent ambulance treatment is required.

An opioid overdose is characterised by respiratory problems. Help by the ambulance personnel to free respiratory passages and facilitate breathing has not changed in this trial.

After receiving the medicine, you will be closely monitored and will receive breathing assistance as required for 10 minutes. If you are not awake after 10 minutes, the trial treatment will be discontinued. You will then receive more naloxone of the type the ambulance normally uses, and they will assess whether other medical measures are required.

If your condition worsens before ten minutes have passed, the trial will be discontinued and the ambulance personnel will perform the medical measures that are best for the patient.

What does it take to be included in the trial?

- To have a suspected opioid overdose, which means to have:
  - Reduced respiration
  - Small pupils
  - Diminished consciousness
- and a palpable neck pulse

What will prevent you from being included in the trial?

If one or more of the following conditions are present, you will not be included in the trial:

- Cardiac arrest
- That the ambulance personnel do not manage to breathe for you
- That you have an injury to your face or nosebleed
- That the overdose is caused by health care providers
- That the ambulance personnel know or think you are under 18 years of age
- That the ambulance personnel know or suspect that you may be pregnant
- You have received naloxone before the ambulance personnel arrive
- That the overdose occurs in an individual who is imprisoned or in custody
- The ambulance personnel are not approved as trial workers
- No trial medicine is available
- The trial medicine has been frozen or has expired
- That the location where you suffer an overdose is not suitable for research or any other reason why the ambulance personnel cannot manage to include you in the trial
- If you did not consent to the use of your data.

What data is registered?

- Name and national identity number
- Time and place of the treatment and ambulance callout
- Effect of the treatment – your respiration rate before treatment, how much oxygen was in your blood and how long did it took before you breathed normally and were in a normal state of consciousness
- How you were feeling after the treatment
- Whether you were taken to an accident and emergency unit or hospital, or were left where you had the overdose
- Whether you have a new ambulance follow-up for an overdose within 24 hours of the trial
- We do not normally register other contact with the ambulance service, hospital or general practitioner records
- If you are admitted to hospital after the overdose with a side effect of the nasal spray, we will follow up on this together with the hospital, and record the side effect.

Who sees that I have had this overdose?

- The data on you and your treatment will be anonymised and stored in a secure database. This means that your name and national identity number will be registered in a location other than in the database. This is not available to anyone outside of the trial team. All the data is secured as well as your ordinary medical records in the ambulance service.
- Everything will be deleted 15 years after the end of the trial.
- The data shall not be shared or used for anything other than this trial.
- It will not be possible to recognise you when the results are published.
- The data may be shown to the Norwegian Medicines Agency to verify the trial.
- Anonymised data (so that no one can find your identity) may also be shared with researchers or publishers who want to verify the trial.

What are my rights?

- You have the right to withdraw from the trial.
- Even if you said yes on site to the ambulance personnel to join the trial, you may still withdraw afterwards.
- You can contact us to find out what data has been recorded.
- You will receive no benefits from being included in this trial.
- You will be contributing to making it easier to treat and improving the treatment of overdoses in the future.
- You are insured by the Medical Liability Insurance Fund.

Are there side effects of naloxone?

Naloxone is a well-known medicine that is considered very safe to use. In many countries, it is available without a prescription. We register side effects such as nausea, vomiting and headaches. If the side effects are serious, you will be hospitalised.

You are in the trial, but you can have your data deleted

If you have had an overdose and have been included in the trial, you may choose whether or not we can use the data from the trial. Not everyone will be able to take a stand on this

immediately after the overdose, but those who can will be asked by the ambulance personnel for permission to use your data further in the trial. If you say no to our use of the data from your treatment in the trial, all the data related to you will be deleted from the trial. Even if you say yes on the spot, you can still withdraw from the trial afterwards.

What happens if I could not give consent?

If you were not able to give consent after your overdose, you will be registered in the trial. If you still consent now to be included in the trial, you need not do anything.

If you find that you want to withdraw from the trial, then the trial team must be notified by phone or here on this website that you want to withdraw.

I want to withdraw from the trial

Fill in the form at the top of the page; include as much information as you can remember. Your trial number is on the sheet of paper you received from the ambulance personnel. Or call 23 02 61 50 Monday through Friday between the hours of 08:30 and 16:00.

You have had an overdose and have been included in a trial

We are comparing naloxone (heroin antidote) administered by nasal spray or syringe.

Our aim is to create a spray that is just as good as the injections currently used.

Your number in the trial is

Your identity will only be known to the researchers
You can withdraw at any time and obtain more information at

www.nalokson.no

Fill in the form at www.nalokson.no to have the data related to you deleted.

You can also call 23 02 61 50

Sincerely yours, Ambulance Service and NTNU

NTNU

ST. OLAVS HOSPITAL
UNIVERSITETSSYKEHUSET I TRONDHEIM

Oslo universitetssykehus

16.1.3 Informed consent forms

16.1.3 Informed consent forms

Who is responsible? Professor Ola Dale of the Norwegian University of Science and Technology (NTNU), Department of Circulation and Medical Imaging.

What are we researching?
We are researching a new naloxone nasal spray that is simpler to use and just as good as the syringe that is currently used in Norway today, and we want it to be fully approved as a medicine. That is to say that both the efficacy and side effects are well known.

What have we done to you?
You have joined a trial in which you have either received the ordinary antidote by syringe or the new naloxone nasal spray. The usual treatment with respiratory facilitation has not changed.
In this trial, the ambulance has a box of medicines that contains a syringe and nasal spray, both of which are administered to you. One of them contains active medicine (naloxone) and the other contains water without medicine. The syringe contains 0.4 mg/ml of naloxone. The dose is 2 ml intramuscularly = 0.8 mg Naloxone. The syringe dose is the same that is usually administered by ambulance personnel today. The nasal spray has a concentration of 14 mg/ml of naloxone, and the dose is 0.1 ml = 1.4 mg naloxone. We expect a little over half of the nasal spray to reach your blood. It will be random whether you receive naloxone as a spray or a syringe, but everyone will receive the antidote in one way or another.

Is this safe?
Yes, we think that it is safe to research this. The treatment in the trial is practically the same as the treatment that is normally administered, which consists of respiratory facilitation, an antidote and follow-up. We have only changed the way the antidote is administered and the observation period from when the first dose is administered until a new dose of antidote is administered. In the trial, this period is 10 minutes with constant monitoring. If your condition worsens during the first ten minutes, the trial will be discontinued and the ambulance personnel will perform the medical measures that are best for the patient.

What data is registered?
Name and national identity number
Time and place of the treatment and ambulance callout
Effect of the treatment – your respiration rate before treatment, how much oxygen was in your blood and how long did it took before you breathed normally and were in a normal state of consciousness
How you were feeling after the treatment
Whether you were taken to an accident and emergency unit or hospital, or were left where you had the overdose
If you have consented to our use of your data in the research project

We will also register if you have a new ambulance follow-up for an overdose within 24 hours of the trial or if you are admitted to hospital with a side effect. We do not register other contact with the ambulance service, hospitals or general practitioner records.

Who sees that I have had this overdose? Can I withdraw?
The data will be anonymised and stored in a secure database. This is not available to anyone outside of the trial team. All the data is secured as well as your ordinary medical records. What we are asking is that we can use the data we have collected on you in the research project. You can choose whether or not we may use the data from the trial. Not everyone will be able to take a stand on this immediately after the overdose, but those who can will be asked by the ambulance personnel if it is okay. If you say no, all the data related to you will be deleted from the trial. Even if you say yes on the spot, you can still withdraw from the trial afterwards. If you were not able to give consent after your overdose, you will be registered in the trial and must contact us if you wish to withdraw.

<u>You are entitled to withdraw from the trial at any time.</u>
When you withdraw, all the data related to you will be deleted from the trial

Peter A Eseltine

Studie av nalokson som nesespray

Navn på studien: NTNU Intranasal Naloxone Trial (NINA-1)
Registreringsnummer: EudraCT 2016-004072-22

Hvem er ansvarlig?

Norges teknisk-naturvitenskapelige universitet (NTNU), Institutt for sirkulasjon og bildediagnostikk (ISB) ved Arne Skulberg

Ambulansetjenesten i Oslo og Akershus og Ambulansetjenesten i Trondheim er studiesteder.

Studien er godkjent av Regional Etisk Komite og Statens Legemiddelverk. Studien samarbeider med to legemiddelfirma i Norge som heter Sanivo Pharma og DnE Farma.

Hva forsker vi på?

Nalokson, motgiften mot morfinstoffer, brukes i dag hovedsakelig som sprøyte.

Vi forsker på en ny nalokson nesespray som vi mener er enklere og bedre enn den som finnes i dag, og ønsker at den skal bli fullt ut godkjent som medisin. Det vil si at både effekt og bivirkninger er godt kjent.

Vi har prøvd ut nesesprayen på frivillige i Trondheim i 2013 til 2016, og prøver nå ut sprayen på ordentlige overdoser i Oslo og Trondheim.

Hva har vi gjort med deg?

Du har blitt med i en studie der du enten har fått vanlig motgift som sprøyte eller ny nalokson nesespray. Den vanlige behandlingen med pustehjelp er ikke endret.

Når ambulansepersonell finner en pasient med mistenkt overdose er det første de gjør å hjelpe pasienten å puste med maske og pustebag. Dette er ikke forandret i studien.

Vanligvis får pasienter motgift enten rett i blodåra eller i skuldermuskelen. I denne studien har ambulansen med seg en boks medisiner hvor det finnes både sprøyte og nesespray, og begge blir gitt til pasienten. Den ene inneholder aktiv medisin (nalokson) og den andre inneholder vann uten medisin. Alle pasienter får motgift på den ene eller andre måten.

Sprøyten inneholder Nalokson 0,4 mg/ml. Dosen er på 2 ml intramuskulært= en dose på 0,8 mg nalokson til deltageren. Sprøytedosen er den samme som vanligvis blir gitt av ambulansen i dag.

Nesesprayen har en konsentrasjon på 14 mg/ml nalokson og dosen er på 0,1 ml= en dose på 1,4 mg nalokson til deltageren. Vi forventer at litt over halvparten av nesesprayen når blodstrømmen din.

Det er tilfeldig om du får nalokson som spray eller sprøyte, og verken ambulansepersonellet eller de som analyserer data vet hvilken som er hvilken før helt til slutt når studien er over. Dette betyr at studien vår er dobbelt blindet og randomisert. Dette er den vitenskapelige beste måten å få vite hvordan medisinen fungerer på.

Er dette trygt?

Sikkerheten til deltagerne er det viktigste i denne studien. Overdose er en livstruende tilstand, og livreddende førstehjelp og kyndig ambulansebehandling er nødvendig.

Opioidoverdose kjennetegnes av pusteproblemer. Hjelp av ambulansepersonell til frie luftveier og pustehjelp er ikke forandret i denne studien.

Etter at man har fått medisin blir man nøye overvåket og får pustehjelp ved behov i 10 minutter. Hvis man ikke er våken etter 10 minutter avbrytes studiebehandlingen. Da får man mer nalokson av den typen ambulansen vanligvis bruker og de vurderer om andre medisinske tiltak er nødvendige.

Hvis man blir verre før det er gått ti minutter avbrytes studien og ambulansepersonellet gjør de medisinske tiltak som er til beste for pasienten.

Hva skal til for å bli tatt med i studien?

- Ha mistenkt opioidoverdose, det vil si har:
    - Redusert pust
    - Små pupiller
    - Redusert bevissthet
- Og følbar puls i halsen

Hva skal til for at man ikke blir tatt med i studien?

Hvis man har en eller flere av dette blir man ikke tatt med i studien:

- Hjertestans
- At ambulansepersonell ikke klarer å puste for deg
- At du har en skade i ansiktet eller neseblødning
- At overdosen er forårsaket av helsepersonell
- At ambulansepersonellet vet eller tror du er under 18 år
- At ambulansepersonellet vet eller mistenker at du kan være gravid
- Du har fått nalokson før ambulansepersonellet kommer til
- At overdosen skjer hos en som sitter i fengsel eller varetekt
- Ambulansepersonellet er ikke godkjente som studiearbeidere
- Ingen studiemedisin tilgjengelig
- Studiemedisinen har vært frosset eller har gått ut på dato
- At stedet du har overdose ikke egner seg for forskning eller andre grunner til at ambulansepersonellet ikke klarer å ta deg med i studien
- Om du ikke samtykket til bruk av opplysningene dine.

Hvilke opplysninger er registrert?

- Navn og personnummer

- Tid og sted for behandling og ambulanseutrykning
- Effekt av behandlingen- hvor raskt pustet du før behandling, hvor mye oksygen var det i blodet og hvor lang tid tok det er før du pustet normalt og var ved normal bevissthet
- Hvordan du føler deg etter behandlingen
- Blir du tatt med til legevakt, sykehus eller etterlatt der du hadde overdose
- Om du har ny ambulanseoppfølging for overdose innen 24 timer etter studien
- Vi registrer ikke rutinemessig annen kontakt med ambulansetjenesten, sykehus eller fastlegejournal
- Hvis du blir lagt inn på sykehuset etter overdosen med en bivirkning av nesesprayen vil vi følge opp dette sammen med sykehuset, og registrere bivirkningen.

Hvem ser at jeg har hatt denne overdosen?

- Opplysningene om deg og behandlingen blir avidentifisert og lagret i en sikker database. Det betyr at navnet og personnummeret ditt blir registrert et annet sted enn i databasen. Dette er ikke tilgjengelig for noen utenfor studieteamet. Alle opplysningene er like godt sikret som den vanlige sykejournalen din i ambulansetjenesten.
- Alt blir slettet 15 år etter studien er avsluttet.
- Dataene skal ikke deles eller brukes til noe annet enn denne studien.
- Det vil ikke være mulig å gjenkjenne deg når resultatene publiseres.
- Dataene kan vises til Legemiddelverket for å kontrollere studien.
- Avidentifiserte data (slik at ingen kan finne identiteten din) kan også deles med forskere eller utgivere som vil kontrollere studien.
- Om du trekker deg vil kun bivirkninger registreres, alle opplysninger om hvem du er, når du hadde overdose og annet som kan identifisere deg blir slettet.

Hvilke rettigheter har jeg?

- Du har rett til å trekke deg fra studien.
- Selv om du sa ja til å være med i studien til ambulansepersonellet på stedet kan du trekke deg i etterkant.
- Du kan kontakte oss og se hvilke opplysninger som er registrert.
- Du har ingen fordeler av å være med i denne studien.
- Du bidrar til å gjøre det enklere og bedre å behandle overdoser i framtiden.
- Du er forsikret i Legemiddelansvarsforsikringen.

Er det bivirkninger av nalokson?

Nalokson er en kjent medisin som er regnet som svært trygg i bruk. I mange land er den tilgjengelig uten resept. Vi registrer bivirkninger som for eksempel kvalme, oppkast og hodepine. Hvis bivirkningene er alvorlige blir du innlagt på sykehus.

Du er med i studien, men kan få din informasjon slettet

Dersom du har hatt en overdose og er tatt med i studien kan du velge om vi får bruke informasjonen fra forsøket eller ikke. Ikke alle vil kunne ta stilling til det rett etter overdosen, men de som kan, vil bli spurt av ambulansepersonellet om tillatelse til å bruke opplysningene dine videre i studien. Om du sier nei til at vi kan bruke opplysningene fra din behandling i studien blir alle opplysninger som kan identifisere deg slettet fra studien. Selv om du sier ja på

stedet, så kan du trekke deg i etterkant.

Hva skjer om jeg ikke kunne samtykke?

Dersom du ikke var i stand til å gi samtykke etter din overdose, så blir du registrert i studien. Dersom du nå samtykker til å være med studien trenger du ikke gjøre noe mer.

Hvis du finner ut at du vil trekke deg fra studien må studietemaet få beskjed på telefon eller her på denne hjemmesiden om at du vil trekke deg.

Jeg vil trekke meg fra studien

Fyll ut skjemaet øverst på siden, ta med så mange opplysninger du husker. Ditt studienummer står på arket du fikk av ambulansepersonellet. Eller ring 23026150 mandag-fredag mellom klokken 08.30 – 16.00.

Du har hatt en overdose og er tatt med i en studie

Vi sammenlikner nalokson (heroinmotgift) gitt i nesespray eller sprøyte.

Hensikten er å lage en spray som er like god som injeksjonen brukt i dag.

Ditt nummer i studien er

Din identitet blir kun kjent for forskerne
Du kan trekke deg når som helst og få mer info på

www.nalokson.no

Fyll inn skjema på www.nalokson.no for å få opplysningene om deg slettet.
Du kan også ringe 23026150

Vennlig hilsen Ambulansetjenesten og NTNU

NTNU ST. OLAVS HOSPITAL UNIVERSITETSSYKEHUSET I TRONDHEIM Oslo universitetssykehus

16.1.3 Informed consent forms

Hvem er ansvarlig? NTNU, Institutt for sirkulasjon og bildediagnostikk ved professor Ola Dale.

Hva forsker vi på?
Vi forsker på en ny nalokson nesespray som er enklere og like bra som sprøyta som brukes i Norge i dag, og ønsker at den skal bli fullt ut godkjent som medisin. Det vil si at både effekt og bivirkninger er godt kjent.

Hva har vi gjort med deg?
Du har blitt med i en studie der du enten har fått vanlig motgift som sprøyte eller ny nalokson nesespray. Den vanlige behandlingen med pustehjelp er ikke endret.
I denne studien har ambulansen med seg en boks medisiner hvor det finnes både sprøyte og nesespray, og begge blir gitt til deg. Den ene inneholder aktiv medisin (nalokson) og den andre inneholder vann uten medisin. Sprøyten inneholder Nalokson 0,4 mg/ml. Dosen er på 2 ml intramuskulært= 0,8 mg nalokson. Sprøytedosen er den samme som vanligvis blir gitt av ambulansen i dag. Nesesprayen har en konsentrasjon på 14 mg/ml nalokson og dosen er på 0,1 ml= 1,4 mg nalokson. Vi forventer at litt over halvparten av nesesprayen når blodstrømmen din. Det er tilfeldig om du får nalokson som spray eller sprøyte, men alle får motgift på den ene eller andre måten.

Er dette trygt?
Ja, vi mener dette er trygt å forske på. Behandlingen i studien er nesten helt lik behandlingen som gis til vanlig, med pustehjelp, motgift og oppfølging. Vi har bare endret måten motgift gis på og observasjonstiden fra første til eventuell ny dose motgift. I studien er den på 10 minutter med konstant overvåkning. Hvis man blir verre i løpet av de ti første minuttene så avbrytes studien og ambulansepersonellet utfører medisinske tiltak som er til pasientens beste.

Hvilke opplysninger er registrert?
Navn og personnummer
Tid og sted for behandling og ambulanseutrykning
Effekt av behandlingen- hvor raskt pustet du før behandling, hvor mye oksygen var det i blodet og hvor lang tid tok det er før du pustet normalt og var ved normal bevissthet
Hvordan du føler deg etter behandlingen
Blir du tatt med til legevakt, sykehus eller etterlatt der du hadde overdose
Om du har samtykket til at vi får bruke informasjonen om deg i forskningsprosjektet

Vi vil også registrere om du har ny ambulanseoppfølging for overdose innen 24 timer etter studien eller om du blir lagt inn på sykehus med en bivirkning. Vi registrer ikke annen kontakt med ambulansetjenesten, sykehus eller fastlegejournal.

Hvem ser at jeg har hatt denne overdosen? Kan jeg trekke meg?
Opplysningene blir avidentifisert og lagret i en sikker database. Dette er ikke tilgjengelig for noen utenfor studieteamet. Alle opplysningene er like godt sikret som den vanlige sykejournalen. Det vi ber om er at vi kan få bruke opplysningene vi har samlet om deg i forskningsprosjeket. Du kan du velge om vi får bruke informasjonen fra forsøket eller ikke. Ikke alle vil kunne ta stilling til det rett etter overdosen, men de som kan, vil bli spurt av ambulansepersonellet om det er greit. Om du sier nei blir alle opplysninger om deg slettet fra studien. Selv om du sier ja på stedet, så kan du trekke deg i etterkant. Dersom du ikke var i stand til å gi samtykke etter din overdose, så blir du registrert i studien og må ta kontakt om du ønsker å trekke deg.

<u>Du har rett til når som helst å trekke deg fra studien.</u>

Når du trekker deg blir alle opplysninger om deg slettet fra studien