Sedation Practice in Intensive Care Evaluation
SPICE IV

Early Sedation with Dexmedetomidine vs. Placebo in Older Ventilated Critically Ill Patients

A Prospective, Multi-Centre, Double-Blind, Randomized, Controlled Trial

ANZICS CTG Endorsed Trial

STUDY PROTOCOL
V2.2

PROTOCOL No YS004

31ST Aug 2022

Early Sedation with Dexmedetomidine vs. Placebo in Older Ventilated Critically Ill Patients

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Clinical trial registration: ACTRN12620001088932p

WHO Universal Trial Number U1111-1255-5885

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1. MANAGEMENT COMMITTEE AUTHORIZATION PAGE

We, the management committee, have read the attached protocol and authorize it as the official protocol for the study entitled **Early Sedation with Dexmedetomidine vs Placebo in Older Ventilated Critically Ill Patients**: A Prospective, Multi-centre, Double-blind, Randomised, Controlled Trial

Chief Investigator Prof Yahya Shehabi	
Professor Rinaldo Bellomo	
Ms Belinda Howe	
Professor Carol Hodgson	
Professor Michael Reade	
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Professor Steve Webb	
Professor Ian Seppelt	
Dr Lewis Campbell	
Dr Colin McArthur	
Ms Rebecca Gresham	
Ms Rima Song	
Dr Zahra Thompson	
Ms Anna Hunt	

All signatures were completed by 31ST Aug 2022.

1.1. PROJECT AND DATA MANAGEMENT:

The project and data management will be based at Monash University, School of Clinical Sciences, Melbourne, Australia.

The study management committee will be responsible for all aspects of the trial and will oversee the conduct of the trial. The study project manager will report to the Chief Investigator and the Study Management Committee.

1.2. MANAGEMENT COMMITTEE:

The Management Committee will be chaired by the Chief Investigator Professor Yahya Shehabi. The investigators listed on page 5, in addition to any future appointed members, will constitute the Management Committee for the study. The Management Committee will meet as required for the efficient conduct and monitoring of the study.

1.3. CONTACT DETAILS:

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1.4. DATA SAFETY MONITORING COMMITTEE:

The independent Data Safety Monitoring Committee (DSMC) will be led by Professor Richard Riker. Professor of Medicine, Tufts University School of Medicine, Neurosciences Institute, Maine Medical Centre, Portland Maine, USA.

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2. ABBREVIATIONS

AE	Adverse Event
ANZ	Australia and New Zealand
ANZICS	Australian and New Zealand Intensive Care Society
APACHE	Acute Physiology and Chronic Health Evaluation
CAM-ICU	Confusion Assessment Method for the Intensive Care Unit
CARM	Centre for Adverse Reactions Monitoring
CRF	Case Report Form
CPOT	Critical Care Pain Observation Tool
CTG	Clinical Trials Group
DEX	Dexmedetomidine
DSMC	Data Safety and Management Committee
EQ-5D	EuroQOL 5D
FDA	Food and Drug Administration of the United States
GCP	Good Clinical Practice
HCL	Hydrochloride
HR / h	Hour
HREC	Human Research and Ethics Committee
HRQoL	Health Related Quality of Life
ICDSC	Intensive Care Delirium Screening Checklist
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IPDMA	Individual patient data meta-analysis
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
IQR	Interquartile Range
IV	Intravenous
KDIGO	Kidney Disease Improving Global Outcome
Kg	Kilogram
MAKE-28	Major Adverse Kidney Events at day 28
MAP	Mean Arterial Pressure
Mg	milligrams
Ml	Milliliters
NHMRC	National Health and Medical Research Council
NMB	Neuromuscular blockade
RASS	Richmond Agitation-Sedation Scale
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SD	Standard Deviation
SDM	Substitute Decision Maker
Sec	seconds
SOFA	Sequential Organ Failure Assessment
SPICE	Sedation Practices in Intensive Care Evaluation
TGA	Therapeutic Goods Administration
µg	Microgram

3. SYNOPSIS

3.1. BACKGROUND

• Experimental evidence suggests that Dexmedetomidine (DEX) has renal (1), neuronal (2, 3) and myocardial (4) protective effects in animal models of hypoxia, ischaemia and reperfusion injury. It also reduced mortality and inflammatory response in an animal model of sepsis (5).

• Small phase II studies have suggested reduced mortality in septic patients treated with DEX (6, 7).

• Several phase II equivalent randomised controlled trials have shown a significant decrease in delirium with DEX sedation compared to placebo in critically ill ventilated patients (8, 9) and in older patients undergoing non-cardiac surgery(10). A phase III trial (SPICE III) showed increased coma-delirium free and ventilator free day (11).

• Older adults exhibit different DEX pharmacokinetics and pharmacodynamics compared to younger adults (12) and need lower doses of DEX to achieve an equivalent level of sedation to younger patients (13).

• Finally, and crucially, the SPICE III study, a randomised controlled trial of 4000 patients, compared early DEX with usual care (11). In a pre-specified sub-group analysis, this study found a significant ($p=0.003$) effect modification according to age dichotomised at the median of 63.7 years for the entire cohort, with a 4.4% absolute reduction in mortality in DEX-treated patients older than the median age.

3.2. AIM

The **primary aim** is to determine whether, in invasively mechanically ventilated patients who are ≥ 65 years of age, early sedation with DEX as the primary sedative agent reduces 90-day all-cause mortality.

The **secondary aims** are to assess the effect of DEX on ventilator free days, coma and delirium free days, major adverse kidney events (MAKE-28) at day 28, duration of ventilation, and hospital stay in survivors.

3.3. HYPOTHESIS

Early sedation with DEX as the primary sedative agent reduces 90-day all-cause mortality in invasively mechanically ventilated patients who are ≥ 65 years of age.

3.4. METHODS

This is a prospective, double-blind, placebo controlled, randomised trial of early sedation with dexmedetomidine in invasively mechanically ventilated patients who are ≥ 65 years of age and who are expected to remain ventilated more than one calendar day after randomization.

Randomization will occur via a secured website and will be stratified by participating centre and operative status. A total of 3500 patients will be recruited and assigned in a 1:1 ratio to either: early dexmedetomidine (Intervention arm) or placebo (Control arm).

Following randomization, analgesia will be optimised for patients in both groups as chosen by the attending physician as clinically indicated. Patients in the active intervention arm will receive a dexmedetomidine infusion starting at a recommended dose of 1 µg/kg/h without a loading dose. Patients in the control arm will receive normal saline at equivalent doses.

The sedation target is defined by the Richmond Agitation-Sedation Scale (RASS) (14) score of -1 to +1 at all times, unless otherwise clinically indicated. If study medication alone is insufficient, propofol or midazolam will be administered as dictated by the treating clinician at the lowest possible dose, to achieve the targeted level of sedation.

Study measurements will include a pain assessment (every 4 hours); the RASS score (every 4 hours); the Intensive Care Delirium Screening Checklist (ICDSC) or the Confusion Assessment Method for Intensive Care (CAM-ICU) (15) daily (at least Monday to Friday) in patients lightly sedated with a RASS score -2 to +1.

3.5. SIGNIFICANCE

As suggested by the SPICE III study (11), DEX given early as the primary sedative agent in older adults may decrease mortality. This has implications for the care of an estimated 25,000 patients/year in Australia and millions worldwide. It is, therefore, important to validate the SPICE III findings in a complementary multi-centre double-blind randomized clinical trial that utilises this prior knowledge and the extensive study network and infrastructure assembled to conduct SPICE III.

3.6. SUMMARY SYNOPSIS – TABLE 1:

Title	Early Sedation with Dexmedetomidine vs. Placebo in Older Ventilated Critically Ill Patients: A Prospective, Multi-centre, Double-Blind, Randomized Controlled Trial
Background	The SPICE III trial, in a predefined sub-group analysis, reported that early sedation with DEX was associated with lower mortality in patients older than the median age of 63.7 years.
Objectives	To evaluate mortality and other key clinical outcomes in older patients receiving early sedation with DEX as the primary sedative agent.
Hypothesis	Early sedation with dexmedetomidine as the primary sedative agent reduces 90-day all-cause mortality in ventilated critically ill patients who are ≥ 65 years old.
Design	Prospective, multi-centre, double-blind, placebo-controlled, randomized trial.
Outcomes	1. *Primary outcome:* 90-day all-cause mortality. 2. *Secondary outcomes*: a. Number of days alive and free of coma and delirium at 28 days b. Number of days alive and ventilator free at 28 days c. Major Adverse Kidney Events at 28 days (16) (Mortality + Acute Kidney Injury > stage II, defined by Kidney Disease Improving Global Outcome (KDIGO) definition) (17). d. Duration of mechanical ventilation in survivors e. Hospital length of stay in survivors 3. Tertiary and Safety outcomes 4. Process related outcomes 5. Health economic evaluation
Intervention	Intravenous infusion of dexmedetomidine or blinded matched placebo, starting at a recommended dose of 1 µg/kg/h administered until sedation is no longer required, up to ICU discharge or day 28, whichever occurs first.
Sample size	3500 participants
Population	Patients admitted to a participating intensive care unit, who are ≥ 65 years old, and require mechanical ventilation.
Eligibility criteria	**Inclusion criteria: Must fulfil ALL inclusion criteria** 1. Age ≥ 65 years 2. Intubated and receiving invasive mechanical ventilation in an intensive care unit 3. The treating clinicians believe that the patient will remain intubated and ventilated until the day after tomorrow (unlikely to be extubated next day) 4. The patient requires immediate ongoing sedative medication for comfort, safety and to facilitate the delivery of life support measures.

	Exclusion criteria: Must have NIL exclusion criteria 1. Has been intubated (excluding time spent intubated within an operating theatre or transport) for greater than 12 hours, with an additional 6 hours grace period, a total of 18 hours, in an intensive care unit 2. Proven or suspected acute primary brain lesion such as traumatic brain injury, intracranial haemorrhage, stroke, or hypoxic brain injury 3. Proven or suspected spinal cord injury or other pathology that may result in permanent or prolonged weakness 4. Admission with a suspected or proven drug overdose or burns. 5. Administration of ongoing neuromuscular blockade 6. Mean arterial blood (MAP) pressure that is less than 50 mmHg despite adequate resuscitation and vasopressor therapy at time of randomization 7. Heart rate less than 55 beats per minute unless the patient is being treated with a betablocker or a high grade atrio-ventricular block in the absence of a functioning pacemaker 8. Known sensitivity to dexmedetomidine 9. Acute fulminant hepatic failure 10. Receiving full time residential nursing care 11. Death is deemed to be imminent or inevitable during this admission and either the attending physician, patient or substitute decision maker is not committed to active treatment 12. Patient has an underlying disease that makes survival to 90 days unlikely 13. Previously enrolled in the SPICE IV study
Funding	The SPICE IV is funded by a NHMRC Clinical Trial and Cohort Studies Grant 2019

4. BACKGROUND

4.1. CURRENT STATUS OF SEDATION IN VENTILATED CRITICALLY ILL PATIENTS

Millions of patients are mechanically ventilated worldwide every year. The bi-national ANZICS Adult Patient Database 2018, which includes over 80% of all ICU admissions in Australia and New Zealand (ANZ), recorded 165,400 ICU admissions in 2018 with a median [Interquartile range IQR] age of 65[50-75] years. The overall ventilation rate in the first 24 hours in patients ≥ 65 years old is 48%(18). More importantly, the overall 90-day mortality was significantly higher in ventilated patients enrolled in the SPICE III trial, who were ≥ 65 yrs. old compared with younger adults (38.2% versus 21.0%), (unpublished data from SPICE III trial).

Sedation remains a ubiquitous component of intensive care treatments in critically ill ventilated patients (19, 20) to relieve anxiety, reduce distress and promote tolerance of endotracheal intubation and associated life-sustaining interventions, including mechanical ventilation. Thus, providing optimal choice of sedative agent is vital to patient comfort and safety. The results of SPICE III have raised substantially the likelihood that the choice of sedative agent does influence survival.

Despite more than 20 years of intensive care sedation research, there is still no consensus on what constitutes best sedation practice. In 2018, the Society of Critical Care Medicine, the peak critical care organisation in North America, published the updated Clinical Practice Guidelines on the management of Pain, Agitation/Sedation, Delirium, Immobility and Sleep Disruption(21). These guidelines issued weak recommendations to provide analgesia before sedation, to target light sedation whenever clinically feasible and to use either DEX or propofol over midazolam for the sedation of ventilated critically ill patients. Similarly, the American Thoracic Society produced a set of Clinical Practice Guidelines to promote the weaning and liberation from mechanical ventilation in critically ill patients with weak recommendations for the use of non-benzodiazepines as primary sedatives and to target light sedation when clinically possible (22). These guidelines, however, do not consider age dependent pharmacokinetics and pharmacodynamics, illness severity, timing of sedative administration or the changing dynamics of sedation practice using multiple agents at different phases of critical illness (11). These guidelines identified evidence gaps to be addressed in future sedation trials, in particular, the need for adequately powered trials to evaluate the impact of sedative choice in special patient sub-groups and on long-term outcomes such as mortality.

Different sedation strategies have been proposed to improve sedation related outcomes. A multicentre French study, the AWARE trial, compared an algorithm to prevent over-sedation with usual care, however is under powered due to early termination due to futility (23). A recently completed multicentre Danish study, the NONSEDA trial, compared a minimal sedation protocol with usual care, albeit with significant limitations. This study was also inadequately powered and failed to impact on the primary or any of the secondary outcomes (24). These trials, however, did not use DEX as a sedative agent and focused on sedative strategies independent of sedative agents used. A recent Cochrane systematic review (25) demonstrated that implementing sedation protocols was not superior to usual care practice for the primary outcome of mortality or the duration of ventilation and hospital stay. It further suggested the need for well-designed clinical trials considering contextual differences and bias reduction. All the above suggests that sedation trials must consider the sedative agents to be used.

The lack of high-level evidence to inform sedation practice in the critically ill has led to approaches that are mainly opinion based and lack the support of evidence from large multicentre, international randomized clinical trials (26-28). While these approaches may provide a framework for sedation strategy in critically ill patients, they have failed to impact global sedation practice.

4.2. DEXMEDETOMIDINE FOR SEDATION OF VENTILATED CRITICALLY ILL ICU PATIENTS

The last 10 years have seen several small to medium-sized trials evaluate the use of DEX in ICU patients. Taken together, these trials support the hypothesis that, when compared with conventional sedatives, DEX facilitates a unique arousable sedation status (29), reduces delirium (30), leads to a shorter duration of mechanical ventilation and faster resolution of agitated delirium (9) and, in low doses, reduces transition to delirium in mechanically ventilated patients (8). These studies, however, share multiple limitations and none were powered to detect an effect on mortality, or any other patient centred outcomes. As such, their impact on practice change remains limited.

The SPICE IV study, like SPICE III, is designed to overcome many of the limitations of previous studies. Unlike SPICE III, however, this study will be a blinded trial conducted in the patients shown to have the greatest likelihood of deriving benefit from the intervention.

First: the time to randomization and commencement of sedative intervention will be significantly shorter than previous DEX studies (except for SPICE III). The time to randomization in the SEDCOM trial, was up to 96 hours (30), and in the PRODEX and MIDEX, it was up to 48 hours (29).

Second: the sample size will be sufficient to enable detection of differences in important patient-centred outcomes, unlike earlier smaller trials: SEDCOM (n=375), PRODEX (n=500), MIDEX (n=501) and MENDS (n=106) (6).

Third: best-practice light sedation will be targeted. The SEDCOM trial targeted light sedation, defined by the Richmond Agitation-Sedation Scale (14) (RASS, ranging from +4 indicating combative to -5 indicating unarousable), of -2 to +1 (-2 corresponding to light sedation; -1, drowsy; 0, alert and calm; +1, restless), the PRODEX and MIDEX targeted a RASS of -3 to 0 (moderate sedation to alert and calm) while the MENDS study did not target a sedation level. Thus, SPICE IV will target light sedation defined as a RASS of -1 to +1 (make eye contact > 10 sec in response to verbal command, awake and calm or slightly restless).

Fourth: the primary outcome of these studies was not patient centred. In the SEDCOM study it was time in target sedation; the PRODEX and MIDEX studies were non-inferiority studies with a primary outcome of time at target sedation and mechanical ventilation time and in MENDS the primary outcome was time spent within one RASS point of target and the number of coma-delirium free days.

Fifth: the duration of treatment and follow-up in these trials, apart from SEDCOM, was short. In PRODEX and MIDEX, the median duration of treatment was 42 hours. In the MENDS trial, maximum treatment duration and follow-up were short at 5 and 14 days respectively.

Finally, all these trials were conducted by commercial sponsors for regulatory purposes, mandated by either the FDA or the European Medicine Agency.

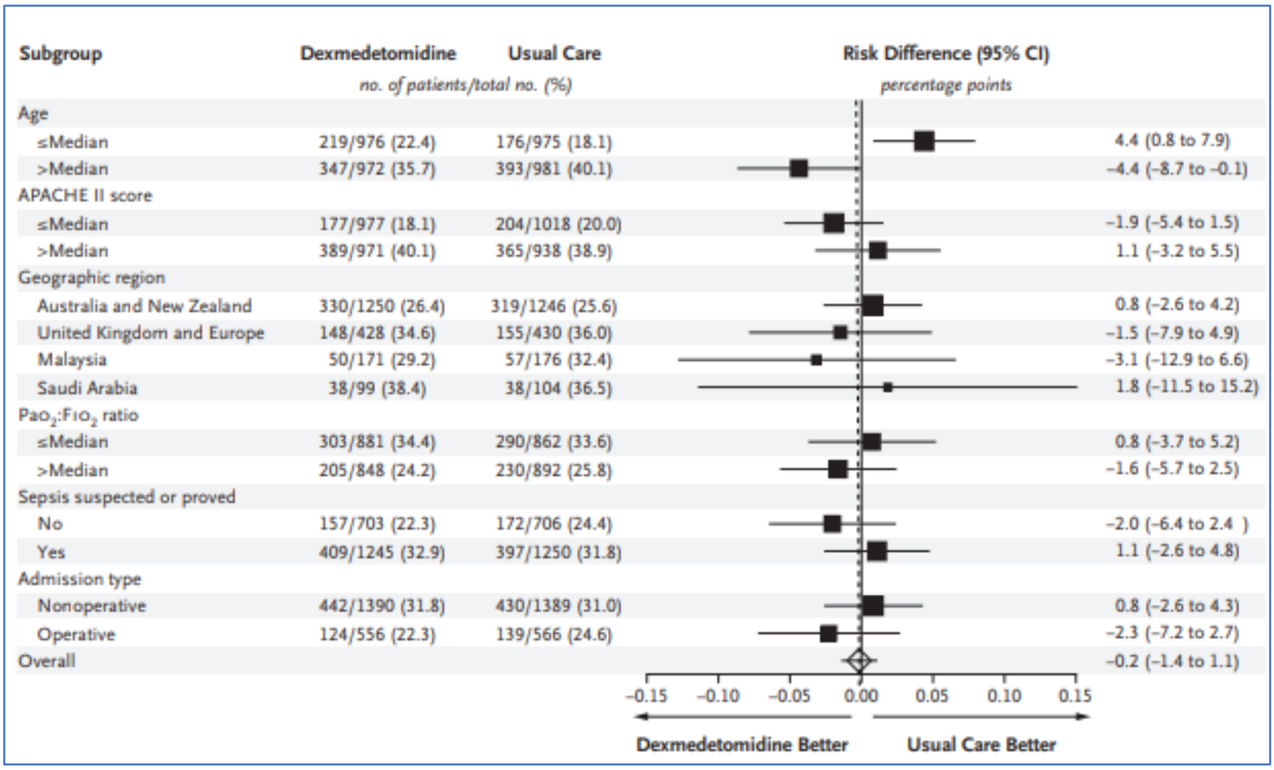
4.3. THE SPICE III: EARLY SEDATION WITH DEX IN VENTILATED CRITICALLY ILL PATIENTS

In 2018 the largest sedation trial to date, SPICE III was completed. It was a pivotal, randomized controlled trial comparing early sedation with DEX as a primary sedative agent with usual care sedation in mechanically ventilated critically ill adults. The SPICE III trial recruited 4000 patients in 74 intensive care units in 8 countries.

Although the SPICE III trial showed no difference in overall 90-day mortality at 29%, in post-hoc analysis, DEX treatment showed a significant 4.7% absolute risk reduction in 90-day mortality in patients who were ≥ 65 yrs. old at 35.96% compared with usual care at 40.64% (P=0.04).

SPICE III included a pre-specified sub-group analysis of 6 baseline variables, including age at randomization dichotomised at the median age of the cohort, which revealed significant heterogeneity (P=0.003 for the interaction) between the effects of age and treatment on mortality. These findings, like all sub-group analyses within large RCTs, remain exploratory (31) and need to be confirmed to change practice.

Forest plot for the 6 pre-specified sub-groups analysis in SPICE III



5. STUDY OBJECTIVES

The study objectives are:

1. To evaluate mortality among patients ≥ 65 years of age given early DEX as a primary sedative agent to verify the findings of the sub-group analysis in SPICE III

2. To compare other key clinical outcomes with early sedation with DEX compared with placebo in the age group ≥ 65 years

3. Explore possible mechanistic explanations for the observed effect in older patients in the SPICE III study.

5.1. AIM

The **primary aim** of this study is to determine whether early sedation with DEX as the primary sedative agent in ventilated patients who are ≥ 65 years old and expected at randomization to require ventilation beyond the day after tomorrow, reduces 90-day all-cause mortality.

The **secondary aims** are to assess the effect of DEX on ventilator free days, coma and delirium free days, major adverse kidney events (MAKE-28) at day 28(16), duration of ventilation and hospital stay in survivors.

5.2. HYPOTHESIS

Early sedation with dexmedetomidine as the primary sedative agent reduces 90-day all-cause mortality in ventilated critically ill patients who are ≥ 65 years old.

6. STUDY OUTCOME MEASURES

6.1. PRIMARY OUTCOME:

The study primary outcome is 90-day all-cause mortality.

6.2. SECONDARY OUTCOMES:

- Number of days alive and free of coma and delirium at 28 days
- Number of days alive and ventilator free at 28 days
- Major Adverse Kidney Events at 28 days(16) (Mortality + Acute Kidney Injury > stage II, defined by Kidney Disease Improving Global Outcome (KDIGO) definition (17).
- Duration of mechanical ventilation in survivors
- Hospital length of stay in survivors

6.3. TERTIARY AND SAFETY OUTCOMES:

Tertiary and Safety outcomes will include the use of tracheostomy, physical restraints, re-intubation, and the administration of neuromuscular blockade, clinically relevant bradycardia, hypotension, cardiac arrest, and serious arrhythmias.

6.4. PROCESS RELATED OUTCOMES

- Percentage of randomised patients deemed suitable for light sedation (RASS -1 to +1) following randomisation and commencement of study medication.

Time-weighted proportion of RASS measurements in target range

- Cumulative daily dose of study medication, other sedatives and opioids given in ICU

- Duration of treatment with study medication and with supplemental sedatives and opioids

6.5. HEALTH ECONOMIC EVALUATION

A health economic evaluation will be done after the conclusion of the trial as a cost effectiveness analysis, should the trial primary endpoint be significant, or cost minimization otherwise. Ten percent of patients recruited in Australia will participate to compare outcomes that reflect cost drivers including ICU length of stay, hospital length of stay, mechanical ventilation hours, and dialysis days. Cost models will be based on contemporary available data. A detailed health economic evaluation will be conducted by a dedicated health economist.

7. OVERALL STUDY DESIGN AND POPULATION

7.1. STUDY DESIGN

The proposed trial is a pragmatic, prospective, multi-centre, double-blind placebo-controlled randomized trial of early sedation with DEX as the primary sedative agent in mechanically ventilated critically ill patients. The study will maximise external validity by including patients admitted to ICUs in tertiary hospitals, as well as metropolitan, rural, and regional hospitals.

7.2. STUDY POPULATION

Patients ≥ 65 years old, ventilated via an endotracheal tube in the ICU.

7.3. INCLUSION CRITERIA

Must fulfil **ALL inclusion criteria**

1. Age ≥ 65 years
2. Intubated and receiving invasive mechanical ventilation in an intensive care unit
3. The treating clinicians believe that the patient will remain intubated and ventilated until the day after tomorrow (i.e. unlikely to be extubated the following day)
4. The patient requires immediate ongoing sedative medication for comfort, safety and to facilitate the delivery of life support measures.

7.4. EXCLUSION CRITERIA

The following exclusion criteria will apply:

1. Has been intubated (excluding time spent intubated within an operating theatre or transport) for greater than 12 hours, with an additional 6-hour grace period, a total of 18 hours, in an intensive care unit
2. Proven or suspected acute primary brain lesion such as traumatic brain injury, haemorrhage, stroke, or hypoxic brain injury
3. Proven or suspected spinal cord injury or other pathology that may result in permanent or prolonged weakness
4. Admission as a consequence of a suspected or proven drug overdose or burns
5. Administration of or need for ongoing neuromuscular blockade
6. A mean arterial blood (MAP) pressure that is less than 50 mmHg, despite adequate resuscitation and vasopressor support at time of randomization

7. Heart rate less than 55 beats per minute unless the patient is being treated with a beta-blocker, or a high grade atrio-ventricular block in the absence of a functioning pacemaker
8. Known sensitivity to dexmedetomidine
9. Acute fulminant hepatic failure
10. Receiving full time residential nursing care
11. Death is deemed both imminent and inevitable and either the attending physician, patient or substitute decision maker is not committed to active treatment
12. Underlying disease that makes survival to 90 days unlikely
13. Previously enrolled in the SPICE IV study

8. STUDY PROCEDURES

8.1. RANDOMIZATION AND MEDICATION KIT ALLOCATION

Randomization will be conducted through a password-protected, encrypted secure website using a central, computer-based randomization program. This will be available 24 hours a day, 7 days a week. Patients will be randomized using computer-generated, permuted block randomization and will be stratified by participating centre and operative status. Patients who satisfy all inclusion criteria and have no exclusion criteria will be randomized in a 1:1 ratio into the dexmedetomidine or the saline placebo arm.

Upon randomization, the website will assign a unique study number and a unique 'medication kit number' to each participant. The unique medication kit number is matched to blinded study drug according to the patient's treatment allocation, supplied to the site. Each medication kit will contain either: dexmedetomidine 200 μg/2 ml vials or normal saline vials. Further supplies of study medication, as required, can be allocated through the study website.

Blinding of study medications within the medication kit will be achieved by identical labelled 2 ml vials.

8.2. CONSENT

By virtue of the study's entry criteria none of the patients who are eligible for this study will be competent to provide informed consent. The approach to obtaining consent in this study will be based on that developed from the guidelines in Chapter 4.4 of the NHMRC National Statement (32). The process for obtaining consent will follow the procedures applied to consent in the SPICE III study, with the following hierarchy:

1. Informed consent from substitute decision maker (SDM): Where possible, and as authorised by law, which varies between countries, states and territories, consent will be obtained from the participant's legally authorised representative.

2. Consent to continue: Where it is not possible or practicable for the SDM to consider the study and give consent within an appropriate timeframe, the patient may be enrolled without prior consent, provided the procedure is in accord with the requirements of the Human Research Ethics Committee and applicable legislation. As soon as possible after randomization, the SDM, and, in turn, the participant, will be informed of the study and will be able to withdraw or consent for ongoing participation at any time.

8.3. STUDY ASSESSMENT

The following study assessments will be collected from randomization until Day 14 or ICU discharge, whichever occurs first:

- Pain assessment (every 4 hours);
- RASS score (every 4 hours);

The following study delirium assessments will be collected from randomization until Day 28 or ICU discharge, whichever occurs first:

- Confusion Assessment Method for Intensive Care (CAM-ICU) (15) in patients lightly sedated with a RASS score of -2 to +1, or the Intensive Care Delirium Screening Check List (ICDSC) (33), daily (at least Monday to Friday).

8.4. STUDY MEDICATION

8.4.1. ACCOUNTABILITY

Drug accountability is the responsibility of the Principal Investigator, which may be delegated to the study research staff at each site.

The site's allocated supply of study medication can only be administered to patients enrolled in this study and in accordance with this protocol.

A study medication accountability log will be kept for recording the study medication kit:

a) Receipt

b) Dispensed to each patient; and

c) Date of dispensing.

Any expired study medication can be destroyed on site after documentation in the Inventory Log. Expired drug can be destroyed according to local standard practice. All records and study medication accountability log should be available for inspection by Project Manager.

8.4.2. STUDY TREATMENT BLINDING

The dexmedetomidine vial contains 236 µgs of dexmedetomidine HCl (equivalent to 200 µgs dexmedetomidine base) and 18 mg of sodium chloride in water for injection. The dexmedetomidine has been sourced from the manufacturer of the registered product and is supplied in a plain glass vial. The powder is a white or nearly white odourless, hygroscopic amorphous solid which is very soluble in water. The placebo is a matching vial containing 2 mL sterile normal saline for injection. Both dexmedetomidine and placebo vials will be covered in identical blinding label. Four study drug vials will be packaged in one medication kit which will be labelled with the appropriate medication kit number.

Coordination and management of study medication storage and distribution will be via an interactive purpose-built web-based database. The website, which will also manage the randomization process, will track full drug inventory including orders to sites, first delivery and reordering when stock is low, allocation of medication kit at randomization and further study medication as required and reconciliation of drug usage.

8.4.3. PREPARATION OF STUDY TREATMENT MEDICATION

The study medication kit number should be obtained in a printout from the study website immediately following randomization.

The study medication will be reconstituted by mixing 4 vials (8 ml) into a 100 ml bag of normal saline or 5% dextrose, this is the preferred dilution, or 2 vials (4ml) into 50 ml syringe to an equivalent concentration of 8 mcg/ml of dexmedetomidine. The constituted infusion is stable at room temperature for up to 24 hours.

8.4.4. ADMINISTRATION OF STUDY TREATMENT MEDICATION

Study treatment medication will be administered via a dedicated intravenous line as a continuous infusion and titrated as per study algorithm. The recommended starting infusion rate is equivalent to 1 µg/kg/h of dexmedetomidine, without loading or bolus. This will be titrated to an equivalent dexmedetomidine dose of 0 to 1.0 µg/kg/h according to study algorithm to maintain target sedation of Richmond Agitation-Sedation Scale (RASS) score of -1 to +1.

The maximum body weight for the infusion rate will be 100 kg.

8.4.5. ADMINISTRATION OF OPEN LABEL DEXMEDETOMIDINE

Open label administration of dexmedetomidine is prohibited in ALL study participants. The use of open label (non-study) dexmedetomidine is allowed in patients with refractory agitation or delirium if not responding to conventional therapy as described below. As the blinded study medication may be dexmedetomidine, study medication MUST be stopped if open label dexmedetomidine is to be given.

8.5. BACKGROUND TREATMENT

8.5.1. ANALGESIA

Patients in both groups will, simultaneously, receive **analgesia** with opioid or other medications as clinically indicated either by bolus or continuous infusion. Other agents including paracetamol, low dose ketamine and/or regional analgesia, may be administered as determined by the treating clinician. Patients in both arms will have 4 hourly pain assessments using a Yes/No (if able to report pain on a numeric visual scale or equivalent) or the modified Critical Care Pain Observation Tool (CPOT, if unable to report pain). Analgesic medications will be titrated and given according to pain assessments.

Administration of **remifentanil and IV clonidine** will be precluded during the study period. Due to increased hyperalgesia, associated bradycardia, narrow therapeutic window and dose dependent transition into opioid based sedation, remifentanil infusion will be precluded in all patients. Similarly, due to its interaction with DEX, injectable clonidine will be precluded in all patients. Oral clonidine may be administered at the discretion of the treating clinician.

8.5.2. PRE-RANDOMIZATION & SUPPLEMENTAL SEDATIVE AGENTS

Prior to study enrolment, most patients would have received **sedative medications**, such as propofol, midazolam, dexmedetomidine or other agents, for the purpose of intubation, transport, diagnostic or therapeutic procedures and other clinical indication. Therefore, once study treatment medication has been commenced, pre-randomization sedatives will be titrated, weaned, and/or stopped, whichever is applicable, to maintain target RASS score, as per study algorithm. The target RASS score will be -1 to +1, unless otherwise clinically indicated. RASS score will be assessed at least every 4 hours following randomization. If dexmedetomidine is being administered prior to randomization, it must be stopped prior to study medication being commenced.

Supplemental sedatives such as propofol and/or midazolam and other agents can be given at the discretion of the treating clinician. These supplemental sedatives will be given at the lowest possible dose, while keeping the study medication infusion at the maximum clinically tolerable rate, to maintain the default target RASS of -1 to +1 or the clinically required RASS target. If the clinically required RASS is not the default target of -1 to +1, the RASS target will be reviewed at least twice daily.

8.5.3. CONTINUOUS NEUROMUSCULAR BLOCKADE

Patients who subsequently require **continuous neuromuscular blockade** (NMB) post randomization must be given adequate sedation using supplemental sedatives to prevent awareness. The choice of supplemental sedatives will be at the discretion of the treating clinician. Study medication may be stopped during this period. If continuous NMB is no longer required, the study medication should be restarted.

8.5.4. BREAKTHROUGH AGITATION

Breakthrough agitation, in the intubated patient, will be treated at the discretion of the clinician by optimization of analgesia using opioids or other medications, increasing the rate of study medication (the SPICE IV protocol recommended maximum DEX rate is 1 µg/kg/h however this rate of study medication administration may be exceeded if the treating clinician deems appropriate and safe for an individual patient to a maximum of 1.4 µg/kg/h), optimization of ongoing sedatives and boluses of propofol, midazolam and/or the addition of an appropriate dose of an antipsychotic agent such as quetiapine, haloperidol, and/or other benzodiazepines. Open label dexmedetomidine should only be used after failure of the above measures. Study treatment medication must be stopped before open label DEX is commenced.

In all patients, daily delirium assessment will be performed using the Confusion Assessment Method for Intensive Care (CAM-ICU) when the RASS score is -2 to +1 or the Intensive Care Delirium Screening Checklist (ICDSC)

8.5.5. MOBILIZATION, SLEEP PROMOTION & FAMILY ENGAGEMENT

According to site protocols, all patients will be **mobilised** as early as clinically safe and feasible. In addition, available means of **sleep promotion** and attention to circadian rhythm, including day-night orientation and environmental awareness, will occur for all patients. Furthermore, **family engagement** and visits should be encouraged for all participating patients.

All aspects of treatment, other than the sedation treatment medication, will be determined by the treating clinician according to routine and usual care in participating ICUs.

8.6. STUDY INTERVENTIONS, SEDATIVE ALGORITHM

Enrolled patients will have a default sedation target of light sedation, as determined by the RASS score of -1 to + 1 (making eye contact for > 10 sec to slightly restless but easily reassured).

Following randomization and commencement of study medication as below, patients who are deemed clinically inappropriate for light sedation target, as determined by the treating clinician, should have a sedation target assigned and the reason for deeper sedation recorded. In these patients, sedation target MUST be reviewed twice daily (am and pm) to determine appropriateness for light sedation. Study drug should be given at max clinically tolerable rate.

Once randomized, study treatment medication should be started at a recommended infusion rate equivalent to 1.0 µg/kg/h of dexmedetomidine. It is expected that a clinically relevant sedative effect would be apparent within 60 minutes of commencing the infusion. Therefore, an hourly and as needed RASS assessment during the transition period should be conducted and sedative infusions titrated accordingly to achieve target RASS as below. **(See Appendix 1).**

The following recommended interventions can be given in combination or in sequence as clinically appropriate to achieve target RASS.

1. Deeply sedated, RASS -4 to -5 (No response to verbal stimuli):
    a. Stop or substantially reduce, as clinically appropriate, any ongoing non-study sedatives, such as propofol or midazolam, and excessive opioids, such as fentanyl or morphine, and reassess hourly and as needed. Keep study medication running at the starting rate.
    b. If deep sedation persists after 4 to 6 hours with only study medication running, reduce the study medication infusion rate by an equivalent of 0.2 to 0.3 µg/kg/h every 2 hours while assessing RASS levels hourly and as needed.
    c. Repeat the above until the target RASS of -1 is achieved.
2. Moderately sedated, RASS of -3 to -2 (open eyes to voice but no or brief eye contact):
    a. Reduce ongoing non-study sedatives infusion, such as propofol or midazolam, and opioids such as fentanyl and morphine and titrate as judged clinically appropriate. Reassess RASS hourly and as needed and titrate accordingly. Keep study medication running at the starting rate.
    b. If moderate sedation persists after 4-6 hours, stop ongoing non-study medication, and reassess at hourly intervals.
    c. If moderate sedation persists after 4 to 6 hours with only study medication running, reduce the study medication infusion rate by an equivalent of 0.2 to 0.3 µg/kg/h every 2 hours while assessing RASS levels at hourly intervals.
    d. Repeat the above until the target RASS of -1 is achieved.
3. Light sedation, RASS of -1 to +1 (sustained eye contact > 10 seconds, calm or slightly restless)

a. Minimize and titrate ongoing non-study sedatives as clinically appropriate.

b. Maintain/titrate Study drug infusion rates to replace conventional sedatives.

c. Reassess RASS hourly and as needed and titrate accordingly.

4. Distressed, very anxious or agitated, RASS ≥ +2:

a. Optimize analgesia - increase the dose of ongoing opioid infusion or introduce an opioid infusion or consider adding another analgesic agent/s.

b. Continue the study medication at the starting recommended maximum rate.

N.B. Assess delirium when possible. If delirium is suspected, consider using an antipsychotic agent, early and before using other non-study sedatives as described below.

c. Increase the rate of infusion of supplemental sedative, such as propofol, midazolam or other sedatives, at the discretion of the treating clinician, by infusion or repeated boluses. Reassess RASS levels at frequent intervals until appropriate comfort sedation has been achieved. Continue to titrate sedative agents according to RASS levels assessed hourly and as needed.

d. If the above does not induce comfort or adequate sedation despite high doses of sedative medications, increase study medication rate to a maximum equivalent dose of 1.4 μg/kg/h.

e. Add an antipsychotic agent such as enteral quetiapine, injectable haloperidol, or a benzodiazepine, as necessary.

8.6.1. STUDY INTERVENTION, HAEMODYNAMIC MANAGEMENT

Patients enrolled in this study are critically ill and can be unstable during the early phase of acute illness. Therefore, it is common for these patients to require vasopressors and inotropes to treat hypotension or low cardiac output state.

The study medication, like all sedative agents, can produce untoward haemodynamic sequelae such as bradycardia, hypotension, and/or low cardiac output state. Therefore, the following is provided as a guide to manage emerging haemodynamic events:

1. A transient mild hypotension (10 to 15% drop) may occur within 20-30 minutes during the initial infusion of the study medication. This can be treated by a suitable fluid bolus and/or vasopressor drug such as metaraminol, norepinephrine or other agents routinely used on site.

2. The initial hypotension can be exaggerated if the patient is inadequately volume resuscitated, especially in the presence of other vasodilating sedatives such as propofol. Therefore, there is no need to stop the study medication during this period unless severe hypotension occurs. In such instances, the patient should be stabilised first, and study medication reintroduced once haemodynamic stability has been achieved.

3. Study medication can produce a dose dependent bradycardia (a drop-in heart rate of 10-15%). If clinically relevant bradycardia occurs, it MUST be treated initially with glycopyrrolate or

atropine and if it persists by a chronotropic agent such as dobutamine. Reducing or stopping the study medication will not resolve the bradycardia effect (which may last for 4-6 hrs). A reduction by 50%, temporary or permanent cessation of study medication is warranted if bradycardia persists despite the above treatment.

8.6.2. DISCONTINUATION OF STUDY TREATMENT MEDICATION

The study treatment medication will be discontinued if the following occur:

- Sedation is no longer required.
- 28 days after randomization.
- Transfer out of ICU or to another ICU not participating in the study.
- Adverse event or serious adverse event.
- Uncontrolled breakthrough agitation requiring open label DEX.

The study medication can be stopped, temporarily or permanently, whenever there is a significant safety concern with patient management.

Study treatment medication and other sedatives or analgesic infusions may continue after extubation, if clinically required. If sedation is deemed necessary beyond 28 days after enrolment, the choice of sedative regimen will be determined solely by the treating clinician.

8.6.3. UNBLINDING OF STUDY TREATMENT MEDICATION

DEX is a commonly used drug, with which treating clinicians are familiar and it is not anticipated there would be any need for unblinding. The unblinding of a patient's allocated study treatment should only be performed when knowledge of the treatment allocation will influence the participant's management in a significant fashion. The treating clinician or study investigator should contact the coordinating centre if they consider there is a need for unblinding. Unblinding a patient occurs through the study website.

9. ETHICS

9.1. GUIDING PRINCIPLES

This study is to be performed in accordance with the ethical principles of the Declaration of Helsinki (June 1964 and amended 1975, 1983, 1989, 1996, 2000, 2008, 2013 and Note of Clarification 2002 and 2004), ICH GCP Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) E6(R2) addendum annotated with Therapeutic Goods Administration comments and NHMRC National Statement on Ethical Conduct in Human Research 2007 (updated 2018) and the New Zealand Interim Good Clinical Research Practice Guidelines (Volume 2 1998 and Volume 3 2000).

9.2. ETHICAL ISSUES OF THE STUDY

Patients who will be eligible for this study are mechanically ventilated and critically ill, and require sedative medications for comfort, safety and to facilitate standard life saving ICU procedures. Critical illness commonly leads to an altered mental state which will affect the patient's mental capacity. In addition, their cognitive capacity is temporarily diminished due to a combination of factors such as the severity of their illness and standard intensive care treatments including ventilatory assistance, sedatives, and analgesics. The presence of agitation and or delirium and the need for comfort sedation further delays the return of the patient's ability to make informed decisions during their stay in the intensive care unit.

Eligible patients will need immediate administration of sedative medications by infusion. The decision about which medication is to be prescribed therefore needs to be made urgently. The sedative medications to be given in this trial, including dexmedetomidine, are all currently and commonly used, and have been shown to be safe and effective to achieve comfort and safety for patients who are receiving, mechanical ventilation in an ICU.

As a consequence of the immediacy of the situation and the urgent need to commence and titrate sedative interventions as per study protocol it is proposed to enrol patients in the study without prior informed consent [see paragraphs 4.4.13 and 4.4.14, National Statement on Ethical Conduct in Human Research, at

https://www.nhmrc.gov.au/about-us/publications/national-statement-ethical-conduct-human-research-2007-updated-2018

For the purposes of this protocol, the descriptor ‘legal surrogate’ describes the person who is legally allowed to give consent for the patient according to each site’s local law and ethical approval conditions. The patient’s ‘legal surrogate’ will be approached for consent to continue in the study. The legal surrogate will be able to withdraw their consent for the patient to continue participation in the study at any time without any reduction in quality of care, and if they choose to withdraw the patient, permission will be asked to use the data collected up to that time.

Patients who recover sufficiently to consent for themselves will be asked to consent to continue in the study or be offered the chance to withdraw. If the patient chooses to withdraw from the study, they will be asked for permission to use their data up to the time of withdrawal.

9.3. ETHICS COMMITTEE APPROVAL

In Australia, this protocol will be submitted to a Human Research and Ethics Committee constituted according to the NHMRC National Statement on Ethical Conduct in Human Research 2007 (updated 2018) for each institution or a Lead HREC. In New Zealand, this protocol will be submitted to the appropriate Health and Disability Ethics Committee, accredited by the Health Research Council and constituted in accordance with the Operational Standard for Ethics Committees March 2002. Approval of the protocol and related documents will be obtained prior to the start of the study at each site. It is the Investigator’s responsibility to ensure that all conditions for approval of the study are met and that amendments to the protocol are reported to the HREC as required by that Committee.

9.4. CONFIDENTIALITY OF PATIENT DATA

Patients will be randomized via a secure website and will be allocated a unique study number. The site research coordinator will compile an enrolment log including the patient’s name, date of birth, hospital identification number, unique study number and date and time of randomization. The enrolment log which contains identifiable information will not leave the research office of the study site. The enrolment log and study data will be kept separately at the study site. All other study data will be identified by the unique study number only. Study data is entered into a secure, password protected data base. No identifying data will be entered into the database.

Follow up of patients at day 90 will be conducted by the research staff at the study site via telephone call. The research staff at the study site will perform the follow up IQCODE and EQ-5D surveys via telephone at 180 days after randomization. Sites can have the option of posting the surveys prior to the telephone call if they deem this will streamline the telephone interview.

10. DATA MANAGEMENT

10.1. DATA COLLECTION METHODS

All data will be collected by trained staff at each study site using the paper/electronic CRF. Coded data, identified by the unique study number only, is entered into the secure online database. Data queries will be automatically generated via the electronic data collection database.

Information recorded in the CRF should accurately reflect the participants' medical/ hospital notes and must be completed as soon as it is made available. The intent of this process is to improve the quality of the clinical study by providing prompt feedback to the Investigators on the progress of the data submitted and to enhance the ability to collect early safety information in a timely fashion to fully comply with the intent of GCP requirements.

10.2. DATA VARIABLES COLLECTED

10.2.1. AT ENROLMENT

- Demographic data (age, sex, ethnicity, estimated body weight)
- Date and time of hospital admission
- Date and time of ICU admission
- Source of ICU admission
- APACHE II score
- ICU admission diagnosis (APACHE III diagnosis code)
- Date and time of first intubation
- Sepsis status, temperature, creatinine, and albumin
- Clinical frailty score
- Name of all sedatives and analgesics, and highest dose of vasopressors/inotropes intravenously administered in this hospital between time of intubation and randomization.

10.2.2. ICU DATA

Every 4 hours until ICU discharge or day 14, whichever occurs first:

- Actual RASS
- Target RASS
- Pain assessment: (assessed by bed side nurse)o (Critical Care Pain Observation Tool C-POT) (34)

Daily until ICU discharge or day 14, whichever occurs first:

• Name and daily dose of all administered parenteral bolus and infusion of sedative and analgesic agents

• Name and daily dose of all administered oral sedative and analgesic agents

• Administration of dialysis

• Name and highest daily dose of all IV administered vasoactive infusion agents

• If deeply sedated, indication for deep sedation

• Use of neuromuscular blockade other than for intubation/ Tracheostomy /procedure

• Use of physical restraints

• Occurrence of active mobilization episode

• Highest temperature

Daily until ICU discharge or day 28, whichever occurs first:

• CAM-ICU (when RASS -2 to +1) or the ICDSC (Monday to Friday) and weekends as possible

• Name and daily dose of all administered parenteral bolus and infusion of sedative and analgesic agents

• Name and daily dose of all administered oral sedative and analgesic agents

• Administration of dialysis

• Administration of vasoactive agents

• Tracheostomy

• One or more episodes of extubation or de-cannulation

• Time of extubation or decannulation, if occurred on that day

• Unplanned extubation or decannulation

• Invasive Ventilation time, re-intubation or re-cannulation

• Time of re-intubation or re-cannulation if occurred on that day

• Tracheostomy performed and, if yes, date and time

Daily until <u>hospital</u> discharge or day 28, whichever occurs first:

• Peak daily serum creatinine

10.2.3. EPISODE OUTCOME DATA AT ICU AND HOSPITAL DISCHARGE

• Duration of study drug, other sedatives, and open label dexmedetomidine infusions given

• Date and time of ICU discharge

• Duration of invasive mechanical ventilation

- Survival status at ICU discharge
- Readmission to same ICU within same hospital stay
- Date and time of hospital discharge
- Survival status at hospital discharge
- Readmission to hospital prior to day 90

10.2.4. EPISODE END OF STUDY OUTCOMES

- Survival status at 90, 180 day.
- Dependency status at 180 day.
- Cognitive function measured by Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) at 180 days post randomization by phone (35)
- HRQoL measured by EQ-5D at 180 days post randomization by phone (36)

10.3. DATA QUALITY

Several procedures to ensure data quality and protocol standardisation will help to minimise bias.

These include:

- Start-up meeting for all research coordinators and investigators will be held prior to study commencement to ensure consistency in procedures
- A detailed dictionary will define the data to be collected on the case report form
- The data management centre will perform timely validation of data, queries, and corrections if errors are found during quality control checks
- Data monitoring will occur as described below.

10.4. MONITORING

The study monitoring will be coordinated/monitored by the Project Manager or his/her delegate according to the study monitoring plan which utilises a risk-based approach in line with ICH GCP E6 (R2). A site initiation teleconference or visit will be conducted before site activation; at least 1 routine monitoring visit will be conducted during the recruitment period; and a close out visit. Email and telephone communication will supplement site visits.

Medical records, any other relevant source documents and the site investigator files must be made available to the study representative for these monitoring visits during the course of the study and at the completion of the study as needed.

A monitoring report will be prepared following each visit and reviewed by the management committee if appropriate. A follow up letter/report on the monitoring visit will be sent to the principal investigator and research coordinator at the site and will be filed in the site investigator file.

11. STATISTICAL CONSIDERATIONS

11.1. SAMPLE SIZE

A total sample size of 3500 patients equally distributed across treatment and control groups will be recruited to detect a 4.7% reduction in mortality (as seen in SPICE III) from a baseline mortality of 40.6 % with 80% power and an 0.05 significance level. This sample size allows for up to a 3% proportion of patient losses to follow up, and also allows for one interim safety analysis at 50% recruitment. The combined loss to follow-up and consent withdrawal in SPICE III, at 2.4%, was within this margin. It is planned that the results from SPICE IV will be combined with the results of SPICE III (which included 1828 patients ≥ 65 years of age) to conduct an individual patient data meta-analysis (IPMDA). This future combined analysis of more than 5000 ICU patients over the age of 65 years may return a more precise estimate of the effect of dexmedetomidine on mortality in ICU patients aged 65 years or older.

11.2. STATISTICAL ANALYSIS PLAN

Statistical analyses will be conducted on an intention-to-treat basis. Comparison of 90-day mortality between treatment arms will be performed using a chi-square test for equal proportion and hierarchical logistic regression to account for multi-centre variability. Sensitivity to missingness and baseline imbalance will be conducted using multiple imputation and covariate adjusted logistic regression respectively. Secondary outcomes will be analysed using standard statistical methods for binomial and continuous data with Bonferroni adjustment for multiplicity. Time-to-event data will be assessed using Cox regression and presented as Kaplan Meier curves with log-rank comparison. A detailed **statistical analysis plan** will be developed in accordance with the SPICE III analysis plan and published prior to study completion.

12. SAFETY

12.1. DATA SAFETY MANAGEMENT COMMITTEE

An independent Data and Safety and Monitoring Committee (DSMC), comprising experts in clinical trials, biostatistics and intensive care medicine will be established before patient enrolment to review all trial protocols.

The Data Safety and Monitoring Committee will oversee the trial's safety data and independently evaluate adverse and serious adverse events. A single blinded interim analysis will be conducted and performed for the purpose of efficacy and safety after 50% (n=1750) of enrolled patients have had their survival status at 90-days collected, using a symmetric 3 SD Haybittle-Peto interim analysis boundary design. The DSMC may, in its absolute discretion, request assessment of any trial data at any time.

The DSMC will be forwarded a copy of all serious adverse events (SAE) reports as soon as they become available to the Project Manager. The DSMC will review all SAE reports that they receive and report back to the management committee of the study if any further action is required.

The DSMC will review any Adverse Drug Reaction Reports to the Therapeutic Goods Administration (TGA) in Australia, the Centre for Adverse Reactions Monitoring (CARM) under the guidance of the Medicines Adverse Reactions Committee in New Zealand and any relevant jurisdiction or regulatory body.

12.2. ADVERSE EVENTS

Adverse events (AEs) are defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational intervention, and which does not necessarily have to have a causal relationship with this treatment (adapted from the Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95 July 2000).

It is recognised that the intensive care patient population will experience a number of common aberrations in laboratory values, signs and symptoms due to the severity of the underlying disease and the impact of standard therapies. These will not necessarily constitute an adverse event unless they require significant intervention or are considered to be of concern in the investigator's clinical judgement. Coded AEs will be collected as specified in the Data Dictionary.

In all cases, the condition or disease underlying the symptom, sign or laboratory value should be reported e.g. bradycardia rather than low blood pressure due to bradycardia, and agitation rather than self-extubation.

12.3. SERIOUS ADVERSE EVENTS

12.3.1. DEFINITION OF A SAE

SAEs are defined in accordance with the Note for Guidance on Clinical Safety Data Management:

Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95- annotated with TGA comments) (July 2000) as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event which may require intervention to prevent one of the previously listed outcomes.

The baseline mortality of intensive care patients enrolled in trials will be high due to the critical illness that has necessitated their ICU admission. They will frequently develop life-threatening organ failure(s) unrelated to study interventions and despite optimal management. Therefore, consistent with the advice of Cook et al, events that are part of the natural history of the primary disease process or expected complications of critical illness (37) and, events already defined and reported as study outcomes (e.g. mortality, re-admission to ICU) will not be labelled and reported separately as adverse events or SAEs unless they are considered to be causally related to the study intervention or are otherwise of concern in the investigator's judgement

12.3.2. SAE REPORTING

SAEs which occur from the time of commencement of study treatment to day 90 will be reported within 24 hours of study staff becoming aware of the event.

All SAEs will be reported to the coordinating centre via entry into the secure, online website. Minimum information to report will include:

- Patient initials and study number
- Nature of the event
- Commencement of the event
- An investigator's opinion of the relationship between study involvement and the event (not-related, unlikely, possibly, probably or definitely related).
- Whether treatment was required for the event and what treatment was administered.

Coordinating centre staff will be responsible for following-up SAEs to ensure all details are available. This may involve follow-up within a limited time frame (8-15 calendar days) if the event meets criteria for expedited reporting.

SAEs which are both unexpected and have a causal relationship with the study drug will be reported as Adverse Drug Reactions by the Coordinating Centre to the TGA, CARM. These reports will then be forwarded to all sites for reporting to their HRECs as required.

13. FUNDING

This study is funded by the National Health and Medical Research Council's Clinical Trials and Cohort Studies Grant APP1186863.

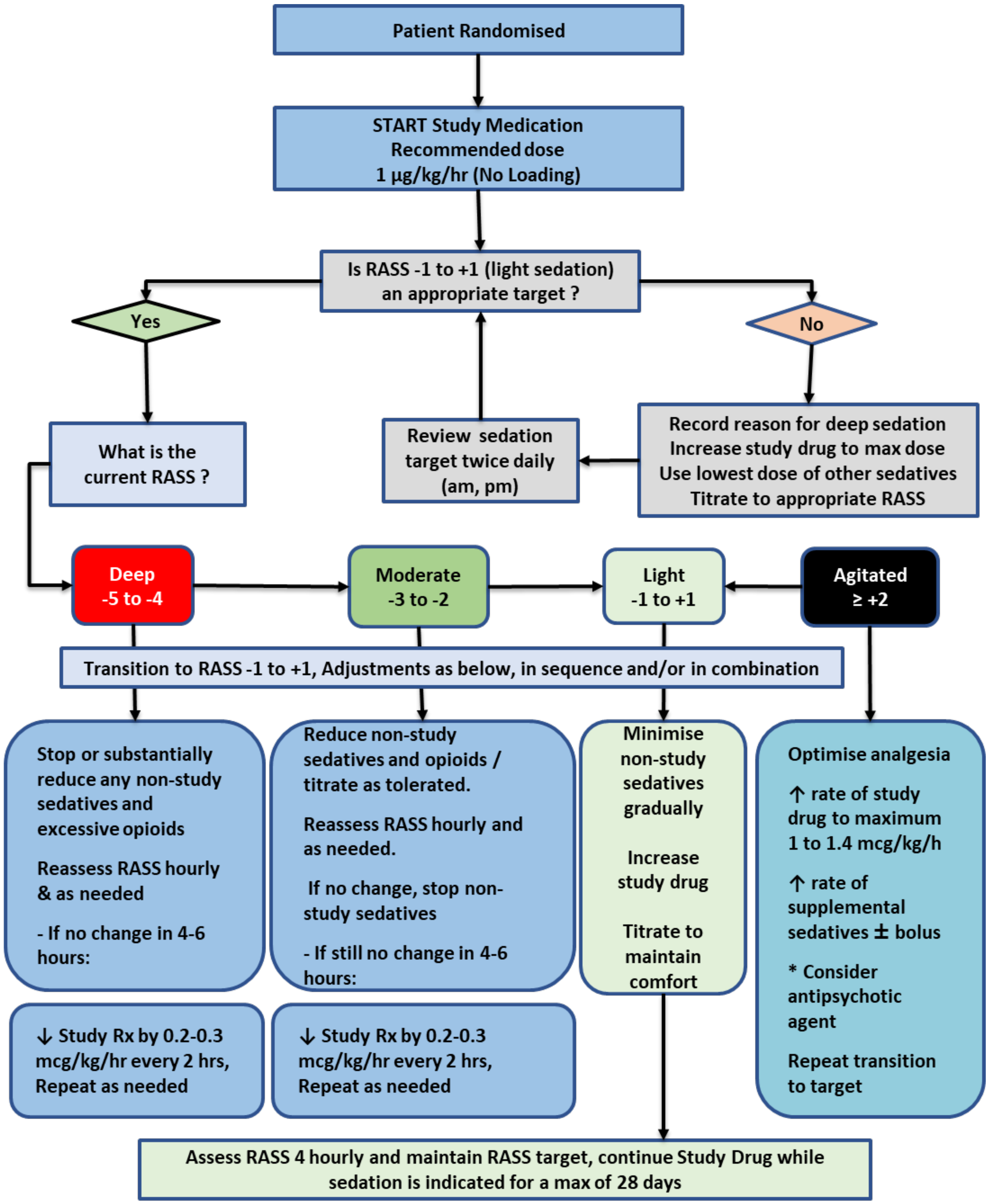
14. PUBLICATION

The principal publication from the study will be in the name of the SPICE IV Investigators with full credit assigned to all collaborating Investigators, Research Coordinators and Institutions. Where individual names are required for publication, they will be those of the Writing Committee, with the Chair of the Writing Committee listed first and subsequent authors listed alphabetically. Appropriate acknowledgement will be given to the coordinating centre and the ANZICS CTG once endorsed.

15. DATA-SHARING STATEMENT

The SPICE IV study will comply with data-sharing policies and procedures of Monash University and the guidelines set by the ANZICS Clinical Trials Group. A detailed statement can be found on the ANZICS CTG website.

16. APPENDIX I SPICE IV TREATMENT AND INTERVENTIONS ALGORITHM



*Assess delirium when possible. Consider using antipsychotics, such as quetiapine or haloperidol, before non-study sedatives such as midazolam or propofol if delirium is suspected.

Allow 20-30 min for any change in study drug to take effect .

❑ Remifentanil and IV clonidine not permitted in ALL patients

17. REFERENCES

1. Si Y, Bao H, Xu L, Wang X, Shen Y, Wang J, et al. Dexmedetomidine protects against ischemia/reperfusion injury in rat kidney. Eur Rev Med Pharmacol Sci. 2014;18(13):1843-51.
2. Ren X, Ma H, Zuo Z. Dexmedetomidine Postconditioning Reduces Brain Injury after Brain Hypoxia-Ischemia in Neonatal Rats. J of Neuroimmune Pharmacol. 2016;11(2):238-47.
3. Sato K, Kimura T, Nishikawa T, Tobe Y, Masaki Y. Neuroprotective effects of a combination of dexmedetomidine and hypothermia after incomplete cerebral ischemia in rats. Acta Anaesthesiol Scand. 2010;54(3):377-82.
4. Ueki M, Kawasaki T, Habe K, Hamada K, Kawasaki C, Sata T. The effects of dexmedetomidine on inflammatory mediators after cardiopulmonary bypass. Anaesthesia. 2014;69(7):693-700.
5. Taniguchi T, Kidani Y, Kanakura H, Takemoto Y, Yamamoto K. Effects of dexmedetomidine on mortality rate and inflammatory responses to endotoxin-induced shock in rats. Critical Care Med 2004;32(6):1322-6.
6. Pandharipande PP, Sanders RD, Girard TD, McGrane S, Thompson JL, Shintani AK, et al. Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an a priori-designed analysis of the MENDS randomized controlled trial. Crit Care. 2010;14(2):R38.
7. Kawazoe Y, Miyamoto K, Morimoto T, Yamamoto T, Fuke A, Hashimoto A, 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):1321-8.
8. Skrobik Y, Duprey MS, Hill NS, Devlin JW. Low-Dose Nocturnal Dexmedetomidine Prevents ICU Delirium. A Randomized, Placebo-controlled Trial. Am J Respir Crit Care Med. 2018;197(9):1147-56.
9. Reade MC, Eastwood GM, Bellomo R, Bailey M, Bersten A, Cheung B, 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.
10. Li CJ, Wang BJ, Mu DL, Hu J, Guo C, Li XY, et al. Randomized clinical trial of intraoperative dexmedetomidine to prevent delirium in the elderly undergoing major non-cardiac surgery. British Journal of Surgery. 2020;107(2):e123-e32.
11. Shehabi Y, Howe B, Bellomo R, Arabi YM, Bailey M, Bass FE, et al. Early sedation with dexmedetomidine in critically ill patients. New England Journal of Medicine. 2019;380(26):2506-17.
12. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol. 2004;57(1):6-14.
13. Kim J, Kim WO, Kim H-B, Kil HK. Adequate sedation with single-dose dexmedetomidine in patients undergoing transurethral resection of the prostate with spinal anaesthesia: a dose–response study by age group. BMC Anesthesiology. 2015;15(1):17.
14. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, et al. The Richmond agitation–sedation scale validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002;166(10):1338-44.
15. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). JAMA. 2001;286:8.
16. McKown AC, Wang L, Wanderer JP, Ehrenfeld J, Rice TW, Bernard GR, et al. Predicting major adverse kidney events among critically ill adults using the electronic health record. Journal of medical systems. 2017;41(10):156.
17. Levey AS, Eckardt K-U, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2005;67(6):2089-100.
18. ANZICS. https://www.anzics.com.au/adult-patient-database-apd/. 2018.
19. Shehabi Y. Bellomo R MG, Riker R, Takala J. Intensive care sedation, The past, present and the future. Critical Care. 2013;17(322).
20. Wunsch H, Kahn JM, Kramer AA, Rubenfeld GD. Use of intravenous infusion sedation among mechanically ventilated patients in the United States. Crit Care Med. 2009;37(12).
21. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJ, Pandharipande PP, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Critical Care Medicine. 2018;46(9):e825-e73.
22. Girard TD, Alhazzani W, Kress JP, Ouellette DR, Schmidt GA, Truwit JD, et al. An Official American Thoracic Society/American College of Chest Physicians Clinical Practice Guideline: liberation from mechanical ventilation in critically ill adults. Rehabilitation protocols, ventilator liberation protocols, and cuff leak tests. American Journal of Respiratory and Critical Care Medicine. 2017;195(1):120-33.
23. Group ST. Impact of oversedation prevention in ventilated critically ill patients: a randomized trial—the AWARE study. Ann of Intensive Care. 2018;8(1):93.

24. Olsen HT, Nedergaard HK, Strøm T, Oxlund J, Wian K-A, Ytrebø LM, et al. Nonsedation or light sedation in critically ill, mechanically ventilated patients. New England Journal of Medicine. 2020;382(12):1103-11.
25. Aitken LM, Bucknall T, Kent B, Mitchell M, Burmeister E, Keogh SJ. Protocol-directed sedation versus non-protocol-directed sedation in mechanically ventilated intensive care adults and children. Cochrane Database of Systematic Reviews. 2018(11,CD009771).
26. Mehta S, Spies C, Shehabi Y. Ten tips for ICU sedation. Intensive Care Med. 2017:1-3.
27. Vincent J-L, Shehabi Y, Walsh TS, Pandharipande PP, Ball JA, Spronk P, et al. Comfort and patient-centred care without excessive sedation: the eCASH concept. Intensive Care Med. 2016;42(6):962-71.
28. Pandharipande P, Banerjee A, McGrane S, Ely EW. Liberation and animation for ventilated ICU patients: the ABCDE bundle for the back-end of critical care. Critical Care. 2010;14(3):1.
29. Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA. 2012;307(11):1151-60.
30. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, et al. Dexmedetomidine vs Midazolam for Sedation of Critically Ill Patients A Randomized Trial. JAMA. 2009;301(5):489-99.
31. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine—reporting of subgroup analyses in clinical trials. New England Journal of Medicine. 2007;357(21):2189-94.
32. NHMRC. the National Statement on Ethical Conduct in Human Research consists of a series of guidelines on ethical conduct in human research. https://servicesanueduau/files/guidance/national-statement-2018-updatedpdf. 2018.
33. Bergeron N, Dubois M-J, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. Intensive care medicine. 2001;27(5):859-64.
34. Gélinas C, Fillion L, Puntillo KA, Viens C, Fortier M. Validation of the critical-care pain observation tool in adult patients. Am J Crit Care. 2006;15(4):420-7.
35. Jorm AF. A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): development and cross-validation. Psychol Med. 1994;24:9.
36. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life research. 2011;20(10):1727-36.
37. Cook D, Lauzier F, Rocha MG, Sayles MJ, Finfer S. Serious adverse events in academic critical care research. Cmaj. 2008;178(9):1181-4.