Academic and Clinical Central Office for Research and Development

An ICU Sedation Study

Study Protocol

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

Co-sponsors	The University of Edinburgh & Lothian Health Board ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
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PROTOCOL APPROVAL SIGNATURE PAGE

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The undersigned accept the content of this protocol in accordance with the appropriate regulations and agree to adhere to it throughout the execution of the study.

Professor Timothy Walsh **Chief Investigator**		**Signature**	28/8/2018 **Date**
Professor Chris Weir **Trial Statistician**		**Signature**	11/09/2018 **Date**
Dr Fiach O'Mahony **Lead Co-Sponsor Representative**		**Signature**	24 Aug 2018 **Date**

For multi-site trials, the Principal Investigator must sign below to document that the protocol has been read and understood.

Name **Principal Investigator**		**Signature**	**Site**	**Date**

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LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
AE	Adverse Event
APACHE II	Acute Physiology and Chronic Health Evaluation
AR	Adverse Reaction
CAM-ICU	Confusion Agitation Method for delirium in ICU
CHI	Community Health Index
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
COS	Core Outcomes dataset
CPAP	Continuous positive airway pressure
CRF	Case Report Form
CSR	Clinical Study Report
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
ECTU	Edinburgh Clinical Trials Unit
EQ-5D-5L	Euroqual Tool
EudraCT	European Clinical Trials Database
FCI	Functional Comorbidity Index
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HR	Hazard Ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment Agency
IB	Investigator Brochure

ICE-Q	Intensive Care Experience Questionnaire
ICER	Incremental cost-effectiveness ratio
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
IES-R	Impact of Events Scale (Revised)
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
LFT	Liver Function Tests
MAR	Missing At Random
MCID	Minimally Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
MV	Mechanical Ventilation
PI	Principal Investigator
PRE-DELERIC	Prediction of Delirium in ICU patients
NIHR	National Institute of Healthcare Research
NIMP	Non-Investigational Medicinal Product
NIV	Non-invasive Mechanical ventilation
NMB	Net monetary benefit
OR	Odds Ratio
PE	Process Evaluation
PerLR	Personal legal Representative
PIS	Patient Information Sheet
PPI	Patient and Public Involvement
ProLR	Professional Legal Representative
PSS	Personal Social Services

QA	Quality Assurance
QALY	Quality-adjusted Life Year
R&D	Research And Development
RASS	Richmond Agitation Sedation Scale
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RR	Risk Ratio
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC/IB	Summary of Product Characteristics
SOC	Systems Organ Class
SOFA	Sequential Organ Failure Assessment Score
SOP	Standard Operating Procedure
SQAT	Sedation Quality Assessment Tool
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TMoCA	Montreal Cognitive Assessment Tool (Telephone version)
TSC	Trial Steering Committee
VFD	Ventilation Free Days

TRIAL SUMMARY

Trial Title	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
Study Acronym	A2B Trial
Clinical Phase	Phase 3
Trial Design	A randomised, parallel-group, allocation concealed, controlled, open, phase 3 pragmatic clinical and cost- effectiveness trial with internal pilot. Patients will be randomised via a web-based system to receive sedation using dexmedetomidine or clonidine or to continue on the 'usual care' control arm in a 1:1:1 ratio.
Trial Participants	Adult ICU patients within 48 hours of starting mechanical ventilation (MV), expected to require at least 24 hours further MV at randomisation. Exclusions include patients with primary brain injury; post-cardiac arrest; status epilepticus; and peripheral nervous system disease.
Planned Number of Participants	1737
Planned Number of Sites	Approximately 40 Intensive Care Units
Countries Anticipated to be Involved in Trial	UK only
Treatment Duration	Variable
Follow up Duration	6 months
Total Planned Trial Duration	6 months
Primary Objective	The primary outcome is time to successful extubation (in hours post-randomisation) using an internationally agreed definition.
Secondary Objectives	Secondary outcomes *in ICU* comprise: delirium, time to optimum sedation, average sedation depth, mortality, overall sedation quality, ability to communicate with staff, ICU length of stay, pre-defined drug related adverse events. Secondary outcomes *during 6 month follow-up* comprise: mortality, patients' recalled experience of ICU stay, anxiety and depression, post-traumatic stress, cognitive function, health-related quality of life (HRQoL).

Primary Endpoint	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. Note: the use of non-invasive mechanical ventilation (NIV) will be counted as MV; the use of high flow nasal oxygen will not be counted as MV. b) From tracheostomy: time of extubation will be defined as the first time 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.
Secondary Endpoints	1) Length of ICU stay 2) Delirium during ICU stay 3) Sedation and analgesia quality 4) Time to optimum sedation 5) Proportion of patients achieving primary outcome without experiencing agitation 6) Patient's ability to communicate pain and ability to cooperate with care 7) Relative/Partner/Friend assessment of comfort and communication 8) Drug-related adverse events 9) Mortality 10) Patient experience of ICU care 11) Anxiety and depression 12) Post-traumatic stress 13) Cognitive function 14) Health related Quality of Life
IMP(s)	Alpha-2 agonists sedation agents 1) Clonidine 2) Dexmedetomidine 3) Propofol
IMP Route of Administration	IV Infusion
NIMP(s)	N/A

Lay Summary of Trial	Many patients in intensive care (ICU) need help to breathe on a breathing machine and need pain killers and sedatives to keep them comfortable and pain free. However, keeping patients too deeply sedated can make their ICU stay longer, can cause ICU confusion (delirium), and afterwards may cause distressing memories. Ideally, we want to keep patients less sedated, but it is difficult to get the balance of sedation and comfort right. For sedation, most ICUs use a drug called 'propofol' that is good at reducing anxiety and making people sleepy, but is not a pain killer, so additional pain killers are needed. There are two other drugs used less often called 'alpha-2 agonists' that have both sedative and pain-killing actions, which may make it easier for patients to be more awake and comfortable on the ventilator. The two drugs are called clonidine and dexmedetomidine. We want to know whether starting an alpha2-agonist drug early in ICU, and using this instead of propofol as much as possible, can help keep patients more lightly sedated but still comfortable, and whether patients spend less time on the ventilator with these drugs. We also want to know how safe they are and if they can improve important outcomes during ICU stay (like delirium, comfort, and safety) and during recovery (like bad memories, anxiety, and depression). We also want to know if they are value for money. Our trial will include 1737 patients needing to be on a ventilator for at least 2 days. Patients will be allocated to one of three groups by chance. One group will continue to receive propofol; one group will receive dexmedetomidine; and one group will receive clonidine. All patients will receive extra pain relief if needed, and patients in the dexmedetomidine and clonidine groups will continue to receive propofol if they need this in addition. Nurses and doctors will alter the doses of sedation drugs to try and reduce or stop them, but always aiming to have patients lightly sedated and comfortable. We will compare if patients on dexmedetomidine or clonidine come off the ventilator quicker than those just on propofol. We will also see if there was a difference between the groups in the number of people who experienced delirium in ICU, compare how comfortable people were, and measure if participants memories of being in the ICU differed. Patients who were in the trial will be followed up for 180 days afterwards because we want to compare if there were differences in the after-effects of being ill in ICU between the groups. We will ask patients to complete questionnaires that will assess their memories of the ICU experience at 30 and 90 days after entering the trial. At 90 and 180 days, we will also ask patients to complete questionnaires so that we can detect how they feel about their quality of life or if they suffer from anxiety, depression or stress. Alongside this trial, we will be looking at value for money, which is important because clonidine, dexmedetomidine, and propofol costs are quite different. Clonidine, in particular, is relatively inexpensive. We will also find out ICU nurses' and doctors' views on how easy or difficult it was to adjust and use the drugs. This will give us valuable practical information that can be shared with other ICUs, particularly if alpha2-agonists are found to be better and other ICUs want to start using them.

	We have a large experienced team of people guiding this study. They include doctors, nurses, pharmacists, health economists, statisticians, ex-patients and others who have expertise in the study methods. Together they will ensure that the trial runs smoothly, safely and finishes on time.

1. INTRODUCTION

1.1 BACKGROUND

1.1.1 Relationship between sedation practice and patient outcomes

Around 20 million patients worldwide require intubation and MV in ICUs each year.[1] Almost all require ongoing sedation and analgesia for comfort, to relieve pain and anxiety, and to facilitate treatments. International guidelines and professional societies recommend that ICU patients who require MV are kept awake or lightly sedated whenever possible, and at the earliest opportunity during ICU care.[2-4] Observational studies consistently show an association between deep sedation and a range of clinically important adverse short-term outcomes including prolonged ventilation and ICU stay, hospital acquired infections, and greater mortality.[2 5] Deeper sedation is most prevalent during the first 2-3 days of ICU care, when patients typically require high levels of organ support and are subject to most invasive procedures. Observational studies indicate an association between deeper sedation and higher mortality even during early ICU stay.[6 7] Several randomised controlled trials have compared usual care with protocols designed to decrease the incidence of deep sedation. Most used a nurse-led protocol and/or regular interruption of sedation drugs followed by reassessment (a sedation 'hold' or 'break').[8 9] Although results are inconsistent, most support a clinical benefit from lighter sedation especially for reducing duration of MV.

An unproven concern regarding patient wakefulness and/or discomfort during ICU is that it could increase the prevalence of long-term psychological morbidity, such as post-traumatic stress, anxiety, and depression all of which are prevalent among survivors.[10-12] Frightening and delusional memories are common among ICU survivors, and these may increase long-term psychological morbidity.[13 14] However, it is uncertain whether 'light sedation' strategies or the choice of sedative agent can modify this, either directly or by decreasing delirium.[11 13 15]

1.1.2 Implications for healthcare costs

The main driver for ICU cost is duration of ICU stay, which is largely determined by the duration of MV. Other factors such as delirium are also important.[16] ICU costs dominate both short and long-term healthcare costs for critically ill patients.[17 18] Interventions that decrease MV duration or complications associated with prolonged ICU and hospital stay, such as delirium, could be highly cost-effective and relieve bed pressures on ICU services.

1.1.3 Delirium

Delirium is a prevalent complication during critical illness, occurring in >40% of MV patients.[16] Delirium is associated with higher mortality, longer duration of MV and ICU stay, and long-term cognitive decline.[16 19] It remains unproven whether this association is causative, in part because trials designed to decrease delirium in the ICU setting have mostly failed to modify delirium prevalence. The biological mechanisms of delirium pathogenesis are uncertain, but sedative use especially with benzodiazepines significantly increases delirium risk.[2 4 20] Whether the choice of ICU sedative modifies delirium prevalence is controversial. Current guidelines recommend using opioid drugs for analgesia as first-line therapy, introducing the short-acting GABA-agonist propofol for sedation, and avoiding benzodiazepines.[2 3] Alpha-2 agonists are the major alternative sedative class. There is biological

plausibility that these decrease delirium, but evidence is inconclusive and the importance of agent choice unknown.

1.1.4 Current sedation practice in the UK

We recently showed that only 55-65% of patient time in UK ICUs is optimally sedated, defined as the absence of deep sedation, agitation, and pain.[21] Unnecessary deep sedation was present for 20% of MV treatment, primarily during early ICU stay (the first 2-3 days). Conversely, agitation was also prevalent and occurred during 10% of MV treatment. Propofol was the most widely used sedative, and α2-agonist use was infrequent and inconsistent. A recent point prevalence study and survey undertaken in the UK included 214 (91 %) of 235 eligible ICUs.[22] Propofol was the preferred sedative and alfentanil and fentanyl the preferred opioid analgesics. Most ICUs (83%) used combinations of sedatives and analgesics. In the point prevalence study 72% of patients were receiving propofol, but only 8% clonidine and 2% dexmedetomidine. We surveyed UK ICUs in Dec 2016 via the NIHR network (159 responses from different units). We found 58% of ICUs reported using dexmedetomidine, but in less than 10% of patients. More than 90% used clonidine, in up to 25% of patients, but administration route and protocols varied widely. Less than 5% of ICUs had clear protocols defining indications or which agent to use first. Widespread practice variation was clear.
From these data, and our clinical experience, we know that current UK practice is usually to establish sedation and analgesia following intubation with propofol and an opioid and continue this until sedation is no longer clinically indicated (usually at the time of extubation or tracheostomy). At present α2-agonists are mostly used in a small group of selected patients, for example with established agitation and/or delirium, and typically late in ICU stay after usual care has failed to achieve comfortable awake sedation. There is wide variation in the choice of α2-agonist and dosage regimen between clinicians.

1.1.5 Current evidence relating to dexmedetomidine and clonidine for ICU sedation

Three recent systematic reviews summarise current evidence for dexmedetomidine and clonidine compared to usual care in critically ill patients.
A Health Technology Assessment Agency (HTA) review (published 2016) underpinning an HTA commission that funded this trial included 18 RCTs (2489 adult patients).[23] One small low quality trial compared dexmedetomidine with clonidine (N = 70), finding that target sedation was achieved in a higher number of dexmedetomidine treated patients.[23] The remaining 17 trials compared dexmedetomidine with propofol or benzodiazepines, but varied considerably in relation to population, comparators, dose of sedative agents, and outcome measures. Risk of bias was generally high or unclear. Meta-analysis suggested dexmedetomidine did not alter mortality [risk ratio (RR) 1.03, 95% confidence interval (CI) 0.85 to 1.24], but length of ICU stay (mean difference -1.26 days, 95% CI -1.96 to -0.55 days) and time to extubation (mean difference -1.85 days, 95% CI -2.61 to -1.09 days) were significantly shorter among patients who received dexmedetomidine. Dexmedetomidine increased the risk of bradycardia (RR 1.88, 95% CI 1.28 to 2.77). There was no clear evidence that dexmedetomidine reduced delirium, but with a suggestion of a reduced incidence (RR 0.83, 95% CI 0.65 to 1.06) albeit with statistical heterogeneity.

A Cochrane review (last updated January 2015) also summarised the evidence about dexmedetomidine and clonidine, but restricted trial populations to long-term sedation during MV in the ICU (>24 hours).[24] This review included seven RCTs (1624 adult patients) comparing dexmedetomidine with propofol or benzodiazepines. No trials with clonidine were identified. Findings were similar to the HTA review.

Dexmedetomidine reduced mean duration of MV by 22% (95% CI 10% to 33%), and ICU length of stay by 14% (95% CI 1% to 24%). The effect on delirium was similar to the HTA review (RR 0.85; 95% CI 0.63 to 1.14), with statistical heterogeneity. Dexmedetomidine did not alter mortality (RR 0.99; 95% CI 0.79 to 1.24). There was a doubling of bradycardia risk (RR 2.11; 95% CI 1.39 to 3.20).

A review restricted to clonidine (published 2017) reviewed studies in critically ill patients requiring MV.[25] Eight studies (642 patients) were included. There was important and relevant heterogeneity in multiple areas: four trials were in children; the routes of administration varied (6 intravenous and 2 oral); the dosage regimens varied widely (especially for intravenous administration; range 0.88 to 3 µg/kg/hour); and in 7 of 8 trials clonidine was used for adjunctive rather than stand-alone sedation. The only evaluation of clonidine as a single agent was the comparison with dexmedetomidine included in the HTA review. There was no difference in the duration of MV, ICU mortality, or ICU length of stay but quality and precision of estimates were low. In contrast to dexmedetomidine, clonidine was associated with increased hypotension (RR 3.11; 95% CI = 1.64 to 5.87), but not bradycardia (RR 1.34; 95% CI 0.45 to 3.98).

Three additional relevant trials have been published during the past 2 years. Su et al did a double blind placebo controlled RCT in patients aged >65 years admitted to the ICU after elective non-cardiac surgery.[26] Patients received either a short (<24 hours) low dose intravenous dexmedetomidine infusion or placebo (350 per group). The incidence of the primary outcome of postoperative delirium was significantly lower in the dexmedetomidine group (9% versus 23%; odds ratio [OR] 0.35; 95% CI 0.22-0.54). However, this population had low illness severity, only 55% were MV, and sedatives were only used in 51% of patients. The time to extubation among intubated patients was also very short (mean 6.9 hours (control) versus 4.6 hours (dexmedetomidine). These data support effectiveness in reducing delirium among elective low risk post-surgical patients, but the population was not relevant to that defined in the HTA brief or proposed in the current proposal. Reade and colleagues did a small double blind placebo-controlled RCT in Australian ICUs.[27] The population was 74 adult patients in whom extubation was considered inappropriate because of the severity of agitation and delirium, and most patients had been MV for >2-3 days at randomisation. Dexmedetomidine or placebo was titrated to achieve physician-prescribed sedation goals for up to 7 days. The primary outcome of ventilator-free hours in the 7 days following randomisation was increased by dexmedetomidine (median 144.8 vs 127.5 hours; P=0.01)). There was a reduced time to extubation (median difference 19.5 hours (95%CI 5.3 to 31.1 hours); P<0.001)) and quicker resolution of delirium (median difference 16.0 hours (95%CI 3.0 to 28.0 hours; P=0.01)). Although a small study, this trial suggests that dexmedetomidine may reduce time to extubation in a sub-population of patients with difficult agitation after 2-3 days of usual care management. Finally, Kawazoe et al recently published an open-label, RCT conducted in 8 ICUs in 201 consecutive adult patients with sepsis requiring MV for at least 24 hours.[28] Patients were randomized to receive either sedation with dexmedetomidine (n = 100) or usual care without dexmedetomidine (n = 101). Other agents used in both groups were fentanyl, propofol, and midazolam. The trial hypothesis was based on a *post-hoc* analysis of a trial comparing dexmedetomidine with lorazepam in ICU patients in which a mortality benefit was observed in a sub-population with sepsis (84% versus 59%).[29] The authors powered their trial for a large absolute mortality difference (20%) with only 80% power (80% versus 60%) and also had co-primary outcomes (mortality and ventilator-free days (VFDs; over 28-days)). Mortality was not significantly different between the groups (22.8% (dexmedetomidine) vs 30.8% (usual care); hazard ratio (HR) 0.69; 95% CI 0.38-1.22; *P* = 0.20), but the absolute difference (8%) could be important if confirmed

in an adequately powered RCT. There was also a trend to reduction in ventilation time (dexmedetomidine median 20 VFDs; control group median 18 VFDs). Sedation quality was better in the dexmedetomidine group.

1.2 RATIONALE FOR STUDY

Our project is in response to an HTA commissioned brief (16/93). This noted the shift from benzodiazepine towards propofol-based sedation, but highlighted growing use of the α2-agonists clonidine and dexmedetomidine, but without clear evidence for effectiveness and cost-effectiveness in the NHS (particularly for clonidine). A key recommendation of the systematic review underpinning the brief was that *'well-designed RCTs are needed to assess the use of clonidine in ICUs'.* Research concurrently comparing dexmedetomidine and clonidine is especially needed because: widespread practice variation exists within UK ICUs, clonidine is unlicensed for ICU sedation, the pharmacokinetics and dynamics of these agents differ considerably which could influence relative risk-to-benefit profiles, and the cost differential is substantial.

Dosage regimens based on patient weight are well established for dexmedetomidine. We estimate that the average daily dose used in our trial will be around 0.7μg/kg/hour (1200μg/day), which at current NHS list price will cost around £94 per day. In contrast, for clonidine we estimate an equipotent drug cost (1μg/kg/hour (1700μg/day)), will cost only around £5-10 per day. If both α2-agonists were superior to usual care with equivalent safety and effectiveness, the x10-20 fold lower cost of clonidine would represent very substantial cost savings to the NHS. For comparison, we estimate daily mean propofol costs are currently around £5-10.

Improving ICU sedation practice and delirium management is also a priority for patients. In the James Lind/Intensive Care Foundation patient/professional collaboration 'improving agitation and delirium management' was a top three, and 'enhancing patient comfort during Intensive Care' a top 10 priority (see: www.jla.nihr.ac.uk/priority-setting-partnerships/intensive-care). Our work with PPI colleagues has strongly supported the need for this trial.

We searched clinical trial databases for ongoing large trials. We found no trials in which dexmedetomidine and clonidine are being concurrently evaluated. For clonidine, we found no large trials comparing clonidine to usual care in MV ICU patients. For dexmedetomidine, we identified two large trials. The SPICE III trial (NCT01728558) is an international trial (N = 4000) led from Australia, comparing dexmedetomidine with usual care. The primary outcome is mortality, and secondary outcomes include delirium and duration of MV. An important difference between SPICE III and the current trial is that recruitment to SPICE III requires randomisation within 12 hours, which in many cases may exclude patients considered too unstable or not suitable for early 'light' sedation by clinicians, many of whom subsequently experience prolonged ICU stays. Our design aims to include a higher proportion of MV patients by extending the recruitment period to up to 48 hours and allowing safe transition to α2-agonists in patients with cardiovascular instability (for example, requiring vasopressor support); we believe this will increase generalisability. The MENDS II trial (NCT01739933) is a US based trial (N = 530) comparing dexmedetomidine with propofol in MV septic patients. The primary outcome is delirium/coma free days with a range of secondary outcomes. This trial is restricted to patients with infection. These trials will provide new data about dexmedetomidine, but none for clonidine.

We have designed our trial to directly compare dexmedetomidine with clonidine in the context of UK practice and provide both clinical and cost-effectiveness comparisons with current practice. The greater UK use of clonidine than dexmedetomidine further highlights this need. Our 'usual care' group will receive propofol, which recent surveys indicate is the most widely used sedative in UK ICUs.

2. STUDY OBJECTIVES

2.1 OBJECTIVES

Our overall objective is to determine whether the α2-agonists clonidine or dexmedetomidine (or both) are clinically and cost-effective in MV ICU patients compared to current usual care. We also aim to determine which agent is most clinically effective and offers best value to the NHS given important differences in properties and cost between the drugs.

2.1.1 Primary Objective

Our primary objective is 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.

2.1.2 Secondary Objectives

Secondary objectives are to assess the effects of dexmedetomidine and clonidine, compared with usual care, on other **clinical**, **patient-centred**, and **economic** outcomes in the ICU, hospital, and during up to 6 months follow up post-randomisation. These will address all outcomes specified in the HTA brief, and some additional outcomes suggested by core outcome datasets, biological plausibility for clinically important effects, and advice from PPI collaborators co-developing the project.

2.1.2.1 Clinical and Person-centred objectives

During ICU stay we will compare rates and duration of delirium, time to optimum sedation, average sedation depth, the ability of patients to communicate with staff and relatives, the quality of sedation, and duration of ICU stay. We will also compare safety based on pre-defined adverse events relevant to sedation and α2-agonist agents.

Following discharge from the ICU we will compare patient outcomes for which sedation and ICU experience may be on the causal pathway, namely patients' memories of their ICU stay, psychological wellbeing, and cognitive function. We will follow up patients for 6 months for survival, HRQoL, and healthcare resource use.

2.1.2.2 Economic evaluation

We will include a detailed cost-effectiveness analysis; we will compare costs and cost-effectiveness from an NHS and personal social services (PSS) perspective.

2.1.2.3 Process evaluation

The trial, by necessity, is a complex healthcare intervention trial evaluating a novel class of sedative agents. We will include a process evaluation, consistent with Medical Research Council (MRC) guidance[30 31], to understand how α2-agonists were used in the trial, how this may explain the results, how best to use the drugs safely in a heterogeneous population, and how to implement trial findings into practice.

2.1.2.4 Mechanistic study

There is some evidence that in addition to sedative effects, α2-agonists have anti-inflammatory and immune modulating properties. In a sub-group of patients in whom consent is obtained we will collect two blood samples to study whether α2-agonists alter inflammation in comparison to current usual care.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

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.

   Note: the use of non-invasive mechanical ventilation (NIV) will be counted as MV; the use of high flow nasal oxygen will not be counted as MV. CPAP support not exceeding 5cm H_2O via mask will not be counted as MV.

b) From tracheostomy: time of extubation will be defined as the first time 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.

The 48 hours of successful extubation is included in the definition to exclude patients with failed extubations, i.e. those patients requiring reintubation within 48 hours. This occurs in 5-10% of ICU patients. If a re-intubation occurs within this time window it is likely to be related to the original episode of respiratory failure requiring intubation; in contrast if beyond 48 hours it is likely to represent a new episode of respiratory failure. This definition is a core outcome in the MV outcome set (COS).

2.2.2 Secondary Endpoints

Secondary outcomes are shown in table 1, together with the measurement tool and timing.

Table 1: secondary outcomes, measurement tool or method, and timing.

Outcome	Measurement tool or method	Timing
Length of ICU stay	Days randomisation to ICU discharge	ICU discharge
Delirium during ICU stay	Confusion-Agitation method for ICU (CAM-ICU)[32] Occurrence during ICU stay (binary outcome) and delirium days during ICU stay (continuous outcome)	Twice daily during ICU stay
Sedation and analgesia quality	Richmond Agitation and Sedation Scale (RASS) Plots of lowest and highest RASS score over time Sedation Quality (based on Sedation Quality Assessment Tool (SQAT).[33] Defines four states for sedation quality: 1. Overall optimum sedation (no agitation; no unnecessary deep sedation; no pain behaviour) 2. Agitation	Four hourly during mechanical ventilation Derived from daily sedation and analgesia quality data during mechanical ventilation in ICU

	3. Unnecessary deep sedation (RASS -4/-5 without clinical indication) 4. Pain (presence of pain behaviour based on limb movement and ventilation compliance)	
Time to first Optimum sedation	Hours from randomisation to first RASS score of -2 or greater Days from randomisation to first day with optimum sedation (based on SQAT definition)	Based on daily sedation and pain assessments
Patients' Ability to Communicate Pain and Ability to Cooperate with Care	Binary assessment for each 12 hours nursing shift completed by bedside nurse (based on overall assessment of period of care). Answer to the following questions: 1. Was your patient able to communicate pain? 2. Was your patient able to cooperate with care?	Twice daily during mechanical ventilation in ICU
Relative/partner/friend *(PerLR)* assessment of comfort and communication	Relative/partner/friends response to the following questions (based on their opinion at time of assessment): 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?	Daily at a visit
Drug-related adverse events	Bradycardia; hypotension; hypertension; cardiac arrhythmias; cardiac arrest (defined in protocol)	Daily during drug administration
Mortality	Medical records check	ICU, hospital, 90 and 180 days
Patient experience of ICU care	Intensive Care Experience Questionnaire (ICE-Q)[34] Provides numeric score in four domains: 1. Awareness of Surroundings 2. Frightening Experiences 3. Recall of Experiences 4. Satisfaction with Care	30 and 90 days post ICU discharge
Anxiety and depression*	Hospital Anxiety and Depression Scale (HADS) questionnaire	90 and 180 days post ICU discharge
Post-traumatic stress*	Impact of Events Scale-revised (IES-R)	90 and 180 days post ICU discharge
Cognitive function*	Montreal Cognitive Assessment Tool (Postal or Telephone version) (TMoCA)	90 and 180 days post ICU discharge
Health-related Quality of Life	Euroqol tool (EQ-5D-5L)	Recalled HRQoL prior to hospital admission; 30, 90 and 180 days

In addition to these clinical endpoints, a mechanistic sub-study will measure inflammation and immune function and compare whether this is different between the three groups.

3. STUDY DESIGN

3.1 HYPOTHESIS

The primary hypothesis is that sedation with α2-agonists will decrease the time to extubation in adult MV ICU patients compared with usual care.

3.2 TYPE OF STUDY

This is a randomised, parallel-group, allocation concealed, controlled, open-label, phase 3, pragmatic, clinical and cost-effectiveness trial with an internal pilot.

After intubating and stabilizing patients, we will randomise patients (1: 1: 1) as early as possible to receive sedation-analgesia based on clonidine *or* dexmedetomidine *or* to continue on propofol (usual care) plus opioid analgesia as required.

3.3 'PICO' QUESTION

Population:	Adult MV ICU patients within 48 hours of initiation of MV
Interventions:	A: Sedation based on clonidine ± opioid analgesic
	B: Sedation based on dexmedetomidine ± opioid analgesic
Comparator:	Usual care sedation with propofol ± opioid analgesic
Outcome (primary):	Time from randomisation to successful extubation

3.4 DESIGN AND ANALYTIC/CONCEPTUAL FRAMEWORK

Our analytic framework has been devised to address all the important questions in the HTA brief in a staged hierarchical fashion.[35 36] This enables a highly efficient trial design that maximises efficiency and restricts overall Type 1 error rate to below 5%. Importantly, the trial will determine whether α2-agonists are superior to current practice but also, if superiority is found, which agent is most clinically and cost-effective. We propose three analytic stages, where progression to hypothesis testing in sequential stages is dependent on preceding results:

Stage 1 will test whether dexmedetomidine or clonidine (or both) are superior to propofol (usual care). If neither test is significant we consider further testing is not important because we will have fulfilled our main objective.

Stage 2 will test whether dexmedetomidine is superior to clonidine or if clonidine is non-inferior to dexmedetomidine (if stage 1 testing is significant). This stage is important because of the large differences in cost between the drugs.

Stage 3 will test if clonidine is superior to dexmedetomidine, but only if clonidine has been shown to be non-inferior in stage 2. A more detailed description is provided in section 11.

3.5 PRE-PLANNED SUB-GROUP ANALYSIS

We plan sub-group analyses for patients with:

1. sepsis *(because of possible beneficial anti-inflammatory effects from α2-agonists, which may be most pronounced in sepsis)*[29 37]
2. higher delirium risk as defined by the validated PRE-DELIRIC delirium risk prediction score, using the version assessing at 24 hours post-admission[38] *(because α2-agonists may decrease delirium, which might modify many of the other outcomes)*

3. organ dysfunction at randomisation *(because this could differentially alter the safety profile of the three groups)*

These analyses will be exploratory.

3.6 BLINDING

This will be an *open-label* trial. Issues that were considered justification for an open-label trial were:

1. Dynamic adjustment of blinded drugs with different pharmacokinetics and dynamics would be extremely challenging to clinical staff (and be potentially unsafe) in sick patients.
2. The cost to supply blinded drugs 24/7 to ICUs was extremely high.
3. After discussing the pros/cons of blinding with PPI collaborators, they felt a more relevant and safe assessment of the drugs was likely if clinicians were aware of allocation.
4. The co-applicants were concerned that blinding might increase enrolment bias and slow recruitment, because of safety concerns (this may have contributed to low recruitment in a previous trial of clonidine in paediatric ICUs[39]).
5. Overall, it was thought that an open-label trial would provide a population and intervention with greater generalisability, and not compromise internal or external validity.

Individuals drafting and updating the trial analysis plan will be blinded from any outcome data identifying intervention group until the data base is locked. Outcome assessors for the post hospital discharge outcomes will be concealed from group allocation. It will not be feasible to blind outcome assessors for outcomes measured during the ICU stay.

3.7 STUDY DETAIL

3.7.1 Internal pilot and overall recruitment strategy

Participants will be recruited from approximately forty sites and we aim to set these up at an average rate of 3 sites per month over the first 14 months of trial recruitment. The internal pilot study will comprise those sites recruiting from months 4-9 (6 months). Our target recruitment rate is around 2 patients per month per centre. This assumes 40-50% recruitment of eligible cases, which is similar to our recent sedation and delirium trials.[21 40]

With this approach, during the internal pilot we aim to have 3, 6, 9, 12, 15, and 18 sites contributing over months 4-9. Assuming, on average, sites are ready to contribute by the middle of the month, they will generate 1.5, 4.5, 7.5, 10.5, 13.5 and 16.5 centre-months (total 54 centre months) during this internal pilot period. At an average of 2 recruits per centre per month, the internal pilot should achieve around 100 randomisations.
Continuing to add 3 sites per month after the end of the internal pilot the aim is to reach 40 sites by recruitment month 14 (another 239 centre months), and steady state of 40 sites for the final 16 months of recruitment (640 centre months).

The total centre months will be 933 over a total recruitment period of 30 months. This requires a mean 1.9 recruits per centre per month assuming the staged set-up is achieved.

For the internal pilot, we will use a Green-Amber-Red statistical approach. Assuming each centre month follows an independent identically distributed Poisson distribution

with mean 1.9, the total will be approximately normally distributed with mean 100 and SD 10. *'Green'* will be within 2 standard deviations of 100 i.e. if we have randomised 80 or more we will continue unchanged. *'Amber'* will be within 2-4 standard deviations i.e. if we have recruited 60-79 we will consider adding new centres and/or extending the recruitment window. *'Red'* will be triggered with <60 randomisations and serious consideration, in conjunction with HTA, around stopping the study.

During the internal pilot we will audit screening logs, recruitment, reasons for exclusion and protocol compliance. We will also measure the completeness of datasets, and the completeness of the primary outcome, which we anticipate should be >95% (the only exceptions will be patients transferred to other ICUs before reaching the primary outcome or withdrawing). Process evaluation data during this phase will be important and will establish protocol fidelity, inform clarifications/modifications, and facilitate efficient set-up in other sites. We will also optimise the educational materials for use in the wider site recruitment and set-up.

3.7.2 Centres

The trial will be undertaken in approximately 40 UK ICUs with clinical equipoise for using either α2-agonist as per protocol. Participating centres must use sedation and weaning practices consistent with the protocol, which represents best practice. We will select ICUs from those who have successfully recruited to recent UK multicentre critical care trials. Selection will occur through existing trial networks and the NIHR critical care network.

4. STUDY POPULATION

4.1 TARGET POPULATION

The target population are critically ill patients requiring MV, recruited as early during ICU stay as possible, with an anticipated total requirement for MV of *at least* two days. Patients expected to require short periods of MV are unlikely to experience clinically or cost-effective benefits, especially for the primary outcome.

Patient consent and randomisation is unlikely in most cases to be feasible prior to endotracheal intubation, and attempts to obtain it might delay life-saving emergency care. Screening will only be undertaken in patients after MV is started in the ICU.

Alpha2-agonists are not appropriate as single agents for intubation and early sedation for most acutely ill patients due to their pharmacokinetic and pharmacodynamic properties and cardiovascular side effects. Anaesthesia to undertake endotracheal intubation and establish initial ICU sedation-analgesia will follow current usual care (almost always intravenous propofol or other anaesthetic induction agent, and opioid). It is anticipated that many patients will be established on MV prior to ICU admission.

4.2 NUMBERS OF PARTICIPANTS

The total number of participants is 1737 (579 per trial group).

4.3 INCLUSION CRITERIA

1. Patient requiring MV in an ICU
2. Aged 18 or over
3. Within 48 hours of starting MV in an ICU

4. Requiring sedation with propofol
5. Expected to require *a total* of 48 hours of MV or more in ICU
6. Expected to require a further 24 hours of MV or more *at the time of randomisation* in the opinion of the responsible clinician

Note: Criteria 5 and 6 are intended to ensure that all participants require at least 48 hours of MV in the ICU and that all patients receive at least 24 hours of the allocated intervention after randomisation.

4.4 EXCLUSION CRITERIA

The following exclusions will apply

1. Acute brain injury (traumatic brain injury; intracranial haemorrhage; ischaemic brain injury from stroke or hypoperfusion)[1]
2. Post-cardiac arrest (where there is clinical concern about hypoxic brain injury)[1]
3. Status epilepticus[1]
4. Continuous therapeutic neuromuscular paralysis at the time of screening or randomisation[1]
5. Guillain-Barre Syndrome[1]
6. Myasthenia gravis[1]
7. Home ventilation[1]
8. Fulminant hepatic failure[2]
9. Patient not expected to survive 24 hours by responsible clinician
10. Decision to provide only palliative or end-of-life care
11. Pregnancy
12. Known allergy to one of the study drugs
13. Untreated second or third degree heart block[3]
14. Transferred from another Intensive Care Unit in which MV occurred for >6 hours
15. Prisoners
16. Enrolled on another CTIMP
17. Previously enrolled on the A2B Trial

Note:

[1]For these conditions the neuromuscular condition will dominate the primary outcome unrelated to sedation practice

[2]Uncertain pharmacokinetics of α-2 agonist; potential for cerebral oedema mandating deep sedation

[3]Patients with treated heart block, for example with a pacemaker, are eligible for inclusion

4.5 CO-ENROLMENT

Co-enrolment to other studies will be allowed where the PIs and/or trial management teams have considered the scientific and practical implications of co-enrolment and agreed that co-enrolment is permitted, referring to UK guidance for critical care trials and/or local standard operating procedures. Co-enrolment to other concurrent Clinical Trials of Investigational Medicinal products (CTIMPs) will not be permitted. The option for co-enrolment will only apply where agreement has been reached between the two studies prior to an individual participant being considered for inclusion, and this has been documented in the trial materials and site files.

5. PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Participants will be identified by clinical ICU teams in collaboration with research teams using regular screening of patients on a daily basis, or as often as feasible, from the time of ICU admission.

5.2 CONSENTING PARTICIPANTS

Patients will lack mental capacity at the time of screening and enrolment as a result of critical illness and the effects of sedative drugs. The appropriate approaches to consent according to UK law will be used, approaching Personal and Professional legal representatives. The use of the "emergency provision" will be used in selected patients for deferred consent when a legal representative is not available within 2 hours of meeting eligibility criteria according to procedures agreed with the ethics committees.

5.2.1 Informed Consent

All patients who are potentially eligible for the trial will be critically ill and receiving sedative drugs by continuous infusion. They will therefore lack mental capacity. The Investigator is responsible for ensuring agreed consent procedures are followed before any protocol specific procedures are carried out. These are detailed in the flowchart in appendix 2. The process for obtaining informed consent must be documented in the patient's medical records.

5.2.2 Consent process

In clinical trials that include patients with diminished capacity requiring treatment in a critical care environment, a common approach is to seek declaration of agreement from a personal consultee or personal legal representative and once the participant has regained capacity, to seek retrospective informed consent. For this trial, however, any delays in allocation to the treatment group may decrease the potential effectiveness of the intervention and would also mean the intervention was not being evaluated in the way it would be used in routine care. This issue arises because sedation is an early essential intervention following mechanical ventilation, and the benefits of alpha2 agonists may be from early use.

In the majority of participants a legal representative will provide consent prior to randomisation. The A2B trial also allows deferred consent for patients in whom a legal representative is not present in the ICU or does not attend within 2 hours from the time patients become eligible. This model has been developed in conjunction with the Patient and Public coinvestigators and collaborators.

In ICUs, research teams are integrated into clinical teams and/or work closely with them. Once the clinical and/or research teams have identified a patient is eligible for enrolment in the trial, the aim is to randomise the patient and start the allocated intervention as soon as possible. This will maximise the potential benefit from the intervention and ensure it is evaluated in the manner it would be used in routine care. It is relevant that both intervention drugs are already widely used in UK ICUs, and the comparator is current usual care.

There will be three scenarios through which randomisation may occur:

Patient's personal legal representative (PerLR) is present at the time eligibility occurs or attends within the next 2 hours.

In this situation the PerLR will be consulted and provided with the Patient Information Sheet (PIS) sheet. After the opportunity to ask questions of the research team,

patients for whom consent is provided will be randomised. This is the default approach to be used wherever possible.

Patient's personal legal representative (PerLR) is not present at the time eligibility occurs and does not attend within 2 hours of fulfilling eligibility criteria, but a professional legal representative (ProfLR) is identified who is immediately available after two hours.
In this situation the ProfLR will be consulted. If the ProfLR provides consent the patient will be randomised.

Patient's personal legal representative (PerLR) is not present at the time eligibility occurs and does not attend within 2 hours of fulfilling eligibility criteria and a professional legal representative (ProfLR) is NOT immediately available after two hours from meeting eligibility criteria.
In this situation deferred consent will be used under the 'emergency provision' of the Medicines for Human Use (Clinical Trials) Regulations. This will enable the patient to be randomised to the trial intervention at a time when the intervention is most likely to be associated with benefit, and is the time at which the intervention (alpha2-agonist based sedation) would be used in routine care.

These situations may arise because relatives are frequently present for a significant time around the period of admission and stabilisation in ICU, but frequently then need to rest before returning and may have recently left the ICU around the time of eligibility. This period is frequently also during night-time hours. A delay in approach of more than 2 hours is likely to result in randomisation occurring after at least 6-12 hours, because the PerLR will require time to be approached and consider consent, and then randomisation procedures undertaken and treatment started. This delay is important in this trial because early deep sedation, even during the first 24-48 hours, has been strongly associated with worse patient outcomes. A key goal of sedation with α2-agonists is to reduce early deep sedation (during the first 24-48 hours).

If deferred consent or ProfLR consent is used, the PerLR will be consulted and provided with the PIS at the earliest possible time following randomisation, and consent requested to continue in the study. If following deferred consent available information suggests that the patient does not have a PerLR who will be able to attend, then a Professional Legal Representative (ProfLR) opinion will be sought at the earliest opportunity and consent requested to continue in the study.

If enrolment and randomisation have occurred under emergency provisions, but the PerLR or the ProfLR dos not provide consent when consulted, the patient will be withdrawn from the study and continuing care will be follow usual care according to the direction of the clinical team.

5.2.3 Obtaining consent from participants who regain capacity
Once a patient has regained capacity, they will be approached by an authorised member of the site research team for informed consent to continue in the trial. This will be done as soon as practically possible. A Participant Information Sheet (PIS) will be provided to the patient by an authorised staff member. The PIS will provide information about the purpose of the study, what participation means for the patient (e.g. follow-up questionnaires at 90 and 180 days), confidentiality and data security, and the future availability of the trial results.
Timing of approach for informed consent from the patient:

- The majority of enrolled patients will have their invasive mechanical ventilation discontinued through removal of the endotracheal tube, prior to

them having demonstrated capacity and will therefore only be approached for informed consent following collection of primary outcome data.

- A small proportion of enrolled patients (estimated to be <10%) will have a tracheostomy performed as part of their routine clinical care and may be able to demonstrate capacity and be approached for informed consent prior to the primary outcome endpoint having been reached.
- A minority of enrolled patients will have an endotracheal tube in place yet still be able to demonstrate capacity and be approached for informed consent prior to the primary outcome endpoint having been reached.

In the unusual event that a patient is not able to be approached for consent to remain in the trial prior to hospital discharge, the local research team with seek written consent at the time of 30 day follow-up (via post).

A Consent Form will be provided indicating that: the information given, orally and in writing, has been read and understood; participation is voluntary and can be withdrawn at any time without consequence; and that consent is given for access to medical records for data collection. The Consent Form will cover consent for use of data already collected for the trial, as well as ongoing data collection and follow-up. Patients will be given time to read the PIS and have an opportunity to ask any questions they may have about participation in the A2B Trial. After verifying that the PIS and Consent Form are understood, the person seeking consent will invite the patient to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the patient, a copy placed in the patient's medical notes and the original kept in the Investigator Site File. If the patient is unable to physically sign the Consent Form (e.g. due to weakness, reduced dexterity), an independent witness can sign on their behalf.
Patients and their representatives will only be approached by authorised staff members who have received training in A2B Trial processes and procedures and in Good Clinical Practice (GCP). The recruitment process will be done in such a way to mitigate any potential undue influence or coercion. No therapeutic promises will be made.

Information about the A2B trial will be displayed on posters in waiting areas. This promotes understanding of the study in anticipation of the participants regaining capacity and will provide some background for the personal consultees that may inform their discussions with the participant when they have regained capacity and are considering providing informed deferred consent.

5.3 SCREENING FOR ELIGIBILITY

All patients admitted to the participating ICUs will be screened for eligibility. Screening will start as early as possible post-ICU admission, ideally within 6 hours. The maximum benefit from the interventions is likely to occur if patients commence treatment as early as possible after starting mechanical ventilation and sedation. Specifically, deep sedation during the first 1-2 days in the ICU is associated with worse outcomes including higher mortality. The interventions aim to decrease deep sedation and enable patients to be awake and comfortable. Screening will continue for up to 48 hours following the start of MV in the ICU. Periods of MV prior to ICU admission, for example in the operating theatre or the emergency department, will not count as part of the 48 hours recruitment window. Patients can be screened on multiple occasions during the 48 hours if appropriate

A screening log will be maintained at each site including reasons for non-enrollment to enable reporting according to the CONSORT statement.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Ineligible patients who are not randomised will continue to receive usual care as directed by the clinical care team.

5.5 RANDOMISATION

5.5.1 Randomisation Procedures

Eligible patients will be randomised by staff delegated to undertake this task at the earliest opportunity, but within 48 hours from the start of MV in the ICU. Randomisation should be undertaken immediately after consent is obtained from a legal representative, or when deferred consent is used if this is triggered.

The individual undertaking randomisation will be responsible for assigning patients to the randomisation group and communicating this to clinical teams. The aim is to randomise eligible patients as close to the time sedation is used clinically, which in routine care is continuously from the time of MV. Participants will be randomised to the trial using a remote web-based randomisation system.

5.5.2 Treatment Allocation

Randomisation will use a remote web-based randomisation system to allocate patients in a 1:1:1 ratio to the three trial groups using permuted blocks (randomly arranged sizes of 3, 6, 9, 12) stratified by centre. We will not stratify for any other variables to simplify enrolment and decrease time delays. The allocation sequence will be stored on a secure server and concealed from all personnel involved in the trial, and will be generated by a clinical trials unit member of staff who is not involved in clinical care.

5.6 INTERVENTION GROUPS

Patients will commence intravenous infusion of open-label study drug according to a weight-based dose regimen (see appendix 1) as early as possible post-randomisation, and within a maximum of two hours.
Bedside clinical staff will transition patients to achieve sedation with the allocated α2-agonist agent as quickly as clinically feasible and safe, to replicate the way these drugs would be used in routine practice. Additional opiate will be used for analgesia using clinical judgement. Once established, additional propofol will only be used when the maximum α2-agonist dose is reached or because cardiovascular or other side-effects limit dose escalation.

5.6.1 Dexmedetomidine group

For dexmedetomidine, the regimen will follow the manufacturer's guidance and regimens used in previous trials. Dexmedetomidine will be up and down titrated against sedation targets set by clinical staff and reviewed at regular intervals, and documented at least daily. 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}. Lower starting doses will be used at clinical discretion for patients with cardiovascular instability.

5.6.2 Clonidine group

For clonidine, the regimen is 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. Clonidine will be up and down titrated against sedation targets set by clinical staff and reviewed at regular intervals, and at least daily. 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^{-1}. Lower starting doses will be used at clinical discretion for patients with cardiovascular instability.

5.7 USUAL CARE GROUP

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.

5.8 DURATION OF INTERVENTION

The intervention period will continue until the patient is weaned from MV and sedation in the ICU. The timing of discontinuation of sedative agents will be at the discretion of the clinical team. This may include discontinuation prior to ending MV (for example in patients who have undergone tracheostomy), or discontinuation after extubation (for example in agitated or delirious patients).

The intervention period will last for whichever of the following occurs first;

- The patient is successfully extubated according to the definition of the primary outcome and sedative drugs have been discontinued
- The patient dies during MV in the ICU
- The patient is transferred to another non-participating ICU prior to achieving the primary outcome, or
- 28 days of MV in ICU have been required without achieving the primary outcome.

Once the primary outcome has occurred any further periods of sedation, for example after later reintubation or ICU readmission, will follow usual care practice.

If the patient is re-intubated before achieving the primary outcome, they should continue the group allocated treatment until the primary outcome is successfully achieved.

If patients are transferred to another ICU that is participating in the trial, the intervention and follow up will be continued wherever feasible.

5.9 MANAGEMENT DURING INTERVENTION PERIOD

5.9.1 Titration to sedation targets

The default sedation target will be the most awake and comfortable state considered safe by clinical staff. Bedside clinical nurses will be asked to document, for each 12 hours nursing shift, whether there is a clinical indication for deep sedation (after consultation with medical staff). If there is no requirement for deep sedation, the <u>least awake</u> target sedation state will be 'brief eye contact made in response to voice'. This is equivalent to a Richmond Agitation Sedation Scale (RASS) score of -2[41]. Targeting a sedation state at this level or more awake throughout ICU care is considered best practice, was used in most previous trials, and is generally considered 'light' sedation.[2 3]

Bedside ICU nurses will be asked to document RASS score every 4 hours while patients are receiving interventions up to the point of achieving the primary outcome. A bedside algorithm will recommend changes to sedation drug (according to group allocation) based on responses to RASS scores. When patients do not make brief eye contact to voice and there is no requirement for deep sedation, clinical nurses will be asked to decrease propofol dose (if administered in any intervention group) or decrease the intervention drug dose if no propofol is being administered (according to the dose administration algorithm).

All patients will receive opioid infusions for analgesia as clinically indicated at the discretion of clinical teams. Patients that require additional sedation, for example for agitation, will receive additional propofol as required, but only once the maximum tolerated dose of intervention drug is reached.

5.9.2 Weaning from mechanical ventilation

All patients should have regular assessments and attempts to wean and discontinue mechanical ventilation throughout treatment. The approach used in individual ICUs and patients will not be mandated, but should follow the following 'best practice' principles:

- Continuous or regular attempts to decrease sedation drug dose to achieve the most awake and comfortable state considered safe by clinical staff, with a minimum target of 'brief eye contact made in response to voice'.
- Regular sedation interruption or hold if appropriate (regular or protocolised sedation interruption is not required unless local practice)
- Early attempts to transition patients from mandatory ventilation modes (for example Synchronised Intermittent Mandatory Ventilation, Pressure Control Ventilation) to spontaneous modes (for example Pressure Support Ventilation or Assisted Spontaneous Breathing)
- Regular attempts to decrease mechanical support from the ventilator, for example by reducing pressure support or undertaking spontaneous breathing trials.
- Regular assessment of readiness for extubation by clinical teams.

5.10 WITHDRAWAL OF STUDY PARTICIPANTS

Participants or their representatives, if appropriate, are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case record form, if possible. The participant will have the option of withdrawal from:

(i) study medication with continued study procedures and collection of clinical and safety data

(ii) all aspects of the trial but continued use of data collected up to that point or

Patients who are withdrawn during the intervention and participants who do not provide consent to remain in the trial after regaining capacity will not be replaced, as the sample size allows up to 5% loss to follow-up before the primary outcome. However, rates of withdrawal will be monitored, especially in relation to withdrawal following deferred consent when this approach is used. If withdrawal rates are high a strategy to address this will be agreed to ensure study power is maintained.

5.11 STOPPING CRITERIA

There are no pre-defined statistical stopping criteria in this trial. The DMC will provide oversight of the trial and make their recommendations to the Trial Steering Committee.

6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1 ALPHA-2 AGONIST DRUGS

Alpha-2 agonists induce sedation by dose-dependent decrease in activity of noradrenergic neurons in the brain stem via post-synaptic receptor-mediated inhibition.[42] This increases the activity of inhibitory gamma-aminobutyric acid (GABA) neurons, resulting in inhibitory neurotransmitter release, especially via GABA neurones. This mechanism contrasts with established sedatives, propofol and benzodiazepines, which are direct GABA agonists in the central nervous system. Unlike GABAergic sedatives, α-2 agonists have analgesic properties, which can reduce opioid requirements. Analgesia probably occurs via multiple sites, but primarily at the level of the spinal cord.[43]

Alpha-2 agonists can have biphasic cardiovascular effects especially after loading or bolus dosing.[43] Initial hypertension can occur due to activation of receptors on peripheral vascular smooth muscle. More frequent is hypotension and bradycardia due to centrally mediated sympathetic outflow inhibition and vagotonic actions. Cardiovascular instability is more likely in shocked and hypovolaemic patients and when concurrently administered with other anaesthetic agents. However, α2-agonists have minimal negative inotropic effects and may increase coronary blood flow. These effects explain why bolus doses or rapid changes to infusion rates are generally avoided in critically ill patients, or should be used with caution. The cardiovascular effects also explain the relative contraindication in patients with untreated second/third degree heart block. Alpha-2 agonists have minimal effect on respiratory function, in contrast to GABAergic agents which can decrease respiratory drive and respiratory muscle activity. Other effects include diuresis, dry mouth, constipation, and ileus. After prolonged administration, an acute hypertensive withdrawal syndrome after rapid discontinuation is described, mainly following long-term clonidine treatment for hypertension.

6.1.1 Dexmedetomidine

Dexmedetomidine is a highly selective α2-agonist with a α2:α1 receptor selectivity ratio of 1620:1.[44] It was developed specifically as a sedative agent and is licensed by the US Food and Drug Administration (FDA; initially in 1999) for ICU sedation and subsequently procedural sedation in non-intubated patients. In the European Union (EU) the license (2011) is for ICU sedation of intubated adult patients requiring light to moderate sedation (RASS score 0 to -3). Dexmedetomidine sedation is characterized by spontaneous and evoked movements, and by awakening by external stimuli. Roused patients are more likely to be cooperative and obey instructions. Dexmedetomidine sedation more closely resembles normal physiological sleep than seen with GABA-ergic sedatives. Bolus doses and rapid infusions of the drug should be used with caution (see above). The drug is >90% protein bound; unbound drug freely crosses the blood–brain barrier to exert central effects. The distribution half-life is 6 min. Metabolism is by glucuronidation, hydroxylation, and N-methylation in the liver to inactive metabolites which are then renally excreted. Hepatic impairment will decrease metabolism, but renal impairment and renal replacement therapy should not alter activity. The terminal elimination half-life is around 2 h. A high steady-state volume of distribution (>100 litres in adults) is increased in patients with low plasma albumin concentration (common during critical illness), prolonging the terminal half-life.

6.1.2 Clonidine

Clonidine was the prototype α2-agonist (developed in the 1960s), licensed for hypertension (1966), but subsequently used therapeutically for a wide range of neuropsychiatric conditions, including attention deficit hyperactivity disorder, anxiety disorders, migraine, drug withdrawal syndromes, and in pain medicine.[45] The drug is available in multiple formulations (including oral; transdermal; and intravenous); many clinical uses are unlicensed (including ICU sedation via any route). Clonidine has significantly lower α2-receptor selectivity than dexmedetomidine; α2:α1 selectivity is 220:1 (x8 less than dexmedetomidine). The α1-receptor mediated effects may therefore be more frequent than with dexmedetomidine when titrated to similar α2-mediated sedation states, which could increase cardiovascular side effects. Clonidine is less protein bound than dexmedetomidine (20-40%). It undergoes hepatic metabolism through similar mechanisms to dexmedetomidine to inactive metabolites that are excreted in the urine, but importantly around 65% is excreted unchanged in the urine. The elimination half-life is therefore significantly longer (6-23 hours, mean 7 hours), and (unlike dexmedetomidine) is prolonged by renal failure (18-41 hours; important in critical illness). Peak effects after a single dose occur after 10-60 minutes, but may last 3-7 hours. A single widely agreed evidence-based intravenous dosage regimen has not been developed for intravenous clonidine.

6.2 PROPOFOL (USUAL CARE)

Propofol (2, 6-diisopropylphenol) is a short-acting general anaesthetic agent with a rapid onset of action of approximately 30 seconds. Recovery from anaesthesia is usually rapid. The mechanism of action, like all general anaesthetics, is poorly understood. However, propofol is thought to produce its sedative/anaesthetic effects by the positive modulation of the inhibitory function of the neurotransmitter GABA through the ligand-gated GABAA receptors. In general, falls in mean arterial blood pressure and slight changes in heart rate are observed when propofol is administered for induction and maintenance of anaesthesia. However, the haemodynamic parameters normally remain relatively stable during maintenance and the incidence of untoward haemodynamic changes is low. Although ventilatory depression can occur following administration of propofol, any effects are are readily manageable in clinical practice.

Propofol reduces cerebral blood flow, intracranial pressure and cerebral metabolism. The reduction in intracranial pressure is greater in patients with an elevated baseline intracranial pressure.

Propofol is extensively distributed and rapidly cleared from the body (total body clearance 1.5–2 litres/minute). The decline in propofol concentrations following a bolus dose or following the termination of an infusion can be described by a three compartment open model with very rapid distribution (half-life 2 –4 minutes), rapid elimination (half-life 30 – 60 minutes), and a slower final phase, representative of redistribution of propofol from poorly perfused tissue. Clearance occurs by metabolic processes, mainly in the liver where it is blood flow dependent, to form inactive conjugates of propofol and its corresponding quinol, which are excreted in urine.

6.3 STUDY DRUG IDENTIFICATION

6.3.1 Study Drug Identification

The IMP is defined by the active substance only, therefore all authorised brands/ concentrations may be used. Several concentrations and brands of these drugs are

marketed in the UK, examples are given below and in the summaries of product characteristics.

Clonidine:	Catapres Ampoules 150 micrograms in 1ml solution for injection
Dexmedetomidine:	Dexdor 100 micrograms/ml concentrate for solution for infusion
Propofol:	Diprivan 10 mg/ml (1%) emulsion for injection or infusion Diprivan 20 mg/ml (2%) emulsion for injection or infusion

6.3.2 Study Drug Manufacturer

Details of one manufacturer of each of the trial drugs are given below. Pharmacies may provide the brand of each drug that is available to them. Examples of manufacturers are given below.

Catapres – Boehringer Ingelheim Limited, Ellesfield Avenue, Bracknell, Berkshire, RG12 8YS, United Kingdom

Dexdor – Orion Corporation, Orionintie 1, FI-02200 Espoo, Finland

Diprivan – Aspen Pharma Trading Limited, 3016 Lake Drive, Citywest Business Campus, Dublin 24, Ireland

6.3.3 Marketing Authorisation Holder

Details of one marketing authorisation holder are given below.

Catapres - Boehringer Ingelheim Limited, Ellesfield Avenue, Bracknell, Berkshire, RG12 8YS, United Kingdom under marketing authorisation number PL 00015/5008R

Dexdor – Orion Corporation, Orionintie 1, FI-02200 Espoo, Finland under marketing authorisation numbers EU/1/11/718/001-002, EU/1/11/718/004, EU/1/11/718/006-007

Diprivan – Aspen Pharma Trading Limited, 3016 Lake Drive, Citywest Business Campus, Dublin 24, Ireland under marketing authorisation number PL 39699/0074 (10mgs/ml) and PL 39699/0076 (20mgs/ml).

6.3.4 Labelling and Packaging

The trial has been classified as a Type A risk adapted CTIMP as any potential risk is no higher than that of standard medical care. Dexmedetomidine and propofol are being used as licensed. Clonidine is a licensed drug in the UK but is not licensed for ICU sedation. However the use of clonidine as a sedative for MV patients in ICU is common practice in the UK and pre-trial work showed that more than 90% of ICU units that responded used clonidine, in up to 25% of patients. Guidelines for use of clonidine as a sedative agent are those recommended by the UK Intensive Care Society (www.ics.ac.uk/ICS/guidelines-and-standards.aspx) and are detailed in appendix 1.

The IMPs will therefore not require any specific labelling or packaging.

Detailed prescribing and administration instructions are provided in the protocol.

6.3.5 Storage

Drugs will be procured through NHS routes via pharmacy and stocked within ICUs. Drugs will be stored unblinded within ICUs under usual clinical conditions, as for current routine clinical use. No special monitoring will be performed.

6.4 DOSING REGIMEN

Both interventional drugs will be used according to a weight based dosing algorithm with regular increments or decrements according to sedation state (appendix 1).

Dexmedetomidine will be diluted to a concentration of 8μg.mL^{-1} in 50mL syringes with 5% glucose solution.

Clonidine will be diluted to a concentration of 15μg.mL^{-1} in 50mL syringes with 5% glucose solution.

Dosing charts will be presented indicating mLs.hour^{-1} for a range of doses, for a range of patient weight estimations from 45kg to 100kg in 5kg increments. Dosing concentrations for infusion are those recommended by the UK Intensive Care Society (www.ics.ac.uk/ICS/guidelines-and-standards.aspx). Patients who weigh greater than 100kg will be dosed using the regimen suggested for 100kg weight.

Flow charts will provide a bedside guide for increasing or decreasing dexmedetomidine or clonidine dose according to clinical sedation state and cardiovascular status.

6.5 PARTICIPANT COMPLIANCE

Control of drug dose will be by the bedside clinical team. Participant compliance will not therefore be relevant.

Compliance by the clinical teams will be monitored as part of the process evaluation. Training materials to support protocol compliance will be provided to sites.

6.6 OVERDOSE

Patient-initiated overdose will not be relevant because dosing will be controlled by clinical staff. Dosing algorithms will provide guidance when to reduce or limit dexmedetomidine or clonidine dose according to heart rate and blood pressure. If an overdose does occur it will be managed as per standard care. Details of symptoms and management of overdose are detailed in the SPC. All patients will be in an intensive care unit when receiving the IMP, and closely monitored by staff with expertise in managing the IMP use and the common complications that may occur.

6.7 OTHER MEDICATIONS

6.7.1 Prohibited Medications

There are no medications that are prohibited in the clonidine or dexmedetomidine groups. Clinical staff will be asked to titrate study drug to a clinical sedation target, with a default of ‘brief eye contact made in response to voice’, while minimising and wherever possible discontinuing propofol. If sedation with clonidine or dexmedetomidine at the maximum recommended dose does not control agitation of achieve comfort, then propofol can be used to provide additional sedation. In these situations propofol should be the first sedative drug to be decreased if patients become deeply sedation or sedation is being decreased for other reasons.

Clonidine should not be used for sedation in patients allocated to the dexmedetomidine group; conversely dexmedetomidine should not be used for sedation in patients allocated to the clonidine group.

6.7.2 Medications used with caution and clinical judgement

Medications that may exacerbate the bradycardic and hypotensive effects of clonidine and dexmedetomidine can be used, but caution and clinical judgement should be used. For a list of drugs to be used with caution, refer to the summary of product characteristics.

The clonidine, dexmedetomidine and propofol Summary of Product Characteristics (SPC) is provided in a separate document with a cover sheet and signature page (signed and verified by the CI and Sponsor) and is filed in the TMF.

7. STUDY ASSESSMENTS AND DATA COLLECTION

7.1 SCREENING DATA

Anonymised screening data will be recorded on screening logs and entered onto the database by research teams at site. This data will be used to generate a CONSORT diagram at the end of the trial.

7.2 BASELINE DATA

The following patient demographic variables will be collected pre-randomisation:

Date of birth, CHI/hospital number, gender, estimated weight, RASS score, CAM-ICU status (unless RASS is -4 or -5), final eligibility review

The remaining patient demographic variables will be collected post-randomisation:

Past medical history (including liver co-morbidities), functional comorbidity index (FCI), HRQoL prior to hospital admission (assessed by proxy; EQ-5D-5L), APACHE II score collected at 24 hours, Sequential Organ failure Score (SOFA) excluding neurologic score, diagnosis at ICU admission, type of admission, time from mechanical ventilation in ICU to randomisation, dose of sedative and opiate at randomisation, sepsis status, baseline blood results (FBC, urea/electrolytes, LFTs, coagulation), arterial blood gas at baseline, baseline delirium risk (PRE-DELIRIC score; collected at 24 hours).

7.3 DAILY DATA COLLECTION DURING ICU STAY

The following data will be collected on a daily basis during ICU stay for up to 28 days after randomisation. Data relating to mechanical ventilation will be collected until the patient is successful extubated.

7.3.1 Data recorded by bedside clinical nurse

Clinician decision to maintain deep sedation during nursing shift; RASS score every 4 hours; behavioural pain assessment (limb movement and ventilation compliance elements) every 12 hours; CAM-ICU assessment every 12 hours (at end of nursing shift); 12 hourly assessment of patient's ability to communicate pain (binary assessment); 12 hourly assessment of patient's ability to cooperate with care (binary assessment). These data will be used to collect the following in the CRF (transcribed by research staff): highest and lowest RASS score for each ICU day; 'least' and 'greatest' pain behaviour for each ICU day; CAM-ICU status on each ICU day;

whether patient was able to communicate pain on each ICU day; and whether patient was able to cooperate with care on each ICU day.

7.3.2 Data collected from a visiting relative/partner/friend

This data will be collected from the personal legal representative (PerLR) who provided consent for participation on days they visit the patient. Relative/ partner/friends response to the following questions (based on their opinion at time of assessment):

Does the patient appear awake to the visitor?

Does the patient seem comfortable to the visitor?

Does the visitor feel they can communicate with the patient?

7.3.3 Data collected by research staff

MV status, MV mode and settings. Extubation events (time); Use of Non-invasive Ventilation (NIV); Reintubation events (time). Tracheostomy events

Total dose of propofol during 24 hours; dose of study drug in 24 hours. Use of any other drugs for sedation (benzodiazepines; others); use of any other drugs for delirium or agitation (haloperidol; other antipsychotic agents)

SOFA score (excluding neurologic score)

Sedation-related adverse events: unplanned removal of nasogastric tube, central line, arterial line or drain; unplanned extubation; peripheral line removal; staff injury; or patient injury

Cardiovascular adverse events: highest vasopressor dose during 24 hours; severe bradycardia (HR <50/minute; yes/no); hypotension (lowest systolic blood pressure); cardiac arrhythmia (including cardiac arrest; yes/no; type of arrhythmia);

Other adverse events: ileus (yes/no)

7.4 ICU DISCHARGE DATA

Patient status (alive; dead; transfer to other ICU). Date/time of discharge, Date/time of final extubation

7.5 HOSPITAL DISCHARGE DATA

Date of hospital discharge

7.6 POST HOSPITAL DISCHARGE ASSESSMENTS

Survival status will be confirmed by the participating sites prior to follow-up. All assessments will be done via post or telephone contact, unless the patient is an inpatient in the participating hospital at the time of follow up. Follow up at 30 days will be undertaken by staff at study sites. Follow up at 90 and 180 days will be undertaken by staff based in the Edinburgh trial coordinating centre who will be blinded to group allocation.

7.6.1 30 days post-randomisation assessments (up to 45 days)

ICE-Q questionnaire; recalled pre-ICU EQ-5D-5L; EQ-5D-5L at 30 days.

7.6.2 90 days post-randomisation assessments (up to 105 days)

Patient experience of intensive care (ICE-Q questionnaire); anxiety and depression (HADS questionnaire); post-traumatic stress (IES-R questionnaire); cognitive function (TMoCA); health related quality of life (EQ-5D-5L); health resource use questionnaire

7.6.3 180 days post-randomisation assessments (up to 195 days)

Patient experience of intensive care (ICE-Q questionnaire); anxiety and depression (HADS questionnaire); post-traumatic stress (IES-R questionnaire); cognitive function (TMoCA); health related quality of life (EQ-5D-5L); health resource use questionnaire.

7.6.4 Survival status

Survival will be collected up to 180 days post-randomisation

Table 2: Table of Assessments

	Pre-Randomisation	Baseline Data	Daily ICU Data Collection	ICU Discharge	Hospital Discharge	30 days	90 days	180 days
Screening for eligibility and consent, demographics, CHI/hospital number, RASS, CAM-ICU, final eligibility check	X							
Baseline data collection - baseline data, FCI, APACHE II, SOFA, RASS, CAM-ICU, PRE-DELIRIC (collected at 24 hours), EQ-5D-5L (assessed by proxy).		X						
Substudy only - 2 blood samples for inflammatory markers • Baseline sample (within 12 hours of randomisation) • 60 hour sample (within 48-72 hours post randomisation)		X						
Daily data collection during ICU stay – clinical team (4hrly - RASS score and pain assessment; 12hrly – CAM-ICU, SQAT, co-operation and communication assessment)			X					
Daily data collection during ICU stay – research team (MV data collection, IMP and drug usage, SOFA score, adverse event data collection)			X					
Assessment of comfort and communication - informant			X					
Adverse Event data			X					
ICU and hospital discharge data				X	X			
Mortality			X	X	X	X	X	X
Intensive Care Experience Questionnaire (ICE-Q)						X	X	
Hospital Anxiety and Depression Scale (HADS) questionnaire							X	X
Impact of Events Scale – revised (IES-R)							X	X
Montreal Cognitive Assessment Tool (Telephone version - TMoCA)							X	X
Euroqol tool (EQ-5D-5L)						X	X	X
Recalled Euroqol tool (EQ-5D-5L)						X		
Health economic questionnaire (including hospital resource use and return to employment)							X	X

7.7 DATA MANAGEMENT

The Edinburgh Clinical Trials Unit will be responsible for data management and quality. A data management plan will be agreed to cover data entry, coding, security and storage, including quality control.

7.7.1 Personal Data

The following personal data will be collected as part of the research:

Participant's name, address, phone number, date of birth and NHS/Community Health Index (CHI) number will be collected. The name, address and phone number of the

person who acted as your Personal Legal Representative will also be collected if appropriate.

Personal data will be stored securely by the research team at each recruiting site for up to 10 years after the study has finished.

7.7.2 Transfer of Data

Data collected or generated by the study may be transferred to external individuals or organisations outside of the Sponsoring organisation(s). It may be provided to researchers running other research studies outwith NHS Lothian/University of Edinburgh. Participant information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research**.** Where this information includes identifiable information, it will be held securely with strict arrangements about who can access the information.

We intend to perform data linkage with nationally held databases to find out about the participant's long term health. In order to identify them on these databases we will use their NHS/CHI number and other personal details.

7.7.3 Data Processor

The data processor is the Edinburgh Clinical Trials Unit, Usher Institute, University of Edinburgh.

7.7.4 Data Controller

The data controller is the University of Edinburgh and NHS Lothian who are the co-sponsors of this study.

7.8 SOURCE DATA DOCUMENTATION

Source data is defined as all information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents are original documents, data and records where source data are recorded for the first time.

The source data will be the patient's medical records, electronic records, data collection sheets and completed questionnaires.

7.9 CASE REPORT FORMS

Study data will be recorded on the electronic CRF by members of the research team at site. Follow-up study data collected centrally will also be recorded on the eCRF. Paper data collection sheets may be used if required by sites. Case report forms must be reviewed and approved by the ACCORD Monitor prior to use (see ACCORD SOP CR013 CRF Design and Implementation).

7.10 TRIAL DATABASE

A trial database developed by the Clinical Trials Unit in Edinburgh will be used to collect all study data. Individuals will be issued log-in details and access will be restricted to necessary fields only. The study teams at site and individuals at ECTU involved in follow-up data collection or data entry will enter data. Participants contact details will be held in an encrypted part of the database.

8. STATISTICS AND DATA ANALYSIS

8.1 SAMPLE SIZE CALCULATION

8.1.1 Modelling primary outcome

Minimum clinically important difference (MCID):

Based on clinical consensus, likely economic benefit, and the findings of systematic reviews, a MCID of a mean difference of 2 days has been chosen for all superiority tests. For non-inferiority of clonidine versus dexmedetomidine, a non-inferiority margin of 1 day has been chosen.

Sample size and power were modelled based on the analytic framework outlined in figure 1, which includes a hierarchical approach to hypothesis testing. We used a large prospective data set from a recent sedation trial in 8 UK ICUs for modelling (N=708).[21] Based on this data set, we estimate that 53% of patients in the "usual care" group will be extubated and around 14% will have died prior to extubation at 7 days.

STAGE ONE:

If either dexmedetomidine or clonidine are superior to usual care by an overall mean difference of 2 days in time to extubation, this translates to an estimated extubation rate of 63% in the dexmedetomidine or clonidine arm at 7 days. The death rate of 14% was assumed to remain the same as for the usual care arm. The minimum follow-up period will be 28 days in ICU for all patients. Under these conditions, using nQuery version 8 software (log-rank test accounting for competing risks), a sample size of 550 per arm (1650 patients in total, 1328 extubation events across the three arms) has 99% power to detect hazard ratios of 1.37 indicating superiority of clonidine or dexmedetomidine over usual care, assuming a one-sided 2.5% significance level.

STAGE TWO:

These analyses are only undertaken if one or other or both of the stage one tests are significant. For the non-inferiority test of clonidine relative to dexmedetomidine (test H3), the non-inferiority margin is fixed on the original scale to be a 1 day absolute mean difference in time to extubation. Based on the real dataset from an untreated ICU population, a 1 day absolute mean difference translates into an estimated survival probability of 63% in the dexmedetomidine arm at 7 days and 57% in the clonidine arm at 7 days. This then equates to an estimated non-inferiority margin on the hazard ratio scale of 0.83 according to nQuery version 8 software (log-rank test accounting for competing risks). As before the death rates in both arms were assumed to be 14% at 7 days. The minimum follow-up period is 28 days in ICU for all patients. Using this information in nQuery version 8 software (log-rank test accounting for competing risks), 550 patients per arm (1100 in total, 888 extubation events) provides 81% power to conclude non-inferiority of clonidine, using a one-sided 2.5% significance level. The power calculation for the superiority comparison of dexmedetomidine versus clonidine (test H4) is the same as that for STAGE ONE.

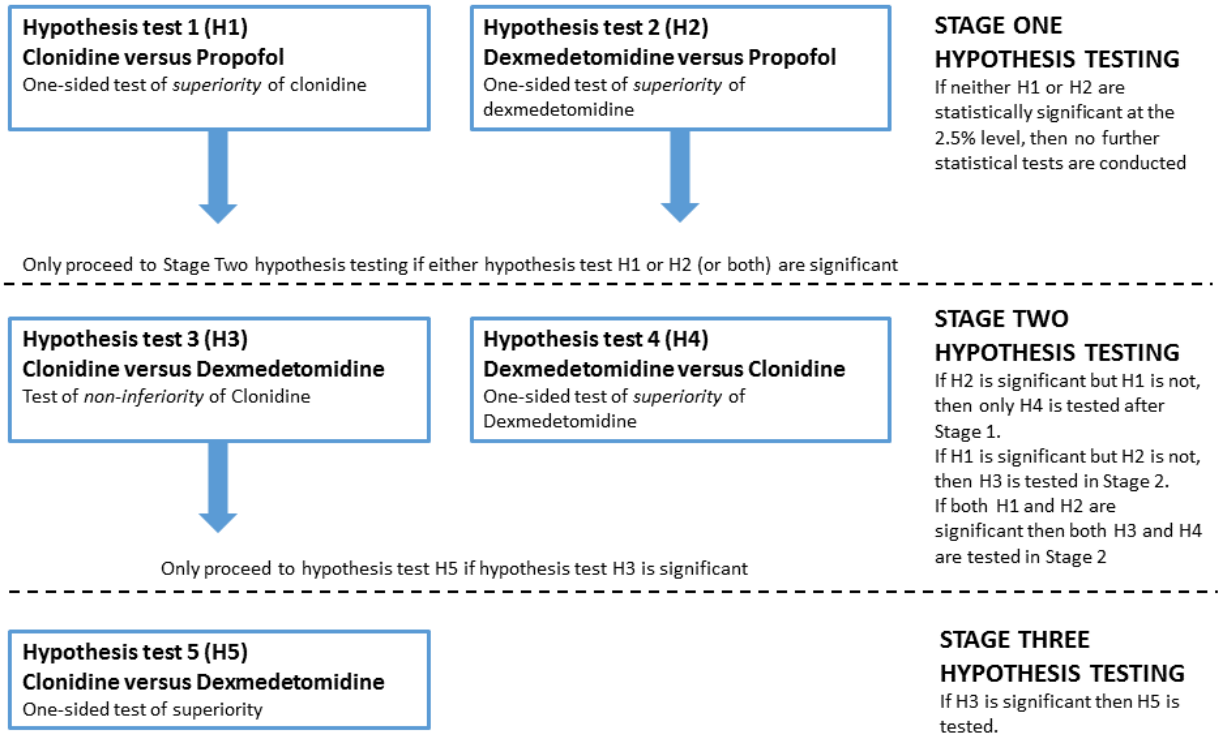

Figure 1: Analytic framework which efficiently tests the trial questions using a hierarchical analytic structure with serial gatekeeping to preserve study power.

Simulation work was used to calculate the overall power of test H1 (clonidine superiority test versus propofol) *and* test H3 (clonidine non-inferiority test versus dexmedetomidine) being statistically significant using Fine and Gray proportional sub-distribution hazards regression analysis based on 2000 trials simulated from the real ICU dataset (median 7 days on ventilation).[21] Assuming that dexmedetomidine and clonidine are both superior to usual care by an overall true mean difference of 2 days, and there is no difference between dexmedetomidine and clonidine, then a total sample size of 1650 (550 per group) provides 81% power of concluding non-inferiority of clonidine over dexmedetomidine (test H3) *and* concluding clonidine is superior to usual care (test H1) based on simulation, using a one-sided 2.5% significance level.

STAGE THREE: The power calculation for the superiority comparison of clonidine versus dexmedetomidine (test H5), which will only be done if stage one demonstrates superiority (tests H1 or H2) *and* clonidine is non-inferior to dexmedetomidine (test H3), is the same as that given in STAGE ONE.

8.1.2 Loss to follow-up

Withdrawal rates have been <5% in recent NIHR-funded RCTs.[46-48] Some other patients may be lost if transferred to another ICU before reaching the primary endpoint. Sample size is therefore inflated by 5% to allow for drop-out or loss to follow-up (579 per group (1737 in total).

8.1.3 Final sample size

A sample size of 1737 (579 per group) provides a highly efficient trial to address the key research questions, namely whether either (or both) α2-agonists are superior to usual care and which agent provides best value for money to the NHS.

8.1.4 Mortality

For the key outcome of mortality in ICU prior to extubation, a sample size of 550 per group provides 83% power to detect a difference in mortality of 7% (equivalent to a HR of approximately 1.5) using Cox regression assuming mortality in the usual care group is 23% and 16% in the clonidine/dexmedetomidine group, using a 2-sided 5% significance level.

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 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).[49-51] Site will be included in the model as a random effect.

(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. The impact on efficacy of the extent of this departure from the randomised treatment strategy will be explored using a complier average

causal effect analysis. Full details of this approach will be documented in the statistical analysis plan.

Similar approaches will be used for the secondary outcomes. A detailed trial analysis plan will be finalised prior to locking the trial data base.

8.2.3 Analysis populations

Unless otherwise stated in the statistical analysis plan, efficacy analysis will be performed on the **full analysis set**: all randomised participants analysed according to their allocated treatment group, regardless of the treatment actually received.

The **safety analysis set** will be formed of all randomised participants who received one of the study regimens, analysed according to the treatment received (dexmedetomidine, clonidine, or usual care)

9. PROCESS EVALUATION

We have included a process evaluation (PE) in the A2B trial given that ICU sedation is a complex healthcare intervention that involves multiple members of the healthcare team, assessing and delivering multiple agents using a series of interrelated activities. Based on previous evidence, it is highly likely that sedation practices vary across site. Therefore it is essential that we develop a detailed understanding of how the study intervention is operationalised in individual sites with a view to developing an understanding of the relationship between implementation and trial outcomes. The results of the process evaluation, in the content of the trial outcomes, will help us to distinguish between intervention failure and implementation failure, which will be essential information for interpreting trial results and guiding implementation into practice beyond the trial, if appropriate.

9.1 AIMS AND OBJECTIVES

The aim of the process evaluation is to explore the processes involved in intervention delivery, and identify factors and the mechanisms of their interaction likely impacting on trial outcomes. Specific objectives that will guide data collection are:

1. Establish the extent to which the intervention is implemented as intended (implementation fidelity), over time and across different ICUs;
2. Ascertain how clinical staff understand and respond to the intervention, over time and across different ICUs;
3. Explore the importance of context (inter-ICU differences, changes over time) and determine factors (including managerial support, economic, organisational and work level) that affect intervention use and implementation.

9.2 DATA COLLECTION METHODS

Pre-trial: information collected from potential sites during the site recruitment process regarding usual sedation practices will be used to ensure units with a mix of sedation practices are included in the pilot phase so that ability to implement the intervention in various settings is confirmed.

During internal pilot: At site visits we will interview staff responsible for caring for patients in the trial to determine acceptability of the trial protocol and trial drugs, including barriers, concerns and enablers, culture & work processes affecting sedation practice and any other processes that might affect operationalisation of the study. Assessment of inter-rater reliability of sedation, delirium & SQAT assessment

tools will also occur. These data will inform feasibility and any changes required to maximise recruitment and fidelity of the trial protocol.

During main study: A purposeful selection of sites (approximately 10) will be contacted via telephone to obtain information regarding the implementation process including acceptability of the intervention, barriers and facilitators to implementation, and clinical decisions affecting the protocol.

Final site visits: Individual and small group interviews with staff involved in implementation and/or intervention delivery will be conducted. We will employ maximum variation sampling to obtain 10 – 15 sites and purposive sampling to obtain a range of participants according to grade, profession and role. We will explore reflections on use of the trial protocol and trial drugs, including perceived barriers, concerns, enablers and work processes affecting sedation practice. Assessment of inter-rater reliability of sedation, delirium & SQAT assessment will also occur.

9.3 DATA ANALYSIS

We will use the framework approach to analyse qualitative data. This will allow us to use themes identified *a priori* alongside those that emerge *de novo* in the development of the final analytical framework. To ensure confirmability and trustworthiness, a sample of textual data will be double coded and the independent analyses shared to identify key difference and similarities in pursuit of an agreed final analysis.

We will synthesise this evidence with that derived from researcher observations of unit context and practice by looking for patterns and exceptions that cross-cut the entire body of data. Using this overarching approach, we will generate a collective body of evidence on the barriers and facilitators related to the implementation, including intervention fidelity.

9.4 INTEGRATION OF PROCESS AND OUTCOME DATA

The integration of process and trial outcome data and subsequent analyses will be secondary and explanatory, and separate from the primary effectiveness analysis. The qualitative evidence will be systematically combined with process and outcome data to identify the dose of the intervention that has been implemented (in regard to both frequency of assessments and dose of sedatives), the coverage of the intervention (including number and characteristics of included and excluded patients and reasons for not recruiting), and intervention fidelity (including extent of protocol implementation), and how these relate to observed outcomes.

10. HEALTH ECONOMIC EVALUATION

10.1 OVERVIEW

A detailed health economic evaluation will be included. The significant cost differences between dexmedetomidine and both usual care and clonidine make this especially relevant (estimated mean daily cost in the trial £80 for dexmedetomidine, £6 for propofol; and £5 for clonidine). Additional drug costs associated with α2-agonists should be balanced against potential cost savings from reductions in ICU and hospital stay and altered outcomes. We will undertake a detailed analysis of the cost and cost-effectiveness of dexmedetomidine, clonidine and usual care. Our analysis will conform to accepted economic evaluation methods in the UK[52]. The comparisons made in the economic evaluation will reflect those of the staged hypothesis tests for the primary outcome (figure 1). We will estimate costs and cost-effectiveness for the 'within-trial' period (6 months/short-run model) and also over the

expected lifetime of the patient ('lifetime'/long-run model). Costs will be assessed from the perspective of the NHS and personal social services (PSS). For both the within-trial and lifetime analyses we will undertake cost-utility analyses, estimating incremental cost per quality-adjusted life year (QALY) gained[52].

10.2 WITHIN-TRIAL ANALYSIS

For the within-trial analysis we will calculate detailed cost information on index hospitalisation for every patient from ICU admission to hospital discharge and during 6 months follow-up. Patient-level resource use data will be collected on items including: sedative drugs; costs associated with managing adverse events (e.g., delirium); length of ICU stay and hospital wards; use of MV; and co-prescribed medications. Patient-level resource use data will be collected post-discharge up to 6 months using questionnaires at 3 and 6 month follow-up: hospital re-admissions; A&E and outpatient visits; GP and nurse visits in clinic and at home; medications; care home admissions; any other contacts with primary and social care (e.g., physiotherapist, occupational therapist, social worker, counsellor). Unit costs will be obtained from published sources and inflated where appropriate before being applied to the volume of resource use data.[53] [54] [55]

QALYs will be calculated based on the HRQoL and mortality data collected during the trial. HRQoL will be measured using the EQ-5D-5L (www.euroqol.org), which we will collect at 30 days, 3 and 6 months (see table 1). As patients recruited to the trial will be critically ill, completion of the EQ-5D-5L at baseline will not be possible. Previous studies have assumed a common baseline value for all patients (e.g., zero).[56] We will use this approach, and also two alternatives. First, we will estimate baseline utility scores for patients using proxy responses from a person who knows the patient. In this case we will use the proxy version of the EQ-5D-5L (by the patient's spouse, parent or (adult) child).[57] The type of proxy respondent will be controlled for in subsequent analyses. Second, we will ask patients to retrospectively record their baseline EQ-5D-5L at the 30 day follow-up point. We will evaluate QALYs associated with each strategy using all three approaches; the base case approach will use the proxy responses. Patients who die will be assigned a utility value of zero at the date of death and all subsequent time periods. Patient-specific utility profiles will be constructed assuming a straight line relation between each of the patients' EQ-5D-5L scores at each follow-up point. The QALYs experienced by each patient from baseline to 6 months will be calculated as the area underneath this profile.

Multiple imputation by chained equations will be used to deal with missing HRQoL and resource use values. Subsequent analyses of imputed data will include variance correction factors to account for additional variability introduced into parameter values as a result of the imputation process. Cost-effectiveness will be calculated as the mean cost difference between groups divided by the mean difference in outcomes (QALYs) to give the incremental cost-effectiveness ratio (ICER). We will also calculate net monetary benefits (NMBs). We will subject the results to extensive deterministic (one-, two- and multi-way) and probabilistic sensitivity analysis. For the latter, non-parametric methods for calculating confidence intervals around the ICERs and NMBs based on bootstrapped estimates of the mean cost and QALY differences will be used.[58] These methods will appropriately account for the multiple imputation of the missing data. The bootstrap replications will also be used to construct cost-effectiveness acceptability curves, which will show the probability that each strategy is cost-effective at 6 months for different values willingness to pay for additional QALYs by the NHS.

10.3 LIFETIME ANALYSIS

In the lifetime model cost-effectiveness will be calculated in terms of the incremental cost per QALY gained. A review of the NIHR HTA website (www.hta.ac.uk/project/htapubs.asp) and the NHS Economic Evaluation Database (NHS-EED, www.crd.york.ac.uk https://www.crd.york.ac.uk/CRDWeb/) (last search 15/05/2017) reveals there have been no previous analyses to evaluate lifetime cost-effectiveness of the study strategies[59]. Given this paucity of evidence, we will develop a *de novo* cost-effectiveness model that will be populated based on available evidence, including the data collected during the trial. We will: [1] design a lifetime model to characterize health states of ICU survivors; [2] populate the model using data identified from the trial and published literature and routine sources; [3] relate outcomes from the trial to final outcomes, expressed in terms of QALYs; and [4] identify which parameters in the model are most uncertain and are important drivers of cost-effectiveness. The model is likely to use a similar structure to a previous economic evaluation of long-term cost-effectiveness for ICU patients in the UK[60]. Survival analysis of the RCT data will provide the basis for extrapolating any within-trial differences in costs and QALYs[61]. The model will use external data on long-term survival of ICU survivors, including from co-applicants expert in this area (Lone, Walsh).[18] Specific details of the data to be used to populate the model will be determined following the development of the structure and the systematic searches of the literature to identify existing models. We will undertake deterministic (one-, two- and multi-way) and probabilistic sensitivity analysis, the latter assuming appropriate distributions and parameter values.[61] We will combine data on incremental costs with epidemiological data on projected patient numbers and undertake a budget impact analysis to evaluate what the total cost impact of each strategy would be were it to be scaled up; budget impact will be calculated separately for ICU-related costs only, the within-trial period and using a lifetime time horizon, as each might be appropriate for different decision-makers. We will also use the probabilistic sensitivity analyses combined with the epidemiological information on projected patient numbers to undertake a value of information analysis to evaluate the potential economic value of future research on this topic.[61]

11. MECHANISTIC SUB-STUDY

In a sub-group of participants, consent will be sought to collect blood samples. For the sub-group in whom consent is obtained, a20mL blood sample will be collected at two timepoints:

- Baseline sample - collect within 12 hours of randomisation
- 60 hour sample – collect at 60 hours (+/- 12 hours) post randomisation (i.e between 48-72 hours)
- at

We will analyse blood samples in laboratories in the University of Edinburgh, or laboratories in other institutions or organisations if required for particular techniques. We will measure a panel of pro- and anti-inflammatory mediators in order to explore whether alpha2-agonists have anti-inflammatory properties that might contribute to or mediate some of their beneficial effects during critical illness. When consent has been provided, we will also explore whether changes in gene expression occur that are modified by alpha2-agonists, for example using whole blood transcriptomics.

12. PHARMACOVIGILANCE

Local investigators will be responsible for the detection and documentation of events meeting the criteria and definitions detailed below.
Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the relevant Summary of Product Characteristics.

The interventions with IMP are limited to the period of mechanical ventilation, which will exclusively occur in the ICU. Clinical and research staff will monitor participants for adverse events (AEs) and serious adverse events (SAEs) during ICU stay. Patients will typically spend several additional days in the ICU after completing the intervention (with the exception of patients who die during the intervention period). The IMP is expected to be completely cleared from the participant's body before ICU discharge, based on their pharmacokinetics. All adverse events (AE) that occur in ICU after joining the trial will be documented in the medical notes and those that are not considered to be expected in this population must be reported in detail in the Case Report Form (CRF). In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment. Participants with AEs must be followed up until resolution of the event or hospital discharge, whichever occurs sooner.

12.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An **adverse reaction** (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that at any dose:

- results in death of the clinical trial participant;
- is life threatening*;
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

*Life-threatening in the definition of an SAE or SAR refers to an event where the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

^Any hospitalisation that was planned prior to randomisation will not meet SAE criteria. Any hospitalisation that is planned post randomisation will meet the SAE criteria.

A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be caused by the IMP, that it is not consistent with the information about the IMP in the Summary of Product Characteristics (SPC).

12.2 IDENTIFYING AES AND SAES

AEs and SAEs will be recorded from the time a participant signs the consent form to take part in the study until discharge from the ICU.

As this study is based in an ICU setting, and involves critically ill patients, it is anticipated and expected that many patients will experience events that might be considered AEs or SAEs, but are expected features of critical illness requiring ICU care. Furthermore, as patients will usually be incapacitated for part or all of the intervention period, the identification of AEs and SAEs will largely be the responsibility of the clinical team and research teams reviewing patient records. Screening and identification of AEs and SAEs will be based on clinical events (from daily charts and reviews) and review of laboratory and other investigations undertaken as part of routine care. There will be no testing or investigation additional to routine care undertaken for the purpose of detection of AEs or SAEs

12.3 RECORDING AES AND SAES

When an AE/SAE considered relevant to the trial by clinical or research teams occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will then record all relevant information in the CRF and on the SAE form (if the AE meets the criteria of serious).
Information to be collected includes dose and intervention group, type of event, onset date, investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome

12.3.1 AEs and SAEs that do not require recording in the CRF

AEs and SAEs that are considered consistent with the patient's critical illness do not require recording or reporting unless the Investigator considers they may relate to participation in the trial. These include, but are not limited to:

- new or deterioration in organ function
- new infections
- complications of ICU procedures
- requirement for further interventions (eg surgery) related to the presenting diagnosis
- reactions to co-prescribed medications.

Death during and after ICU discharge is expected to occur in around 20% of participants in the trial and is a key secondary outcome. Deaths only need to be recorded as AEs and/or SAEs if the Investigator considers they may relate to participation in the trial.

Sedation related adverse events, and well recognised defined potential side effects of alpha-2 agonists (bradycardia, hypotension, ileus), are collected daily during ICU care and are important secondary outcomes in the trial. These events do not need to be routinely recorded as AEs or SAEs.

12.3.2 Pre-existing Medical Conditions

Pre-existing medical conditions (i.e. existed prior to informed consent) should be recorded as medical history and only recorded as adverse events if medically judged to have worsened during the study.

12.3.3 Worsening of the Underlying Condition during the Trial

Medical occurrences or symptoms of deterioration that are expected due to the participant's underlying condition should be recorded in the patient's medical notes and only be recorded as AEs on the AE log if medically judged to have unexpectedly

worsened during the study. Events that are consistent with the expected progression of the underlying disease should not be recorded as AEs.

12.4 ASSESSMENT OF AES AND SAES

Seriousness, causality, severity and expectedness will be assessed by the Principal Investigator. As this is an unblinded trial, Investigators can take group allocation into account when assessing AEs and SAEs.

The Investigator or a delegated member of the local research team is responsible for assessing each AE.

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

12.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 12.1.

12.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the IMP according to the definitions below.

- Unrelated: where an event is not considered to be related to the IMP.
- Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug.

Causality assessment decisions will be made by a medically qualified doctor, using medical and scientific judgement as well as knowledge of the subject concerned.

Where non Investigational Medicinal Products (NIMPs) e.g. rescue/escape drugs are given: if the AE is considered to be related to an interaction between the IMP and the NIMP, or where the AE might be linked to either the IMP or the NIMP but cannot be clearly attributed to either one of these, the event will be considered as an AR. Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated.

12.4.3 Assessment of Expectedness

If an event is judged to be an AR, the evaluation of expectedness will be made based on knowledge of the reaction and the relevant Reference Safety Information documented in the SPC (usually section 4.8, although Investigators should consider any safety information presented in other SPC sections also).

The event may be classed as either:

Expected: the AR is consistent with the toxicity of the IMP listed in the SPC.

Unexpected: the AR is not consistent with the toxicity in the SPC.

12.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE and record this on the CRF or SAE form according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

12.5 REPORTING OF SAES/SARS/SUSARS

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance & QA Office **immediately or within 24 hours**. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.
The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 12.4.2, Assessment of Causality and 12.4.3, Assessment of Expectedness.
The SAE form will be transmitted by fax to ACCORD on **+44 (0)131 242 9447** or may be transmitted by hand to the office or submitted via email to Safety@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email.
Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the investigator and request the missing information.
All reports faxed to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

12.6 REGULATORY REPORTING REQUIREMENTS

The ACCORD Research Governance & QA Office is responsible for pharmacovigilance reporting on behalf of the co-sponsors (Edinburgh University and NHS Lothian).

The ACCORD Research Governance & QA Office has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD or delegate will inform Investigators at participating sites of all SUSARs and any other arising safety information.

ACCORD will be responsible for providing safety line listings and assistance; however, it is the responsibility of the Investigator to prepare the Development Safety Update Report. This annual report lists all SARs and SUSARs reported during that time period. The responsibility of submitting the Development Safety Update Report to the regulatory authority and RECs, lies with ACCORD.

12.7 FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator will follow each participant until resolution or death of the participant, or until hospital discharge (whichever occurs sooner). Follow up information on an SAE will be reported to the ACCORD office.

AEs still present in participants at the last study visit will be monitored until resolution of the event or until no longer medically indicated.

12.8 PREGNANCY

Pregnancy is an exclusion criteria for the trial, and is extremely unlikely to occur during hospitalisation for critical illness. Data concerning pregnancy post hospital discharge will not be collected.

13. TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

13.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Project Management Group, consisting of the grant holders (Chief Investigator and Principal Investigator in Edinburgh), A Trial Manager and coordinating nurse.
The Trial Manager will oversee the study and will be accountable to the Chief Investigator. The Trial Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.
A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

13.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The terms of reference of the Trial Steering Committee, the draft template for reporting and the names and contact details are detailed in CR015 DMC & TSC Charters.

13.3 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. The terms of reference of the Data Monitoring Committee and the names and contact details are detailed in CR0015 DMC & TSC Charters.

The DMC Charter will be signed by the appropriate individuals prior to the trial commencing.

13.4 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

13.5 RISK ASSESSMENT

A study specific risk assessment will be performed by representatives of the co-sponsors, ACCORD monitors and the QA group, in accordance with ACCORD governance and sponsorship SOPs. Input will be sought from the Chief Investigator or designee. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans. The risk assessment outcomes will also indicate which risk adaptions could be incorporated into to trial design.

13.6 STUDY MONITORING AND AUDIT

ACCORD clinical trial monitors, or designees, will perform monitoring activities in accordance with the study monitoring plan. This will involve on-site visits and remote monitoring activities as necessary. ACCORD QA personnel, or designees, will perform study audits in accordance with the study audit plan. This will involve investigator site audits, study management audits and facility (including 3rd parties) audits as necessary.

14. GOOD CLINICAL PRACTICE

14.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

14.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

14.3 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

14.3.1 Study Site Staff

The Investigator must be familiar with the IMP, protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the IMP, protocol and their trial related duties.

14.3.2 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

14.3.3 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the ACCORD Research Governance & QA Office, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents);
- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.

- ACCORD will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF) or Sponsor File, where required. The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs. Under certain circumstances the TMF responsibilities may be delegated to the research team by ACCORD.

14.3.4 GCP Training

All study staff must hold evidence of appropriate GCP training.

14.3.5 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

14.3.6 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated identifiable participant data will be restricted to individuals from the research team treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

15. STUDY CONDUCT RESPONSIBILITIES

15.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Proposed amendments will be submitted to the Sponsor for classification and authorisation.

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to implementation.

15.2 PROTOCOL NON COMPLIANCE

15.2.1 Definitions

Deviation - Any change, divergence, or departure from the study design, procedures defined in the protocol or GCP that does not significantly affect a subjects rights, safety, or well-being, or study outcomes.

Violation - A deviation that may potentially significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being

15.2.2 Protocol Waivers

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

15.2.3 Management of Deviations and Violations

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. Deviation logs / violation forms will be transmitted via email to QA@accord.scot Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be sent by fax to ACCORD on **+44 (0)131 242 9447** or may be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

15.3 URGENT SAFETY MEASURES

The Investigator may implement a deviation from or change to the protocol to eliminate an **immediate hazard** to trial participants without prior approval from the REC and the MHRA. This is defined as an urgent safety measure and the investigator must contact the Clinical Trial Unit at the MHRA and discuss the issue with a medical assessor immediately (+44 (0) 20 3080 6456).

The Investigator will then notify the MHRA (clintrialhelpline@mhra.gsi.gov.uk), the REC and ACCORD, in writing of the measures taken and the reason for the measures within 3 days by submitting a substantial amendment.

15.4 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (QA@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to regulatory authorities and research ethics committees as necessary.

15.5 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

15.6 END OF STUDY

The end of study is defined as the last participant's final follow-up.

The Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, Regulatory Authority, R&D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@ed.ac.uk.

In accordance with ACCORD SOP CR011, a Clinical Study Report (CSR) will be provided to the Sponsor (QA@accord.scot) and REC within 1 year of the end of the study.

Upon completion of the study, the Investigator will upload clinical trial results onto the EudraCT database on behalf of the Sponsor.

The Investigator will submit a short confirmatory e-mail to the MHRA (CT.Submission@mhra.gsi.gov.uk) once the result-related information has been uploaded to EudraCT, with 'End of trial: result-related information: EudraCT XXXX-XXXXXX-XX' as the subject line. The Sponsor(s) will be copied in this e-mail (QA@accord.scot). It should be noted that you will not get an acknowledgment e-mail or letter from the MHRA.

15.7 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

Trial drug will not be continued following the end of the study as participants will only receive trial drug in the acute phase of their illness.

15.8 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been authored by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities. Sites which are part of the United Kingdom's National Health Service have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.
- The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

16. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

16.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

An authorship policy will be agreed prior to completion of recruitment. Authorship of manuscripts and other outputs resulting from the trial will be decided according to the guidelines from the International Committee of Medical Journal Editors (ICMJEs). Authors must demonstrate at least one of the following: substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND drafting the work or revising it critically for important intellectual content; AND final approval of the version to be published; AND agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

16.2 PUBLICATION

The Clinical Study Report (CSR) will be submitted to the Sponsor and REC within 1 year of the end of the study. Where acceptable, a published journal article may be submitted as the CSR. The Chief Investigator will provide the CSR to ACCORD, for review, prior to finalization. The clinical study report may be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. The results of the study, together with other mandated information, will be uploaded to the European clinical trials database within 1 year of the end of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion).

16.3 DATA SHARING

The final trial dataset will be held by the University of Edinburgh on a secure password protected drive. Co-investigators will have the right to access the final data set for the purpose of additional analyses that are consistent with the consent provided by participants. Similarly, any external party can approach the co-investigators to request access to the trial data. In all cases, access to the trial dataset will require approval by a majority of the members of the trial management group and the sponsor (or its delegated representative).

16.4 PEER REVIEW

This study was commissioned by the HTA in response to a detailed commissioned Systematic Review, and prioritization exercise. The study underwent external peer review during the application for funding from the HTA. The study was also presented to the UK Critical Care Research Group (June 2017)) and received support. The study was reviewed on multiple occasions by PPI collaborators during the grants application and protocol development process.

17. REFERENCES

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18. APPENDIX 1: DRUG REGIMENS

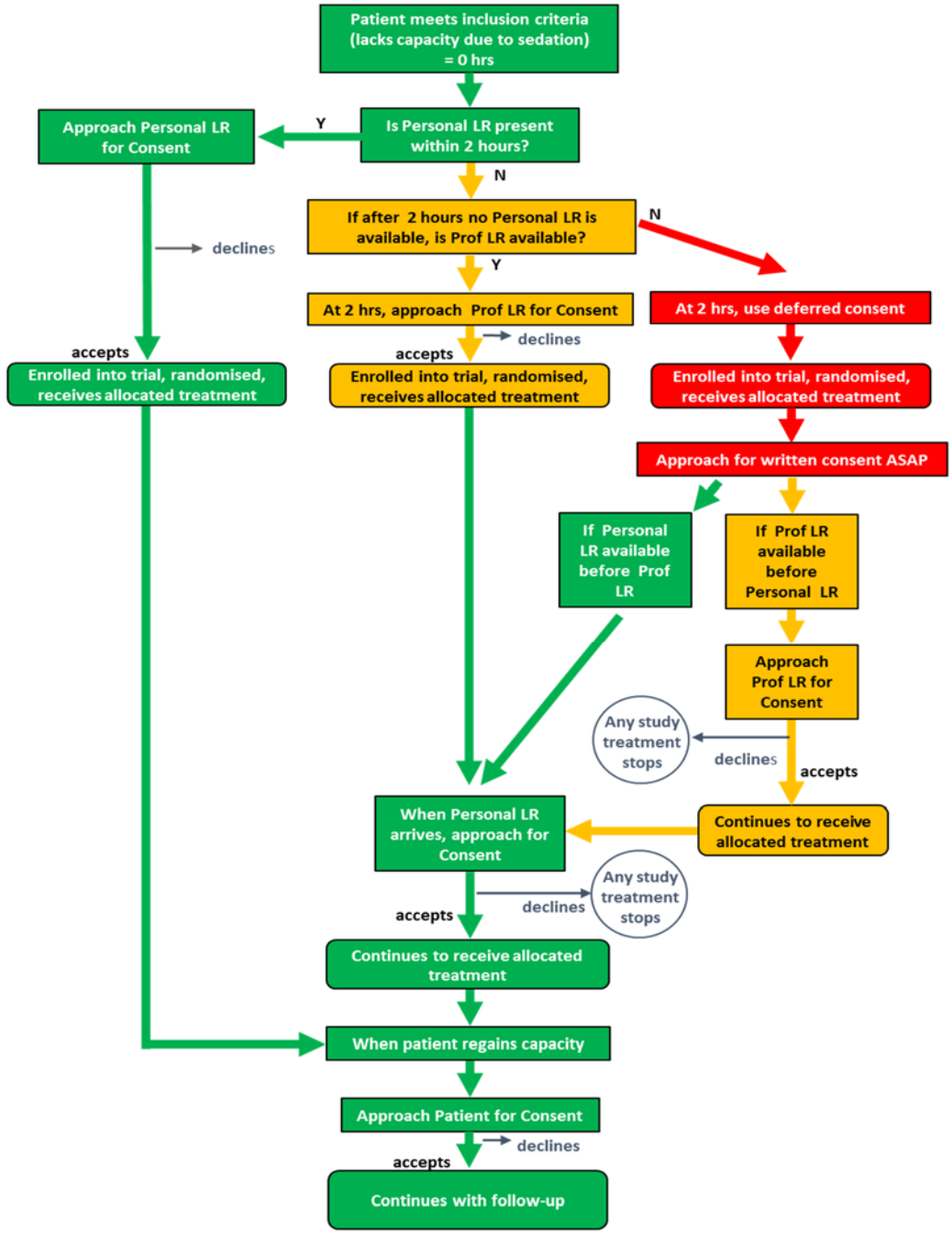
Weight Based Infusion Rates in mls per hour for Clonidine 15micrograms per ml

Dose in micrograms per kilogram per hour	Patient's weight (actual) in kilograms											
	45	**50**	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**	**95**	**≥100**
0.1	0.3	0.3	0.4	0.4	0.4	0.5	0.5	0.5	0.6	0.6	0.6	0.7
0.2	0.6	0.7	0.7	0.8	0.9	0.9	1.0	1.1	1.1	1.2	1.3	1.3
0.3	0.9	1.0	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.0
0.4	1.2	1.3	1.5	1.6	1.7	1.9	2.0	2.1	2.3	2.4	2.5	2.7
0.5	1.5	1.7	1.8	2.0	2.2	2.3	2.5	2.7	2.8	3.0	3.2	3.3
0.6	1.8	2.0	2.2	2.4	2.6	2.8	3.0	3.2	3.4	3.6	3.8	4.0
0.7	2.1	2.3	2.6	2.8	3.0	3.3	3.5	3.7	4.0	4.2	4.4	4.7
0.8	2.4	2.7	2.9	3.2	3.5	3.7	4.0	4.3	4.5	4.8	5.1	5.3
0.9	2.7	3.0	3.3	3.6	3.9	4.2	4.5	4.8	5.1	5.4	5.7	6.0
1.0	3.0	3.3	3.7	4.0	4.3	4.7	5.0	5.3	5.7	6.0	6.3	6.7
1.1	3.3	3.7	4.0	4.4	4.8	5.1	5.5	5.9	6.2	6.6	7.0	7.3
1.2	3.6	4.0	4.4	4.8	5.2	5.6	6.0	6.4	6.8	7.2	7.6	8.0
1.3	3.9	4.3	4.8	5.2	5.6	6.1	6.5	6.9	7.4	7.8	8.2	8.7
1.4	4.2	4.7	5.1	5.6	6.1	6.5	7.0	7.5	7.9	8.4	8.9	9.3
1.5	4.5	5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	9.0	9.5	10.0
1.6	4.8	5.3	5.9	6.4	6.9	7.5	8.0	8.5	9.1	9.6	10.1	10.7
1.7	5.1	5.7	6.2	6.8	7.4	7.9	8.5	9.1	9.6	10.2	10.8	11.3
1.8	5.4	6.0	6.6	7.2	7.8	8.4	9.0	9.6	10.2	10.8	11.4	12.0
1.9	5.7	6.3	7.0	7.6	8.2	8.9	9.5	10.1	10.8	11.4	12.0	12.7
2.0	6.0	6.7	7.3	8.0	8.7	9.3	10.0	10.7	11.3	12.0	12.7	13.3

Weight Based Infusion Rates in mls per hour for Dexmedetomidine 8 micrograms per ml

Patient's weight (actual) in kilograms													
Dose in micrograms per kilogram per hour		45	50	55	60	65	70	75	80	85	90	95	≥100
	0.1	0.6	0.6	0.7	0.8	0.8	0.9	0.9	1.0	1.1	1.1	1.2	1.3
	0.2	1.1	1.3	1.4	1.5	1.6	1.8	1.9	2.0	2.1	2.3	2.4	2.5
	0.3	1.7	1.9	2.1	2.3	2.4	2.6	2.8	3.0	3.2	3.4	3.6	3.8
	0.4	2.3	2.5	2.8	3.0	3.3	3.5	3.8	4.0	4.3	4.5	4.8	5.0
	0.5	2.8	3.1	3.4	3.8	4.1	4.4	4.7	5.0	5.3	5.6	5.9	6.3
	0.6	3.4	3.8	4.1	4.5	4.9	5.3	5.6	6.0	6.4	6.8	7.1	7.5
	0.7	3.9	4.4	4.8	5.3	5.7	6.1	6.6	7.0	7.4	7.9	8.3	8.8
	0.8	4.5	5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	9.0	9.5	10.0
	0.9	5.1	5.6	6.2	6.8	7.3	7.9	8.4	9.0	9.6	10.1	10.7	11.3
	1.0	5.6	6.3	6.9	7.5	8.1	8.8	9.4	10.0	10.6	11.3	11.9	12.5
	1.1	6.2	6.9	7.6	8.3	8.9	9.6	10.3	11.0	11.7	12.4	13.1	13.8
	1.2	6.8	7.5	8.3	9.0	9.8	10.5	11.3	12.0	12.8	13.5	14.3	15.0
	1.3	7.3	8.1	8.9	9.8	10.6	11.4	12.2	13.0	13.8	14.6	15.4	16.3
	1.4	7.9	8.8	9.6	10.5	11.4	12.3	13.1	14.0	14.9	15.8	16.6	17.5

19. APPENDIX 2: CONSENT PROCESS IN THE A2B TRIAL



Personal LR = Personal Legal Representative Prof LR = Professional Legal Representative