Academic and Clinical Central Office for Research and Development

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
Funder	NIHR Health Technology Assessment
Funding Reference Number	HTA 16/93/01
Chief Investigator	Professor Timothy Walsh
Sponsor Reference	AC18022
EudraCT Number	2018-001650-98
REC Number	18/SS/0085
ClinicalTrials.gov	NCT03653832
Version Number and Date	Version7.0, 25th April 2023

FUNDED BY
NIHR | National Institute for Health and Care Research
This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (16/93/01). The views expressed are those of the author(s) and not necessarily of the NIHR or the Department of Health and Social Care.

KEY TRIAL CONTACTS (* Protocol Authors)

Chief Investigator

Name: Professor Timothy Walsh*

Address: Department of Anaesthesia, Critical Care & Pain Medicine
Room S8208, 2nd Floor
Royal Infirmary of Edinburgh
51 Little France Crescent
Edinburgh
EH16 4SA

Telephone: +44 (0) 131 242 6395

Fax:

Email: timothy.walsh@ed.ac.uk

Lead Co-Sponsor Representative

Name: Dr Fiach O'Mahony

Address: Research & Governance
University of Edinburgh
Queen's Medical Research Institute
47 Little France Crescent
Edinburgh
EH16 4TJ

Telephone: +44 (0)131 242 9418

Fax: +44 (0) 131 242 9447

Email: fiach.o'mahony@ed.ac.uk

Trial Manager

Name: Ms Alix Macdonald

Address: Edinburgh Clinical Trials Unit
Usher Institute
The University of Edinburgh
Level 2, Nine Edinburgh BioQuarter
9 Little France Road
Edinburgh
EH16 4UX

Telephone: +44 (0)131 651 9928

Fax:

Email: alix.macdonald@ed.ac.uk

Trial Statistician

Name: Professor Chris Weir*

Address: Edinburgh Clinical Trials Unit
Usher Institute
The University of Edinburgh
Level 2, Nine Edinburgh BioQuarter
9 Little France Road
Edinburgh
EH16 4UX

Telephone: +44 (0)131 651 9957

Fax:

Email: christopher.weir@ed.ac.uk

Academic and Clinical Central Office for Research and Development

PROTOCOL APPROVAL SIGNATURE PAGE

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

EudraCT: 2018-001650-98

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	Tim Walsh (Jun 16, 2023 12:27 GMT+1)	Jun 16, 2023
Chief Investigator	**Signature**	**Date**
Professor Chris Weir	Christopher J Weir (Jun 16, 2023 13:27 GMT+1)	Jun 16, 2023
Trial Statistician	**Signature**	**Date**
Dr Fiach O'Mahony	Fiach O'Mahony (Jun 16, 2023 13:28 GMT+1)	Jun 16, 2023
Lead Co-Sponsor Representative	**Signature**	**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**

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	1437
Planned Number of Sites	Approximately 40-50 Intensive Care Units
Countries Anticipated to be Involved in Trial	UK only
Treatment Duration	Variable
Follow up Duration	6 months with follow up truncated to 1 month from October 2023
Total Planned Trial Duration	58 months (recruitment period)
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	For the purpose of the trial, a successful first extubation from mechanical ventilation (MV) will be defined as follows: a) For patients with an Endotracheal tube: time of successful extubation will be the time of the first extubation that is followed by 48 hours of spontaneous breathing without mechanical support (i.e. the start time of the 48 hours of spontaneous breathing) b) For patients with a tracheostomy: time of successful extubation will be the start time of the patient's first period of 48 hours of spontaneous breathing, where spontaneous breathing is defined as receiving support not exceeding 5 cmH_2O PEEP/CPAP with ≤ 5 cmH_2O pressure support above PEEP c) For patients who are receiving non-Invasive mechanical ventilation (NIV): time of successful extubation will be the start time of the patient's first period of 48 hours of spontaneous breathing, where spontaneous breathing is defined as receiving support not exceeding 5 cmH2O CPAP via mask/hood (NB NIV patients receiving any pressure supported breaths will not be considered to be spontaneously breathing unassisted) NB: The use of high flow nasal oxygen will not be counted as mechanical ventilation, so patients on nasal flow oxygen alone will be considered to be spontaneously breathing unassisted.
Secondary Endpoints	1) Mortality 2) Length of ICU stay 3) Sedation and analgesia quality (RASS) 4) Sedation and analgesia quality (SQAT) 5) Time to first optimum sedation 6) Delirium prior to successful extubation 7) Drug-related adverse events 8) Health related Quality of Life 9) Patient's ability to communicate pain and ability to cooperate with care 10) Patient experience of ICU care 11) Relative/Partner/Friend assessment of comfort and communication 12) Anxiety and depression 13) Post-traumatic stress 14) Cognitive function
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 painkillers 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 painkiller, so additional painkillers 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 1437 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 will always aim to have patients lightly sedated and comfortable. We will compare whether 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 90 days after entering the trial. At 90 and/or 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 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).

Four 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.
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.

The SPICE III trial was an open-label randomized trial that enrolled ICU patients who had been mechanically ventilated for less than 12 hours and were expected to continue to receive ventilatory support for longer than the next calendar day to receive dexmedetomidine as the sole or primary sedative or to receive usual care (propofol, midazolam, or other sedatives).[62] The target range of sedation-scores on the RASS was −2 to +1 (lightly sedated to restless). The primary outcome was the rate of death from any cause at 90 days. The trial enrolled 4000 patients, and found no difference in the primary outcome (29.1% in the dexmedetomidine group versus 29.1% in the usual-care group (adjusted risk difference, 0.0 percentage points; 95% confidence interval, −2.9 to 2.8). Of relevance clinicians indicated a requirement for deep sedation for 50-60% of patients on days 1-2, and 20-40% on subsequent days. Less than 50% of patients achieved the target light sedation on days 1-2 in ICU, and around 60-70% achieved it on subsequent days. To achieve the prescribed level of sedation, patients in the dexmedetomidine group received supplemental propofol (64% of patients), midazolam (3%), or both (7%) during the first 2 days after randomization; in the usual-care group, these drugs were administered as primary sedatives in 60%, 12%, and 20% of the patients, respectively. Bradycardia and hypotension were more common in the dexmedetomidine group. Among the pre-defined secondary outcomes in the dexmedetomidine group there was an increase in ventilator free days (during 28 days follow-up) of 1.0 days (23.0 days versus 22.0 days: 95% CI: 0.4 to 1.6 days). The median duration of ventilation was around 3 days in both groups. In the dexmedetomidine group there was also an increase in the days free of coma and/or delirium during 28 days follow-up (24.0 days versus 23.0 days; difference 1.0 days (95% CI: 0.5 to 1.5). There were no differences in deaths at other time points, or in cognitinve function or HRQoL during follow-up. Among pre-defined subgroup analyses, there were no differences in relation to APACHE II score, oxygenation status, the presence of sepsis, or operative/non-operative groups. There was an interaction with the median population age of 63.7 years. Patients aged <63.7 years who received dexmedetomidine experienced more deaths (mean 4.4%; 95% CI 0.1% to 8.7% more deaths). Patients aged ≥63.7 years who received dexmedetomidine experienced fewer deaths (mean 4.4%; 95% CI 0.8% to 7.9% fewer deaths). This finding was explored in a detailed *post hoc* analysis which confirmed the finding using a range of statistical approaches, but without an explanation for the effect.[30] A cluster analysis suggested that a beneficial effect on mortality may be most marked in operative versus non-operative patients.

The MENDS trial studied 438 adult patients with sepsis randomised double blind to receive either dexmedetomidine or propofol.[31] The trial found no difference in the primary outcome (delirium/coma free days), ventilation outcomes, or mortality between the groups. Only 10% of eligible patients were included, many patients had received MV for 1-2 days before enrolment and overall mean duration of MV was short. The median dose of dexmedetomidine was also low and many patients received midazolam and/or antipsychotics (40%). These features may have compromised the fidelity of the planned intervention and its external validity.

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. 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. This trial 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 up to 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[32 33], 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 (see section 11).

2.2 ENDPOINTS

2.2.1 Primary Endpoint

Time to successful extubation post-randomisation (hours).

For the purpose of the trial, a successful first extubation from mechanical ventilation (MV) will be defined as follows:

a. For patients with an Endotracheal tube:
    a. time of successful extubation will be the time of the first extubation that is followed by 48 hours of spontaneous breathing without mechanical support (i.e. the start time of the 48 hours of spontaneous breathing)
b. For patients with a tracheostomy:
    a. time of successful extubation will be the start time of the patient's first period of 48 hours of spontaneous breathing, where spontaneous

breathing is defined as receiving support not exceeding 5 cmH_2O PEEP/CPAP with ≤ 5 cmH_2O pressure support above PEEP

c. For patients who are receiving non-Invasive mechanical ventilation (NIV):

    a. time of successful extubation will be the start time of the patient's first period of 48 hours of spontaneous breathing, where spontaneous breathing is defined as receiving support not exceeding 5 cmH2O CPAP via mask/hood (NB NIV patients receiving any pressure supported breaths will not be considered to be spontaneously breathing unassisted)

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

The 48 hours of successful extubation is included in the definition in order to exclude patients with early failed extubations, i.e. those patients requiring reintubation within 48 hours. 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 this situation patients should continue to be followed for the start time at which a successful extubation occurs according to the above definitions

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
Mortality	Medical records check	ICU, hospital, 30, 90 and 180 days post randomisation
Length of ICU stay	Days randomisation to ICU discharge	ICU discharge
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).[34] Defines four states for sedation quality: 1. Overall optimum sedation (no agitation; no unnecessary deep sedation; no pain behaviour) 2. Agitation 3. Unnecessary deep sedation (RASS -4/-5 without clinical indication) 4. Pain (presence of pain behaviour based on limb movement and ventilation compliance)	Four hourly during ICU stay until primary outcome is reached Derived from daily sedation and analgesia quality data during intervention period in ICU until primary outcome is reached
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 during the intervention period

Delirium prior to successful extubation	Confusion-Agitation method for ICU (CAM-ICU)[35] Occurrence prior to successful extubation (binary outcome) Days with delirium or coma prior to successful extubation (continuous outcome)	Twice daily during ICU stay until primary outcome is reached
Drug-related adverse events	Severe bradycardia; cardiac arrhythmias; cardiac arrest (defined in protocol)	Daily during the intervention period
Health-related Quality of Life	Euroqol tool (EQ-5D-5L)	Recalled HRQoL prior to hospital admission; 30, 90 and 180 days post randomisation
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 until primary outcome is reached
Patient experience of ICU care	Intensive Care Experience Questionnaire (ICE-Q)[36] Provides numeric score in four domains: 1. Awareness of Surroundings 2. Frightening Experiences 3. Recall of Experiences 4. Satisfaction with Care	90 days post randomisation
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 until primary outcome is reached
Anxiety and depression*	Hospital Anxiety and Depression Scale (HADS) questionnaire	180 days post randomisation
Post-traumatic stress*	Impact of Events Scale-revised (IES-R)	180 days post randomisation
Cognitive function*	Montreal Cognitive Assessment Tool (Telephone version) (TMoCA)	180 days post randomisation

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 (see section 11).

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.[37 38] This enables a highly efficient trial design that maximises efficiency and restricts the overall Type 1 error rate to at most 6.5%, with the upper limit being as low as 5% if the Stage 1 test for superiority of clonidine to propofol does not show a significant benefit. 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 39]
2. higher delirium risk as defined by the validated PRE-DELIRIC delirium risk prediction score, using the version assessing at 24 hours post-admission[40] *(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)*
4. age ≥64 years versus age <64 years *(this cut-off was found to interact with mortality in the SPICE III trial, with younger patients experiencing higher mortality at 90 days with dexmedetomidine, and older patients experiencing*

lower mortality at 90 days with dexmedetomidine; clonidine was not used in the SPICE trial)[62]

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[41]).
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 database is locked. It will not be feasible to guarantee blinding for post hospital discharge outcomes, but blinding will be achieved where possible.

3.7 STUDY DETAIL

3.7.1 Internal pilot and overall recruitment strategy

Participants will be recruited from approximately fifty sites and we aim to set these up at an average rate of 3 sites per month. The internal pilot study will comprise those sites recruiting during the first 9 months of recruitment. Our target recruitment rate is around 2 patients per month per centre. This assumes 40-50% recruitment of eligible cases, which is similar to recent sedation and delirium trials.[21 42]

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 40-50 sites by recruitment month 14 (approximately 239 centre months), and steady state of 40-50 sites for the final 16 months of recruitment (approximately 640 centre months).

The total centre months will be approximately 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 40-50 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 1437 (479 per trial group).

4.3 INCLUSION CRITERIA

1. Patient requiring MV in an ICU

2. Aged 18 or over
3. Within 48 hours of first episode of mechanical ventilation in 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, 4]
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
18. Patient known to have experienced a period with heart rate <50 beats per minute for 60 minutes or longer since commencing mechanical ventilation in the ICU

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]Home ventilation does not include patients receiving night-time CPAP and/or BIPAP therapy for the treatment of obstructive sleep apnoea syndrome.

4.5 CO-ENROLMENT

Co-enrolment to other studies will be permitted in cases where the Chief Investigators and/or trial management teams of both studies agree that co-enrolment is appropriate. In coming to a decision they must consider the scientific and practical implications of co-enrolment, specifically the safety of study participants, the interventions involved, participant burden and the potential impact on the study endpoints. Relevant UK guidance for critical care trials and/or relevant sponsor and local standard operating procedures and policies will be followed (e.g. ACCORD POL008).

Co-enrolment with other concurrent Clinical Trials of Investigational Medicinal products (CTIMPs) will not be permitted.

Co-enrolment with non-CTIMP intervention studies will be permitted if an agreement has been reached between the Chief Investigators and a signed agreement is in place 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 and authorised by the sponsor.

Co-enrolment with purely non-interventional research studies (e.g. questionnaire studies; observational studies) will be permitted if agreement has been reached between the Chief Investigators. A signed co-enrolment agreement is not required, but the agreement of the Cis for both studies will be documented.

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 3. 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 co-investigators 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 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 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 will seek written consent at the time of 30 day follow-up by sending a PIS and consent form by post. The patient will be asked to return the signed consent form if they wish to remain in the trial, or contact the study team if they wish to be withdrawn. If the patient does not return the signed consent form but does not ask to be withdrawn from the trial, the ProfLR and/or PerLR consent will remain valid and the patient will remain in the trial. In this event, a further PIS and consent form will be sent with the 90 days and if necessary the 180 days follow-up questionnaires and the patient will be asked to return a signed consent. As for 30 days, if the patient does not return the signed consent form but does not ask to be withdrawn from the trial, the ProfLR and/or PerLR consent will remain valid and the patient will remain in the trial. No further requests to return a consent form will be sent after the 180 day follow-up.

The Consent Form will indicate 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; 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 irrespective of their duration. 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 the first episode 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. If the randomisation system is not available then please contact the trial office.

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 α2-agonist is 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. 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 e.g. for patients on high doses of norepinephrine or those in whom there is concern about low baseline heart rate.

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. 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 e.g. for patients on high doses of norepinephrine or those in whom there is concern about low baseline heart rate.

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 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.
- 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 following randomisation 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, which may include the use of dexmedetomidine or clonidine.

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. If this is not feasible, the intervention should stop but follow up should be completed wherever possible.

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 least awake 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[43]. 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 (Appendix 2) 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, particularly once the maximum tolerated dose of intervention drug is reached.

5.9.2 Management of participants with cardiovascular instability

5.9.2.1 Patients requiring norepinephrine or other vasopressors for treatment of shock

Patients receiving norepinephrine or other vasopressors at the time of eligibility and randomisation can be commenced on dexmedetomidine or clonidine according to group allocation. The starting dose of allocated sedative is at the discretion of the clinical team. However, as guidance, where the dose of norepinephrine is more than 0.15 micrograms/kg/min it is suggested than a lower starting dose of dexmedetomidine or clonidine may be used, at least until the existing propofol infusion rate is reduced.

5.9.2.2 Patients who develop severe or worsening hypotension during the intervention period

Any patient who develops hypotension should be managed according to local protocols and practice, for example with fluids and vasopressor drugs. All three sedative drugs (propofol, dexmedetomidine, and clonidine) can decrease blood pressure. If changes to sedation are made the first drug to be decreased should be the non-intervention drug according to group allocation, unless this is clinically contraindicated. The guidance for adjusting drug doses in relation to sedation state provided in appendix 2 applies equally whether or not patients are receiving vasopressors.

If a patient experiences worsening hypotension and/or escalating doses of norepinephrine/vasopressors during treatment, the use of sedative drugs should be

reviewed especially when deep sedation is required and/or combinations of sedative agents are being used. Medical review is recommended. For patients in the dexmedetomidine and clonidine groups it is recommended that the rate of the drug infusion is reduced or if necessary, stopped until cardiovascular stability is achieved (see appendix 2). It is important to remember that both the sedative and cardiovascular effects of dexmedetomidine and clonidine can persist for several hours after reducing or stopping the drug dose. Clonidine is likely to take longer than dexmedetomidine to wear off, especially in the presence of renal impairment or failure (see section 5.9.4 below). The drugs can be re-started and/or up-titrated again once the patient is more stable. The research team should encourage re-establishing the clonidine or dexmedetomidine, but the decision to do so will be at the discretion of the clinical teams.

5.9.2.3 Patients who develop significant bradycardia during the intervention period
Dexmedetomidine and clonidine both commonly decrease heart rate. If a participant in the trial develops severe bradycardia during the intervention, the dose of sedative drug can be reduced or if necessary, stopped.
In the dexmedetomidine or clonidine groups, if the patient's heart rate decreases to less than 50/minute, the dexmedetomidine or clonidine should be temporarily stopped until the heart rate increases to greater than 50/minute.
Advice from the medical team should be obtained when the bedside nurse has clinical concerns. Treatment should follow usual local practices for managing bradycardia. This may include the use of glycopyrolate, atropine, dobutamine, norepinephrine or epinephrine, according to advice from the medical team.

Once the patient is more stable, clonidine or dexmedetomidine can be re-started and/or up-titrated again at a dose appropriate to the sedation target, but caution should be used when the clinical target is deep sedation . The research team should encourage re-establishing the clonidine or dexmedetomidine, but the decision to do so will be at the at the discretion of the clinical teams.

5.9.3 Management of participants with other dose limiting side effects.

If a participant in the trial develops other suspected sedation related side effects, medical review is recommended. For patients in the dexmedetomidine and clonidine groups it is recommended that the rate of the drug infusion is reduced or if necessary, stopped to determine whether symptoms improve. If symptoms do resolve, clonidine or dexmedetomidine can be re-started and/or up-titrated again. The research team should encourage re-establishing the clonidine or dexmedetomidine, but the decision to do so will be at the at the discretion of the clinical teams.

5.9.4 Patients in whom deep sedation is requested by the clinical team

Where the clinical team has requested deep sedation this should be recorded on the daily nursing shift form. The way deep sedation is maintained is under the guidance of the clinical team, but it is suggested that for patients receiving dexmedetomidine or clonidine these drugs are titrated up to the maximum tolerated dose according to the infusion algorithm. If additional sedative drug is needed to achieve target sedation this can be achieved with propofol or benzodiazepine according to the preference of the caring clinician.
Caution should be used in the dexmedetomidine and clonidine groups when deep sedation is indicated and the patient develops bradycardia (heart rate <50/minute) and/or worsening hypotension or increasing norepinephrine requirements. In these situations the clonidine or dexmedetomidine should be reduced or if necessary, stopped and medical advice obtained (see sections 5.9.2.2 and 5.9.2.3 above).

Sedation may need to be provided using a lower dose of dexmedetomidine or clonidine with addition of other sedatives if required. It should be remembered that it may take several hours for effects from dexmedetomidine and clonidine to wear off (see section 5.9.4 below)

When deep sedation is no longer requested by the caring clinician, Clonidine or dexmedetomidine should be re-established as the main IV sedative according the the algorithm in Appendix 2. It is suggested that any propofol or benzodiazepine sedation is decreased and stopped prior to reducing the dose of dexmedetomidine or clonidine. However, management is at the discretion of the caring clinician.

5.9.5 Duration of effects following reduction or discontinuation of study drug

The 'elimination half life' of dexmedetomidine is typically around 2 hours and is not altered by renal failure. This means that after a dose change a new steady state of clinical sedation effect is expected after around 2-4 hours. After completely stopping the drug, the sedation effects would be expected to disappear substantially over the next 1-2 hours and be almost completely gone after 4-6 hours.

The 'elimination half life' for clonidine is significantly longer than for dexmedetomidine and is typically around 13 hours ranging between 10 and 20 hours. In addition, renal failure can substantially prolong the elimination of clonidine from the body. More variation between individuals is expected for clonidine than for dexmedetomidine. This means that after a dose change a new steady state of clinical sedation effect could take longer to achieve with clonidine than with dexmedetomidine. Similarly, after completely stopping the drug, the sedation effects of clonidine may be slower to wear off than dexmedetomidine. This is likely to be more pronounced for patients who have received the drug for longer periods at higher doses or who have renal impairment.

5.9.6 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 adhere to 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.

Advice for weaning participants on each intervention is given in Appendix 2, in the bedside advice sheets.

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) Intervention only – follow-up and data linkage permitted

(ii) Intervention and follow-up only – data linkage permitted

(iii) All aspects of the trial and follow-up

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 4.1% 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.[44] 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.[45]

Alpha-2 agonists can have biphasic cardiovascular effects especially after loading or bolus dosing.[45] 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.[46] 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.[47] 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 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:
Propofol 10mg/ml (1%) emulsion for injection or infusion
Propofol 20mg/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 – Glenwood GmbH, Pharmazeutische Erzeugnisse, Arabellastr. 17, 81925 Munich, Germany.

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

Propofol– 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 - Glenwood GmbH, Pharmazeutische Erzeugnisse, Arabellastr. 17, 81925 Munich, Germany under marketing authorisation number PL 22824/0009.

Dexdor – Orion Corporation, Orionintie 1, FI-02200 Espoo, Finland under marketing authorisation number PLGB 27925/0104

Propofol – 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 with 5% glucose or 0.9% sodium chloride solution to a concentration of 8 micrograms per mL in syringes or fluid bags with a total volume according to local practice.

Clonidine will be diluted with 5% glucose or 0.9% sodium chloride solution to a concentration of 15 micrograms per mL in syringes or fluid bags with a total volume according to local practice.

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). Lower starting doses can be used at clinical discretion for patients with cardiovascular instability. Patients who weigh greater than 100kg will be dosed using the regimen suggested for 100kg weight. The trial management team can be contacted for specific advice prior to randomisation if required. For patients who weigh less than 45kg, it is suggested that advice is sought from the trial management team prior to randomisation.

For individual patients, it is recommended that the weight-based dose regimen closest to the weight on the dosing chart is used.

Flow charts (Appendix 2) 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 evaluated as part of the process evaluation. Training materials to support protocol compliance will be provided to sites, and uptake and engagement with these materials will also be examined as part of the process evaluation.

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 or 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.

During the intervention period, clonidine should not be used for first line (post-randomisation) sedation in patients allocated to the dexmedetomidine group and conversely dexmedetomidine should not be used for first line sedation (post-randomisation) in patients allocated to the clonidine group.

In the usual care (propofol) group, neither clonidine nor dexmedetomidine should be used as first line sedation during the intervention period. Either drug can be used at the discretion of the clinical teams for specific indications such as agitation or severe delirium or during difficult weaning. In these situations, the use of clonidine or dexmedetomidine should be recorded in the CRF.

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.

Caution should be used when large doses of propofol are required in addition to clonidine or dexmedetomidine to achieve the desired sedation state, because of the potential for cardiovascular instability.

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, or is -3 but the assessor is unable to assess CAM-ICU status), 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 (based on first 24 hours in ICU), 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; based on first 24 hours in ICU).

7.3 DAILY DATA COLLECTION DURING ICU STAY

The following data will be collected on a daily basis during ICU stay until the participant has had the primary outcome confirmed or for up to 28 days after randomisation (whichever occurs sooner).

7.3.1 Data recorded by bedside clinical nurse

Clinician decision to maintain deep sedation during nursing shift; reason for deep sedation (if required); 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 until the primary outcome is confirmed (or day 28) 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). No other drugs need to be recorded.

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 from study ICU (and other ICU if applicable), Date/time of final extubation

7.5 HOSPITAL DISCHARGE DATA

Date of acute 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 locally by staff at study sites. Follow-up at 90 days and 180 days will be undertaken either locally by staff at study sites or centrally, by staff based in Edinburgh. We will also send a short study update with the 90 day and 180 day follow-up questionnaires (if being completed by post)..

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

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); health related quality of life (EQ-5D-5L); health resource use questionnaire. (Note: these outcomes will not be collected for patients recruited during the final months of the trial recruitment period, as agreed with the funder and TSC as a strategy to enable trial completion within budget).

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

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. (Note: these outcomes will not be collected for patients recruited during the final months of the trial recruitment period, as agreed with the funder and TSC as a strategy to enable trial completion within budget).

7.6.4 Survival status

Survival will be collected up to 180 days post-randomisation. (Note: this outcome will not be collected for patients recruited during the final months of the trial recruitment period, as agreed with the funder and TSC as a strategy to enable trial completion within budget).

Table 2: Table of Assessments. $Note that for patients recruited during the final months of

	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						
Sepsis substudy only - 2 blood samples for inflammatory markers • Baseline sample (within 12 hours post randomisation) • 60 hour sample (within 48-72 hours post randomisation)		X						
Daily data collection during ICU stay until primary outcome confirmed or day 28 – clinical team (4hrly - RASS score and pain assessment; 12hrly – CAM-ICU, SQAT, co-operation and communication assessment)			X					
Daily data collection during ICU stay until primary outcome confirmed or day 28 – research team (MV data collection, IMP and drug usage, SOFA score, adverse event data collection)			X					
Assessment of comfort and communication by informant until primary outcome confirmed or day 28			X					
Adverse Event data collection until ICU discharge			X					
ICU and hospital discharge data				X	X			
Mortality			X	X	X	X	X	X
Intensive Care Experience Questionnaire (ICE-Q)							X	
Hospital Anxiety and Depression Scale (HADS) questionnaire								X
Impact of Events Scale – revised (IES-R)								X
Montreal Cognitive Assessment Tool (Telephone version - TMoCA)								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

trial recruitment, the 90 and 180 days follow will be truncated and not collected. This was agreed with the TSC and funder to reduce trial costs and enable trial completion.

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 as well as the name of the Personal Legal representative who gave their consent.

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. Following data analysis the database will be archived by programmers in ECTU. This archived database will be stored on University of Edinburgh servers once user access has been disabled. Access to the archived database will be controlled by the Chief Investigator.

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 459 per arm (1377 patients in total, 1093 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), 459 patients per arm (918 in total, 741 extubation events) provides 80% power to conclude non-inferiority of clonidine, using a one-sided 4% significance level. The power calculation for the superiority comparison of dexmedetomidine versus clonidine (test H4) is the same as that for STAGE ONE.

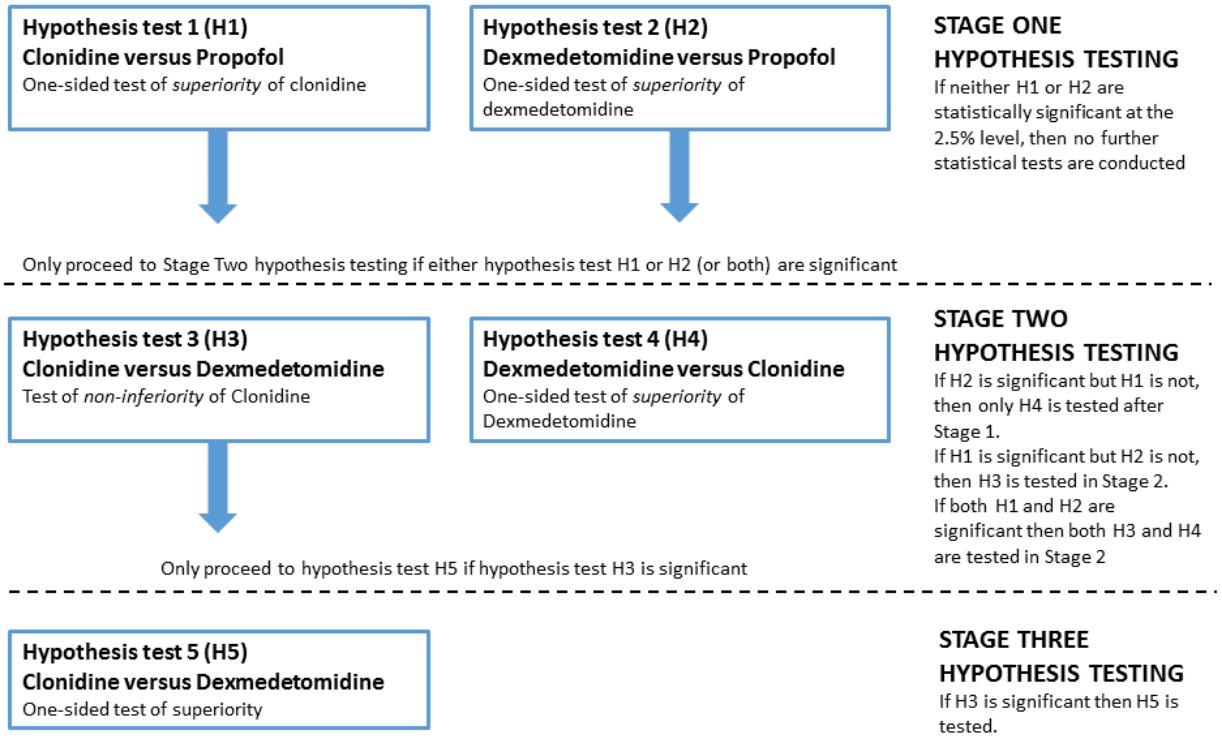


Figure 1: Analytic framework which efficiently tests the trial questions using a hierarchical analytic structure with serial gatekeeping to preserve study power. Hypothesis tests will be performed using a 2.5% one-sided significance level, with the exception of the non-inferiority test H3 which will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

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 (mean 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 1377 (459 per group) provides 80% 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 for H1 and a one-sided 4% significance level for H3.

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.[48-50] Some other patients may be lost if transferred to another ICU before reaching the primary endpoint. Experience during the first 950 participants randomised to A2B indicated a primary outcome loss to follow-up rate of 4.1%. Sample size is therefore inflated by this amount to allow for drop-out or loss to follow-up (479 per group (1437 in total).

8.1.3 Final sample size

A sample size of 1437 (479 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 459 per group provides 76% 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).[51-53] 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. As an exploratory analysis, the main analysis of the primary outcome will be repeated using the adherence analysis set (section 8.2.3) rather than the full analysis set.

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

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

8.2.4 Exploratory analyses

Exploratory analyses will be undertaken where appropriate to explore whether the effects of the interventions on important outcomes were associated with differences in the way the intervention protocol was implemented, either at a centre level or a patient level. These analyses will be exploratory and will include the use of data from the process evaluation if appropriate. Details of a priori defined analyses will be included in the Statistical Analysis Plan; any post-hoc analyses will be documented separately.

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 context 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 delivered as intended (fidelity, dose, and reach), 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 organisational structure and processes) that affect intervention implementation and delivery.

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 deliver 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 and enablers, organisational processes affecting sedation practice, and any other processes that might affect operationalisation of the study. These data will inform feasibility and any changes required to maximise recruitment and fidelity to the trial protocol.

During main study: A purposive sample of sites (approximately 10) will selected at which staff will be interviewed (either in-person or remotely via tele/video conference) to obtain information regarding the implementation process including acceptability of the intervention, barriers and facilitators to implementation and delivery, and clinical decisions impacting upon fidelity to the protocol.

Final site visits or consultations: Individual and small group interviews with staff involved in trial implementation and/or intervention delivery will be conducted either in-person or remotely via tele/video conference. 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, and enablers, and organisational processes affecting sedation practice.

9.3 DATA ANALYSIS

We will use a 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 trial implementation and intervention delivery.

Routinely collected quantitative trial data will be interpreted using descriptive statistics, and examined alongside the qualitative data to understand intervention fidelity, dose, and reach.

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. Of importance, the cost of dexmedetomidine has decreased substantially during the conduct of the trial, such that the cost-effectiveness of the

interventions may be different in the context of pricing in the 'post trial' era. 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[54]. 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[54].

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.[55 56 57]

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).[58] We will use this approach and 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).[59] 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.[60] 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[61]. 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[62]. Survival analysis of the RCT data will provide the basis for extrapolating any within-trial differences in costs and QALYs[63]. 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.[63] 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.[63]

11. MECHANISTIC SUB-STUDY

In the sub-group of participants with sepsis, consent will be sought to collect blood samples. For the sub-group in whom consent is obtained, a 20mL blood sample will be collected at two timepoints:

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

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 use several methods to explore whether there are differences in inflammation

and/or immune function between the trial sub-groups with sepsis at baseline, and how these relate to trial outcomes. 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. Where appropriate, we will also measure a panel of circulating 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.

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 intervention period will continue until the patient is weaned from MV and sedation in the ICU.

The interventions with IMP will continue until the patient is weaned from MV which will exclusively occur in the ICU. The protocolised intervention will also end if the participant has been on the study for 28 days and has not reached the primary outcome or is transferred to an ICU at another non-participating hospital. Clinical and research staff will monitor participants for adverse events (AEs) and serious adverse events (SAEs) until ICU discharge. 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 (e.g. 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/SAEs if the Investigator considers they may relate to participation in the trial or if they were not consistent with the patient's critical illness and/or expected worsening of an underlying medical condition

Sedation related adverse events, and well recognised defined potential side effects of alpha-2 agonists (bradycardia, hypotension, ileus), are collected daily during the intervention period 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 or if the medical Investigator considers that it may be related to trial participation

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 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 unless the medical Investigator considers that they may be related to trial participation.

12.4 ASSESSMENT OF AES AND SAES

Seriousness, causality, severity and expectedness will be assessed by the Principal Investigator or another Investigator who is a suitably qualified physician, trained in recording and reporting AEs, who has been delegated this role. As this is an unblinded trial, Investigators can take group allocation into account when assessing AEs and SAEs.

The Investigator 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 involving 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 2018-001650-98' 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).

The publication plan will be consistent with the policy of the funder.

16.3 DATA SHARING

The final trial dataset will be held by the University of Edinburgh on a secure password protected drive. A file, or set of files, containing an anonymised version of the final analysis data set will be prepared, along with a data dictionary. These will be made available to the Chief Investigator at the end of the analysis phase. 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 follow locally approved governance proesses.

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

1. Adhikari NK, Fowler RA, Bhagwanjee S, et al. Critical care and the global burden of critical illness in adults. *Lancet (London, England)* 2010;376(9749):1339-46. doi: 10.1016/s0140-6736(10)60446-1 [published Online First: 2010/10/12]
2. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Critical care medicine* 2013;41(1):263-306. doi: 10.1097/CCM.0b013e3182783b72 [published Online First: 2012/12/28]
3. Vincent JL, Shehabi Y, Walsh TS, et al. Comfort and patient-centred care without excessive sedation: the eCASH concept. *Intensive care medicine* 2016;42(6):962-71. doi: 10.1007/s00134-016-4297-4 [published Online First: 2016/04/15]
4. Reade MC, Finfer S. Sedation and delirium in intensive care. *The New England journal of medicine* 2014;370(16):1567. doi: 10.1056/NEJMc1402402 [published Online First: 2014/04/18]
5. Jackson DL, Proudfoot CW, Cann KF, et al. A systematic review of the impact of sedation practice in the ICU on resource use, costs and patient safety. *Critical care (London, England)* 2010;14(2):R59. doi: 10.1186/cc8956 [published Online First: 2010/04/13]
6. Shehabi Y, Bellomo R, Reade MC, et al. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. *American journal of respiratory and critical care medicine* 2012;186(8):724-31. doi: 10.1164/rccm.201203-0522OC [published Online First: 2012/08/04]
7. Balzer F, Weiss B, Kumpf O, et al. Early deep sedation is associated with decreased in-hospital and two-year follow-up survival. *Critical care (London, England)* 2015;19:197. doi: 10.1186/s13054-015-0929-2 [published Online First: 2015/05/01]
8. Burry L, Rose L, McCullagh IJ, et al. Daily sedation interruption versus no daily sedation interruption for critically ill adult patients requiring invasive mechanical ventilation. *The Cochrane database of systematic reviews* 2014(7):Cd009176. doi: 10.1002/14651858.CD009176.pub2 [published Online First: 2014/07/10]
9. Aitken LM, Bucknall T, Kent B, et al. Protocol-directed sedation versus non-protocol-directed sedation to reduce duration of mechanical ventilation in mechanically ventilated intensive care patients. *The Cochrane database of systematic reviews* 2015;1:Cd009771. doi: 10.1002/14651858.CD009771.pub2 [published Online First: 2015/01/07]
10. Nikayin S, Rabiee A, Hashem MD, et al. Anxiety symptoms in survivors of critical illness: a systematic review and meta-analysis. *General hospital psychiatry* 2016;43:23-29. doi: 10.1016/j.genhosppsych.2016.08.005 [published Online First: 2016/11/01]
11. Parker AM, Sricharoenchai T, Raparla S, et al. Posttraumatic stress disorder in critical illness survivors: a metaanalysis. *Critical care medicine* 2015;43(5):1121-9. doi: 10.1097/ccm.0000000000000882 [published Online First: 2015/02/06]
12. Rabiee A, Nikayin S, Hashem MD, et al. Depressive Symptoms After Critical Illness: A Systematic Review and Meta-Analysis. *Critical care medicine* 2016;44(9):1744-53. doi: 10.1097/ccm.0000000000001811 [published Online First: 2016/05/07]
13. Aitken LM, Castillo MI, Ullman A, et al. What is the relationship between elements of ICU treatment and memories after discharge in adult ICU survivors? *Australian critical care : official journal of the Confederation of Australian Critical Care Nurses* 2016;29(1):5-14; quiz 15. doi: 10.1016/j.aucc.2015.11.004 [published Online First: 2016/01/19]
14. Rattray JE, Johnston M, Wildsmith JA. Predictors of emotional outcomes of intensive care. *Anaesthesia* 2005;60(11):1085-92. doi: 10.1111/j.1365-2044.2005.04336.x [published Online First: 2005/10/19]

15. Wade D, Hardy R, Howell D, et al. Identifying clinical and acute psychological risk factors for PTSD after critical care: a systematic review. *Minerva anestesiologica* 2013;79(8):944-63. [published Online First: 2013/04/06]
16. Salluh JI, Wang H, Schneider EB, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. *BMJ (Clinical research ed)* 2015;350:h2538. doi: 10.1136/bmj.h2538 [published Online First: 2015/06/05]
17. Lone NI, Seretny M, Wild SH, et al. Surviving intensive care: a systematic review of healthcare resource use after hospital discharge*. *Critical care medicine* 2013;41(8):1832-43. doi: 10.1097/CCM.0b013e31828a409c [published Online First: 2013/06/21]
18. Lone NI, Gillies MA, Haddow C, et al. Five-Year Mortality and Hospital Costs Associated with Surviving Intensive Care. *American journal of respiratory and critical care medicine* 2016;194(2):198-208. doi: 10.1164/rccm.201511-2234OC [published Online First: 2016/01/28]
19. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *The New England journal of medicine* 2013;369(14):1306-16. doi: 10.1056/NEJMoa1301372 [published Online First: 2013/10/04]
20. Zaal IJ, Slooter AJ. Delirium in critically ill patients: epidemiology, pathophysiology, diagnosis and management. *Drugs* 2012;72(11):1457-71. doi: 10.2165/11635520-000000000-00000 [published Online First: 2012/07/19]
21. Walsh TS, Kydonaki K, Antonelli J, et al. Staff education, regular sedation and analgesia quality feedback, and a sedation monitoring technology for improving sedation and analgesia quality for critically ill, mechanically ventilated patients: a cluster randomised trial. *The Lancet Respiratory medicine* 2016;4(10):807-17. doi: 10.1016/s2213-2600(16)30178-3 [published Online First: 2016/07/31]
22. Richards-Belle A, Canter RR, Power GS, et al. National survey and point prevalence study of sedation practice in UK critical care. *Critical care (London, England)* 2016;20(1):355. doi: 10.1186/s13054-016-1532-x [published Online First: 2016/10/30]
23. Cruickshank M, Henderson L, MacLennan G, et al. Alpha-2 agonists for sedation of mechanically ventilated adults in intensive care units: a systematic review. *Health technology assessment (Winchester, England)* 2016;20(25):v-xx, 1-117. doi: 10.3310/hta20250 [published Online First: 2016/04/02]
24. Chen K, Lu Z, Xin YC, et al. Alpha-2 agonists for long-term sedation during mechanical ventilation in critically ill patients. *The Cochrane database of systematic reviews* 2015;1:Cd010269. doi: 10.1002/14651858.CD010269.pub2 [published Online First: 2015/04/17]
25. Wang JG, Belley-Cote E, Burry L, et al. Clonidine for sedation in the critically ill: a systematic review and meta-analysis. *Critical care (London, England)* 2017;21(1):75. doi: 10.1186/s13054-017-1610-8 [published Online First: 2017/03/24]
26. Su X, Meng ZT, Wu XH, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. *Lancet (London, England)* 2016;388(10054):1893-902. doi: 10.1016/s0140-6736(16)30580-3 [published Online First: 2016/10/19]
27. Reade MC, Eastwood GM, Bellomo R, et al. Effect of Dexmedetomidine Added to Standard Care on Ventilator-Free Time in Patients With Agitated Delirium: A Randomized Clinical Trial. *Jama* 2016;315(14):1460-8. doi: 10.1001/jama.2016.2707 [published Online First: 2016/03/16]
28. Kawazoe Y, Miyamoto K, Morimoto T, et al. Effect of Dexmedetomidine on Mortality and Ventilator-Free Days in Patients Requiring Mechanical Ventilation With Sepsis: A Randomized Clinical Trial. *Jama* 2017;317(13):1321-28. doi: 10.1001/jama.2017.2088 [published Online First: 2017/03/23]
29. Pandharipande PP, Sanders RD, Girard TD, et al. Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an a priori-designed analysis of the MENDS randomized controlled trial. *Critical care (London,*

England) 2010;14(2):R38. doi: 10.1186/cc8916 [published Online First: 2010/03/18]
30. Shehabi Y, Serpa Neto A, Howe BD, et al. Early sedation with dexmedetomidine in ventilated critically ill patients and heterogeneity of treatment effect in the SPICE III randomised controlled trial. *Intensive Care Med* 2021;47(4):455-66. doi: 10.1007/s00134-021-06356-8 [published Online First: 2021/03/10]
31. Hughes CG, Mailloux PT, Devlin JW, et al. Dexmedetomidine or Propofol for Sedation in Mechanically Ventilated Adults with Sepsis. *N Engl J Med* 2021;384(15):1424-36. doi: 10.1056/NEJMoa2024922 [published Online First: 2021/02/03]
32. Moore GF, Audrey S, Barker M, et al. Process evaluation of complex interventions: Medical Research Council guidance. *BMJ (Clinical research ed)* 2015;350:h1258. doi: 10.1136/bmj.h1258 [published Online First: 2015/03/21]
33. Craig P, Dieppe P, Macintyre S, et al. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ (Clinical research ed)* 2008;337:a1655. doi: 10.1136/bmj.a1655 [published Online First: 2008/10/01]
34. Walsh TS, Kydonaki K, Lee RJ, et al. Development of Process Control Methodology for Tracking the Quality and Safety of Pain, Agitation, and Sedation Management in Critical Care Units. *Critical care medicine* 2016;44(3):564-74. doi: 10.1097/ccm.0000000000001463 [published Online First: 2016/02/24]
35. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *Jama* 2001;286(21):2703-10. [published Online First: 2001/12/26]
36. Rattray J, Johnston M, Wildsmith JA. The intensive care experience: development of the ICE questionnaire. *Journal of advanced nursing* 2004;47(1):64-73. doi: 10.1111/j.1365-2648.2004.03066.x [published Online First: 2004/06/10]
37. Alosh M, Bretz F, Huque M. Advanced multiplicity adjustment methods in clinical trials. *Statistics in medicine* 2014;33(4):693-713. doi: 10.1002/sim.5974 [published Online First: 2013/10/10]
38. Dmitrienko A, Tamhane, A. C., & Bretz, F. (Eds.). (2009). Chapman and Hall/CRC. Multiple testing problems in pharmaceutical statistics.: Chapman and Hall/CRC 2009.
39. Sanders RD, Hussell T, Maze M. Sedation & immunomodulation. *Anesthesiology clinics* 2011;29(4):687-706. doi: 10.1016/j.anclin.2011.09.008 [published Online First: 2011/11/15]
40. van den Boogaard M, Pickkers P, Slooter AJ, et al. Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study. *BMJ (Clinical research ed)* 2012;344:e420. doi: 10.1136/bmj.e420 [published Online First: 2012/02/11]
41. Wolf A, McKay A, Spowart C, et al. Prospective multicentre randomised, double-blind, equivalence study comparing clonidine and midazolam as intravenous sedative agents in critically ill children: the SLEEPS (Safety profiLe, Efficacy and Equivalence in Paediatric intensive care Sedation) study. *Health technology assessment (Winchester, England)* 2014;18(71):1-212. doi: 10.3310/hta18710 [published Online First: 2015/06/23]
42. Page VJ, Ely EW, Gates S, et al. Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial. *The Lancet Respiratory medicine* 2013;1(7):515-23. doi: 10.1016/s2213-2600(13)70166-8 [published Online First: 2014/01/28]
43. Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale

(RASS). *Jama* 2003;289(22):2983-91. doi: 10.1001/jama.289.22.2983 [published Online First: 2003/06/12]
44. Gertler R, Brown HC, Mitchell DH, et al. Dexmedetomidine: a novel sedative-analgesic agent. *Proceedings (Baylor University Medical Center)* 2001;14(1):13-21. [published Online First: 2005/12/22]
45. Nguyen V, Tiemann D, Park E, et al. Alpha-2 Agonists. *Anesthesiology clinics* 2017;35(2):233-45. doi: 10.1016/j.anclin.2017.01.009 [published Online First: 2017/05/21]
46. Li A, Yuen VM, Goulay-Dufay S, et al. Pharmacokinetics and pharmacodynamics of dexmedetomidine. *Drug development and industrial pharmacy* 2016;42(12):1917-27. doi: 10.1080/03639045.2016.1232727 [published Online First: 2016/09/07]
47. Jamadarkhana S, Gopal S. Clonidine in adults as a sedative agent in the intensive care unit. *Journal of anaesthesiology, clinical pharmacology* 2010;26(4):439-45. [published Online First: 2011/05/07]
48. Young D, Lamb SE, Shah S, et al. High-frequency oscillation for acute respiratory distress syndrome. *The New England journal of medicine* 2013;368(9):806-13. doi: 10.1056/NEJMoa1215716 [published Online First: 2013/01/24]
49. McAuley DF, Laffey JG, O'Kane CM, et al. Simvastatin in the acute respiratory distress syndrome. *The New England journal of medicine* 2014;371(18):1695-703. doi: 10.1056/NEJMoa1403285 [published Online First: 2014/10/01]
50. Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal-directed resuscitation for septic shock. *The New England journal of medicine* 2015;372(14):1301-11. doi: 10.1056/NEJMoa1500896 [published Online First: 2015/03/18]
51. Andersen PK, Geskus RB, de Witte T, et al. Competing risks in epidemiology: possibilities and pitfalls. *International journal of epidemiology* 2012;41(3):861-70. doi: 10.1093/ije/dyr213 [published Online First: 2012/01/19]
52. Noordzij M, Leffondre K, van Stralen KJ, et al. When do we need competing risks methods for survival analysis in nephrology? *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 2013;28(11):2670-7. doi: 10.1093/ndt/gft355 [published Online First: 2013/08/27]
53. Varadhan R, Weiss CO, Segal JB, et al. Evaluating health outcomes in the presence of competing risks: a review of statistical methods and clinical applications. *Medical care* 2010;48(6 Suppl):S96-105. doi: 10.1097/MLR.0b013e3181d99107 [published Online First: 2010/05/18]
54. NICE. Guide to the methods of technology appraisal 2013. 2013 April 2013. https://www.nice.org.uk/process/pmg9/chapter/foreword.
55. Campbell HE, Stokes EA, Bargo DN, et al. Quantifying the healthcare costs of treating severely bleeding major trauma patients: a national study for England. *Critical care (London, England)* 2015;19:276. doi: 10.1186/s13054-015-0987-5 [published Online First: 2015/07/08]
56. Curtis L BA. Unit Costs of Health and Social Care. In: Unit PSSR, ed. Kent, 2015.
57. Health. Do. National Schedule of Reference Costs. In: Health Do, ed. London, 2015.
58. Endovascular strategy or open repair for ruptured abdominal aortic aneurysm: one-year outcomes from the IMPROVE randomized trial. *European heart journal* 2015;36(31):2061-69. doi: 10.1093/eurheartj/ehv125 [published Online First: 2015/04/10]
59. [Available from: http://www.euroqol.org/eq-5d-products/eq-5d-5l/proxy-version.html accessed May 15th 2017.
60. Briggs AH, Wonderling DE, Mooney CZ. Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. *Health economics* 1997;6(4):327-40. [published Online First: 1997/07/01]

61. Dexmedetomidine for Sedation in the ICU or PICU: A Review of Cost-Effectiveness and Guidelines: Canadian Agency for Drugs and Technologies in Health; 2014 [Available from: https://www.cadth.ca/sites/default/files/pdf/htis/jan-2015/RC0617_Dexmedetomidine%20final.pdf accessed May 1st 2017.
62. Ridley S, Morris S. Cost effectiveness of adult intensive care in the UK. *Anaesthesia* 2007;62(6):547-54. doi: 10.1111/j.1365-2044.2007.04997.x [published Online First: 2007/05/18]
63. Briggs A SM, Claxton K. , editor. *Decision Modeling for Health Economic Evaluation*: Oxford University press, 2006.

18. APPENDIX 1: DRUG REGIMENS

18.1 CLONIDINE DRUG REGIMEN

Weight Based Infusion Rates in mls per hour for Clonidine 15micrograms 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	0.3	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

For patients who weigh less than 45kg, please contact the trial management team for specific advice prior to randomisation.

Patients who weigh greater than 100kg will be dosed using the regimen suggested for 100kg weight. Please contact the trial management team for advice if required prior to randomisation.

18.2 DEXMEDETOMIDINE DRUG REGIMEN

Weight Based Infusion Rates in mls per hour for Dexmedetomidine 8 micrograms 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	0.6	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

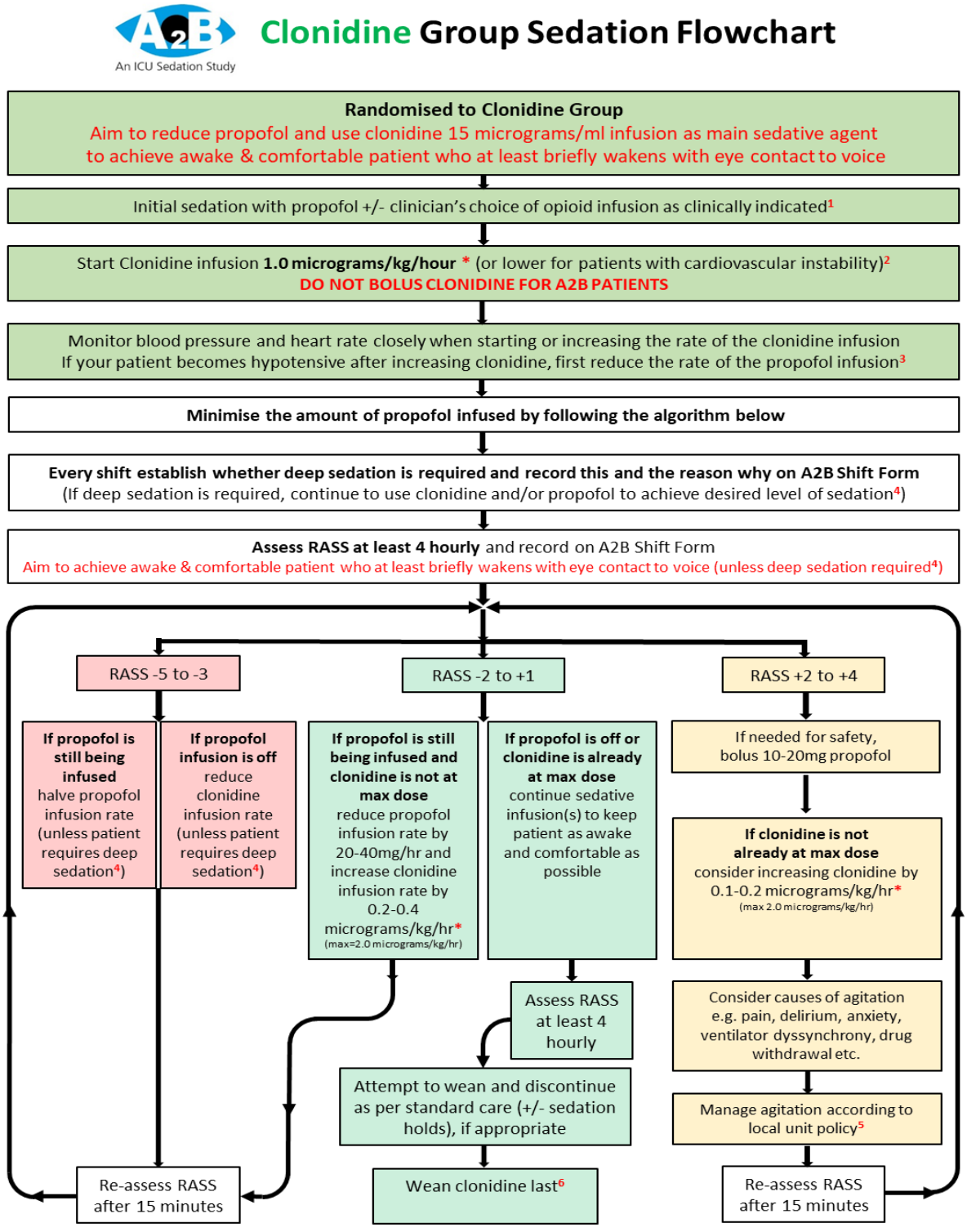
For patients who weigh less than 45kg, please contact the trial management team for specific advice prior to randomisation.

Patients who weigh greater than 100kg will be dosed using the regimen suggested for 100kg weight. Please contact the trial management team for advice if required prior to randomisation.

19. APPENDIX 2: GROUP SEDATION FLOWCHARTS

These flowcharts are intended as guidance for clinical teams, especially bedside nurses managing the patients. Decisions about sedation management that divert from this guidance can be made at the discretion of the clinical team, and do not necessarily need to be reported as protocol deviations.

19.1 CLONIDINE FLOWCHART



* See A2B Clonidine infusion table for mls/hr infusion rates for patient weight

[1] additional opioid boluses can be given as required

[2] if on more than 0.15 micrograms/kg/min noradrenaline to maintain target MAP, use lower starting dose initially

[3] PTO for advice on managing severe bradycardia or hypotension on the reverse of this page

[4] PTO for deep sedation advice on the reverse of this page

[5] dexmedetomidine should not be prescribed for the Clonidine group

[6] PTO for weaning advice on the reverse of this page

Academic and Clinical Central Office for Research and Development

CLONIDINE FLOWCHART – REVERSE

An ICU Sedation Study

An ICU Sedation Study

Clonidine Group Sedation

TARGET: most awake and comfortable state considered safe (the least awake target will be "briefly wakens with eye contact to voice")

- Primary sedative agent is **CLONIDINE** (diluted with 5% glucose or 0.9% NaCl solution to a concentration of **15 micrograms per ml**)
- **Aim to reduce/stop propofol infusion.**
- All patients should receive opioid infusions for analgesia as clinically indicated at the discretion of clinical teams.
- **NB Clonidine has analgesic properties, so it may be possible to reduce opioids if pain is well controlled.**

Drugs you should not give:

- **Dexmedetomidine should not be used as first line sedation during the intervention period.**

How to manage agitation (RASS +2 TO +4)

- Maintain patient/staff safety by bolusing propofol if needed.
- Once agitation is under control, try to identify and manage the cause, using local unit policy for the management of pain/delirium/anxiety/withdrawal etc.
- Anticipate and avoid agitation; use opioid analgesia in advance of uncomfortable or painful interventions or procedures.

What to do if my patient develops severe bradycardia

- **If your patient's heart rate decreases to less than 50 beats per minute, clonidine should be temporarily stopped.**
- Clonidine commonly decreases heart rate. If a participant in the trial develops significant bradycardia during the intervention, the clonidine rate can be reduced (or temporarily stopped, if HR<50).
- NB Clonidine's effect on heart rate can take several hours to resolve, so stopping the clonidine infusion may not immediately resolve bradycardia.
- Seek advice from medical staff who can review and prescribe glycopyrronium, atropine, dobutamine, adrenaline or other agents, as per your ICU policy.
- **Once the patient is more stable, clonidine can be re-started and/or up-titrated again at a dose appropriate to the sedation target,** but caution should be used when the clinical target is deep sedation (see below).

What to do if my patient becomes hypotensive

- **Hypotension should be treated as per local unit policy**. Continuous fluid infusions, fluid challenges and vasopressor infusions are all permitted for patients in the A2B Trial.
- If changes to sedation are required as a result of hypotension, propofol should be decreased before clonidine, unless clinically contraindicated e.g. if patient requires propofol for neuromuscular blockade (see below).
- Continue clonidine infusion unless causing haemodynamic compromise, such that target MAP cannot be maintained with 0.15 micrograms/kg/min of noradrenaline. If haemodynamically compromised, consider halving the rate of the clonidine infusion, then halving again, or stopping, as needed.
- NB Clonidine's effect on heart rate can take several hours to resolve, so stopping the clonidine infusion may not immediately resolve hypotension.
- **Once the patient is more stable, clonidine can be restarted and/or up-titrated again, at a dose appropriate to the sedation target**, but caution should be used when the clinical target is deep sedation (see below).

What if my patient requires deep sedation (RASS -3 TO -5) e.g. for neuromuscular blockade (muscle relaxant)?

- If medical staff have asked to keep your patient deeply sedated, please record the reason deep sedation was requested on the A2B Shift Form.
- **Patients who require neuromuscular blockade after randomisation must receive adequate sedation as per standard care, at the discretion of the treating clinician, to prevent awareness during paralysis. Clonidine alone may not provide adequate sedation to prevent awareness.**
- It is suggested that clonidine is titrated up to the maximum tolerated dose, but if additional sedative drugs are needed to achieve target deep sedation this can be achieved with propofol or benzodiazepine.
- When deep sedation is no longer requested by the caring clinician, aim to use clonidine as main sedative agent as per flowchart over page. It is suggested that any propofol or benzodiazepine sedation is decreased and stopped prior to reducing the dose of clonidine.

What if my patient needs an operative procedure/CT scan/MRI etc.?

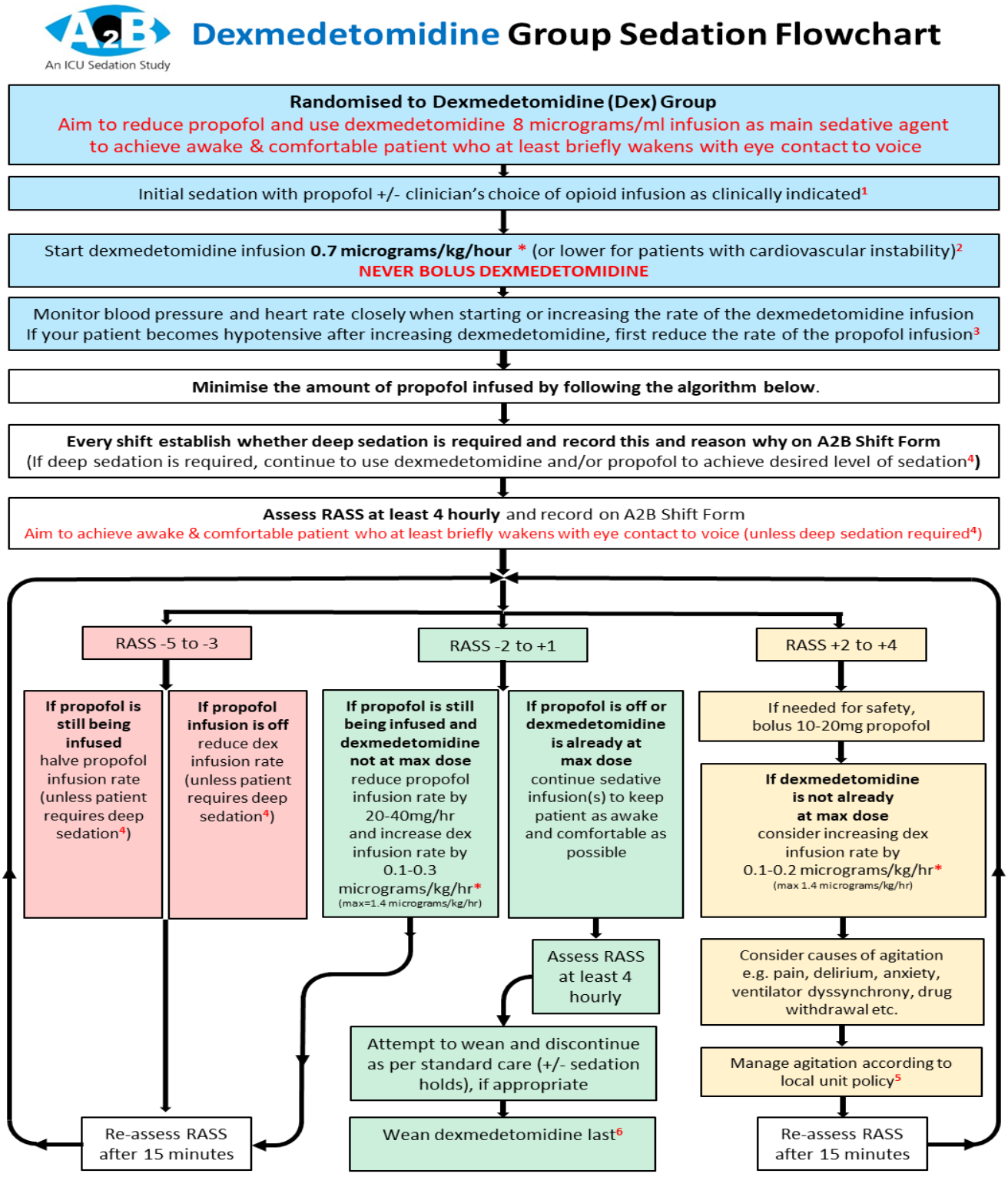
- Increase sedation for transfer if needed, using clonidine and/or propofol.
- If required, anaesthesia should be administered as per local perioperative guidelines.
- Continue clonidine infusion unless haemodynamically compromised, in which case consider halving infusion rate and halving again or stopping, as needed.
- Following the procedure, again aim to reduce propofol and use clonidine as main sedative agent as per flowchart over page.

Weaning and discontinuing Clonidine

- **Clonidine can be abruptly discontinued, but slower weaning should be used if withdrawal reactions occur (rebound hypertension or tachycardia, agitation, sweating etc.). However, this should not delay weaning from ventilation, as clonidine is relatively free from respiratory depressive effects, so can be safely continued post-extubation.**

PTO for Clonidine Group Sedation Flowchart on reverse of this page

19.2 DEXMEDETOMIDINE FLOWCHART



* See A2B Dexmedetomidine infusion table for mls/hr infusion rates for patient weight

[1] additional opioid boluses can be given as required

[2] if on more than 0.15 micrograms/kg/min noradrenaline to maintain target MAP, use lower starting dose initially

[3] PTO for advice on managing severe bradycardia or hypotension on the reverse of this page

[4] PTO for deep sedation advice on the reverse of this page

[5] clonidine should not be prescribed for the dexmedetomidine group

[6] PTO for weaning advice on the reverse of this page

DEXMEDETOMIDINE FLOWCHART – REVERSE

Dexmedetomidine (Dex) Group Sedation

An ICU Sedation Study

An ICU Sedation Study

TARGET: most awake and comfortable state considered safe (the least awake target will be "briefly wakens with eye contact to voice")

- Primary sedative agent is **DEXMEDETOMIDINE** (diluted with 5% glucose or 0.9% NaCl solution to a concentration of **8 micrograms per ml**)
- **Aim to reduce/stop propofol infusion.**
- All patients should receive opioid infusions for analgesia as clinically indicated at the discretion of clinical teams.
- **NB Dexmedetomidine has analgesic properties, so it may be possible to reduce opioids if pain is well controlled.**

Drugs you should not give:

- **Clonidine should not be used as first line sedation during the intervention period.**

How to manage agitation (RASS +2 TO +4)

- Maintain patient/staff safety by bolusing propofol if needed.
- Once agitation is under control, try to identify and manage the cause, using local unit policy for the management of pain/delirium/anxiety/withdrawal etc.
- Anticipate and avoid agitation; use opioid analgesia in advance of uncomfortable or painful interventions or procedures.

What to do if my patient develops severe bradycardia

- **If your patient's heart rate decreases to less than 50 beats per minute, dexmedetomidine should be temporarily stopped.**
- Dexmedetomidine commonly decreases heart rate. If a participant in the trial develops significant bradycardia during the intervention, the dexmedetomidine rate can be reduced (or temporarily stopped, if HR<50).
- NB Dexmedetomidine's effect on heart rate can take several hours to resolve, so stopping the dexmedetomidine infusion may not immediately resolve bradycardia.
- Seek advice from medical staff who can review and prescribe glycopyrronium, atropine, dobutamine, adrenaline or other agents, as per your ICU policy.
- **Once the patient is more stable, dexmedetomidine can be re-started and/or up-titrated again at a dose appropriate to the sedation target**, but caution should be used when the clinical target is deep sedation (see below).

What to do if my patient becomes hypotensive

- **Hypotension should be treated as per local unit policy**. Continuous fluid infusions, fluid challenges and vasopressor infusions are all permitted for patients in the A2B Trial.
- If changes to sedation are required as a result of hypotension, propofol should be decreased before dexmedetomidine, unless clinically contraindicated e.g. if patient requires propofol for neuromuscular blockade (see below).
- Continue dexmedetomidine infusion unless causing haemodynamic compromise, such that target MAP cannot be maintained with 0.15 micrograms/kg/min of noradrenaline. If haemodynamically compromised, consider halving the rate of the dexmedetomidine infusion, then halving again, or stopping, as needed.
- NB Dexmedetomidine's effect on blood pressure can take several hours to resolve, so stopping the dexmedetomidine infusion may not immediately resolve hypotension.
- **Once the patient is more stable, dexmedetomidine can be restarted and/or up-titrated again, at a dose appropriate to the sedation target**, but caution should be used when the clinical target is deep sedation (see below).

What if my patient requires deep sedation (RASS -3 TO -5) e.g. for neuromuscular blockade (muscle relaxant)?

- If medical staff have asked to keep your patient deeply sedated, please record the reason deep sedation was requested on the A2B Shift Form.
- **Patients who require neuromuscular blockade after randomisation must receive adequate sedation as per standard care at the discretion of the treating clinician, to prevent awareness during paralysis. Dexmedetomidine alone may not provide adequate sedation to prevent awareness.**
- It is suggested that dexmedetomidine is titrated up to the maximum tolerated dose, but if additional sedative drugs are needed to achieve target deep sedation this can be achieved with propofol or benzodiazepine.
- When deep sedation is no longer requested by the caring clinician, aim to use dexmedetomidine as main sedative agent as per flowchart over page. It is suggested that any propofol or benzodiazepine sedation is decreased and stopped prior to reducing the dose of dexmedetomidine.

What if my patient needs an operative procedure/CT scan/MRI etc.?

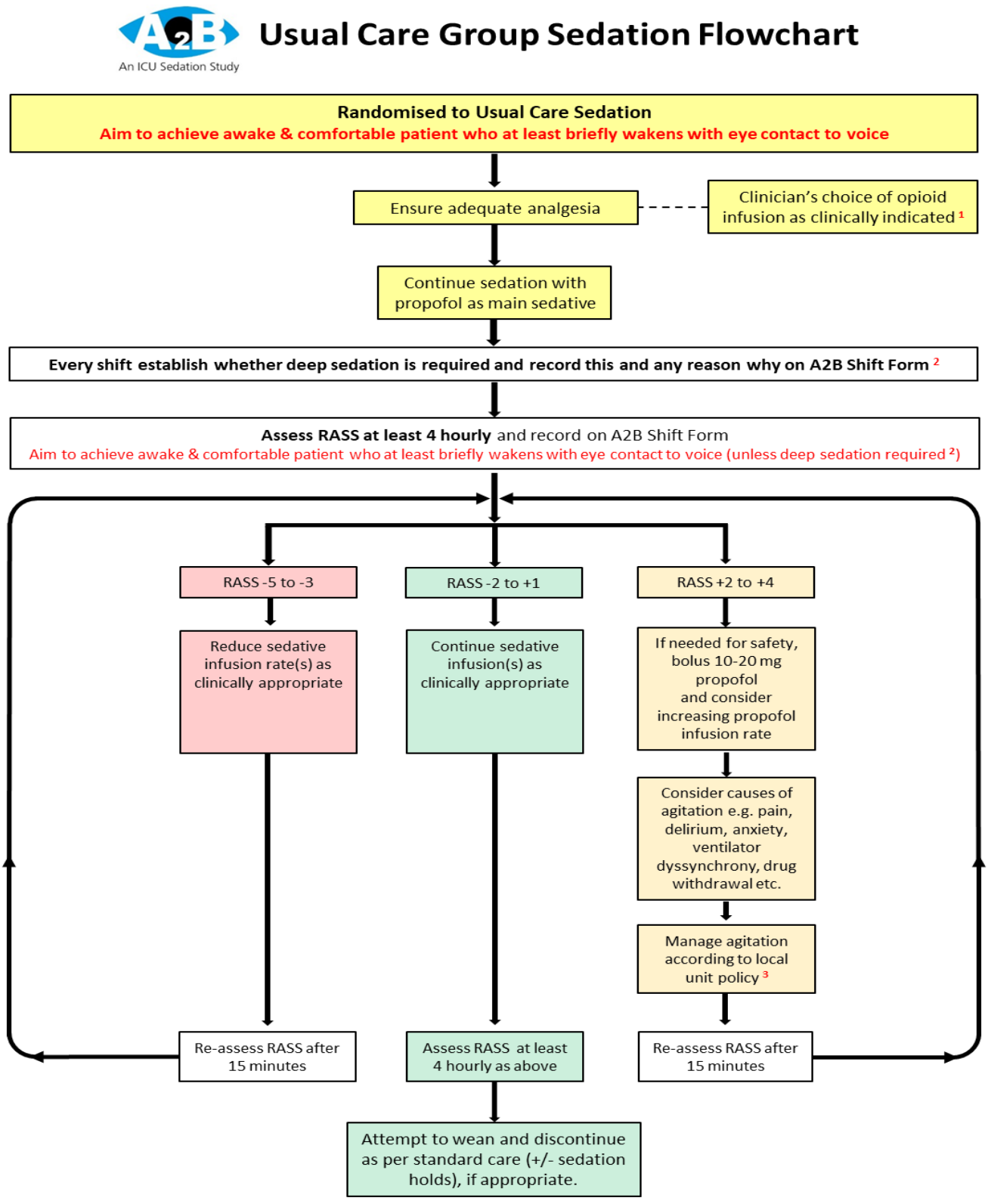
- Increase sedation for transfer if needed, using dexmedetomidine and/or propofol.
- If required, anaesthesia should be administered as per local perioperative guidelines.
- Continue dexmedetomidine infusion unless haemodynamically compromised, in which case consider halving infusion rate and halving again or stopping, as needed.
- Following the procedure, again aim to reduce propofol and use dexmedetomidine as main sedative agent as per flowchart over page.

Weaning and discontinuing Dexmedetomidine

- **Dexmedetomidine can be abruptly discontinued, but slower weaning should be used if withdrawal reactions occur (rebound hypertension or tachycardia, agitation, sweating etc.). However, this should not delay weaning from ventilation, as dexmedetomidine is relatively free from respiratory depressive effects, so can be safely continued post-extubation.**

PTO for Dexmedetomidine Group Sedation Flowchart on reverse of this page

19.3 USUAL CARE (PROPOFOL) FLOWCHART



[1] additional opioid boluses can be given as required
[2] PTO for deep sedation advice on the reverse of this page
[3] See advice in "Drugs you should not give" on the reverse of this page before using Dexmedetomidine or Clonidine

USUAL CARE (PROPOFOL) FLOWCHART - REVERSE

Usual Care Group Sedation

TARGET: most awake and comfortable state considered safe (the least awake target will be "briefly wakens with eye contact to voice")

- Primary sedative agent is **PROPOFOL** (either **1% or 2%**).
- All patients should receive opioid infusions for analgesia as clinically indicated at the discretion of clinical teams

Drugs you should not give:

- **Neither clonidine nor dexmedetomidine should be used as first line sedation during the intervention period.**
- However, either clonidine or dexmedetomidine can be used at the discretion of the clinical teams for specific indications such as agitation, severe delirium or during difficult weaning.

How to manage agitation (RASS +2 TO +4)

- Maintain patient/staff safety by bolusing propofol if needed.
- Once agitation is under control, try to identify and manage the cause, using local unit policy for the management of pain/delirium/anxiety/withdrawal etc.
- Anticipate and avoid agitation; use opioid analgesia in advance of uncomfortable or painful interventions or procedures.

What to do if my patient develops severe bradycardia (HR<50/min)

- Seek advice from medical staff who can review and prescribe, glycopyrronium, atropine, dobutamine, adrenaline or other agents, as per your ICU policy.

What to do if my patient becomes hypotensive

- Hypotension should be treated as per local unit policy. Continuous fluid infusions, fluid challenges and vasopressor infusions are all permitted for patients in the A2B Trial.

What if my patient requires deep sedation (RASS -3 TO -5) e.g. for neuromuscular blockade (muscle relaxant)?

- If medical staff have asked to keep your patient deeply sedated, please record the reason deep sedation was requested on the A2B Shift Form.
- **Patients who require neuromuscular blockade after randomisation must receive adequate sedation as per standard care at the discretion of the treating clinician, to prevent awareness during paralysis.**
- If additional sedative drugs are needed to achieve target deep sedation this can be achieved with benzodiazepine.
- When deep sedation is no longer requested by the caring clinician, aim to use propofol as main sedative agent as per flowchart over page.

What if my patient needs an operative procedure?

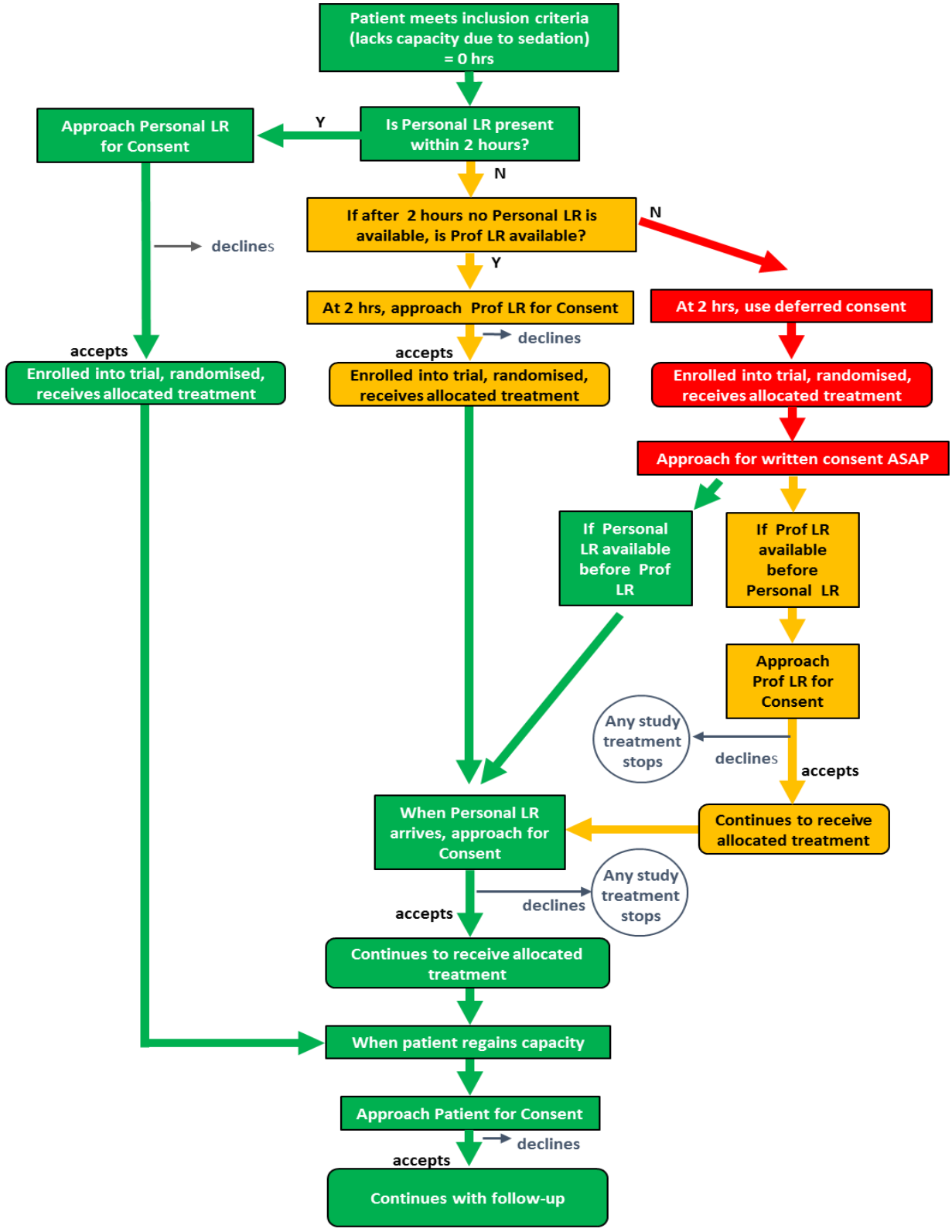
- Increase sedation for transfer if needed.
- If required, anaesthesia should be administered as per local perioperative guidelines.
- Following the operative procedure, again aim to use propofol as main sedative agent as per flowchart over page.

What if my patient needs an operative procedure/CT scan/MRI etc.?

- Increase sedation for transfer to theatre if needed using propofol.
- If required, anaesthesia should be administered as per local perioperative guidelines.

PTO for Usual Care Group Sedation Flowchart on reverse of this page

20. APPENDIX 3: CONSENT PROCESS IN THE A2B TRIAL



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

A2B Protocol V7.0 CLEAN 25042023 Final

Final Audit Report 2023-06-16

Created:	2023-06-14
By:	Alix Macdonald (alix.macdonald@ed.ac.uk)
Status:	Signed
Transaction ID:	CBJCHBCAABAAdoAKy8d-k3cuArppZ1Mf8lmXxILJ-ku4

"A2B Protocol V7.0 CLEAN 25042023 Final" History

Document created by Alix Macdonald (alix.macdonald@ed.ac.uk)
2023-06-14 - 3:05:54 PM GMT- IP address: 109.154.25.160

Document emailed to timothy.walsh@ed.ac.uk for signature
2023-06-14 - 3:07:20 PM GMT

Email viewed by timothy.walsh@ed.ac.uk
2023-06-16 - 11:26:10 AM GMT- IP address: 104.28.40.147

Signer timothy.walsh@ed.ac.uk entered name at signing as Tim Walsh
2023-06-16 - 11:27:23 AM GMT- IP address: 31.94.32.185

Document e-signed by Tim Walsh (timothy.walsh@ed.ac.uk)
Signature Date: 2023-06-16 - 11:27:25 AM GMT - Time Source: server- IP address: 31.94.32.185

Document emailed to christopher.weir@ed.ac.uk for signature
2023-06-16 - 11:27:28 AM GMT

Email viewed by christopher.weir@ed.ac.uk
2023-06-16 - 12:25:40 PM GMT- IP address: 82.2.76.54

Signer christopher.weir@ed.ac.uk entered name at signing as Christopher J Weir
2023-06-16 - 12:27:09 PM GMT- IP address: 82.2.76.54

Document e-signed by Christopher J Weir (christopher.weir@ed.ac.uk)
Signature Date: 2023-06-16 - 12:27:11 PM GMT - Time Source: server- IP address: 82.2.76.54

Document emailed to Fiach O'Mahony (fiach.o'mahony@ed.ac.uk) for signature
2023-06-16 - 12:27:12 PM GMT

Email viewed by Fiach O'Mahony (fiach.o'mahony@ed.ac.uk)
2023-06-16 - 12:27:53 PM GMT- IP address: 94.173.110.34

Document e-signed by Fiach O'Mahony (fiach.o'mahony@ed.ac.uk)

Signature Date: 2023-06-16 - 12:28:02 PM GMT - Time Source: server- IP address: 94.173.110.34

Agreement completed.

2023-06-16 - 12:28:02 PM GMT