A crossover, cluster randomised controlled trial of Selective Decontamination of the Digestive Tract in Intensive Care Unit patients in Australian and New Zealand

(SuDDICU-ANZ)

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STATEMENT OF COMPLIANCE

This document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007), the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95) annotated with Therapeutic goods Administration comments and the New Zealand interim Good Clinical Research Practice Guidelines (Volume 2 1998 and Volume 3 2000)
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# 2 Protocol synopsis

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<td>Acronym</td>
<td>SuDDICU-ANZ</td>
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<tr>
<td>Overview</td>
<td>A randomised trial comparing the effect of using selective decontamination of the digestive tract (SDD) plus standard care, to standard care alone on hospital mortality in patients receiving mechanical ventilation in the intensive care unit (ICU). Secondary outcomes include an ecological assessment and a long-term health economic analysis.</td>
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<tr>
<td>Design</td>
<td>A bi-national, multicentre, crossover, cluster randomised controlled trial (x-cRCT) of eligible patients in participating ICUs using two 12-month interventional trial periods separated by a 3-month inter-period gap. An observational ecological assessment will be conducted in all eligible patients during the two 12-month intervention periods and in all patients admitted to participating ICUs during the first week of each month over three 3-month surveillance periods before, during the inter-period gap and after the second 12-month interventional period.</td>
</tr>
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<td>Participants</td>
<td>General ICUs that admit mechanically ventilated patients will be randomised in the first 12-month period to either implement the SDD protocol in addition to standard care or to continue standard care without SDD, and then to cross over to the other arm during the second 12-month period. Eligible patients are defined as: 1. All patients who are mechanically ventilated via an endotracheal tube on admission to the ICU and who are predicted to remain ventilated beyond the end of the calendar day after the day of ICU admission, or 2. All patients who become mechanically ventilated via an endotracheal tube during their ICU stay and who are predicted to remain ventilated beyond the end of the calendar day after the day they are first ventilated, or 3. All patients who not already recruited but are receiving mechanical ventilation via an endotracheal tube and are expected to receive ongoing ventilation for a further 48-hours or more despite an earlier prediction that ventilation would be discontinued earlier. When units are allocated to the SDD arm, SDD will be prescribed and will be commenced as soon as possible. When units are allocated to the control group, the same patients will identified and followed, without receiving SDD.</td>
</tr>
<tr>
<td>Intervention</td>
<td>In the SDD arm, all eligible patients will receive: 1. A six-hourly topical application of 0.5g paste containing colistin 2%, tobramycin 2% and nystatin 2%, to the buccal mucosa and oropharynx 2. A six-hourly administration of 10 mL of a suspension containing 100 mg colistin, 80 mg tobramycin and 2 x 10^6 IU nystatin, to the gastrointestinal tract via a gastric/post-</td>
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pyloric tube
3. A four-day course of an intravenous (IV) antibiotic. Patients not already receiving a therapeutic antibiotic will be prescribed cefotaxime 1g six-hourly or ceftriaxone 1g daily, with dose adjusted as appropriate for organ dysfunction. Ciprofloxacin (400mg 12-hourly) may be used as an alternative if there is a contraindication to cephalosporins, such as allergy. Patients already receiving an alternative IV antibiotic as clinically indicated will not receive an additional IV antibiotic, but will continue the prescribed antibiotic for the usual duration of therapy.

<table>
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<th>Primary outcome</th>
<th>All-cause hospital mortality</th>
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<td>b) The incidence of <em>Clostridium difficile</em> infections</td>
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<th>Statistical considerations and sample size</th>
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<td>SuDDICU-ANZ will recruit 8,000 patients from 25-30 ICUs and will be able to detect a 3.6-3.7% absolute reduction in hospital mortality from a baseline mortality of 29%, using 80% power, $\alpha &lt;0.05$.</td>
</tr>
</tbody>
</table>
3 Administrative information

3.1 Investigator and Management Committee contacts

3.1.1 Study sponsor / trial co-ordinating centre

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3.1.3 SuDDICU-Globa

Name: Professor Brian Cuthbertson (SuDDICU-Globa Chair)  
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University of Toronto, Toronto, Canada  
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3.2 SuDDICU-ANZ management structure

Terms of Reference for SuDDICU-ANZ Management Committee are defined in the SuDDICU-ANZ charter.

3.2.1 Management Committee members

1. Professor John Myburgh AO (Chair), The George Institute for Global Health
2. Dr Maryam Correa (Project Manager), The George Institute for Global Health
3. Dr Parisa Glass, (Director of Operations), The George Institute for Global Health
4. Associate Professor Ian Seppelt, Intensive Care Unit, Nepean Hospital
5. Dr Paul Young, Wellington Regional Hospital, Wellington
6. Professor Simon Finfer, Intensive Care Unit, Royal North Shore Hospital
7. Professor Brian Cuthbertson, Sunnybrook Health Sciences Centre, University of Toronto
8. Associate Professor Laurent Billot, Director, Statistics Division, The George Institute for Global Health
9. Professor Jon Iredell, Director, Infectious Diseases, Westmead Hospital
11. Dr Colman Taylor Health Economics Fellow, The George Institute for Global Health

3.3 Funding

The study is funded by a Project Grant from the Australian National Health and Medical Research Council (NHMRC) - Project Grant ID 1084244.

3.4 Trial registration

This protocol has been registered on the following registries:
1. Australian New Zealand Clinical Trials Registry, Number: ACTRN12615000411549.
2. ClinicalTrials.gov register, Identifier: NCT02389036.
4 Introduction

4.1 Background and rationale

Sepsis is the most common cause of death in critically ill patients, with a quarter of those who develop severe sepsis dying during their hospitalisation. While outcomes from severe sepsis have improved over time, the prevalence of sepsis in the community has increased. There are no effective treatments for severe sepsis apart from effective resuscitation, prompt administration of antibiotics, source control and supportive care. While many patients are admitted to hospital with severe sepsis, others will develop sepsis while in the hospital. Hospital-acquired infections are recognised as an increasing public health problem, causing more than one million deaths annually worldwide.

Each year, more than 20 million people are treated in an ICU of which between 20% and 50% will develop a hospital-acquired infection. Between 18 and 30% of these patients will die during their admission and a further 30% will die within a year after admission. Hospital-acquired infection is also associated with increased hospital length of stay and associated health-care costs. The prevention of ICU-acquired sepsis is critical and therefore the subject of a number of infection-control protocols and patient safety initiatives including ‘bundles of care’ directed at reducing catheter-related bloodstream infections, ventilator-associated pneumonia, and infections from antibiotic resistant microorganisms.

SDD is an infection-control strategy designed to reduce mortality by preventing sepsis. The aim of SDD is to reduce the mortality of critically ill patients by preventing hospital-acquired infection by altering the balance of potentially pathogenic and normal gastrointestinal flora. Specifically, the aim is to eradicate aerobic Gram-negative bacilli and pathogenic fungi from the digestive tract while maintaining normal populations of Gram-positive and anaerobic bacteria. The mechanism by which SDD prevents infection is primarily by the prevention of gastric colonisation by these organisms with subsequent micro-aspiration into the lungs and possibly by preventing direct translocation of organisms through the bowel mucosa.

Selective decontamination is achieved by the application of topical non-absorbable antibiotics and antifungals to the oropharynx and stomach combined with a short course of IV antibiotics, in addition to strict hand hygiene and other infection control measures. While exact compositions of SDD regimens have varied, SDD usually consists of an oral paste and enteral suspension of an aminoglycoside (e.g. tobramycin), peptide antibiotic (e.g. polymyxin B/colistin) and an antifungal (e.g. amphotericin or nystatin), combined with a short course of IV third generation cephalosporin (e.g. cefotaxime) or fluoroquinolone (e.g. ciprofloxacin).

The concept of SDD originated from attempts to prevent infections in immunocompromised haematological patients. The first trial of SDD in intensive care was in trauma patients in the early 1980s. In the subsequent 25 years, at least 36 randomised controlled trials (RCTs) have been published that have consistently reported a reduction in hospital-acquired infections in patients assigned to receive SDD, with an associated reduction in mortality reported in the majority of the RCTs.
Our group published a systematic review and updated meta-analysis of all SDD trials on the effect on mortality among other endpoints\(^1\). The meta-analysis reported that both topical and topical-systemic SDD regimens were associated with reductions in mortality (odds ratio [OR] 0.73, 95% confidence interval [CI] 0.64 to 0.84) and ventilator-associated pneumonia (OR 0.40, 95% CI 0.15 to 0.60)\(^1\). There was marked statistical heterogeneity due to the long historical inception period, small sample sizes, and methodological limitations\(^1\).

**Figure 1: Effect of SDD on mortality\(^1\)**

Despite the emerging evidence of potential benefit, there has been limited uptake of SDD into clinical practice. SDD is used routinely in many, but not all ICUs, in the Netherlands, where much of the existing evidence has been generated\(^1\). There has been limited uptake in the United Kingdom and minimal uptake in Australia, New Zealand and North America. This may be explained in part by concerns about methodological limitations of many of the trials, particularly small sample sizes and ascertainment bias.

Reflecting this clinical uncertainty, the 2012 Surviving Sepsis Guidelines recommended that SDD be ‘investigated as a method to reduce the incidence of ventilator-associated pneumonia’ and that it ‘can then be instituted in healthcare settings and regions where (it) is found to be effective’\(^1\).3.

The principal concern limiting the uptake of SDD is that the use of SDD will lead to an increase in antibiotic resistance. The association between overuse of antibiotics and the emergence of infections due to multi-resistant organisms (especially methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus*), is well established and these organisms are highly prevalent in many hospitals\(^1\). Broad-spectrum antibiotics are also associated with an increased prevalence of *Clostridium difficile* and multi-resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa* due to alterations in intestinal flora. The increasing problem of antibiotic resistance has resulted in policies that restrict both the use of prophylactic and therapeutic antibiotics and the enforcement of good antibiotic stewardship.

While many SDD trials report antibiotic resistance in study patients\(^9\) or short-term studies of ICU ecology,\(^15,16\) none of these trials have simultaneously studied the microbiological ecology of the whole ICU during and after the introduction of SDD. Much of the existing data on the impact of SDD on antibiotic resistance patterns comes from the Netherlands that has an atypical and low prevalence of
endemic bacterial resistance. Consequently the applicability of data from the Netherlands to countries, such as Australia, where antibiotic resistance is more prevalent is unclear.

Given the uncertainty about the efficacy, safety and potential health economics of SDD, its role in clinical practice has been vigorously debated for the last 20 years. There is therefore an ethical, scientific and financial imperative to design an integrated research program to address all aspects about the effectiveness of SDD and to inform clinicians and policy makers.

4.2 The SuDDICU international research collaboration

The SuDDICU collaboration is an international, investigator-initiated research collaboration that was established through research networks in Australia, New Zealand, Canada and the UK in 2009 with the aim of addressing the controversy about the role of SDD in intensive care practice.

The international SuDDICU research program consists of six phases:

1. Systematic review of the literature (completed)
2. Exploratory study of risks, benefits, and barriers to the use of SDD (completed)
3. Inception cohort pilot study (completed)
4. Cluster randomised controlled trial (cRCT) with ecological and health economic evaluations (the protocol for this study)
5. Knowledge translation / implementation study (to be completed)
6. Post-implementation surveillance of effectiveness and antibiotic resistance pattern study. (to be completed)

4.2.1 Systematic review of antibiotic resistance

In addition to our updated systematic review looking at the effect of SDD on mortality, we conducted a meta-analysis of all available trials that looked at the development of antibiotic resistance with SDD.

As a major concern with SDD is whether it increases antibiotic resistance, this is a crucial factor to consider in the design of an RCT. We found no statistical difference in colonisation or infection with methicillin-resistant *Staphylococcus aureus* (OR 1.46, 95% CI 0.90 to 1.68) or vancomycin-resistant *Enterococcus* (OR 0.63, 95% CI 0.39 to 1.02). There was no difference in development of aminoglycoside (OR 0.73, 95% CI 0.51 to 1.05) or quinolone resistance (OR 0.52, 95% CI 0.16 to 1.68) and a significant decrease in polymyxin (OR 0.58, 95% CI 0.46 to 0.72) and third-generation cephalosporin resistance (OR 0.33, 95% CI 0.20 to 0.52) in those patients infected with Gram-negative organisms who were treated with SDD.

Despite valid concerns that SDD might increase the prevalence of antibiotic resistant organisms, there is evidence that SDD is associated with a reduction in overall antibiotic use and that these concerns may be misplaced.

This strengthens the case to conduct a definitive RCT to address these concerns.
4.2.2 Exploratory studies of the risks, benefits and barriers related to use of SDD

Our group has studied the perceived risks, benefits and barriers to the use of SDD in ICUs in Australia, New Zealand, Canada and the United Kingdom. We performed a Delphi survey of 120 key international stakeholders and opinion-leaders from critical care medicine, nursing, pharmacy, infectious diseases, and medical microbiology from the United Kingdom (33%), Canada (33%) and Australia / New Zealand (33%)\(^9\).

No clear patterns in favour of or against the use of SDD were observed indicating clinical equipoise among the respondents. Respondents clearly indicated they considered that further research was required to establish efficacy of SDD in terms of patient-centred outcomes and development of antibiotic resistance and that they would be willing to participate in a high quality RCT. Mortality was favoured as the primary outcome\(^9\).

Concern about the development of antibiotic resistance was not identified as a barrier to participation in a trial, provided that appropriate pre-, intra- and post-trial monitoring of antibiotic resistance was conducted.

Figure 2: The prevalence of Gram-negative organisms resistant to (A) aminoglycosides, (B) polymyxin E or B, (C) fluoroquinolones, or (D) third generation cephalosporins\(^\text{18}\)
4.2.3 Inception cohort pilot study

We conducted an inception cohort pilot study in five centres in Australia, New Zealand, United Kingdom, Canada and the USA to determine the number of ICU patients eligible for the present study, to describe the baseline characteristics of the study population, to establish the duration of study treatment that would be required and to prospectively determine the in-hospital mortality rate for the study population.

We established that 36.4% (95% CI 32.6% to 40.2%) of all patients admitted to the five ICUs met the inclusion criteria for the planned RCT and the average duration of study treatment would be 7.8 days (95% CI 7.1 to 8.6 days). The hospital mortality rate was 29.9% (95% CI 23.7 to 36.0%). 61% of patients were already being prescribed therapeutic antibiotics at the time of ICU admission. The potential duration of therapy for patients identified as fulfilling the study eligibility criteria was 10 days. The time to first dose of trial intervention was 4.5 hours.

A second pilot study of the delivery of the intervention has been completed in one centre in Canada. It demonstrated a very high fidelity of delivery of the IV and oral/gastric intervention (>90%) and concluded the intervention delivery for a cRCT was feasible.

To address the question of whether or not to include the IV component of SDD, we conducted a comparative cohort study of patterns and outcomes from infection in ICUs using SDD in the UK. After adjustment for severity of illness and unit-level random effects, there were no statistically significant differences in mortality, but a lower rate of ICU-acquired infections in SDD units that used an IV antimicrobial component (OR 0.09, 95% CI 0.01 to 0.63, p=0.015).

4.2.4 A cRCT of SDD

Our preparatory studies indicated that a high-quality comparative effectiveness study of SDD, including a study of the ecology of infection and microbial resistance is acceptable, necessary and feasible.

SDD is both an individual patient-based intervention and an ecological intervention. It, may have direct individual patient-centred effects and reduces the carriage of potentially pathogenic microorganisms that may lead to a hospital acquired infection. SDD may also alter the ecology of a unit and may have indirect effects both among patients receiving SDD but also in those patients in the unit not receiving the intervention.

Individual patient randomisation, as opposed to unit randomisation will not replicate the manner in which SDD would subsequently be deployed in practice and will have a large risk of failing to adequately evaluate the influence of SDD on antibiotic resistance. For the prophylaxis to be maximally effective it should be introduced as soon as possible after ICU admission - this is only feasible in a cluster design where the prophylactic SDD regime becomes the participating ICUs standard practice for the trial period.

Originally planned as an international, multi-centred, cRCT that was to be simultaneously conducted in Canada, UK, Australia and New Zealand and designed using metrics from these countries to determine a 3.5% absolute reduction in hospital mortality and a 2% non-inferiority increase in antibiotic resistance, a study population of 22500 patients from 100 ICUs was projected. This international trial was dependent on success in simultaneous applications to national research funding agencies in the four countries.

However, only the Australian NHMRC was successful and a decision was made to conduct the RCT in Australia and New Zealand as a stand-alone trial (SuDDICU-ANZ), with a modification to a crossover
cRCT, primarily directed at determining a consistent 3.5% absolute reduction in hospital mortality. Due to lack of statistical power with a revised study population of 8000 patients for the primary outcome, the ecological assessment was modified to an observational study to determine secular trends in antibiotic resistance patterns before, in between and after the intervention periods.

The crossover design is consistent with the original cRCT design and allows each ICU to serve as its own control, minimising the risk of imbalance between participating ICUs, and significantly improving statistical power compared to a parallel group cRCT.

The results of SuDDICU-ANZ would provide definitive information about the effect of SDD on hospital mortality compared to standard care and would form the vanguard for subsequent parallel trials conducted within the international SuDDICU collaboration with the ultimate aim of conducting a pre-specified individual patient-data meta-analysis of all SDD trials using harmonised databases and outcomes.

5  Study design

5.1  Aim

To determine whether SDD is clinically effective and cost-effective at reducing hospital mortality in mechanically ventilated critically ill patients in the ICU without increasing antibiotic resistance, and is cost-effective compared to the standard care.

5.2  Design

The SuDDICU-ANZ trial is a bi-national, multicentre, x-cRCT of eligible patients in participating ICUs using two 12-month interventional trial periods separated by a 3-month inter-period gap.

An observational ecological assessment will be conducted in all eligible patients during the two 12-month intervention periods and in all patients admitted to participating ICUs during the first week of each month over three 3-month surveillance periods before, during the inter-period gap and after the second 12-month interventional period.

Figure 3: The elements of the trial design
6 Study outcomes

6.1 Primary outcomes

All-cause hospital mortality related to ICU index admission.

6.2 Secondary outcomes

6.2.1 Ecology assessments

1. The incidence of AROs isolated from all clinical and surveillance specimens, including the incidence of AROs in cultures from blood or other sterile sites, the incidence of AROs in non-sterile clinical and surveillance specimens, and the incidence of bacteraemia in all blood culture specimens
2. The incidence of Clostridium difficile infections
3. Total antibiotic usage (as daily defined doses)

6.2.2 Clinical assessments

1. Duration of mechanical ventilation
2. ICU length of stay
3. ICU mortality
4. Hospital length of stay

6.2.3 Health economic assessment

1. Health economic analysis from a healthcare system perspective

7 Study population

7.1 Study setting

SuDDICU-ANZ will be conducted in 25-30 general ICUs in Australia and New Zealand.

7.2 Site eligibility criteria

7.2.1 Inclusion

1. A general ICU or complex of ICUs (medical, surgical, mixed) capable of treating mechanically ventilated critically ill patients.

7.2.2 Exclusions

1. Unwilling or unable to follow trial protocols
2. Unable to capture the minimum data set required for the study
3. Isolated specialty ICUs not co-located with a general ICU, such as solely cardiac, neurological/neurosurgical and burns ICUs, but such specialty patients cared for in general ICUs will be included
4. Specialty paediatric ICUs.
7.3 Patient eligibility criteria

7.3.1 Inclusions

1. All patients who are mechanically ventilated via an endotracheal tube on admission to ICU and who are predicted to remain ventilated beyond the end of the calendar day after the day of ICU admission, or
2. All patients who become mechanically ventilated via an endotracheal tube during their ICU stay and who are predicted to remain ventilated beyond the end of the calendar day after the day they are first ventilated, or
3. All patients not already recruited who are receiving mechanical ventilation via an endotracheal tube and are expected to receive ongoing ventilation for a further 48 hours or more despite an earlier prediction that ventilation would be discontinued earlier.

7.3.2 Exclusions

1. Patients enrolled in a trial that would interact with the intervention
2. Patients with a known allergy, sensitivity or interaction to trial topical intervention drugs
3. Patients who are known or suspected to be pregnant
4. Patients who are moribund and not expected to survive the next 12 hours
5. Patients less than 16 years of age will not be enrolled in New Zealand

Patients readmitted to the ICU will be re-enrolled into the study and receive study interventions if they meet inclusion criteria and do not have any exclusion criteria. They will be counted as the same enrolment for study analysis.

7.4 Ecology surveillance period eligibility criteria

7.4.1 Inclusion

1. All patients admitted to the study ICUs regardless of ventilation status, during the first full week of every calendar month for 3-months during the pre-trial, inter-period gap and post-trial periods for the duration of their ICU admissions.

7.4.2 Exclusion

1. None

8 Study interventions

ICUs will be randomised in the pre-trial period to either deliver SDD in the first 12-month period or be a control ICU in the second 12-month period, or to be a control ICU first and deliver SDD in the second period.

8.1 Randomisation

All participating ICUs will be randomised by an independent statistician using a computer-based randomisation program.

Once governance and operational clearances have been completed, ICUs will be notified to which order of periods they have been allocated during the 3-month pre-trial phase.
8.2 Intervention group

All patients eligible for the intervention will receive the following in addition to the usual infection control measures:

1. A six-hourly topical application of 0.5g paste, containing colistin 2%, tobramycin 2% and nystatin 2%, to the buccal mucosa and oropharynx
2. A six-hourly administration of 10 mL of a suspension containing 100 mg colistin, 80 mg tobramycin and $2 \times 10^6$ IU nystatin, to the gastrointestinal tract via a gastric/post-pyloric tube
3. A four-day course of an IV antibiotic. Patients not already receiving a therapeutic antibiotic will be prescribed cefotaxime 1g six-hourly or ceftriaxone 1g daily, with dose adjusted as appropriate for organ dysfunction. Ciprofloxacin (400mg 12-hourly) may be used as an alternative if there is a contraindication to cephalosporins (e.g. allergy). Patients already receiving an alternative IV antibiotic to treat infection will not receive this additional IV antibiotic, but will continue the prescribed antibiotic for the usual duration of therapy.

8.2.1 Duration of treatment

SDD will become standard care for that ICU for the intervention period and will be prescribed for all eligible patients in that ICU.

Eligible patients will be treated with SDD within six hours of meeting eligibility criteria.

The topical and enteral intervention will continue until tracheal extubation, removal of the enteral feeding tube, 24-hours unsupported spontaneous ventilation via tracheostomy, or ICU discharge, whichever comes first, for a maximum of 90 days.

The IV antibiotic will be continued for four days or until ICU discharge, whichever comes first. If there is a clinical indication to continue systemic antibiotics for a longer period then that will not be considered part of the trial intervention.

Patients readmitted to the ICU during the same hospital admission will continue to receive the intervention according to trial protocol but not be counted as a separate enrolment.

8.2.2 Provision of product

Colistin, tobramycin and nystatin are licensed antibacterial and antifungal drugs, and are already used in critically ill patients when indicated. The paste and suspension of these agents (1 and 2 above) will be manufactured according to Good Manufacturing Practice standards under contract for the trial and will be supplied in numbered patient-specific boxes to the ICUs.

The study paste and suspension will be registered with the Australian Therapeutic Goods Administration and Medsafe (New Zealand). Copies of an Investigators Brochure and study drug information sheets will be supplied to participating sites.

Most of the IV antibiotics are considered standard practice and the only study specific intervention given is IV ceftriaxone or cefotaxime administered to patients not already treated with antibiotics for clinical purposes. This is predicted to be 40% of eligible patients.

8.3 Control group

When the ICU is allocated to standard care (control) the same group of patients will be identified according to the inclusion and exclusion criteria above and will be followed up in the same way to the primary and secondary endpoints above.
Patients will receive all usual infection control measures but will receive no study-specific interventions.

8.4 Cessation of treatment

At the end of each 12-month SDD intervention period, patients will continue to receive SDD until they meet criteria for cessation of SDD for a maximum of 90 days, or until the end of the 3-month (90-day) inter-period gap and post-trial period.

8.5 Concomitant care and permitted interventions

There are no restrictions on what is considered standard care in each site, aside from the use of SDD or its components.

The Management Committee will consider co-enrolment with other randomised studies on an individual basis. Apart from concurrent antibiotic studies as outlined in the trial exclusion criteria, co-enrolment is generally permitted.

8.6 Blinding

This is an unblinded study. SDD will become usual practice for participating ICUs when allocated to the intervention arms.

Ascertainment bias will be mitigated through blinded randomisation.

8.7 Surveillance swabs

It is recommended that ICUs collect routine surveillance swabs (oral/endotracheal and perineal/rectal) on all patients on admission, at least weekly and on discharge.

If surveillance swabs are not usual practice for the ICU then they are not mandated for this trial.

8.8 Withdrawal of study treatment

Following enrolment all participating patients should continue to receive SDD paste and suspension according to the protocol. Study intervention can be stopped in the following circumstances:

1. Serious adverse reaction to study intervention
2. A definite contraindication to study intervention becomes apparent
3. Request to withdraw by the patient or their substitute / person responsible (if applicable). At this time the patient or substitute will be asked if previously collected data can be used and if the trial primary outcome can be collected and analysed for the study. If this is declined then all patient data will be destroyed and no further analysis undertaken.

9 Data collection

Outcomes will be collected using data that are routinely recorded in the ICU clinical chart and available in hospital databases.

9.1 Screening

Patients will be screened and evaluated to assess eligibility for the study. A screening log will be kept at each site to monitor recruitment and report the size of the patient population from which eligible patients have been recruited.
9.2 Enrolment

Patient demographics will be entered into a web-based patient record system, and each eligibility criterion will be answered with a Yes / No response to confirm eligibility.

9.3 Baseline

Patient demographics, admission diagnosis and clinical information including a routinely collected severity of illness score will be collected.

Specific risk factors for infection (diabetes, immunosuppression and use of systemic steroids) will be documented, as will any use of oral chlorhexidine, and receipt of IV antibiotics at time of enrolment and for >48 hours prior to enrolment.

9.4 Control group

Daily information will be collected up to a maximum of 28 days, documenting the duration of mechanical ventilation, the use of any antibiotics in daily defined doses.

Any positive test for Clostridium difficile, the results of all blood cultures, and the report of any AROs in any other sterile or non-sterile cultures or surveillance swabs will be collected for the duration of the ICU admission censored at 90 days.

All cultures with an ARO from any source will be counted as a single event.

ICU discharge date and time, hospital discharge data and time, and cause of death (if deceased) will be documented.

For the primary analysis, hospital mortality will be censored at 90 days.

Hospital mortality will subsequently be collected for the entire cohort without censoring.

9.5 Intervention group

In addition to all the data points for the control group, in the intervention group daily data will be collected documenting the delivery of any SDD intervention paste, suspension or IV antibiotics.

9.6 Ecology surveillance periods

During the nine discrete ecology surveillance periods (three pre-trial, three during the inter-period gap and three post-trial), data will be collected on all patients admitted to the ICU during the first full week of each calendar month of the periods regardless of mechanical ventilation status.

Demographics, diagnosis and severity of illness score will be documented, the presence and duration of mechanical ventilation, the ICU and hospital length of stay and hospital mortality.

Microbiology results will be collected documenting any positive test for Clostridium difficile, the results of all blood cultures and any positive AROs in sterile or non-sterile sites.
### 10 Study timeline

<table>
<thead>
<tr>
<th>Date</th>
<th>Project Milestone</th>
</tr>
</thead>
<tbody>
<tr>
<td>July 2015 – December 2016</td>
<td>Start-up phase; including site feasibility and selection, and agreement by sites to follow study protocols (intensive care and infectious diseases)</td>
</tr>
<tr>
<td>August 2016</td>
<td>Protocol finalised</td>
</tr>
<tr>
<td>August - October 2016</td>
<td>Case Report Form (CRF) and other study documents finalised</td>
</tr>
<tr>
<td>November 2016</td>
<td>All ethics and other regulatory requirements met</td>
</tr>
<tr>
<td>February – April 2017</td>
<td>3-month pre-trial data collection period (surveillance ecology); site randomisation and initiation</td>
</tr>
<tr>
<td>May 2017 – April 2018</td>
<td>First trial recruitment period (SDD or control)</td>
</tr>
<tr>
<td>May – July 2018</td>
<td>3-month inter-period data collection period (surveillance ecology) and site initiation for crossover</td>
</tr>
<tr>
<td>August 2018 – July 2019</td>
<td>Second trial recruitment period (control or SDD after crossover)</td>
</tr>
<tr>
<td>August – October 2019</td>
<td>3-month post-trial data collection period (surveillance ecology)</td>
</tr>
<tr>
<td>November 2019 – June 2020</td>
<td>Analysis and publication of primary (mortality) and secondary (ecology) endpoints</td>
</tr>
</tbody>
</table>
11 Safety monitoring and reporting

Critically ill patients in the ICU have a number of perturbations in laboratory values, signs and symptoms due to the severity of the underlying disease and the impact of standard medical therapies. These will not necessarily constitute an adverse event or serious adverse event unless they are considered to be related to study treatment or a concern in the principal investigator’s clinical judgement.

In this study, reporting of adverse events will be restricted to events that are considered to be related to study treatment (possibly, probably or definitely).

11.1 Adverse Drug Reactions (ADR)

Regarding marketed medicinal products, a well-accepted definition of an adverse drug reaction is 28:

‘A response to a drug which is noxious and unintended and which occurs in doses normally used in humans for prophylaxis, diagnosis or therapy of disease or for modification of physiological function’.

Any adverse reaction thought to be study treatment related will be reported to the coordinating centre within 7 days of discovery.

The principal investigator will be responsible for determining the causal relationship as either possible, probable or definitely study treatment related.

Notification will be by fax, scanned document sent by email or by notification of a completed ADR form on the web based data management system.

All adverse reactions will be reviewed by the coordinating centre staff and recorded in a safety database which will be monitored by the study management committee on a regular basis.

11.2 Serious Adverse Drug Reactions (SADRs)

Serious adverse events are defined as any untoward medical occurrence that meets one of more of the following criteria:

1. Results in death
2. Is life-threatening
3. Requires inpatient hospitalisation or prolongation of existing hospitalisation
4. Results in persistent or significant disability/incapacity
5. Is a congenital anomaly/birth defect

The classification of ‘serious adverse event’ is not related to the assessment of the severity of the adverse event. An event that is mild in severity may be classified as a serious adverse event based on the above criteria. Given that critically ill patients are likely to experience any of the above listed criteria in the course of their ICU admission, only serious events that are thought to be study treatment related will be reported.

Serious adverse drug reactions should be reported to the coordinating centre within 24-hours of participating site study staff becoming aware of the occurrence. A member of the coordinating centre will be on call 24-hours a day via mobile phone for out of ‘business hours’ reporting.
11.3 Suspected Unexpected Serious Adverse Reactions (SUSARs)

A serious adverse drug reaction whose nature, severity, specificity, or outcome is not consistent with the term or description used in the product information, should be considered unexpected. These will also be reported to the coordinating centre within 24-hours of participating site study staff becoming aware of the occurrence.

11.4 Reporting SADR and SUSARs

The minimum information to report will include:

1. Patient initials and study number
2. Nature of the event
3. Commencement and cessation of the event
4. The principal or co-investigator’s opinion of the relationship between study drug and the event (possibly, probably or definitely related)
5. Whether treatment was required for the event and what treatment was administered.

The coordinating centre staff will be responsible for following-up all SADRs and SUSARs to ensure all details are available. The coordinating centre is also responsible for alerting other participating sites of the report of an SADR or SUSAR and reporting to the regulatory authorities within required time frames.

It is the responsibility of each principal investigator to inform the local or lead Human Research Ethics Committee (HREC) of all SADR and SUSAR events which occur at their hospital, in accordance with local requirements. Copies of any reporting and correspondence to and from the local HREC or Research Governance Officer (RGO) should also be sent to the coordinating centre.

11.5 Data and Safety Monitoring Committee (DSMC)

An independent DSMC from the coordinating centre and investigators will perform an ongoing review of study outcomes and overall study conduct. The DSMC will review all adverse reactions at predetermined intervals during the study or as deemed appropriate by the DSMC.

The primary responsibility of the DSMC is to review interim analyses of outcome data and to recommend to the Study Management Committee whether the study needs to be changed, or terminated based on these analyses.

Full details of the DSMC procedures and processes are documented in the DSMC charter.

11.6 ARO outbreaks

An ARO outbreak is defined by the need for any new infection control interventions that are deemed (by the site investigator) to be directed specifically to outbreak containment. These must be reported to study Management Committee and will be assessed by the DSMC. Usual study procedures should continue while any outbreak is being assessed.

As ARO rates are being assessed as an endpoint of the trial, we do not propose to change the clinical intervention in the event of an observed increase in multi-resistant infections in a participating unit during the trial periods or to discontinue the SDD intervention.
Study sites will decide on the appropriate clinical management as determined by the clinical team and infection control staff of that unit. The study sites will be actively encouraged to resume normal trial conduct after control of the situation.

All cases of Clostridium *difficile* infection will be reported as serious adverse events.

### 11.7 Study termination

The study may be terminated at any time at the request of the study Management Committee in consultation with the DSMD, or by a regulatory authority, with proper and timely notification of all parties concerned.

The local or lead HREC will be informed promptly and the coordinating centre or the investigator will supply reason(s) for the termination or suspension, as specified by the applicable regulatory requirements.

The study will be considered terminated upon completion of all patient treatments and evaluations, and after the end of the 3-month post-trial observation period.

### 12 Ethics and dissemination

The study will be performed in accordance with ethical principles consistent with the Declaration of Helsinki and all relevant national and local guidelines on the ethical conduct of research.

#### 12.1 Independent Ethics Committee

The Principal Investigator is responsible for submitting this protocol to the Independent Ethics Committee. In Australia, an initial application requesting approval to conduct this study will be submitted using a National Ethics Application Form (NEAF) to a lead HREC in NSW. In addition, a review by the New South Wales Civil and Administrative Tribunal (Guardianship Division) has been completed.

Further applications will be submitted to other Independent Ethics Committees in Australia and the New Zealand Multi-region Ethics Committee and/or to the Hospital Research Ethics Committee at each of the participating hospitals. Each application will be submitted according to the requirements of each hospital committee, all of which are formed and are conducted in accordance with the guidelines laid down by the National and Medical Research Council of Australia or the Health Research Council of New Zealand.

During the trial, any amendment or modification to the study protocol should be notified to the Independent Ethics Committee by the Principal Investigator and approved by the Independent Ethics Committee before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the Independent Ethics Committee should be informed as soon as possible.

Each Principal Investigator will be responsible for informing the Independent Ethics Committee of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety.

The Principal Investigator will produce progress reports, adverse event reports, and any other required documentation to the local Independent Ethics Committee in accordance with their guidelines.
Any amendments or additions to the study protocol and material must be notified to the Independent Ethics Committee by the Principal Investigator and approved by the Independent Ethics Committee.

It is the responsibility of the Principal Investigator at each participating hospital to keep an up to date record of all correspondence and applicable documentation with the local Independent Ethics Committee.

12.2 Ethical implications of a x-cRCT design

A x-cRCT is the only feasible, practical and ethical design for this study, because of the nature of the intervention. An individual patient RCT will not be able to address the ecological effects of the intervention, whereas a ‘stepped wedge’ design fails to ethically address a possible harm from the therapy. A x-cRCT is essential in order to study both the patient-related direct effects of SDD (caused by the delivery of SDD to a particular patient) and indirect effects of SDD (caused to all patients by the effects of SDD on the microbiological ecology of the ICU).

As each ICU will be exposed to the study intervention for a defined time it will be possible to study secular trends in resistance in the ICUs before and after the introduction of and then cessation of SDD.

As the intervention will be offered to all eligible patients in participating ICUs as part of ‘standard practice’ for that ICU, recruitment for the study will be without individual patient consent. This is consistent with the NHMRC National Statement on Ethical Conduct in Human Research26 and the Ottawa Statement on the Ethical Design and Conduct of cRCTs27.

12.3 Individual patient consent

We intend to recruit every eligible patient admitted to the study ICU during the study recruitment period.

We will not seek individual patient consent for the period of the study up to hospital discharge (the primary outcome). We will apply for a waiver of consent in Australia, recognising that laws vary from state to state, and in New Zealand.

If the laws of individual jurisdictions do not allow a waiver of consent, then prospective proxy consent by person responsible will be sought as soon as possible for all patients recruited into the intervention arm of the trial.

Patients in the control arm of the trial, and the ecology surveillance periods, will be recruited without consent as no actual intervention is being offered.

12.4 Confidentiality and privacy

All patient data pertaining to the study will be stored in a computer database maintaining confidentiality in accordance with local legislation on privacy and use of health data. When archiving or processing data pertaining to the investigator and/or to the patients, the coordinating centre will take all appropriate measures to safeguard and prevent access to this data by any unauthorised third party.

The investigator will maintain the confidentiality of all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The investigator will retain the study documents at least fifteen years after the completion or discontinuation of the study. The investigator must notify the study management committee prior to
destroying any study essential documents following the study completion or discontinuation. If the investigator’s personal situation is such that archiving can no longer be ensured by him/her, the investigator shall inform the study management committee and the relevant records shall be transferred to a mutually agreed upon designee.

If any investigator retires, relocates, or otherwise withdraws from conducting a study, the responsibility for maintaining records may be transferred to the coordinating centre, or other investigator. The coordinating centre must be notified of and agree to the change. All associated documentation must also be updated.

13 Data collection, management, and analysis

The SuDDICU-ANZ study sponsor and trial co-ordination centre is The George Institute for Global Health who will manage all aspects of data management, oversight and monitoring of data collection, co-ordination of ethical and legal clearances, co-ordination of study drug acquisition and statistical analysis.

The principal means of data collection and data processing will be electronic via a password protected website. All computerised forms will be electronically signed by the authorised study staff and all changes made following the electronic signing will have an electronic audit trail with a signature and date.

Folders will be provided for the research co-ordinator to file any paper documents used for any form of data collection. A comprehensive guide to the data collection with definitions and rationale will be provided together with a paper version of the data collection forms. Paper documents will be stored in secure locked cabinets with access limited to authorized persons.

A comprehensive guide to accessing the data entry forms on the website and entering all follow-up data is also provided in the guideline for CRF completion. All of these documents are also available in PDF format for printing from the study website as required. These aim to assist the research co-ordinator to ensure high-quality data collection and data entry.

14 Quality control and quality assurance monitoring

14.1 Responsibilities of the investigators

The investigators agree to perform the clinical trial in accordance with this clinical trial protocol, ICH guidelines for Good Clinical Practice and the applicable regulatory requirements. The investigators are required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the co-ordinating centre.

The investigators agree to provide reliable data and all information requested by the clinical trial protocol in an accurate and legible manner according to the instructions provided. The investigator agrees to allow representatives of the co-ordinating centre to have direct access to source documents.

14.2 Responsibilities of the co-ordinating centre

The co-ordinating centre, The George Institute for Global Health is responsible for taking all reasonable steps to ensure the proper conduct of the clinical trial protocol.
Prior to initiation of the study at each participating site, the co-ordinating centre will be responsible for providing adequate training to the Principal Investigator and study personnel. The training will cover all aspects of the study protocol and procedures and will include practical training in the use of the CRF website and the study materials. All study materials will be provided at or before the training sessions.

This study will be monitored by a representative of co-ordinating centre (study monitor). During the trial, the site will be contacted, through monitoring visits, letters or telephone calls, by the study monitor to review study progress, investigator and patient compliance with study protocol requirements and any emergent problems. The main duty of the study monitor is to help the investigator and the co-ordinating centre maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the trial.

Site monitoring visits will be performed periodically and in accordance with the Monitoring Plan. The investigator and study personnel will assist the monitoring staff by providing all appropriate documentation, and being available to discuss the study. These monitoring visits will include but not be limited to review of the following aspects:

1. Adherence to the protocol including consistency with inclusion and exclusion criteria
2. The completeness and accuracy of the CRFs and source documentation
3. Patient recruitment
4. Adverse Event documentation and reporting
5. Study treatment allocation
6. Patient compliance with the study treatment regimen
7. Study treatment accountability
8. Compliance with regulations.

At completion of the trial, a final monitoring and close out visit will be conducted by the study monitor in accordance with the Monitoring Plan. Secure facilities for the storage of study data for 15 years will also be re-checked at this visit.

### 14.3 Source document requirements

According to the ICH guidelines for Good Clinical Practice, the monitoring team must check the CRF entries against the source documents. The purpose of source documents is to document the existence of the participant and substantiate the integrity of the study data collected. Source documents include the original documents related to the trial, to medical treatment, and to the history of the subject. Adequate and accurate source documents allow the investigator and the site monitor to verify the reliability and authenticity of data recorded on the electronic CRFs and ultimately to validate that the clinical study was carried out in accordance with the protocol.

### 14.4 Management of protocol deviations

A protocol deviation is an unanticipated or unintentional departure from the expected conduct of an approved study that is not consistent with the current research protocol or consent document. A protocol deviation may be an omission, addition or change in any procedure described in the protocol.

The investigator should not implement any deviation from or changes to the protocol without agreement by the study management committee and documented approval from the Independent Ethics Committee of the amendment, except where necessary to eliminate an immediate hazard(s) to trial participants. In the event of an emergency intended to eliminate an apparent immediate hazard to participants the Investigator may implement any medical procedure deemed appropriate.
Deviations from the protocol must be documented and promptly reported to the study management committee and the Independent Ethics Committee (if applicable). The report should summarise the event and action taken.

14.5 Direct access to data and documents

The study may be audited by government regulatory authorities, local Independent Ethics Committees or qualified representatives of The George Institute for Global Health as permitted by the regulation. Therefore access to medical records, other source documents such as ICU charts and other study related files must be made available at all study sites for monitoring and audit purposes during the course of the study and after its completion.

Participants will not be identified by name, and confidentiality of information in medical records will be preserved. The confidentiality of the participant will be maintained unless disclosure is required by regulations.

15 Statistical methods

15.1 Power calculation and sample size

The baseline mortality has been estimated from previous SDD studies in which a 30% hospital mortality for patients ventilated for more than 48-hours was observed in the control arm\(^1\). This was confirmed in our inception cohort pilot study where the observed mortality was 29.9% (95% CI 23.7 to 36.0%) and is consistent with the mortality of this cohort in other recent large intensive care trials\(^20,21\). For the purposes of this trial we have estimated hospital mortality for our targeted patients of 29%.

The international SuDDICU cRCT was designed to have 90% power to detect an in-hospital mortality difference of 3.5%, that is approximately half the 6% mortality difference seen in the SDD meta-analyses\(^10\) and the mortality difference observed in the most recent European SDD trial\(^8\). This absolute risk reduction is biologically plausible and consistent with the mortality difference seen in other large high quality intensive care trials\(^22\). The original design aimed to detect an absolute risk reduction in hospital mortality from 29% to 25.5% (3.5%), with 90% power, \(\alpha<0.05\).

The inter-cluster correlation coefficient (ICC) is estimated to be 0.01. An ICC of 0.01 was observed for the previous Dutch cluster crossover study of SDD\(^8\). An ICC of 0.01 has been calculated from the UK national intensive care audit data\(^24\) (Prof K. Rowan, personal communication) as well as from data in the Australian and New Zealand Intensive Care Society’s Adult Patient Database.

For the revised SuDDICU-ANZ x-cRCT, the inter-period correlation (IPC) coefficient is estimated at 0.005 and sample size calculations are conservatively based on these assumptions. We have re-calculated sample size using data from the Australian and New Zealand Intensive Care Society Clinical Trials Group x-cRCT PEPTIC study (Dr Paul Young, personal communication) that reported an ICC 0.0093 and IPC 0.0072. Once all sites are committed to the study, we will conduct a pre-specified validation analysis using ICC and IPC data available from the APD, for all ICU patients who either die or are ventilated for 48-hours or more, which approximates the inclusion criteria for this trial.

SuDDICU-ANZ will therefore recruit 8,000 patients from 25 to 30 ICUs and will have 80% power to detect an absolute reduction in hospital mortality between 3.6 and 3.7% from a baseline mortality of 29%, depending on the precise number of clusters.
15.2 Statistical analysis plan

The study is a x-cRCT, where the participating ICU will be the unit of randomisation and will act as its own control in the crossover period.

The primary outcome data will be collected at the level of the individual patient. Characteristics of the trial cohort at baseline will be summarised using descriptive statistics. The primary outcome, hospital mortality, will be analysed within a multi-level modelling framework. As the primary outcome is binary we will use logistic regression models with a random effect for the ICU and a random ICU-period effect23.

We plan both a simple unadjusted analysis and an adjusted analysis that will include prognostic covariates at the level of the participant [e.g. nature of ICU admission (surgery, trauma etc.)] and ICU level covariates (e.g. ICU baseline antibiotic resistance rates).

We will explore potential treatment modification within subgroups by including treatment by subgroup interactions in models. The data collection methods will minimise missing outcome data and our primary analysis strategy will be based on all available data. There will no imputation for missing data, although sensitivity analyses may be considered if the amount of missing data is greater than expected.

All analyses will be conducted on an intention-to-treat basis, unless otherwise specified.

Antibiotic resistance rates will be monitored across the pre-trial, the two trial periods, inter-period gap and post-trial periods within each centre, controlling for heterogeneity in microbiology practices.

We will evaluate resistance with both clinical and surveillance samples, and determine whether rates are different for control and SDD periods for ICUs for each method of resistance detection. Composite outcomes such as incidence of antibiotic resistant organisms will have components analysed individually to determine the direction of individual outcome effects. All outcomes that use routine clinical microbiological data will be normalised ‘per 1000 patient admissions’ to allow for heterogeneity in practice.

Indicators will include the incidence of (i) ICU-acquired antibiotic resistant organisms in cultures from blood or other sterile sites (defined as in reference 8), (ii) ICU-acquired antibiotic-resistant organisms in non-sterile clinical and surveillance specimens and (iii) ICU-acquired Clostridium difficile infections (toxin-positive). Our experience of differential ecological impact of antibiotics in Australian ICUs predicts that one or more antibiotic-resistant bacteraemia will be reported in 64 to 135 of these 8,000 admissions25.

15.3 Planned subgroup analyses

15.3.1 Baseline variables

1. Nature of admission (i.e. surgical, elective and emergency, trauma and medical patients)
2. Unit’s baseline antibiotic resistance rates derived from pre-trial period
3. Number of admissions per year stratified by quartile of participating units
4. Unit ventilator occupancy as a percentage
5. Severity of illness as determined by ICU admission APACHE II score
6. Surveillance showing antibiotic resistant organism
15.3.2 Timelines for analysis

The main primary analysis will be completed immediately after completion of the two trial periods and the 3-month post-trial period when all RCT data and outcomes are available. This analysis will evaluate the primary outcome and some secondary outcomes. A secondary analysis will occur after the completion of all data collection including uncensored hospital mortality and will analyse remaining secondary outcomes including ARO rates in both SDD and control groups in pre-trial, trial and post-trial periods.

16 Health economics evaluation

There will be a separate cost-effectiveness and cost-utility analysis that will use the most appropriate data collected across all settings but will use parameters that are judged context-specific (e.g. unit costs) and taken from local sources.

All health economic analyses will be undertaken from the perspective of the “idealized insurer”/third party payer (i.e. the provincial, state and federal government payer perspective in Australia and New Zealand). In Australia these data will be obtained through routine patient follow up and augmented through data linkage via the Centre for Health Records Linkage to capture hospitalisations and Medicare Australia to capture pharmaceutical and medical service use.

17 Study compliance

17.1 Loss to follow-up

For the primary outcome we predict a very small loss to follow up as the primary outcome is hospital mortality and we intend to record link with reliable data registries. We therefore predict less than a 1% loss to follow up for this outcome. For the primary analysis this outcome will be censored at 90 days but for subsequent analysis this outcome will be complete.

17.2 Compliance with intervention and the process evaluation

Due to the protocolised nature of the intervention and the fact that it will be standard care for that unit for the intervention period, we predict that once centres are randomised and allocated, their patients will receive the intervention during the SDD periods in the vast majority of cases (>90%). To assist with and assure compliance and data quality, the research co-ordinators and data monitors will closely monitor the intervention to ensure high compliance rates, and confirm similar recruitment rates during control and intervention periods. Separate to the trial compliance monitoring we will conduct a trial process evaluation.

The process evaluation will comprise a mixed methods evaluation and consider the three phases of the SuDDICU-ANZ study: pre-trial, the trial periods and post-trial. We will use surveys as well as have repeated visits to ICUs to assess changes over time (e.g. of attitudes to SDD), which will allow us to monitor the process of implementation of the intervention in ICUs.

18 Publications and reports

All outcomes from SuDDICU-ANZ will be published as discrete manuscripts where appropriate in medical journals and presented at professional conferences.
18.1 Public access

The protocol and statistical analysis plan will be made public in 2017. The participant level dataset will not be publicly available immediately but will be available to collaborative researchers after consultation and negotiation with the SuDDICU-ANZ Investigators.

19 References


