Clinical trial results:
The NAPRESSIM trial.
The use of low dose prophylactic naloxone infusion to prevent respiratory depression with intrathecal morphine.

Summary

EudraCT number	2015-003504-22
Trial protocol	IE
Global end of trial date	06 December 2017

Results information

Result version number	v1
This version publication date	29 December 2018
First version publication date	29 December 2018

Trial information

Trial identification

Sponsor protocol code	UCDCRC/015/006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02885948
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College Dublin
Sponsor organisation address	Belfield, Dublin, Ireland,
Public contact	Clinical Research Centre, University College Dublin, +353 017164593, rabia.hussain@ucd.ie
Scientific contact	Clinical Research Centre, UCD Clinical Research Centre, +44 7496459789, davidcosgrave9@hotmail.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 December 2017
Global end of trial reached?	Yes
Global end of trial date	06 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

A reduction in the incidence of respiratory depression in patients who have received intrathecal morphine as part of their analgesic regimen for major hepatobiliary surgery.

Protection of trial subjects:

All patients were cared for in a high dependency setting with 1:1 or 1:2 nursing care at all times.

The clinical staff caring for the patients were allowed to institute whatever treatment including stopping the study infusion if they deemed it necessary. All protocol deviations were recorded.

Background therapy:

All enrolled patients were undergoing major open hepatopancreaticobiliary surgery.
Part of their analgesic regimen included administration of intrathecal morphine 10mcg/kg prior to induction.

Evidence for comparator: -

Actual start date of recruitment	01 December 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Ireland: 95
Worldwide total number of subjects	95
EEA total number of subjects	95

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	74
From 65 to 84 years	21

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment took place from the 20th April 2016 to the 06th December 2017 .
Two sites were involved, on one campus.
St Vincent's University Hospital, Dublin, Ireland.
St. Vincent's Private Hospital, Dublin, Ireland.

Pre-assignment

Screening details:

Inclusion:
-Aged 18 or above
-Eligible surgical procedure
-Able to consent
Exclusion:
-Allergy to naloxone
-Pregnant or breast-feeding
-Recent other investigational agent
-Anticonvulsant medication
-cardiac arrhythmia
-chronic opioid use
-contraindication to intrathecal injection
-history of sleep apnoea
-clinician preference

Pre-assignment period milestones

Number of subjects started	225[1]
Number of subjects completed	95

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Met Exclusion criteria: 22
Reason: Number of subjects	Clinician preference not to randomise: 87
Reason: Number of subjects	Eligible but didnt consent: 12
Reason: Number of subjects	Eligible but logistical reasons not to randomise: 6
Reason: Number of subjects	Randomised, surgery postponed, re-randomised: 1
Reason: Number of subjects	Didn't meet inclusion criteria: 2

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The pre-assignment period contains all candidates screened for the trial. This is a much larger number than subjects recruited to the trial itself.

Period 1

Period 1 title	Baseline Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Treating clinicians, investigators and patients were unaware of the subject allocation
•The study pharmacist prepared the study infusion based on the randomisation code
•Both the placebo and active infusion were clear colourless solutions, prepared in identical packaging
•Labelling of infusions was identical
•The treating physician, investigators, patients and other clinical staff had no access to the randomisation schedule

Arms

Are arms mutually exclusive?	Yes
Arm title	Naloxone

Arm description:

Patients in this arm of the study will receive an infusion of naloxone at a rate of 5mcg/kg/hr from within one hour of extubation post operatively, until 08.00 the first postoperative morning.

Arm type	Experimental
Investigational medicinal product name	Naloxone hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10000mcg naloxone diluted to 500mls with 0.9% Sodium CHloride, to give a concentration of naloxone 20mcg/ml.
This was infused at a rate of 0.25ml/kg/hr for the duration of the study period.

Arm title	Placebo

Arm description:

Patients in this arm received 0.9% Sodium Chloride via intravenous infusion at a rate of 0.25ml/kg/hr from within one hour of extubation postoperatively, until 08.00 the first postoperative morning.

Arm type	Placebo
Investigational medicinal product name	0.9% Sodium CHloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The solution was administered at a rate of 0.25ml/kg/hr for the duration of the study period.

Number of subjects in period 1	Naloxone	Placebo
Started	48	47
Completed	44	43
Not completed	4	4
Protocol deviation	4	4

Period 2

Period 2 title	Trial Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes

Arm title	Naloxone

Arm description:

Patients in this arm of the study will receive an infusion of naloxone at a rate of 5mcg/kg/hr from within one hour of extubation post operatively, until 08.00 the first postoperative morning.

Arm type	Experimental
Investigational medicinal product name	Naloxone hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10000mcg naloxone diluted to 500mls with 0.9% Sodium CHloride, to give a concentration of naloxone 20mcg/ml.
This was infused at a rate of 0.25ml/kg/hr for the duration of the study period.

Arm title	Placebo

Arm description:

Patients in this arm received 0.9% Sodium Chloride via intravenous infusion at a rate of 0.25ml/kg/hr from within one hour of extubation postoperatively, until 08.00 the first postoperative morning.

Arm type	Placebo
Investigational medicinal product name	0.9% Sodium CHloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The solution was administered at a rate of 0.25ml/kg/hr for the duration of the study period.

Number of subjects in period 2	Naloxone	Placebo
Started	44	43
Completed	44	43

Baseline characteristics

Reporting groups	
Reporting group title	Naloxone
Reporting group description:	
Patients in this arm of the study will receive an infusion of naloxone at a rate of 5mcg/kg/hr from within one hour of extubation post operatively, until 08.00 the first postoperative morning.	
Reporting group title	Placebo
Reporting group description:	
Patients in this arm received 0.9% Sodium Chloride via intravenous infusion at a rate of 0.25ml/kg/hr from within one hour of extubation postoperatively, until 08.00 the first postoperative morning.	

Reporting group values	Naloxone	Placebo	Total
Number of subjects	48	47	95
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	57.3	54.8	
standard deviation	± 11.1	± 10.2	-
Gender categorical			
Units: Subjects			
Female	17	21	38
Male	31	26	57
ASA Score			
American Society of Anesthesiologists Score: Baseline health / functional status scoring system.			
Units: Subjects			
ASA 1	3	5	8
ASA 2	40	39	79
ASA 3	4	3	7
Missing data	1	0	1
Type of Surgery			
All surgical procedures were major open hepatopancreaticobiliary procedures.			
Units: Subjects			
Whipples Procedure	20	24	44
Liver resection	21	16	37
Distal Pancreatectomy	3	1	4
Pancreatectomy	0	1	1
Other	4	5	9

BMI			
Body Mass Index			
Units: kilogram(s)/square meter			
arithmetic mean	26.9	26.0	
standard deviation	± 3.1	± 4.4	-

End points

End points reporting groups

Reporting group title	Naloxone
Reporting group description:	
Patients in this arm of the study will receive an infusion of naloxone at a rate of 5mcg/kg/hr from within one hour of extubation post operatively, until 08.00 the first postoperative morning.	
Reporting group title	Placebo
Reporting group description:	
Patients in this arm received 0.9% Sodium Chloride via intravenous infusion at a rate of 0.25ml/kg/hr from within one hour of extubation postoperatively, until 08.00 the first postoperative morning.	
Reporting group title	Naloxone
Reporting group description:	
Patients in this arm of the study will receive an infusion of naloxone at a rate of 5mcg/kg/hr from within one hour of extubation post operatively, until 08.00 the first postoperative morning.	
Reporting group title	Placebo
Reporting group description:	
Patients in this arm received 0.9% Sodium Chloride via intravenous infusion at a rate of 0.25ml/kg/hr from within one hour of extubation postoperatively, until 08.00 the first postoperative morning.	
Subject analysis set title	RespiratoryMotion ExSpiron Xi diagnosis
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects who were monitored for respiratory depression using the RespiratoryMotion ExSpiron Xi	
Subject analysis set title	Clinical observations diagnosis
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Clinical diagnosis of respiratory depression for Subjects who were monitored for respiratory depression using the Exspiron respiratory monitor.	
Subject analysis set title	PaCO2 >6.6kPa RD Diagnosis
Subject analysis set type	Per protocol
Subject analysis set description:	
Diagnosis of respiratory depression by PaCO2 > 6.6kPa in patients who were monitored for respiratory depression using the Exspiron respiratory monitor	

Primary: Rate of respiratory depression in patients receiving naloxone infusion versus placebo

End point title	Rate of respiratory depression in patients receiving naloxone infusion versus placebo
End point description:	
End point type	Primary
End point timeframe:	
16-20 hours post administration of intrathecal morphine	

End point values	Naloxone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: subjects				
Respiratory depression	10	21		
No respiratory depression	34	22		

Statistical analyses

Statistical analysis title	Respiratory depression
Statistical analysis description: A one sided z test for independent proportions was used.	
Comparison groups	Naloxone v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0102
Method	z test for independent proportions
Parameter estimate	Risk ratio (RR)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	0.87

Secondary: Rate of incidence of PaCO2 >/= 6.6kPa in the naloxone group compared to placebo

End point title	Rate of incidence of PaCO2 >/= 6.6kPa in the naloxone group compared to placebo
End point description:	
End point type	Secondary
End point timeframe: 18-24 hours post administration of intrathecal morphine	

End point values	Naloxone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: Subjects	1	11		

Statistical analyses

Statistical analysis title	PaCO2 > 6.6kPa
Statistical analysis description: z-test for independent proportions	
Comparison groups	Naloxone v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	z test for independent proportions
Parameter estimate	Risk ratio (RR)
Point estimate	0.0888
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.012
upper limit	0.6588

Secondary: Maximum pain score

End point title	Maximum pain score
End point description:	
End point type	Secondary
End point timeframe: 18 - 24 hours post administration of intrathecal morphine	

End point values	Naloxone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: Pain score				
median (inter-quartile range (Q1-Q3))	5 (4 to 8)	4 (2 to 6)		

Statistical analyses

Statistical analysis title	Maximum pain score
Comparison groups	Naloxone v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0009
Method	Mann-Whitney U test

Secondary: Rescue fentanyl requirement

End point title	Rescue fentanyl requirement

End point description:

End point type	Secondary

End point timeframe:

18 - 24 hours after administration of intrathecal morphine

End point values	Naloxone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: mcg				
arithmetic mean (standard deviation)	151 (± 117)	54 (± 80)		

Statistical analyses

Statistical analysis title	Rescue fentanyl
Comparison groups	Naloxone v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.000025
Method	t-test, 2-sided

Secondary: Patient Satisfaction score

End point title	Patient Satisfaction score

End point description:

End point type	Secondary

End point timeframe:

18 - 24 hours after administration of intrathecal morphine

End point values	Naloxone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: Satisfaction score Verbal rating 0-10				
median (inter-quartile range (Q1-Q3))	8 (6 to 9)	9 (7 to 10)		

Statistical analyses

Statistical analysis title	Satisfaction scores
Comparison groups	Naloxone v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0017
Method	Mann-Whitney U Test

Secondary: Incidence of nausea in the naloxone vs placebo group

End point title	Incidence of nausea in the naloxone vs placebo group

End point description:

End point type	Secondary

End point timeframe:

18 - 24 hours after administration of intrathecal morphine

End point values	Naloxone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: Subjects	25	29		

Statistical analyses

Statistical analysis title	Nausea
Comparison groups	Naloxone v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.212
Method	z test for independent proportions

Secondary: Vomiting

End point title	Vomiting

End point description:

End point type	Secondary

End point timeframe:

18 - 24 hours after administration of intrathecal morphine

End point values	Naloxone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: Subjects	3	5		

Statistical analyses

Statistical analysis title	Vomiting
Comparison groups	Naloxone v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.343
Method	z test for independent proportions

Secondary: Rate of pruritus in the naloxone group vs placebo

End point title	Rate of pruritus in the naloxone group vs placebo

End point description:

End point type	Secondary

End point timeframe:

18 - 24 hours after administration of intrathecal morphine

End point values	Naloxone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: subjects	15	26		

Statistical analyses

Statistical analysis title	Pruritus
Comparison groups	Naloxone v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0123
Method	z test for independent proportions
Parameter estimate	Risk ratio (RR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.92

Secondary: Incidence of Ramsey score > / = 3 in the naloxone group vs placebo group

End point title	Incidence of Ramsey score > / = 3 in the naloxone group vs placebo group
End point description:	
End point type	Secondary
End point timeframe:	
18 - 24 hours after administration of intrathecal morphine	

End point values	Naloxone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: subjects	2	4		

Statistical analyses

Statistical analysis title	Ramsey score >/= 3
Comparison groups	Naloxone v Placebo

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.326
Method	z test for independent proportions

Other pre-specified: Respiratory depression diagnosed by RespiratoryMotion ExSpiron Xi or clinical observation.

End point title	Respiratory depression diagnosed by RespiratoryMotion ExSpiron Xi or clinical observation.

End point description:

End point type	Other pre-specified

End point timeframe:

18 - 24 hours after administration of intrathecal morphine

End point values	RespiratoryMotion ExSpiron Xi diagnosis	Clinical observations diagnosis	PaCO2 >6.6kPa RD Diagnosis	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	45	45	45	
Units: subjects				
Respiratory depression	36	16	7	
No respiratory depression	9	29	38	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

18 - 24 hours after administration of intrathecal morphine

Adverse event reporting additional description:

Data was continuously collected during the trial period by the high dependency and PACU staff, including adverse events reports.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Naloxone

Reporting group description:

Patients in this arm of the study will receive an infusion of naloxone at a rate of 5mcg/kg/hr from within one hour of extubation post operatively, until 08.00 the first postoperative morning.

Reporting group title	Placebo

Reporting group description:

Patients in this arm received 0.9% Sodium Chloride via intravenous infusion at a rate of 0.25ml/kg/hr from within one hour of extubation postoperatively, until 08.00 the first postoperative morning.

Serious adverse events	Naloxone	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Naloxone	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 44 (13.64%)	5 / 43 (11.63%)	
Injury, poisoning and procedural complications			
Tourniquet application	Additional description: Tourniquet inadvertently left in place on arm following blood sampling for blood cultures during the study period, by a clinician not involved in the study. No morbidity occurred as a result.		
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	0	
Cardiac disorders			

Hypotension	Additional description: Hypotension requiring vasopressor or aggressive fluid resuscitation during the study period.		
subjects affected / exposed	1 / 44 (2.27%)	2 / 43 (4.65%)	
occurrences (all)	1	2	
Respiratory, thoracic and mediastinal disorders			
Respiratory depression	Additional description: Respiratory depression due to intrathecal morphine, requiring treatment with naloxone via intravenous infusion, outside of the trial protocol infusion.		
subjects affected / exposed	0 / 44 (0.00%)	2 / 43 (4.65%)	
occurrences (all)	0	2	
Obstructive airways disorder	Additional description: Excessive sedation postoperatively, leading to airway obstruction, treated with insertion of a nasopharyngeal airway, which successfully treated the complication.		
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 April 2017	Statistics – update to Statistics section mainly to use more conservative, relative risk rather than odds ratio when determining the primary efficacy endpoint. Minor change to Statistical analysis to be more consistent with HPRA recommendations received in September 2015. Non-substantial change as this was already agreed in response back to HPRA. Method of assigning subjects to treatment groups - correction of an error in the description. Determination of sample size subjects – update to sample size. Total of 96 patients expected to participate, to allow for post randomisation loss to follow up / dropout.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29284510