NTNU
Norwegian University of
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SUPPLEMENTARY APPENDIX

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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Supplementary appendix
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List of investigators

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List of local study coordinators

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List of user participation board members

The following were signatories to the original ethics committee application 2016. The board has meet at different points during the study, with varying representation from different organisations 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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List of Data Monitoring and Safety Committee (DMSC) members

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Jørgen Dahlberg, MD, PhD
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Øyvind Thomassen, MD, PhD
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Table S1: Full list of inclusion and exclusion 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
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

Table S2: Primary and secondary endpoints

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

Table S3: Reasons for participants to be excluded from the Per Protocol Set to 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

Table S4: Baseline characteristics of Full analysis set (FAS) and Excluded participants

Overdose characteristics for overdoses in the Full analysis set (FAS) vs. those not in the FAS. Patients that did not give consent are not included. 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

Table S5: Post hoc adjusted estimates of primary endpoint

Table: Estimated marginal risk differences (intramuscular minus intranasal), averaged over the indicated baseline variable which has been adjusted for in the logistic regression model. The same categorization as in Table 1 in the main text is used, unless stated otherwise.

Adjusted for	Risk difference (95% Confidence interval)
unadjusted	17.7% (8.98%, 26.3%)
Center	17.5% (8.98%, 26.1%)
Sex	17.8% (9.09%, 26.5%)
Age[1]	20.2% (10.7%, 29.7%)
Identity known	18.1% (9.44%, 26.8%)
Baseline respiratory rate	20.1% (10.6%, 29.5%)
Glasgow Coma Score	19.9% (10.4%, 29.4%)
Primary Suspected Drug	17.8% (9.15%, 26.5%)
Benzodiazepines, alcohol, gamma hydroxybutyrate, or other drugs suspected	19.8% (10.3%, 29.3%)
Location of overdose	16.1% (7.51%, 24.6%)

[1]Categorized in two groups (≤mean age, >mean age).

Table S6: Results prespecified secondary endpoints

Please consult Figure S4 and Figure S5 for more information

Continuous secondary endpoint (numbered according to S2)	Intramuscular naloxone	Intranasal naloxone	Mean difference
	Margin (95% confidence interval)		
Continuous Secondary Endpoints			
2.1 Changes in Glasgow Coma Scale 0 to 10 minutes[2]	8.50 (7.22 to 9.77)	6.64 (5.20 to 8.09)	1.86 (0.66 to 3.05)
2.2 Changes in oxygen saturation 0 to 10 minutes[2]	21.8 (14.7 to 28.8)	22.1 (18.3 to 25.9)	-0.33 (-11.1 to 10.4)
Dichotomous Secondary Endpoints			
Dichotomous secondary endpoint (numbered according to S2)	Intramuscular naloxone	Intranasal naloxone	Difference in risk
2.3 Overdose complications[1]	0.067 (0.019 to 0.114)	0.055 (0.008 to 0.101)	0.012 (-0.053 to 0.077)
2.4 Opioid withdrawal reaction to naloxone reversal[1]	0.073 (0.027 to 0.119)	0.053 (0.008 to 0.099)	0.020 (-0.046 to 0.085)
2.5 Adverse reactions to naloxone formulation[1]	0.127 (0.068 to 0.185)	0.149 (0.077 to 0.220)	-0.022 (-0.116 to 0.071)
2.6 Need for rescue naloxone [1]	0.095 (0.038 to 0.151)	0.288 (0.202 to 0.375)	-0.194 (-0.297 to -0.090)
2.7 Recurrence of opioid overdose[1]	0.035 (0.000 to 0.071)	0.037 (-0.011 to 0.086)	-0.002 (-0.067 to 0.063)
2.8 Follow up after care. Risk of being followed-up at hospital or by primary care as opposed to being left at the scene without further health service follow up[1]	0.310 (0.220 to 0.399)	0.422 (0.323 to 0.521)	-0.112 (-0.237 to 0.013)

[1]Dichotomous endpoints analysed in the same way as the primary endpoint. [2]Continuous Secondary Outcomes analysed using a linear regression change value as the dependent variable, which is described in detail in the statistical analysis plan.

Other secondary endpoints without inferential statistical analysis:		
2.9 Suitability of spray device in pre-hospital setting	No problems with the spray device were reported by study workers in this trial	
2.10 Rescue dose and route of administration during study visit	Total dose milligram of rescue naloxone (mean (SD))	0.61 (0.35)
2.11 Regarding reasons not to give rescue naloxone to non-responders	Two participants are documented to have had clinical need for rescue naloxone at 10 minutes, but ambulance personnel did not administer One patient responded while ambulance crew prepared the rescue dose, at approximately 12 minutes One patient regained respiration that satisfied the ambulance personnel, but remained unconscious. The patient was transported to hospital where they received further care.	

Table S7: 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)

Table S8: Reasons to exclude participants

Criterion		Number of times criterion used
Inclusion criteria	Reduced (below or equal to 8 breaths per minute) or absent spontaneous respiration	493
	Miosis	75
	GCS below 12/15	226
	Palpable carotid or radial arterial pulse	13
Exclusion criteria	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 administered in-hospital, or 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 has 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

Please note that each overdose event may have been excluded on multiple grounds, and that the total number of reasons not to include patients exceed the number of cases excluded from the trial.

Figure S1: Flow chart of procedure for informed consent

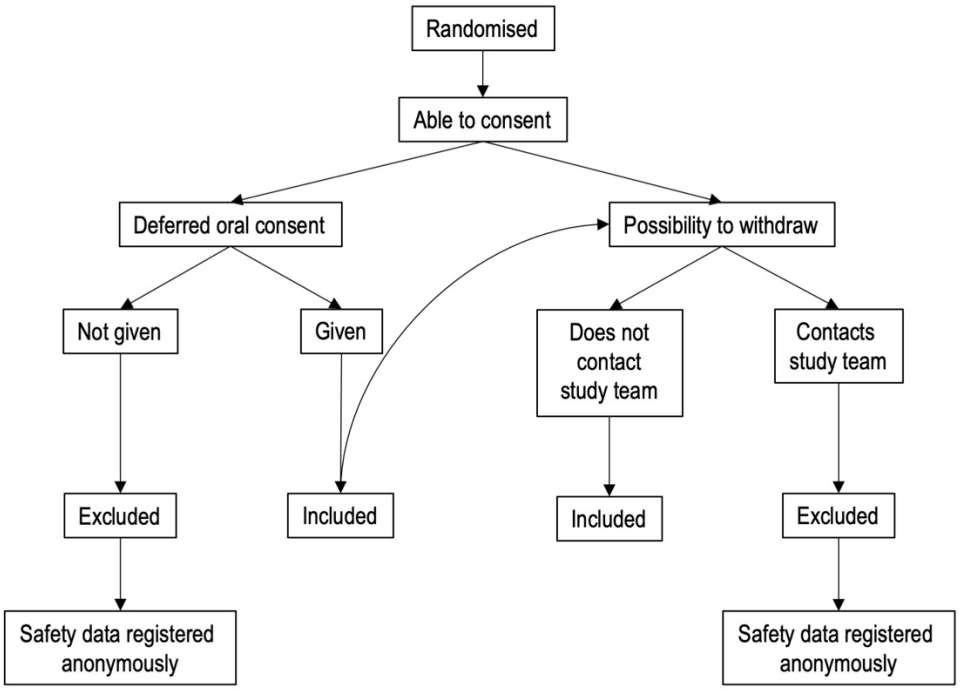


Figure S2: Flow chart trial procedure during study visit

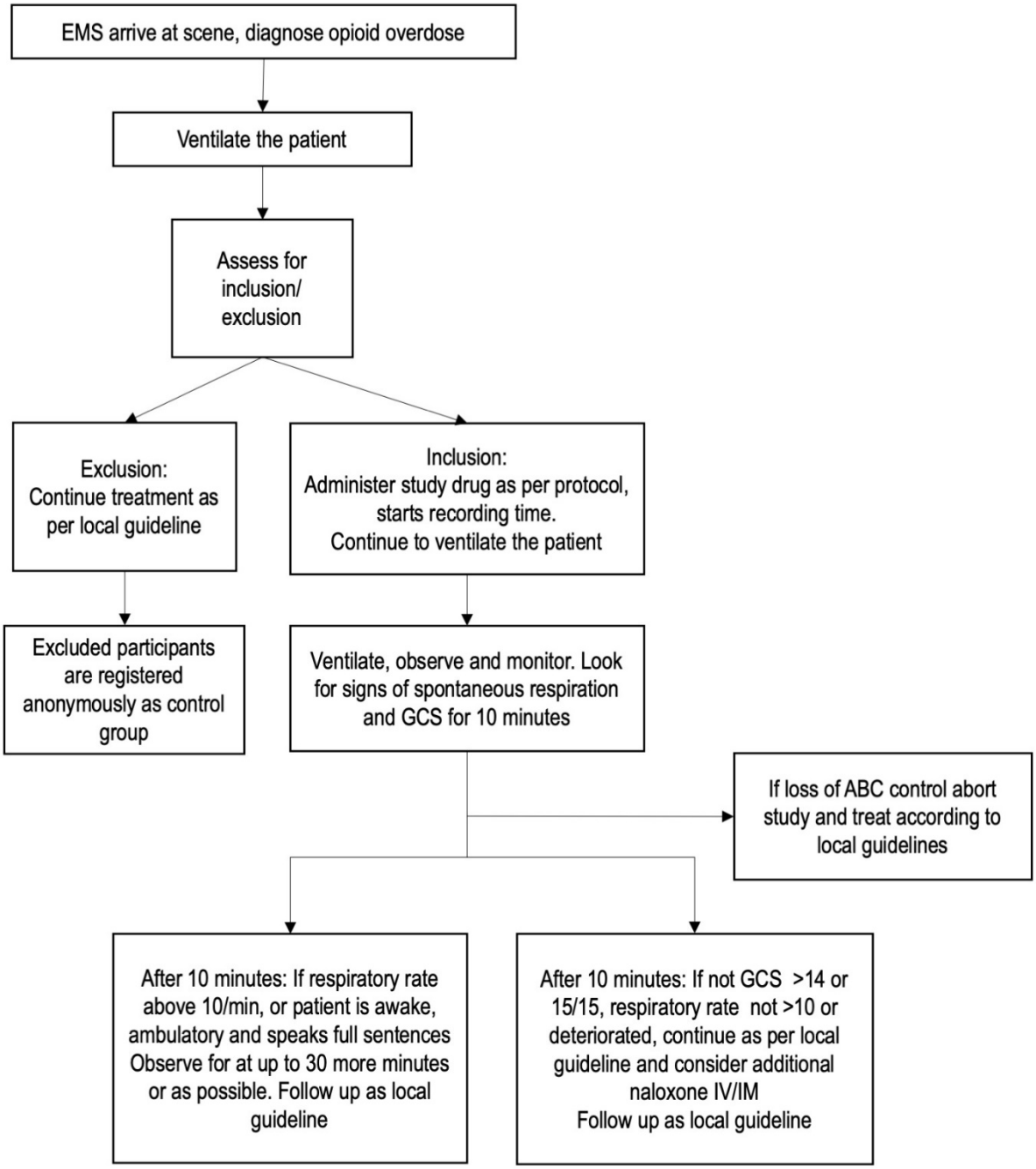
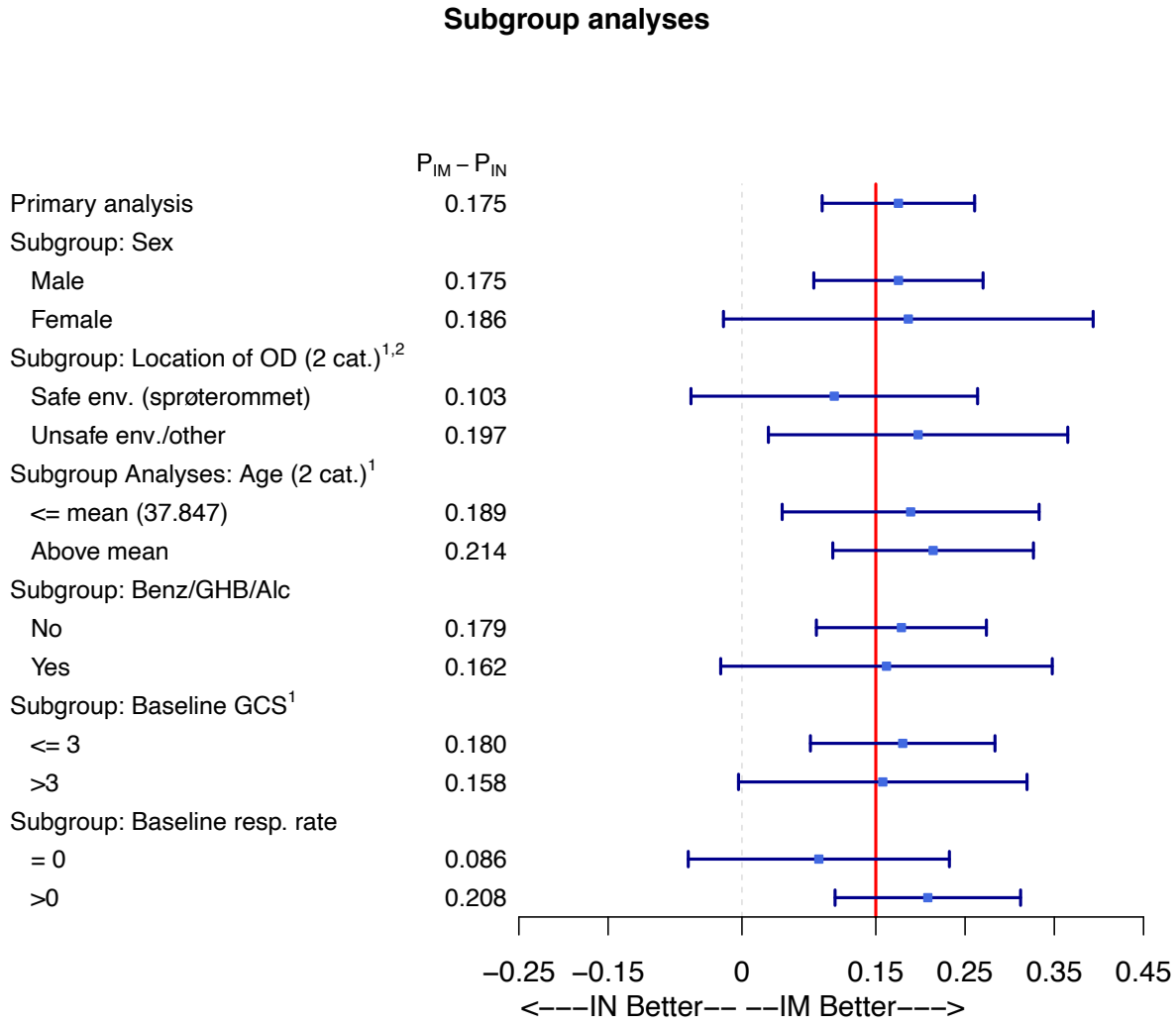


Figure S3: Photo double dummy kit

A sealed A5 size cardboard box contained all equipment for the administration of the study medicine, a paper case report form and serious adverse event reporting form, and an information letter for informed consent. All papers were numbered with randomisation numbers. Kits were randomised and assembled by the hospital pharmacy of the Central Norwegian Regional Health Authority at St. Olavs hospital, Trondheim, Norway

Photography: Ine Eriksen, Oslo University Hospital

Figure S4 Subgroup analysis



OD= Overdose

Benz= Benzodiazepines

GHB= Gamma Hydroxybutyrate

Alc= Alcohol

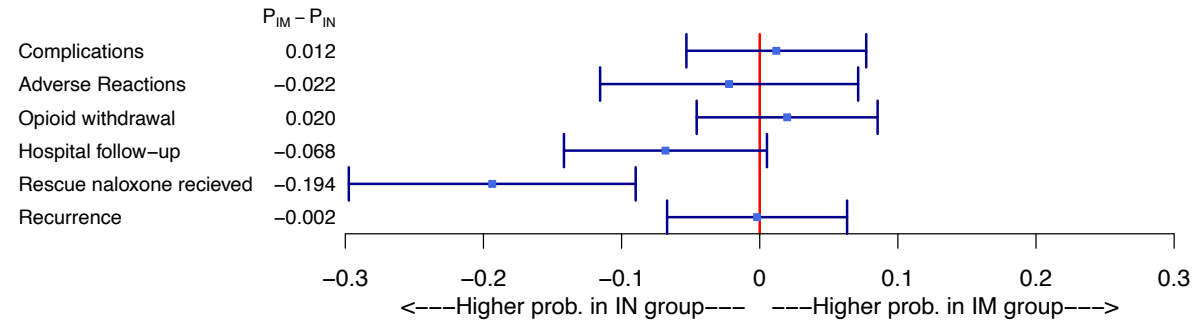
GCS= Glasgow Coma Score

Results of the subgroup analysis of the primary endpoint in the per protocol population. The result of the primary analysis is included for completeness. The red vertical line represents the non-inferiority margin.

[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

Figure S5: Dichotomous secondary endpoints



Forest plots describing dichotomous secondary endpoints calculated from the per protocol set. $P_{IM} - P_{IN}$ indicates the marginal risk difference (Intramuscular group minus intranasal group).

Figure S6: Primary end point in Full Analysis Set