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

A2B Trial

Statistical Analysis Plan

CONFIDENTIAL

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Chief Investigator Name	Professor Timothy Walsh
Chief Investigator Email address	timothy.walsh@ed.ac.uk

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SAP authors

Number	Name	Date involvement started	Date involvement finished	Notes (optional)
1	Richard Parker	04Jul2019	02Aug2019	Authorship ceased following unblinding for data monitoring committee reporting
2	Christopher Weir	04Jul2019		

SAP Approval Signatures	
Trial Statistician: Christopher Weir (Mar 27, 2024 09:51 GMT)	**Date Approved:** Mar 27, 2024
Chief Investigator: Tim walsh Tim walsh (Mar 27, 2024 09:59 GMT)	**Date Approved:** Mar 27, 2024

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1.0	22/01/2021	Initial Creation
2.0	11/01/2024	Incorporated modified sample size calculation. Refinement of modelling for secondary outcome analyses, including addition of Poisson regression where appropriate. Updated to reflect latest ECTU SAP template (V5.0, 16Oct2023).
3.0	27/03/2024	Analysis population change to exclude 14 participants from site 45. Further clarification of analysis population criteria. Sensitivity analysis excluding site 45 added. Change from Poisson regression to time to event analysis for secondary outcome S5.

Table of Contents

List of Abbreviations

Abbreviation	Full name
AE	**Adverse event**
CAM-ICU	**Confusion-Assessment Method for ICU**
CI	**Confidence interval**
CONSORT	**CONsolidated Standards Of Reporting Trials**
CPAP	**Continuous positive airway pressure**
CRF	**Case report form**
EQ-5D-5L	**EuroQol instrument with five levels of severity in each of five dimensions**
EudraCT	**European Clinical Trials Database**
HADS	**Hospital Anxiety and Depression Scale**
HR	**Hazard ratio**
HTA	**Health Technology Assessment**
ICE-Q	**Intensive Care Experience Questionnaire**
ICU	**Intensive care unit**
ICH	**International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use**
IES-R	**Impact of Events Scale – Revised**
MV	**Mechanical ventilation**
NIHR	**National Institute for Health and Care Research**
NIV	**Non-invasive mechanical ventilation**
OR	**Odds ratio**
RASS	**Richmond Agitation and Sedation Scale**
SD	**Standard deviation**
SOFA	**Sequential Organ Failure Assessment**
SQAT	**Sedation Quality Assessment Tool**
T-MoCA	**Montreal Cognitive Assessment tool (telephone version)**

1. Introduction

A2B is a randomised, parallel-group, allocation concealed, controlled, open, multi-centre, phase 3 pragmatic clinical and cost- effectiveness trial with internal pilot. Adult intensive care unit (ICU) patients expected to require at least 24 hours further mechanical ventilation (MV) will be randomised within 48 hours of starting MV. Patients with primary brain injury; post-cardiac arrest; status epilepticus; and peripheral nervous system disease will be excluded. 1437 patients will be randomised to receive sedation using dexmedetomidine or clonidine or 'usual care' sedation in a 1:1:1 ratio. To simplify the enrolment process randomisation will be stratified by site alone.

This statistical analysis plan is written with reference to protocol version 7, dated 25 April 2023. Its scope covers the end of trial analysis for A2B, with the exception of the health economic evaluation, the process evaluation (apart from quantitative descriptions of fidelity to the intervention) and the mechanistic sub-study of pro- and anti-inflammatory mediators which will all be documented separately.

2. Statistical Methods section from the protocol

8.2 PROPOSED ANALYSES

8.2.1 Estimand

Here we define the estimand for the primary analysis of the primary outcome in the trial, in line with the draft addendum to ICH E9 (Statistical Principles for Clinical Trials): ICH E9(R1), Defining the Appropriate Estimand for a Clinical Trial/Sensitivity Analyses.

Population *Adult ICU patients enrolled within 48h of MV starting in ICU and expected to require sedation with propofol and MV for at least 48h, at least 24h of which would be after randomisation. Long-term home ventilation, terminal illness, selected diagnoses, allergy to study medication, pregnancy and expected death within 24h are exclusion criteria.*

Variable *Time to successful extubation post-randomisation (hours).*

Population-level Summary *Cumulative incidence function of time to extubation; sub-distribution hazard ratio (HR)*

*The following **Intercurrent Events** have been identified which would prevent measurement of the primary outcome or change the interpretation of the measured primary outcome:*

1. *Death before the time point at which randomised treatment is due to start.*
2. *(a) Dexmedetomidine allocated in randomisation but not started*
   (b) Clonidine allocated in randomisation but not started
3. *Additional propofol being administered when cardiovascular side effects have limited the escalation of dexmedetomidine or clonidine.*
4. *Additional propofol being administered when non-cardiovascular side effects have limited the escalation of dexmedetomidine or clonidine.*
5. *Death before successful extubation.*

6. *Patient withdrawal from intervention and follow-up (situation where deferred consent is not granted is a subset of such events).*
7. *Transfer to another ICU before successful extubation.*
8. *Use of dexmedetomidine as main sedative in usual care group.*
9. *Use of clonidine as main sedative in usual care group.*
10. *Use of rescue medication [1]in the presence of agitation or delirium.*

Events 1, 2(a), 2(b), 8 and 9 are expected to be rare and no specific actions will be taken: analysis of these events will be by intention to treat, except for event 1 which will be handled in the same way as event 5.

Events 3 and 4 will be dealt with using an intention to treat approach. Non-cardiovascular side-effects will mostly be sedation-related and therefore will be further analysed as secondary outcomes.

Event 5 will be treated as a competing risk for the primary outcome, and will therefore be analysed using a hypothetical strategy.

Event 6 will also be handled using a hypothetical strategy, in which the time to extubation will be censored at the point of withdrawal and the withdrawals will be assumed to lead to missing at random (MAR) data on the primary outcome. Complete follow up should still be possible for most participants in whom event 7 occurs; if not, the hypothetical strategy used for event 6 will also be implemented.

Event 10 is analogous to events 8 and 9 but applies to all treatment arms and medications. An intention to treat approach will be used for this event.

Full details of the methods of dealing with the above intercurrent events will be incorporated in the statistical analysis plan.

8.2.2 Statistical analysis

For the primary analysis, a Fine and Gray proportional sub-distribution hazards regression analysis of time from randomisation to successful extubation will be performed (this method allows us to directly model the cumulative incidence of extubation after taking into account the competing risk of mortality) for each hypothesis test permitted under the analytic structure (Figure 1). Results will be expressed as sub-distribution HRs with corresponding 95% confidence intervals and p-values.

The following supplementary analyses will be performed to provide reassurance about the robustness of the main analysis of the primary outcome, for each between-arm comparison:

(i) A Cox frailty proportional hazards regression model will be fitted to the primary outcome, with censoring for deaths or loss to follow-up in ICU while on MV. Although death in ICU may be considered a competing risk, this modelling approach allows us to estimate the instantaneous risk of experiencing a successful extubation event at time t given that the patient is still alive at time t (in the literature this is called the "cause-specific hazard" of extubation for patients who have not yet died). Site will be included in the model as a random effect.

[1] Rescue medication is recorded as haloperidol, quetiapine, dexmedetomidine, midazolam, olanzapine, clonidine, lorazepam or other

(ii) A Cox frailty regression analysis of time from randomisation to ICU mortality while on ventilation. Patients experiencing successful extubation events or loss to follow-up prior to mortality will be censored. This analysis will provide "cause-specific" HRs for patients on MV to support the primary analysis results. Site will be included in the model as a random effect.

(iii) A Cox frailty regression analysis of time to all-cause mortality, with censoring only for patients lost to follow-up during the six months follow-up period. This analysis will allow us to compare the risk of overall mortality across trial arms for all patients, regardless of whether or not patients are still on MV. Site will be included in the model as a random effect.

(iv) For each participant, the proportion of care periods will be recorded in which propofol treatment was maintained even though dexmedetomidine or clonidine had not been up-titrated to its maximum dose and had no dose-limiting side-effects. As an exploratory analysis, the main analysis of the primary outcome will be repeated using the adherence analysis set (section 8.2.3) rather than the full analysis set.

For the secondary outcomes other than mortality, formal hypothesis testing will not be performed but point estimates and 95% confidence intervals for pairwise differences between randomised groups will be calculated. A trial analysis plan providing full details will be finalised prior to locking the trial data base.

The hierarchical hypothesis testing framework for analysis of the primary outcome, which controls the overall type I error to be at most 6.5% across the multiple analyses being performed, is also outlined in protocol Figure 1:

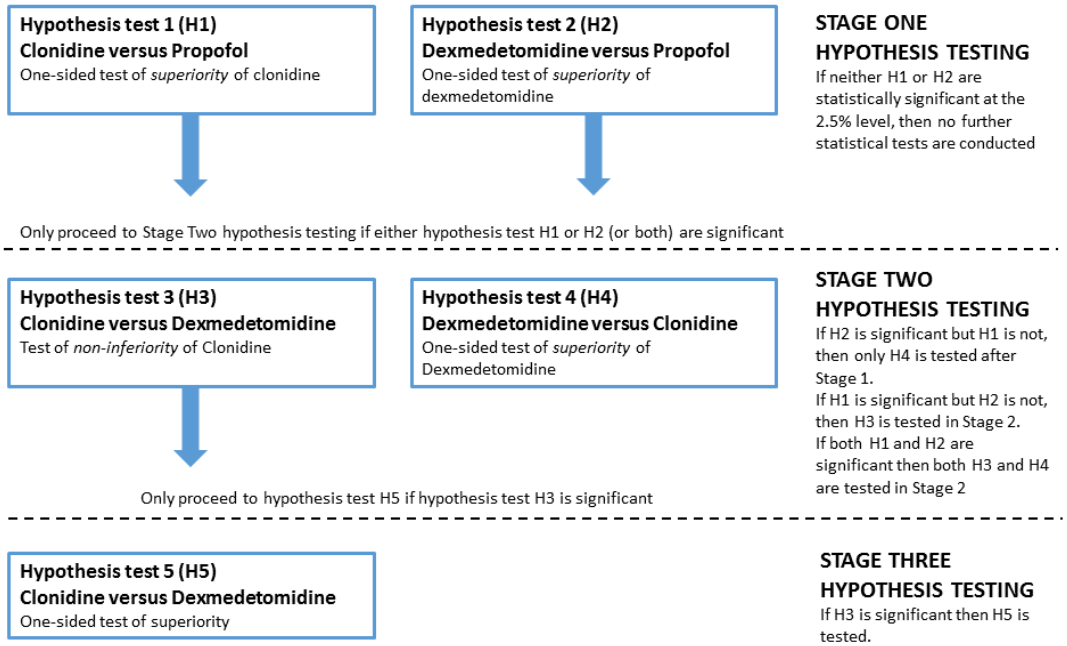

Figure 1: *Analytic framework which efficiently tests the trial questions using a hierarchical analytic structure with serial gatekeeping to preserve study power. Hypothesis tests will be performed using a 2.5% one-sided significance level, with the exception of the non-inferiority test H3 which will use a 4% one-sided significance level.*

3. Overall Statistical Principles

The Stage 1 hypothesis testing of the superiority of each of clonidine and dexmedetomidine versus propofol will be carried out at the one-sided 2.5% significance level. The Stage 2 hypothesis of non-inferiority of clonidine to dexmedetomidine will be performed with a one-sided 4% significance level. The Stage 2 hypothesis of superiority of dexmedetomidine to clonidine will have a one-sided 2.5% significance level. Finally, in Stage 3, there will be a possible test of superiority of clonidine versus dexmedetomidine at the one-sided 2.5% significance level. All hypothesis tests on the primary outcome are arranged in a hierarchical structure, with serial gatekeeping, to ensure overall control of the type 1 error to at most 6.5%.

Although the secondary outcomes are numbered in this analysis plan for ease of reference, note that this does not mean any form of hierarchical testing procedure will be implemented. Instead, to avoid multiplicity concerns, no p-values will be reported in the analysis of secondary outcomes, with the exception of mortality due to its close relationship with the primary outcome. For the other secondary outcomes, unless otherwise specified in Section 4.6, 95% confidence intervals will be reported for treatment effect estimates. These confidence intervals will not be interpreted inferentially as a substitute for hypothesis testing, but instead will be used as supporting information to aid interpretation of the primary outcome and mortality findings.

Categorical variables will be summarised using frequencies and percentages; continuous variables will be summarised using the mean, standard deviation (SD), median, lower quartile, upper quartile, minimum and maximum values.

Analyses of outcomes will adjust for site as a random effect, since site is included as a stratification factor in the randomisation.

Generally speaking, missing data will be handled according to the principles outlined in the A2B estimand, described in protocol section 8.2.1. Participants randomised in error despite ineligibility will be reported in the participant flow summary but will not be included in efficacy or safety analyses as no further data will be gathered on these participants.

Outliers will be identified by viewing boxplots of the outcome variables of interest. All analyses will include outliers as standard; where data are present for a continuous variable which lie more than 4 standard deviations away from the mean, a sensitivity analysis will be performed removing these data values to determine the robustness of the findings in the analysis where outliers were included.

The planned analyses will be performed using the SAS statistical software, version 9.4 or later. Following the end of trial, defined as the date of the last follow-up of the final participant, the planned analyses will be performed and reported in stages according to the National Institute for Health and

Care Research (NIHR)-approved publication plan, once data querying has been completed and the locking of the trial database has been documented.

3.1 Analysis populations

Full analysis set

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.

Adherence analysis set

The **adherence analysis set** will be all randomised participants in the **full analysis set** who, in the dexmedetomidine group received any dexmedetomidine on the day of randomisation; in the clonidine group received any clonidine on the day of randomisation; or in the usual care group received neither dexmedetomidine nor clonidine (except as rescue medication for agitation) on the day of randomisation.

Exclusions resulting from serious breach event at site 45: A further 14 participants from A2B trial site 45 will be excluded from both the **full analysis set** and the **adherence analysis set**. While professional legal representative consent was obtained for these participants, a notified serious breach (REC Reference 18/SS/0085; Breach Reference B23-167) arose in relation to processes followed locally to obtain consent to remain in the trial in these incapacitated patients. Following MHRA reporting, part of the CAPA agreed was to contact next of kin (and one patient) to provide trial information as 'duty of candour'. The Research Ethics Committee were consulted who advised that those contacted should have up to 6 months during which they could decide to request deletion of their relative's data from the A2B trial database. The sponsor and Chief Investigator agreed that it was not therefore feasible to include these patients in the analysis population, due to the reporting timeline required by the funding body, NIHR HTA, and the funding available for the trial analysis.

The A2B study identifiers of those to be excluded are:
45001
45002
45004
45006
45009
45010
45011
45013
45014
45018
45019
45021
45029
45031

The CONSORT flow diagram for A2B will include a summary of the randomised group allocations for these excluded participants.

3.2 Outcomes

Primary outcome

- Time to successful extubation post-randomisation (hours).

A successful first extubation from mechanical ventilation will be defined as follows:

a) From endotracheal extubation: time of first extubation that is followed by 48 hours of spontaneous breathing.

b) From tracheostomy: time of extubation will be defined as the start time of the first period during which a patient receives support not exceeding 5 cmH_2O CPAP with less or equal to pressure support ventilation of 5cmH_2O for a continuous period of 48 hours. Decannulation during this period will count as being free from mechanical ventilation.

c) From non-invasive mechanical ventilation (NIV): time of extubation will be the start time of the first period during which a patient receives support not exceeding 5 cmH_2O CPAP via mask/hood for a continuous period of 48 hours. NIV patients receiving any pressure supported breaths will not be considered to be spontaneously breathing unassisted.

NB: The use of high flow nasal oxygen will not be counted as mechanical ventilation, so a patient on high nasal flow oxygen alone will be considered to be spontaneously breathing unassisted.

Secondary outcomes

Secondary outcomes are listed below. Mortality is of greatest importance, as it forms a component of the primary outcome time to successful extubation. Outcomes listed from Length of ICU Stay to Patient Experience of ICU Care are other outcomes specified in the NIHR HTA briefing document for this commissioned funding call.

S1 Mortality
ICU; hospital; 30 days; 90 days; 180 days post-randomisation

S2 Length of ICU stay (days from randomisation to ICU discharge)

S3 Sedation quality, measured by Richmond Agitation and Sedation Scale (RASS)

- Measured up to four-hourly during mechanical ventilation until primary outcome recorded, summarised as lowest and highest RASS scores for each 12 hours nursing shift and each ICU day (a 12 hours day and night nursing shift)

S4 Sedation quality, measured during mechanical ventilation until primary outcome, recorded by Sedation Quality Assessment Tool (SQAT- Appendix 1). Each component and overall sedation quality summarised for each ICU day based on any occurrence of the item recorded during the two 12 hours nursing shifts.
Four sedation quality states:

1. Overall optimum sedation (no agitation;no unnecessary deep sedation;no pain behaviour)
2. Agitation
3. Unnecessary deep sedation (RASS -4/-5 without clinical indication)
4. Pain (presence of pain behaviour based on limb movement and ventilation compliance)

S5 Time to first optimum sedation (based on highest and lowest RASS score recorded for each 12 hours nursing shift)

- Time from randomisation to start of first 12 hours nursing shift with a highest RASS score of -2 or greater
- Days from randomisation to first day with SQAT demonstrating overall optimum sedation

S6 Delirium prior to successful extubation, assessed by Confusion-Assessment Method for ICU (CAM-ICU)

- Any occurrence prior to successful extubation (binary outcome)
- Days with delirium or coma prior to successful extubation (count outcome)

S7 One or more pre-defined cardiac adverse events
(of those recorded daily: severe bradycardia; cardiac arrhythmias; cardiac arrest)

S8 Health-related Quality of Life, measured by recall prior to hospital admission, and at 30, 90 and 180 days after randomisation using the EuroQol EQ-5D-5L instrument

S9 Patient Ability to Communicate Pain and Ability to Cooperate with Care
Binary assessments for each 12 hours nursing shift:

- Was patient able to communicate pain?
- Was patient able to cooperate with care?

S10 Patient experience of ICU care, measured at 90 days after randomisation using the Intensive Care Experience Questionnaire (ICE-Q)
Provides numeric score in four domains:

1. Awareness of Surroundings (9 items; score range 9-45)
2. Frightening Experiences (6 items; score range 6-35)
3. Recall of Experiences (5 items; score range 5-25)
4. Satisfaction with Care (4 items; score range 4-20)

S11 Relative/partner/friend (PerLR) assessment of comfort and communication, measured daily during mechanical ventilation
Binary assessment for each question:

1. Does the patient appear awake to the visitor?
2. Does the patient seem comfortable to the visitor?
3. Does the visitor feel they can communicate with the patient?

S12 Anxiety and depression, measured at 180 days post randomisation using the Hospital Anxiety and Depression Scale (HADS) questionnaire

S13 Post-traumatic stress, measured at 180 days post randomisation using the Impact of Events Scale-revised (IES-R)

S14 Cognitive function, measured at 180 days post randomisation using the Montreal Cognitive Assessment tool telephone version (T-MoCA)

4. List of Analyses

This analysis plan describes the end of trial statistical analyses to be performed on A2B, excluding analysis of the mechanistic sub-study of putative pro- and anti-inflammatory mediators (protocol section 11), the health economics analyses and the process evaluation components of the trial. However, quantitative assessment of fidelity from the process evaluation is included in the scope of this analysis plan.

4.1 Recruitment, retention and missing data

A CONSORT flow diagram will be constructed. For EudraCT reporting purposes, enrolment will also be summarised into age categories 18-64; 65-84; and 85+ years.

The number and percentage of patients who were later found to be ineligible for the trial even though they were randomised will be summarised by randomised group, as will the number of patients formally withdrawn and the reason for withdrawal (if available). The number and percentage of patients with missing primary outcome data will be reported by randomised treatment allocation. No formal hypothesis testing will be performed.

4.2 Baseline characteristics

The following baseline characteristics will be summarised by treatment group and overall. A further descriptive summary will assess any association between the Covid-19 pandemic and participant characteristics. The baseline characteristics summary will be further stratified by randomisations occurring up to and including 23 March 2020 and those occurring after 23 March 2020.

Age (years)
Age (by EudraCT reporting categories)
Gender
Pre-randomisation:
- Estimated weight (kg)
- RASS
- CAM-ICU (unless RASS -4 or -5, or is -3 but the assessor is unable to assess CAM-ICU status)

Functional comorbidity index (Groll et al, 2005) (total count; and 18 separate items)
Medical history:
- Portal hypertension
- Biopsy proven cirrhosis
- Hepatic encephalopathy
- Alcohol dependence
- Drug dependence

Type of admission (Trauma, Non-trauma medical, Non-trauma surgical; Planned, Unplanned)
Diagnosis at admission (Medical)
Diagnosis at admission (Surgical)
Pre-randomisation sedatives (Propofol, Midazolam, Fentanyl, Alfentanil, Morphine, Remifentanil, Dexmedetomidine, Clonidine, Haloperidol, Diazepam, Other (free text)) For each report frequency and summarise dose, in units specified on CRF.
SOFA score (excluding neurological SOFA) (Singer et al, 2016)
Pre-randomisation blood results:
- Haemoglobin g/L
- Lymphocytes $x10^9$/L
- Sodium mmol/L

Urea mmol/L
Albumin g/L
White cell count x10^9/L
APTT ratio
Potassium mmol/L
eGFR mL/min/1.73m^2
ALT U/L

Blood gases:

H^+
pH
PaO_2 kPa
$PaCO_2$ kPa
Standard bicarbonate mmol/L
Lactate mmol/L

PRE-DELIRIC delirium prediction score (van den Boogaard et al, 2012; Appendix 2) including components:

Apache II score
Infection/sepsis
Antibiotics given during first 24 hours in ICU
Sepsis
Septic shock
Coma RASS -4/-5 for at least 8 hours in first 24 hours in ICU
If yes, by use of medication / other reason / both medication and other
Total morphine dose in first 24 hours in ICU
None / 0.01-7.1mg / 7.2-18.6mg / 18.7-331.6mg
Any propofol, midazolam or lorazepam use in first 24 hours in ICU
Highest urea value in first 24 hours in ICU (mmol/L)
Metabolic acidosis

Proxy baseline EQ-5D

4.3 Primary outcome (primary analysis)

For the primary analysis, performed on the full analysis set, a Fine and Gray proportional sub-distribution hazards regression analysis (Fine and Gray, 1999) of time from randomisation to successful extubation will be performed (this method allows us to directly model the cumulative incidence of extubation after taking into account the competing risk of mortality, thus implementing the hypothetical strategy outlined in the estimand for intercurrent events 1 and 5) for each hypothesis test permitted under the hierarchical testing structure. Site will be accounted for in the analysis by implementing the marginal model approach to the Fine and Gray method for clustered data (Zhou et al, 2012). If this aspect of model fitting proves problematic due to sites which have randomised a small number of participants (fewer than 5), we will consider pooling of data from such sites to address this issue.

Intercurrent events 2(a), 2(b), 8 and 9 are expected to be rare and will therefore be handled using the intention to treat approach in the primary analysis of the primary outcome. Events 3 and 4 (propofol use due to cardiovascular and non-cardiovascular side-effects respectively) will also be handled using the intention to treat approach due the pragmatic exploration of the effects of clonidine and dexmedetomidine in A2B. Withdrawals where the participant has not withdrawn permission to use data collected up to the point of withdrawal will have time to extubation censored at the time of withdrawal (intercurrent event 6, missing at random assumption, hypothetical strategy). In the rare

cases of transfer to another ICU before extubation (intercurrent event 7), follow-up will be continued to extubation where possible but if extubation time is missing it will be censored at the last time at which the extubation status is known (missing at random assumption, hypothetical strategy). Intercurrent event 10 will be handled using intention to treat, again reflecting the treatment policy pragmatic nature of A2B.

Results will be reported as: the sub-distribution hazard ratio (HR) for each of dexmedetomidine and clonidine versus usual care, with corresponding 95% confidence intervals (CI) and p-values from the Fine-Gray model. The exception will be the non-inferiority analysis of clonidine versus dexmedetomidine (hypothesis H3 in protocol figure 1) for which a 96% one-sided non-inferiority CI will be presented. The cumulative incidence function (CIF) obtained from the Fine-Gray model for time to successful extubation will be plotted separately for each treatment group; the median time to successful extubation and its 95% CI will be reported by treatment group. As recommended in the CONSORT reporting guidance, the absolute risk difference (and its 95% CI) for each of dexmedetomidine and clonidine versus usual care will be reported at 7 days after randomisation (the median time on mechanical ventilation under 'usual care' in a real ICU dataset).

Following the strategy recommended by Poythress et al. (2020), the fit of the Fine-Gray model will be evaluated by plotting, by treatment group, the CIF for time to successful extubation from the Fine-Gray model against the nonparametric CIF. If substantial differences occur between the Fine-Gray and nonparametric CIF curves an alternative modelling strategy, such as cause-specific hazards, will be considered.

4.4 Primary outcome (supplementary analyses)

Where the modelling proves to be feasible, the following supplementary analyses will be considered to provide reassurance about the robustness of the primary analysis, for each between-arm comparison:

(i) A mixed effects partially proportional hazards regression model will be fitted to the primary outcome of time from randomisation to successful extubation, with censoring for deaths or loss to follow-up in ICU while on MV. Although death in ICU may be considered a competing risk, censoring for deaths allows us to estimate the instantaneous risk of experiencing a successful extubation event at time t given that the patient is still alive at time t (the "cause-specific hazard" of extubation for patients who have not yet died). Site will be included in the model as a random effect, treatment group as a fixed effect. Results will be expressed as the HR for each of dexmedetomidine and clonidine versus usual care, with its corresponding 95% CI and p-value.

(ii) A mixed effects partially proportional hazards regression analysis of time from randomisation to ICU mortality while on MV. Patients experiencing successful extubation events or loss to follow-up prior to mortality will be censored. For patients on MV, this analysis will provide the mortality "cause-specific" HR (and 95% CI) for each of dexmedetomidine and clonidine versus usual care, to support the primary analysis results. Site will be included in the model as a random effect, treatment group as a fixed effect.

(iii) Overall mortality will be analysed using a mixed effects partially proportional hazards regression analysis, see Section 4.6 for details.

(v) The primary analysis will be repeated, but using the adherence analysis set.

(vi) The primary analysis will be repeated using the full analysis set, but with the exclusion of participants from site 45.

Furthermore, selected baseline characteristics of patients with missing primary outcome data due to withdrawal will be compared descriptively to those with patients who did not withdraw prior to extubation to evaluate the missing at random assumption present in the primary analysis of intercurrent event 6.

Similarly, selected baseline characteristics of patients transferred to another ICU who did not have time to extubation recorded will be compared to those transferred to another ICU who did have it recorded, to assess the missing at random assumption being made in the primary analysis of intercurrent event 7.

Finally, further exploratory analysis will assess any association between the Covid-19 pandemic and the primary outcome. Summary descriptive statistics of time to successful extubation will be reported by treatment group and further stratified by the date of the UK lockdown: randomisations occurring up to and including 23 March 2020 versus those occurring after 23 March 2020.

4.5 Subgroup analyses

The primary analysis of the primary outcome will be repeated for the following subgroups specified in the protocol.

(1) Patients with and without sepsis at enrolment to A2B.
(2) Patients with lower or higher delirium risk, as defined by the PRE-DELIRIC delirium risk prediction score. (van den Boogaard et al, 2012; see Appendix 2) The groups with values above (or including) and below the median PRE-DELIRIC score observed in the trial population will be compared.
(3) Patients with and without organ dysfunction at randomisation. The group with SOFA score values above or equal to the median SOFA score (excluding neurological score) that is present at baseline will be compared with the group with SOFA score values below the median score at baseline.
(4) Age (<64 versus ≥64)

For each subgroup variable, a p-value will be calculated for its interaction with each of dexmedetomidine and clonidine versus usual care. Within each subgroup category, we will calculate the sub-distribution HR and 95% confidence interval for (a) dexmedetomidine versus usual care and (b) clonidine versus usual care and present these in a forest plot. These analyses will be considered exploratory.

For age, an additional exploratory analysis will fit an interaction term based on its continuous value rather than age categories. A cubic B-spline, fractional polynomial or simple quadratic term will be fitted to determine, via a likelihood ratio test, whether there is a significant non-linear relationship between age and the effects of each of dexmedetomidine and clonidine versus usual care.

For the age subgroup, given the findings of the SPICE trial of dexmedetomidine (Shehabi et al., 2019), the above subgroup analysis will also be applied to the mortality secondary outcome **S1** and the cardiac events secondary outcome **S7** and each of its component events. For both of these outcomes the interaction term for each of dexmedetomidine and clonidine versus usual care will be added to

the model for the outcome specified in Section 4.6. For these secondary outcomes, the p-values for the interaction terms will not be reported.

4.6 Secondary outcomes

Each secondary outcome will be summarised using appropriate descriptive statistics, by treatment group and overall. Where informative, graphical summaries will also be created. The remainder of this section describes the formal analyses that will be undertaken on secondary outcomes. The large number of secondary outcomes means that not all will be included in the main trial publication text. Secondary outcomes for which there is substantial missing data will also be considered for transfer from the main publication text to supplementary material or to secondary publications agreed in the NIHR threaded publication plan.

For the secondary outcomes other than **S1**, mortality, formal hypothesis testing will not be performed but point estimates and 95% confidence intervals for pairwise differences between randomised groups will be calculated. P-values will not be reported.

For secondary outcomes measured at more than one time point following ICU discharge, separate analyses will be performed for each measurement occasion.

S1 Mortality. Kaplan-Meier survival curves will be presented by randomised group. A mixed effects partially proportional hazards regression analysis will be used to analyse time to all-cause mortality, with censoring only for patients lost to follow-up or with truncated follow-up during the six months post-randomisation period. This analysis will allow us to compare the risk of overall mortality, using the HR, 95% CI and p-value, for each of dexmedetomidine and clonidine versus usual care for all patients, regardless of whether or not patients are still on MV. Site will be included in the model as a random effect and treatment group as a fixed effect.

The time to event secondary outcome **S2** will be analysed using the same method as for the primary analysis of the primary outcome (Section 4.3), in order to take account of the potential competing risk of death. The supplementary analyses of Section 4.4 will also be applied for this outcome.

For **S3** each of overall daily, day shift and night shift highest and lowest RASS will be summarised using boxplots, by randomised group, up to the occurrence of the successful extubation primary outcome, withdrawal or death, whichever occurred first.

Optimal sedation during the first 7 days from randomisation (outcome **S4**) will be reported descriptively (including a record of the number of missing values) and summarised graphically as a proportion for each combination of study day and treatment group. Each of the **S4** SQAT components (agitation; pain; and unnecessary deep sedation) will be reported descriptively as for optimal sedation. Incidence of each of agitation and unnecessary deep sedation during the first 7 days from randomisation will be modelled using Poisson regression, incorporating an offset term for duration of follow-up and including site as a random effect in the model. A rate ratio and 95% confidence interval will be reported for each of dexmedetomidine and clonidine compared to usual care. Where completeness of data permits, this Poisson regression modelling will also be performed for the pain component and for overall optimum sedation.

Outcome **S5** (time from randomisation to start of the first 12 hours nursing shift with highest RASS recorded of -2 or greater) will be analysed using the same model as for the primary analysis of the primary outcome, but the modelling will be restricted to the first 7 days from randomisation.

Where completeness of data permits the derivation of optimum sedation in a reasonable proportion of participants and time points, outcome **S5** (days from randomisation to first day with SQAT optimum sedation) will be analysed in the same way as **S2**.

Outcome **S6** (occurrence of delirium at any time) and outcome **S6** (days with delirium or coma prior to successful extubation) will be analysed using the same Poisson regression model structure as for **S4**, but the modelling will cover the first 10 days from randomisation. For occurrence of delirium, the Poisson regression model offset term will only include the number of days on which the participant had CAM-ICU data collected and was free from coma (i.e. CAM-ICU data collected and lowest RASS greater than or equal to -2; or had CAM-ICU data collected with a lowest RASS equal to -3). For the outcome of days with delirium or coma prior to successful extubation, the Poisson regression model offset term will only include the number of days on which the participant had CAM-ICU data collected or else was recorded as having RASS -5, -4, or -3. We will consider any patient with RASS -3 as being in a coma unless CAM-ICU data was collected at RASS -3.

Outcome **S7** (occurrence of any of severe bradycardia; cardiac arrhythmias; cardiac arrest) will be analysed using the same Poisson regression model structure as for **S4**, but the modelling will cover the full follow-up period up to successful extubation. The number and proportion of participants experiencing each of these events at any time during follow-up will be reported.

Binary secondary outcomes (**S9**, **S11**) will be analysed by a generalised linear mixed model with a logit link function. Site will be included as a random effect in the model and treatment group as a fixed effect. For outcome **S9** which is measured in multiple care periods, a random effect for participant (nested within site) will also be included. Results will be expressed as the odds ratio (OR) for each of dexmedetomidine and clonidine versus usual care, with corresponding 95% CI.

Continuous secondary outcomes (**S8** (visual analogue scale; derived utility), **S12**, **S13**, **S14**) will be analysed using a normal linear mixed model. Site will be included as a random effect in the model and treatment group as a fixed effect. A proxy for outcome **S8** is measured at baseline and, if data completeness is sufficient, this will be included as a fixed effect in the model. The parameter to be estimated is the adjusted mean difference: dexmedetomidine minus usual care; and clonidine minus usual care. The corresponding 95% CI will also be reported. If the assumption of normality of residuals does not hold (as determined by Q-Q plot), the outcome variable will be transformed to rectify this. In the event that the assumption cannot be satisfied, alternative analyses (for example involving categorising the outcome measure) will be conducted. A similar strategy will be applied when residuals versus fitted values demonstrate non-constant variance for an outcome.

4.6.1 Missing data handling: secondary outcomes

We anticipate minimal rates of missing data for the secondary outcome **S1**, mortality. In cases of missing data, the survival time will be censored at the date last known alive. Missing data on time to event secondary outcomes **S2** and **S5** will be handled using a similar approach to that used for **S1**.

In other secondary outcomes, for which no formal hypothesis testing will be undertaken, the following strategies will be implemented where missing data rates are low (less than 10% overall, and with a no more than 5% difference in the rate across treatment groups). For continuous secondary outcomes a "missing at random" assumption will be applied automatically within the normal linear mixed model, while complete case analyses will be performed for outcomes which are counts or binary variables. In

the event of the missing data rate being greater than 10% overall, or differing by more than 5% across treatment groups, multiple imputation strategies will be considered.

4.7 Safety

Safety data will be reported for the full analysis population, according to treatment allocated.

While death will be analysed as a secondary outcome (Section 4.6), only deaths considered related to participation in A2B will be recorded as serious adverse events. Sedation-related adverse events (including hypotension, hypertension, unplanned NG removal, unplanned central line removal, unplanned arterial line removal, unplanned peripheral line removal, unplanned drain removal, unplanned extubation, staff injury as a result of patient, patient injury and ileus) will be reported descriptively: number and percentage by treatment group and overall.

During the recruiting ICU stay (or up to and including study day 28, whichever is earlier) the number and percentage of patients experiencing each of: any adverse event (AE); non-serious adverse event (NSAE); serious adverse event (SAE) and suspected unexpected serious adverse reaction (SUSAR) will be reported, overall and split by trial arm. Tabulations will be split by events occurring pre- and post-randomisation. The numbers of events will also be reported.

The AE, NSAE, SAE and SUSAR tables will also be further categorised by the number and percentage of patients recording an event in each of the MedDRA system organ class categories, with a further sub-categorisation according to verbatim text or MedDRA preferred term as appropriate.

Data listings of all adverse events will be provided by treatment group, sorted by MedDRA system organ class and reporting participant study number, MedDRA system organ class, verbatim text, severity, seriousness, causality, expectedness and outcome.

Daily data on blood results (platelets, bilirubin, creatinine), respiratory function (FiO_2, PaO_2, SpO_2), blood pressure (lowest systolic BP recorded and corresponding diastolic BP) and urine output (>500mL/day, 200-500mL/day, <200mL/day) will be summarised and presented graphically by ICU study day and treatment group. No formal statistical inference will be performed on these measures. When estimating the mean and SD measures below the limit of quantification (LLQ) will be handled by treating these observations as censored but positive, calculating the likelihood conditional on them being greater than zero. This is strategy M4 from Senn et al., 2012.

4.8 Concomitant medications

Rescue medication for agitation: The frequency and percentage (of all those in the full analysis set) of patients in whom any rescue medication was administered at any time from randomisation to recording of the primary outcome will be reported, overall and by treatment arm. These summaries will be repeated for each rescue medicine separately (haloperidol, quetiapine, dexmedetomidine, midazolam, olanzapine, clonidine, lorazepam).

Use of sedatives and analgesics: The frequency and percentage (of all those in the full analysis set) of patients in whom sedatives or analgesics were administered will be reported overall and by treatment arm. Specific continuous data summaries by treatment group will be:

- total propofol dose (mg)
- propofol dose per kg per day (mg)
- total dexmedetomidine dose (µg)

- dexmedetomidine dose per kg per day (µg)
- total clonidine dose (µg)
- clonidine dose per kg per day (µg)
- fentanyl dose per day (µg)
- alfentanil dose per day (mg)
- midazolam dose per day (mg)
- morphine dose per day (mg)
- remifentanil dose per day (µg)
- haloperidol dose per day (mg)
- diazepam dose per day (mg)

Use of propofol, dexmedetomidine, and clonidine over time:
Usual care group: A boxplot of propofol dose by day will be presented.
Dexmedetomidine: A boxplot of propofol dose and dexmedetomidine dose by day will be presented as upper and lower panels on the same figure, with a common time axis.
Clonidine: A boxplot of propofol dose and clonidine dose by day will be presented as upper and lower panels on the same figure, with a common time axis.

4.9 Intervention dose, fidelity and reach

Dose

The frequency of RASS assessments recorded per shift will be summarised overall, by treatment group and by study site.

Fidelity

The degree of implementation of various components of the A2B interventions will be summarised using the algorithm outlined in Appendix 3. Reporting will cover completeness of day and night shift forms; responses to deep sedation query; completeness of RASS data; completeness of CAM-ICU data on day and night shifts; completeness of pain behaviour data; deep sedation guidance compliance; number and proportion of care periods for each participant in which each of propofol, dexmedetomidine and clonidine was administered will be summarised overall and by treatment group; and propofol, dexmedetomidine and clonidine administration by study day for participants remaining on mechanical ventilation.

For each treatment group, the proportion of participants receiving propofol treatment on each study day will be reported.

For each treatment group, the proportion of patients in whom ‘deep sedation’ was requested by the caring clinical team for each sequential study day will be reported for the period up to successful extubation or death, whichever occurred first.

Further evaluation of fidelity will be reported in the qualitative process evaluation.

4.10 Protocol deviations and violations

For events which are specific to a participant, the number and percentage of each of protocol deviations and violations will be presented, split by site, trial arm and overall.

Deviations and violations which cannot be attributed to an individual participant (for example, an issue with a process in a site) will be presented in a line listing.

5. Validation and QC

The following will be performed by a second statistician:

1. Separate programming and checking of the primary and supplementary analyses for the primary outcome (Sections 4.3 and 4.4).
2. Separate programming and re-analysis of the mortality secondary outcome.
3. The end of trial statistical report will be read and checked for accuracy and consistency.

6. Data sharing

A file, or set of files, containing the de-identified final data will be prepared, along with a data dictionary. These will be made available to the Chief Investigator after the primary results paper based on the final statistical report has been published.

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Appendix 1 Sedation Quality Assessment Tool (SQAT)

For a given ICU shift, the sedation quality states of SQAT will be derived as:

Agitation Highest RASS +3/+4 (Daily Data Collection CRF)

Unnecessary deep sedation Lowest RASS -4/-5 AND Was the bedside nurse asked by medical staff to keep this patient deeply sedated? = "No" (Daily Data Collection CRF)

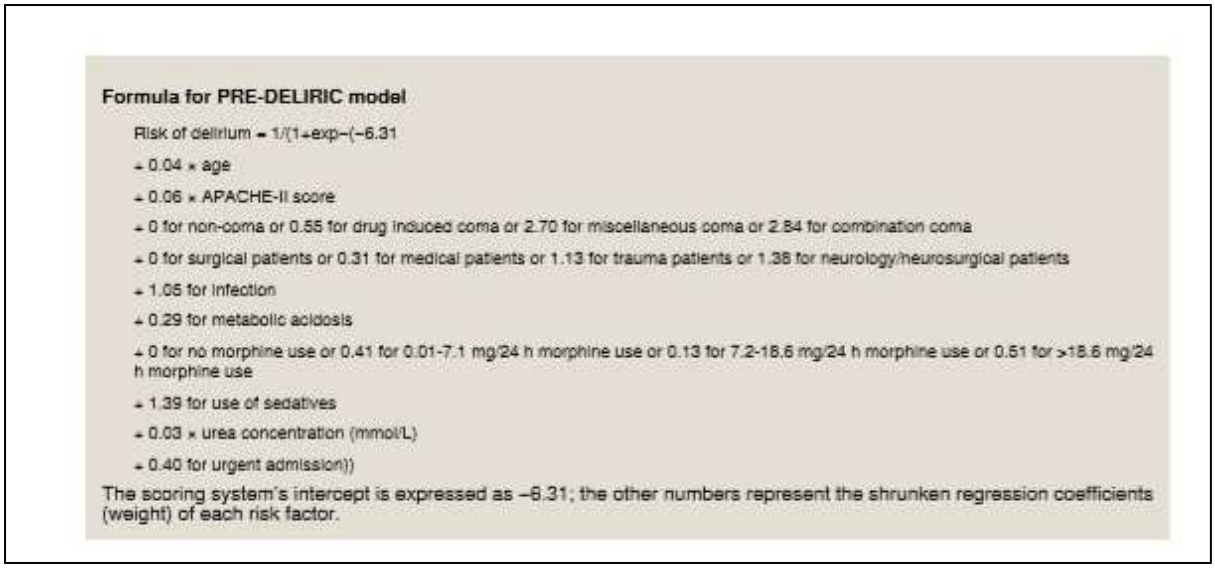
Pain Presence of pain behaviour based on:

Limb movement (Response to moving the participant = "Difficult to move most of the time" OR "Actively resisting movement most of the time") OR
((Compliance with the ventilator = "Tolerating ventilation but coughing/gagging frequently" OR "Unable to control ventilation due to poor patient synchronisation despite different modes tested") AND Was the participant paralysed throughout the entire nursing shift? = "No")
(Daily Data Collection CRF)

Overall optimum sedation is present when there is no agitation; no unnecessary deep sedation; and no pain behaviour.

Appendix 2 PRE-DELIRIC score derivation

The PRE-DELIRIC score will be derived according to the formula in van den Boogaard et al, 2012:



Formula for PRE-DELIRIC model

Risk of delirium = 1/(1+exp−(−6.31

+ 0.04 × age

+ 0.06 × APACHE-II score

+ 0 for non-coma or 0.55 for drug induced coma or 2.70 for miscellaneous coma or 2.84 for combination coma

+ 0 for surgical patients or 0.31 for medical patients or 1.13 for trauma patients or 1.38 for neurology/neurosurgical patients

+ 1.05 for infection

+ 0.29 for metabolic acidosis

+ 0 for no morphine use or 0.41 for 0.01-7.1 mg/24 h morphine use or 0.13 for 7.2-18.6 mg/24 h morphine use or 0.51 for >18.6 mg/24 h morphine use

+ 1.39 for use of sedatives

+ 0.03 × urea concentration (mmol/L)

+ 0.40 for urgent admission))

The scoring system's intercept is expressed as −6.31; the other numbers represent the shrunken regression coefficients (weight) of each risk factor.

Age: Randomisation date minus date of birth (Pre-Randomisation CRF)

APACHE II score: (Baseline CRF)

Coma:

Non-coma	Coma status = ”No coma” (Baseline CRF)
Drug induced coma	Coma status = ”Coma” AND “With use of medication” (Baseline CRF)
Miscellaneous coma	Coma status = ”Coma” AND “Other” (Baseline CRF)
Combination coma	Coma status = ”Coma” AND “Combination” (Baseline CRF)

Surgical/Medical/Trauma/Neurology/Neurosurgery:

Surgical	Type of ICU admission = ”Non-trauma” AND (“Surgical” NOT (Diagnosis at Admission – Surgical Admission = “Intracerebral haemorrhage” OR “Subdural/epidural haematoma” OR “Subarachnoid haemorrhage” OR “Laminectomy / other spinal cord injury” OR “Craniotomy for neoplasm” OR “Other neurologic diseases”))
Medical	Type of ICU admission = ”Non-trauma” AND (“Medical” NOT (Diagnosis at Admission – Medical Admission = “Intracerebral haemorrhage” OR “Subarachnoid haemorrhage” OR “Stroke” OR “Neurologic infection” OR “Neurologic neoplasm” OR “Neuromuscular disease” OR “Seizure” OR “Other neurologic disease”))
Trauma	Type of ICU admission = ”Trauma (without traumatic brain injury)”
Neurology/Neurosurgery	Type of ICU admission = ”Non-trauma” AND

((Diagnosis at Admission – Surgical Admission = "Intracerebral haemorrhage" OR "Subdural/epidural haematoma" OR "Subarachnoid haemorrhage" OR "Laminectomy / other spinal cord injury" OR "Craniotomy for neoplasm" OR "Other neurologic diseases") OR
(Diagnosis at Admission – Medical Admission = "Intracerebral haemorrhage" OR "Subarachnoid haemorrhage" OR "Stroke" OR "Neurologic infection" OR "Neurologic neoplasm" OR "Neuromuscular disease" OR "Seizure" OR "Other neurologic disease"))
(Baseline CRF)

Infection:

Did the participant receive antibiotics for proven or suspected infection during their first 24 hours in ICU? = "Yes" (Baseline CRF)

Metabolic acidosis:

pH < 7.35 (H+ > 44.7) with bicarbonate < 24 mmol/L in the first 24 hours in ICU? = "Yes" (Baseline CRF)

Morphine use:

Total administered morphine dose in first 24 hours in ICU =
"Morphine use: 0.01 – 7.1 mg" cumulative OR
"Morphine use: 7.2 – 18.6 mg cumulative" OR
"Morphine use: 18.7 – 331.6 mg cumulative"
(Baseline CRF)

Sedatives:

Any use of propofol, midazolam, lorazepam or combination in the first 24 hours in ICU? = "Yes" (Baseline CRF)

Urea concentration:

Please specify the highest serum urea value in the first 24 hours in ICU [mmol/L]
(Baseline CRF)

Urgent admission: Planned Admission = "Unplanned" (Baseline CRF)

Appendix 3 Data completeness and intervention adherence

Rule 1: Removing non-intervention period days
Remove days on which answer to 'InvasivelyVentilated_YesNoDesc' and 'NonInvVentilation_YesNoDesc' is NO
This will remove the majority of days on which the patient was no longer ventilated during the intervention period. There will be a small number of days on which the response could be NO but the patient is subsequently re-intubated and the primary outcome has not been reached. However, subsequent ventilated days will be included as the answer to this question should revert to YES. For the purpose of tracking data quality this small discrepancy will not be important.
Remaining data should be all days on which patients was receiving mechanical ventilation as defined in the protocol

Rule 2: completeness of day and night shift forms
After rule 1:
Count proportion of 'DSBedsideNurse_YesNoDesc' that response is YES
Count proportion of 'NSBedsideNurse_YesNoDesc' that response is YES
Report this as proportion of 'shift forms' completed by clinical staff during day shift and night shift and overall by site and overall trial

Rule 3: responses to deep sedation query
After rule 1:
Count proportion of 'DSDeepSedation_YesNoNotCollectedDesc' reported for each category
Count proportion of 'NSDeepSedation_YesNoNotCollectedDesc' reported for each category
Report this for day shift and night shift and for overall by site and overall trial

Rule 4: completeness of sedation RASS data
After rule 1:
Report completeness of:
'DSHighestRASS_RASSScoreDesc'
'DSLowestRASS_RASSScoreDesc'
'NSHighestRASS_RASSScoreDesc'
'NSLowestRASS_RASSScoreDesc'
To provide a measure of ability to report a highest and lowest recorded RASS score on each day report:
Proportion of days on which:
'DSHighestRASS_RASSScoreDesc' OR 'NSHighestRASS_RASSScoreDesc' OR BOTH have a RASS score reported
'DSLowestRASS_RASSScoreDesc' OR 'NSLowestRASS_RASSScoreDesc' OR BOTH have a RASS score recorded

Rule 5: completeness of CAM-ICU data
After rule 1:
Report the following:
Day shift
Proportion of day shifts on which 'DSCAMICUPositive_CAMICUPositiveDesc' is YES OR NO (this is a definite response)
Proportion of day shifts on which 'DSCAMICUPositive_CAMICUPositiveDesc' response is 'RASS -3 but clinical team unable to assess CAM-ICU'

Proportion of day shifts on which 'DSCAMICUPositive_CAMICUPositiveDesc' response is 'Not collected' AND responses to ['DSHighestRASS_RASSScoreDesc' AND 'DSLowestRASS_RASSScoreDesc'] are both [-4 or -5]
Proportion of day shifts on which 'DSCAMICUPositive_CAMICUPositiveDesc' response is 'Not collected' AND responses to ['DSHighestRASS_RASSScoreDesc' AND 'DSLowestRASS_RASSScoreDesc'] are both [-2 or -1 or 0 or +1 or +2 or +3 or +4]
Night shift
Proportion of night shifts on which 'NSCAMICUPositive_CAMICUPositiveDesc' is YES OR NO (this is a definite response)
Proportion of night shifts on which 'NSCAMICUPositive_CAMICUPositiveDesc' response is 'RASS -3 but clinical team unable to assess CAM-ICU'
Proportion of night shifts on which 'NSCAMICUPositive_CAMICUPositiveDesc' response is 'Not collected' AND responses to ['NSHighestRASS_RASSScoreDesc' AND 'NSLowestRASS_RASSScoreDesc'] are both [-3 or -4 or -5]
Proportion of night shifts on which 'NSCAMICUPositive_CAMICUPositiveDesc' response is 'Not collected' AND responses to ['NSHighestRASS_RASSScoreDesc' AND 'NSLowestRASS_RASSScoreDesc'] are both [-2 or -1 or 0 or +1 or +2 or +3 or +4]

Rule 6: completeness of pain behaviour data
After rule 1:
Proportion of day shifts on which 'DSCompliance_VentilatorComplianceDesc' response is missing.
Proportion of day shifts on which 'DSCompliance_VentilatorComplianceDesc' response is missing.
Proportion of night shifts on which 'NSCompliance_VentilatorComplianceDesc' response is missing.
Proportion of night shifts on which 'NSCompliance_VentilatorComplianceDesc' response is missing.

Rule 7: indicative sedation guidance compliance
Shifts during which deep sedation was NOT requested
After rule 1:
Select shifts where response to 'DSDeepSedation_YesNoNotCollectedDesc' AND 'NSDeepSedation_YesNoNotCollectedDesc' are both NO or both missing.
For these shifts:
Proportion of each RASS score response to 'DSHighestRASS_RASSScoreDesc' AND 'NSHighestRASS_RASSScoreDesc'
These cumulative data should indicate how common it is for a patient in whom deep sedation was NOT requested for the patient NOT to achieve a highest recorded RASS of -2 or greater during the intervention period.

Rule 8: Correct administration of drugs according to group
After rule 1:
Patients allocated to usual care group
Number/proportion of days on which propofol administered 'Propofol_YesNoDesc'
Number/proportion of days on which dexmedetomidine administered 'Dexmedetomidine_YesNoDesc'
Number/proportion of days on which clonidine administered 'Clonidine_YesNoDesc'
Patients allocated to dexmedetomidine group
Number/proportion of days on which propofol administered 'Propofol_YesNoDesc'
Number/proportion of days on which dexmedetomidine administered 'Dexmedetomidine_YesNoDesc'

Number/proportion of days on which clonidine administered 'Clonidine_YesNoDesc'
Patients allocated to clonidine group
Number/proportion of days on which propofol administered 'Propofol_YesNoDesc'
Number/proportion of days on which dexmedetomidine administered 'Dexmedetomidine_YesNoDesc'
Number/proportion of days on which clonidine administered 'Clonidine_YesNoDesc'
This plot will give an overall indication of compliance without adjustment for the day of study.

Rule 9: correct administration according to group and day of study
Using Rule 8 data:
For each intervention group separately:
For study day 1, study day 2, study day 3 etc plot
Number/proportion of days on which propofol administered 'Propofol_YesNoDesc'
Number/proportion of days on which dexmedetomidine administered 'Dexmedetomidine_YesNoDesc'
Number/proportion of days on which clonidine administered 'Clonidine_YesNoDesc'
This plot will provide an indication of compliance according to the day of intervention (for patients remaining on mechanical ventilation.