Clinical trial results:
Alpha 2 agonists for sedation to produce better outcomes from critical illness (A2B Trial): A randomised, parallel-group, allocation concealed, controlled, open, phase 3 pragmatic clinical and cost- effectiveness trial with internal pilot

Summary

EudraCT number	2018-001650-98
Trial protocol	GB
Global end of trial date	14 December 2023

Results information

Result version number	v1 (current)
This version publication date	23 October 2025
First version publication date	23 October 2025

Trial information

Trial identification

Sponsor protocol code	AC1802

Additional study identifiers

ISRCTN number	ISRCTN18035454
ClinicalTrials.gov id (NCT number)	NCT03653832
WHO universal trial number (UTN)	-
Other trial identifiers	Eudra CT: 2018-001650-98

Notes:

Sponsors

Sponsor organisation name	The University of Edinburgh
Sponsor organisation address	Little France Road, Edinburgh, United Kingdom, EH16 4UX
Public contact	O'Mahony, University of Edinburgh, 0044 01312429418, fiach.o'mahony@ed.ac.uk
Scientific contact	O'Mahony, University of Edinburgh, 0044 01312429418, fiach.o'mahony@ed.ac.uk
Sponsor organisation name	NHS Lothian
Sponsor organisation address	Little France Road, Edinburgh, United Kingdom, EH16 4UX
Public contact	Kenneth Scott, NHS Lothian, 0044 01312423325, accord@nhslothian.scot.nhs.uk
Scientific contact	Kenneth Scott, NHS Lothian, 0044 01312423325, accord@nhslothian.scot.nhs.uk

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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 January 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 December 2023
Global end of trial reached?	Yes
Global end of trial date	14 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine whether intravenous sedation with the α2- agonist agents, dexmedetomidine or clonidine, can decrease the time to successful extubation from MV among adult critically ill patients.

Protection of trial subjects:

This was a trial of ICU sedation. All patients were incapacitated when eligible for inclusion. The ethical framework used protected participants through the Clinical Trials Directive guidance about including patients lacking mental capacity. Consent was provide by Professional Legal Representative or Personal Legal Representative according to a process agreed with the ethics committee. Deferred consent was also permitted according to agreed circumstances.

All patients were monitored for sedation state and comfort using validated tools. Clinicians adjusted therapy to achieve the desired level of sedation and analgesia. Any pain or distress was managed by clinical teams using clinical judgement and best practice.

Background therapy:

All patients received the following according to individual need and clinical judgement:
- Mechanical ventilation
- Other forms of organ support to treat critical illness
- Any other treatments indicated for critical illness, such as antibiotics for infection
- All other treatments and therapies considered standard of care for ICU patients

Evidence for comparator:

The comparator or usual care treatment was propofol-based sedation. This is the most widely used sedative in critical care practice, and is recommended as first line sedative in clinical guidelines.

Actual start date of recruitment	11 December 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 1404

Worldwide total number of subjects	1404
EEA total number of subjects	0

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)	827
From 65 to 84 years	561
85 years and over	16

Subject disposition

Recruitment

Recruitment details:

Start of recruitment: 11 Dec 2018
End of recruitment: 27 Oct 2023
Recruited from ICU units at 38 UK sites:
4 sites in Scotland
2 sites in Wales
2 sites in Ireland
30 sites in England

Pre-assignment

Screening details:

Screening started as early as possible post-ICU admission, ideally within 6 hours. Screening continued for up to 48 hours following the start of Mechanical Ventilation (MV) in the ICU.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was an open-label trial. Clinicians were not blinded from group allocation or from the treatment during its administration.

Collection of the primary outcome and hospital-based secondary outcomes was not concealed or blinded from local research staff
Collection of long term telephone based secondary outcomes was concealed from research staff

Arms

Are arms mutually exclusive?	Yes
Arm title	Dexmedetomidine

Arm description:

Participants commenced intravenous infusion of open-label dexmedetomidine according to a weight-based dose regimen as early as possible post randomisation, and within a maximum of two hours. Bedside clinical staff transitioned patients to achieve sedation with dexmedetomidine as quickly as clinically feasible and safe, to replicate the way these drugs were used in routine practice. Additional opiate was used for analgesia using clinical judgement. Once dexmedetomidine was established, additional propofol was only used when the maximum α2-agonist dose was reached or because cardiovascular or other side-effects limited dose escalation. The regimen followed the manufacturer's guidance and regimens used in previous trials. No loading dose was administered. The starting dose was 0.7µg/kg/hour titrated to a maximum dose 1.4µg/kg/hour.

Arm type	Experimental
Investigational medicinal product name	Dexmedetomidine - Dexdor 100 micrograms/ml concentrate for solution for infusion
Investigational medicinal product code	PLGB 27925/0104
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

For dexmedetomidine, the regimen will follow the manufacturer's guidance and regimens used in previous trials. No loading dose will be administered. The starting dose will be 0.7µg.kg-1.hour-1 titrated to a maximum dose 1.4µg.kg-1 hour-1.

Arm title	Clonidine

Arm description:

Participants commenced intravenous infusion of open-label clonidine according to a weight-based dose

regimen as early as possible post randomisation, and within a maximum of two hours.
Bedside clinical staff transitioned patients to achieve sedation with clonidine as quickly as clinically feasible and safe, to replicate the way these drugs were used in routine practice. Additional opiate was used for analgesia using clinical judgement. Once clonidine was established, additional propofol was only used when the maximum α2-agonist dose was reached or because cardiovascular or other side-effects limited dose escalation.
For clonidine, the regimen was designed to be equipotent with dexmedetomidine based on known pharmacokinetics and pharmacodynamics. The chosen regimen is similar to that currently used in many UK ICUs as part of routine 'off label' practice. No loading dose was administered. The starting dose was 1.0µg/kg/hour titrated to a maximum dose of 2µg/kg/hour.

Arm type	Experimental
Investigational medicinal product name	Clonidine - Catapres Ampoules 150 micrograms in 1ml Solution for Injection
Investigational medicinal product code	PL 22824/0009
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The regimen was designed to be equipotent with dexmedetomidine based on known pharmacokinetics and pharmacodynamics. The chosen regimen is similar to that currently used in many UK ICUs as part of routine 'off label' practice. No loading dose will be administered. The starting dose will be 1.0µg.kg-1.hour-1 titrated to a maximum dose of 2µg.kg-1.hour.

Arm title	Propofol

Arm description:

Participants received intravenous propofol according to current usual care. The sedation targets, weaning, and sedation discontinuation procedures followed the same clinical targets as for the clonidine and dexmedetomidine groups.

Arm type	Active comparator
Investigational medicinal product name	Propofol 10mg/ml (1%) emulsion for injection or infusion
Investigational medicinal product code	PL 39699/0074
Other name	
Pharmaceutical forms	Emulsion for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients will continue to receive intravenous propofol according to current usual care.
The sedation targets, weaning, and sedation discontinuation procedures will follow the same clinical targets as for the clonidine and dexmedetomidine groups.

Number of subjects in period 1	Dexmedetomidine	Clonidine	Propofol
Started	457	476	471
Completed	457	476	471

Baseline characteristics

Reporting groups	
Reporting group title	Dexmedetomidine

Reporting group description:

Participants commenced intravenous infusion of open-label dexmedetomidine according to a weight-based dose regimen as early as possible post randomisation, and within a maximum of two hours. Bedside clinical staff transitioned patients to achieve sedation with dexmedetomidine as quickly as clinically feasible and safe, to replicate the way these drugs were used in routine practice. Additional opiate was used for analgesia using clinical judgement. Once dexmedetomidine was established, additional propofol was only used when the maximum α2-agonist dose was reached or because cardiovascular or other side-effects limited dose escalation. The regimen followed the manufacturer's guidance and regimens used in previous trials. No loading dose was administered. The starting dose was 0.7µg/kg/hour titrated to a maximum dose 1.4µg/kg/hour.

Reporting group title	Clonidine

Reporting group description:

Participants commenced intravenous infusion of open-label clonidine according to a weight-based dose regimen as early as possible post randomisation, and within a maximum of two hours.
Bedside clinical staff transitioned patients to achieve sedation with clonidine as quickly as clinically feasible and safe, to replicate the way these drugs were used in routine practice. Additional opiate was used for analgesia using clinical judgement. Once clonidine was established, additional propofol was only used when the maximum α2-agonist dose was reached or because cardiovascular or other side-effects limited dose escalation.
For clonidine, the regimen was designed to be equipotent with dexmedetomidine based on known pharmacokinetics and pharmacodynamics. The chosen regimen is similar to that currently used in many UK ICUs as part of routine 'off label' practice. No loading dose was administered. The starting dose was 1.0µg/kg/hour titrated to a maximum dose of 2µg/kg/hour.

Reporting group title	Propofol

Reporting group description:

Participants received intravenous propofol according to current usual care. The sedation targets, weaning, and sedation discontinuation procedures followed the same clinical targets as for the clonidine and dexmedetomidine groups.

Reporting group values	Dexmedetomidine	Clonidine	Propofol
Number of subjects	457	476	471
Age categorical			
All subjects were aged between 18 and 92. No participants were under 18.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	288	274	265
From 65-84 years	164	195	202
85 years and over	5	7	4
Age continuous			
Units: years			
arithmetic mean	58.8	59.6	59.2
standard deviation	± 14.8	± 14.5	± 15.2

Gender categorical Units: Subjects			
Female	160	168	166
Male	297	308	305

Reporting group values	Total		
Number of subjects	1404		
Age categorical			
All subjects were aged between 18 and 92. No participants were under 18.			
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)	827		
From 65-84 years	561		
85 years and over	16		
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	494		
Male	910		

Subject analysis sets

Subject analysis set title	Dexmedetomidine
Subject analysis set type	Full analysis

Subject analysis set description:

All participants randomised, analysed according to their allocated treatment group regardless of the treatment actually received, with the exception of the following groups of participants:
(a) those randomised in error despite ineligibility;
(b) erroneous duplicate randomisations;
(c) those fully withdrawing from the trial who also requested that all of their data be deleted;
(d) exclusions resulting from a serious breach event at site 45 relating to participant consent (14 participants). While professional legal representative consent was obtained for these participants, a notified serious breach arose in relation to processes followed locally to obtain consent to remain in the trial for these incapacitated patients.

Subject analysis set title	Clonidine
Subject analysis set type	Full analysis

Subject analysis set description:

All participants randomised, analysed according to their allocated treatment group regardless of the treatment actually received, with the exception of the following groups of participants:
(a) those randomised in error despite ineligibility;
(b) erroneous duplicate randomisations;
(c) those fully withdrawing from the trial who also requested that all of their data be deleted;
(d) exclusions resulting from a serious breach event at site 45 relating to participant consent (14 participants). While professional legal representative consent was obtained for these participants, a notified serious breach arose in relation to processes followed locally to obtain consent to remain in the trial for these incapacitated patients.

Subject analysis set title	Propofol
Subject analysis set type	Full analysis

Subject analysis set description:

All participants randomised, analysed according to their allocated treatment group regardless of the treatment actually received, with the exception of the following groups of participants:
(a) those randomised in error despite ineligibility;
(b) erroneous duplicate randomisations;
(c) those fully withdrawing from the trial who also requested that all of their data be deleted;
(d) exclusions resulting from a serious breach event at site 45 relating to participant consent (14 participants). While professional legal representative consent was obtained for these participants, a notified serious breach arose in relation to processes followed locally to obtain consent to remain in the trial for these incapacitated patients.

Reporting group values	Dexmedetomidine	Clonidine	Propofol
Number of subjects	457	476	471
Age categorical			
All subjects were aged between 18 and 92. No participants were under 18.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	287	272	268
From 65-84 years	164	193	203
85 years and over	5	7	4
Age continuous			
Units: years			
arithmetic mean	58.8	59.6	59.2
standard deviation	± 14.8	± 14.5	± 15.2
Gender categorical			
Units: Subjects			
Female	160	168	166
Male	297	308	305

End points

End points reporting groups

Reporting group title	Dexmedetomidine

Reporting group description:

Participants commenced intravenous infusion of open-label dexmedetomidine according to a weight-based dose regimen as early as possible post randomisation, and within a maximum of two hours. Bedside clinical staff transitioned patients to achieve sedation with dexmedetomidine as quickly as clinically feasible and safe, to replicate the way these drugs were used in routine practice. Additional opiate was used for analgesia using clinical judgement. Once dexmedetomidine was established, additional propofol was only used when the maximum α2-agonist dose was reached or because cardiovascular or other side-effects limited dose escalation. The regimen followed the manufacturer's guidance and regimens used in previous trials. No loading dose was administered. The starting dose was 0.7µg/kg/hour titrated to a maximum dose 1.4µg/kg/hour.

Reporting group title	Clonidine

Reporting group description:

Participants commenced intravenous infusion of open-label clonidine according to a weight-based dose regimen as early as possible post randomisation, and within a maximum of two hours.
Bedside clinical staff transitioned patients to achieve sedation with clonidine as quickly as clinically feasible and safe, to replicate the way these drugs were used in routine practice. Additional opiate was used for analgesia using clinical judgement. Once clonidine was established, additional propofol was only used when the maximum α2-agonist dose was reached or because cardiovascular or other side-effects limited dose escalation.
For clonidine, the regimen was designed to be equipotent with dexmedetomidine based on known pharmacokinetics and pharmacodynamics. The chosen regimen is similar to that currently used in many UK ICUs as part of routine 'off label' practice. No loading dose was administered. The starting dose was 1.0µg/kg/hour titrated to a maximum dose of 2µg/kg/hour.

Reporting group title	Propofol

Reporting group description:

Participants received intravenous propofol according to current usual care. The sedation targets, weaning, and sedation discontinuation procedures followed the same clinical targets as for the clonidine and dexmedetomidine groups.

Subject analysis set title	Dexmedetomidine
Subject analysis set type	Full analysis

Subject analysis set description:

All participants randomised, analysed according to their allocated treatment group regardless of the treatment actually received, with the exception of the following groups of participants:
(a) those randomised in error despite ineligibility;
(b) erroneous duplicate randomisations;
(c) those fully withdrawing from the trial who also requested that all of their data be deleted;
(d) exclusions resulting from a serious breach event at site 45 relating to participant consent (14 participants). While professional legal representative consent was obtained for these participants, a notified serious breach arose in relation to processes followed locally to obtain consent to remain in the trial for these incapacitated patients.

Subject analysis set title	Clonidine
Subject analysis set type	Full analysis

Subject analysis set description:

All participants randomised, analysed according to their allocated treatment group regardless of the treatment actually received, with the exception of the following groups of participants:
(a) those randomised in error despite ineligibility;
(b) erroneous duplicate randomisations;
(c) those fully withdrawing from the trial who also requested that all of their data be deleted;
(d) exclusions resulting from a serious breach event at site 45 relating to participant consent (14 participants). While professional legal representative consent was obtained for these participants, a notified serious breach arose in relation to processes followed locally to obtain consent to remain in the trial for these incapacitated patients.

Subject analysis set title	Propofol
Subject analysis set type	Full analysis

Subject analysis set description:

All participants randomised, analysed according to their allocated treatment group regardless of the treatment actually received, with the exception of the following groups of participants:

(a) those randomised in error despite ineligibility;
(b) erroneous duplicate randomisations;
(c) those fully withdrawing from the trial who also requested that all of their data be deleted;
(d) exclusions resulting from a serious breach event at site 45 relating to participant consent (14 participants). While professional legal representative consent was obtained for these participants, a notified serious breach arose in relation to processes followed locally to obtain consent to remain in the trial for these incapacitated patients.

Primary: Time to successful extubation

End point title	Time to successful extubation
End point description: Time to successful extubation (in hours post-randomization) Median (95% CI)	
End point type	Primary
End point timeframe: During ICU stay.	

End point values	Dexmedetomidine	Clonidine	Propofol	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	457	476	471	
Units: Hours				
median (full range (min-max))	136 (117 to 150)	146 (124 to 168)	162 (136 to 170)	

Statistical analyses

Statistical analysis title	Primary analysis: Dexmedetomidine versus Propofol

Statistical analysis description:

For the primary analysis, performed on the full analysis set, a Fine and Gray proportional sub-distribution hazards regression model of time from randomisation to successful extubation was fitted to the data. Results are presented as sub-distribution hazard ratios for each of the dexmedetomidine and clonidine versus usual care comparisons, with corresponding 95% confidence intervals (CI) and p-values from the primary analysis model.

Comparison groups	Dexmedetomidine v Propofol
Number of subjects included in analysis	928
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.196
Method	Fine and Gray proportional sub-distribut
Parameter estimate	Sub-distribution hazard ratio
Point estimate	1.093
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.955
upper limit	1.25

Notes:

[1] - Fine and Gray proportional sub-distribution hazards regression analysis

Statistical analysis title	Primary analysis: Clonidine versus Propofol

Statistical analysis description:

For the primary analysis, performed on the full analysis set, a Fine and Gray proportional sub-distribution hazards regression model of time from randomisation to successful extubation was fitted to the data. Results are presented as sub-distribution hazard ratios for each of the dexmedetomidine and clonidine versus usual care comparisons, with corresponding 95% confidence intervals (CI) and p-values from the primary analysis model.

Comparison groups	Clonidine v Propofol
Number of subjects included in analysis	947
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.342
Method	Fine and Gray proportional sub-distribut
Parameter estimate	Sub-distribution hazard ratio
Point estimate	1.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.948
upper limit	1.167

Notes:

[2] - Fine and Gray proportional sub-distribution hazards regression analysis

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Daily during the intervention period and until ICU discharge.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	Dexmedetomidine group
Reporting group description: -	
Reporting group title	Clonidine group
Reporting group description: -	
Reporting group title	Propofol group
Reporting group description: -	

Serious adverse events	Dexmedetomidine group	Clonidine group	Propofol group
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 457 (4.81%)	12 / 476 (2.52%)	5 / 471 (1.06%)
number of deaths (all causes)	132	145	141
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Pyrexia possibly due to Clonidine			
subjects affected / exposed	0 / 457 (0.00%)	1 / 476 (0.21%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension and subsequent hypotension			
subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small bowel ischemia due to pseudo-obstruction			
subjects affected / exposed	0 / 457 (0.00%)	1 / 476 (0.21%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left MCA stroke			

subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Large cerebral bleed			
subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac disorders			
Bradycardic cardiac arrest			
subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MItral regurgitation found on TOE requiring urgent repair SAE documented			
subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Whilst repositioning, patient bit endotracheal tube. Unable to ventilate patient. Saturations droppe			
subjects affected / exposed	0 / 457 (0.00%)	1 / 476 (0.21%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Profound bradycardia requiring CPR			
subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patient lost cardiac output on three occasions			
subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia with loss of cardiac output			

subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brady Arrhythmia			
subjects affected / exposed	0 / 457 (0.00%)	1 / 476 (0.21%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Astystole			
subjects affected / exposed	0 / 457 (0.00%)	1 / 476 (0.21%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac event			
subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Severe bradycardia with HR 28-30 bpm and hypotension with SBP 50-60s for a few minutes at 4AM on 01/			
subjects affected / exposed	0 / 457 (0.00%)	1 / 476 (0.21%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 457 (0.00%)	1 / 476 (0.21%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Bradycardia			
subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MI			
subjects affected / exposed	0 / 457 (0.00%)	0 / 476 (0.00%)	1 / 471 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
VF arrest likely due to sepsis with post myocardial infarction scarring			

subjects affected / exposed	0 / 457 (0.00%)	0 / 476 (0.00%)	1 / 471 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Severe bradycardia with associated hypotension			
subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiovascularly unstable. Bradycardia leading to episodes of asystole that resolved spontaniously.			
subjects affected / exposed	0 / 457 (0.00%)	1 / 476 (0.21%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation with rapid ventricular response followed by ventricular pulseless tachycardia, r			
subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Compromised bradycardia			
subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PEA Cardiac Arrest			
subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral Infarction			
subjects affected / exposed	0 / 457 (0.00%)	0 / 476 (0.00%)	1 / 471 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Participant fond to have multiple infarcts on Head CT done due to reduced consciousness off sedation			

subjects affected / exposed	0 / 457 (0.00%)	1 / 476 (0.21%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sub acute left frontoparietal haematoma found on CT scan			
subjects affected / exposed	0 / 457 (0.00%)	1 / 476 (0.21%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Unconscious			
subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
New right occipital lobe PCA territory infarct			
subjects affected / exposed	0 / 457 (0.00%)	0 / 476 (0.00%)	1 / 471 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MCA infarct with occluded Right ICA			
subjects affected / exposed	0 / 457 (0.00%)	1 / 476 (0.21%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Verified Death after deterioration with rapidly escalating oxygen requirement following vomit.			
subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hyperthermia due to dexmedetomidine			
subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
UGI Bleed			

subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal bleed			
subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic bowel and bowel perforation-pt was palliated and died the same day, SAE has been recorded			
subjects affected / exposed	0 / 457 (0.00%)	1 / 476 (0.21%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory, thoracic and mediastinal disorders			
Significant bilateral pleural effusions causing patient to be peri arrest and requiring emergency re			
subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patient had to be re intubated due to PE and CAP			
subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Significant tracheostomy cuff leak with probable atelectasis post-op			
subjects affected / exposed	0 / 457 (0.00%)	0 / 476 (0.00%)	1 / 471 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Dexmedetomidine group	Clonidine group	Propofol group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 457 (6.13%)	14 / 476 (2.94%)	13 / 471 (2.76%)
Vascular disorders			
Vascular disorder			
subjects affected / exposed	8 / 457 (1.75%)	2 / 476 (0.42%)	3 / 471 (0.64%)
occurrences (all)	8	2	3
Surgical and medical procedures			
Surgery	Additional description: Immediate return to theatre following scan.		
subjects affected / exposed	0 / 457 (0.00%)	1 / 476 (0.21%)	0 / 471 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Hyperthermia			
subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences (all)	1	0	0
Rapidly escalating oxygen requirement	Additional description: Verified Death after deterioration with rapidly escalating oxygen requirement following vomit.		
subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Respiratory disorder			
subjects affected / exposed	6 / 457 (1.31%)	1 / 476 (0.21%)	5 / 471 (1.06%)
occurrences (all)	8	1	8
Psychiatric disorders			
Psychiatric disorder			
subjects affected / exposed	3 / 457 (0.66%)	2 / 476 (0.42%)	1 / 471 (0.21%)
occurrences (all)	4	2	1
Injury, poisoning and procedural complications			
Pyrexia	Additional description: Pyrexia possibly due to Clonidine		
subjects affected / exposed	0 / 457 (0.00%)	1 / 476 (0.21%)	0 / 471 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Cardiac event			
subjects affected / exposed	24 / 457 (5.25%)	14 / 476 (2.94%)	5 / 471 (1.06%)
occurrences (all)	26	15	9
Nervous system disorders			

Nervous system disorder			
subjects affected / exposed	7 / 457 (1.53%)	3 / 476 (0.63%)	3 / 471 (0.64%)
occurrences (all)	8	3	3
Blood and lymphatic system disorders			
Bleeding from tracheostomy	Additional description: Bleeding from tracheostomy and frank blood from NG		
subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	3 / 457 (0.66%)	3 / 476 (0.63%)	1 / 471 (0.21%)
occurrences (all)	3	3	1
Hepatobiliary disorders			
Hepatobiliary disorder			
subjects affected / exposed	2 / 457 (0.44%)	0 / 476 (0.00%)	1 / 471 (0.21%)
occurrences (all)	2	0	1
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 457 (0.00%)	0 / 476 (0.00%)	1 / 471 (0.21%)
occurrences (all)	0	0	1
Endocrine disorders			
Endocrine disorder			
subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Septic episode	Additional description: Septic episode with haemodynamic instability.		
subjects affected / exposed	1 / 457 (0.22%)	0 / 476 (0.00%)	0 / 471 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 November 2018	Change of PI at Belfast, addition of 10 sites
16 May 2019	Addition of 13 sites and removal of one (Dorset)
24 October 2019	NIHR logo and statement updated, various protocol updates, new covering letters, 2 new sites added, PI at Hampton Hospitals changed
27 May 2020	Addition of 5 sites, change of PI at Royal Marsden, removal of one site (Royal Free)
24 August 2020	Change in PI at Oxford and St Georges
01 September 2020	SPC updated, Protocol: changes to follow-up, sites 90 day FU, booklets, reduce Q at 30 and 90 days. Covering letters for 90 day site FU. PIS changes: GDPR info included, sites can do 90 days FU
21 March 2022	SPC and Summary product Ch updated. 8 letters, PIS updated and protocol changes including co-enrolment to CTIMPS
31 August 2022	Am 7 documents resubmitted but removed co-enrolment to CTIMPs. SPC and Summary product Ch updated. 8 letters, PIS updated and protocol changes
03 May 2023	1. The protocol has been updated to change the sample size from 1737 to 1437. Additional updates to the protocol include:- a change in trial manager (the previous trial manager has moved onto a new study)- changes to the follow-up duration to truncate the follow up period - an email from the statistician has been included to confirm this will not cause a significant impact on the outcome of the trial- update to the total planned duration of the trial in line with the extension granted by the Funder to complete the trial- changes to section 3.4 Design and analytical/ conceptual framework in line with the revised sample size- changes to Section 10.1 Overview to Health Economic Evaluation to clarify the changes in cost of the drugs during the trials lifespan- changes in section 6.3.1 Replacing Diprivan with Propofol in line with the updated SPC V5.0 (detailed in number 3). - Change to the follow up duration truncating the follow up to 30 days only for participants recruited in October. There is an email from the statistician included to assure there will be no impact from truncating the follow up period.2. Changes to the PIS, Process Evaluation PIS and addition of two letters as detailed further on in the amendment tool.3. SPC updated: we wish to submit SPC V5.0 25042023. The Catapres and Propofol SPC has been updated with no changes to the RSI. The Dexdor SPC has also been updated with a change to the RSI - in section 4.8 (undesirable effects); Added to adverse reactions is diabetes insipidus (endocrine disorder) with unknown frequency. Removed is "Renal and urinary disorders: Polyuria (Not known)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

11 March 2020	Recruitment to A2B was suspended at all sites from 11th March 2020 due to the COVID-19 pandemic.	03 June 2020

Notes:

Limitations and caveats

None reported