

**A crossover, cluster randomised controlled trial of Selective
Decontamination of the Digestive Tract in Intensive Care Unit
patients
(SuDDICU)**

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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. In Canada, this study will comply with the International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants, as well as applicable regulatory and institutional requirements.

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1 Protocol synopsis

Title	A crossover, cluster randomised controlled trial of selective decontamination of the digestive tract in intensive care patients.
Acronym	SuDDICU
Overview	<p>Selective decontamination of the digestive tract (SDD) is an infection-control strategy designed to reduce mortality by preventing sepsis. This is a randomised trial comparing the effect of using 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.</p>
Design	<p>An international, 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.</p> <p>An observational ecological (microbiological) assessment will be conducted in all ICU patients during one week of each month during the 3-month surveillance period before the first interventional period, in all trial eligible patients during the two 12-month intervention periods, in all ICU patients during one week of each month of the final 3-months of the two interventional periods, and in all ICU patients during one week of each month during the 3-month inter-period and post-trial periods.</p>
Participants	<p>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.</p> <p>Eligible patients are defined as:</p> <ol style="list-style-type: none"> 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. <p>When units are allocated to the SDD arm, SDD will be prescribed and will be commenced as soon as possible.</p> <p>When units are allocated to the control group, the same patients will be identified and followed, without receiving SDD.</p>
Intervention	<p>In the SDD arm, all eligible patients will receive:</p> <ol style="list-style-type: none"> 1. A six-hourly topical application of 0.5g paste containing colistin 10mg, tobramycin 10mg and nystatin 125,000 IU, to the buccal mucosa and oropharynx

	<ol style="list-style-type: none"> 2. A six-hourly administration of 10 mL of a suspension containing 100 mg colistin, 80 mg tobramycin and 2×10^6 IU nystatin, to the gastrointestinal tract via a gastric/post-pyloric tube 3. A four-day course of an intravenous 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 intravenous antibiotic, but will continue the prescribed antibiotic for the usual duration of therapy.
Primary outcome	All-cause hospital mortality
Secondary outcomes	<ol style="list-style-type: none"> 1. Microbiological assessments during ICU index admission: <ol style="list-style-type: none"> 1.1 The incidence of antibiotic resistant organisms isolated from all clinical and surveillance specimens 1.2 Changes in ARO rates between surveillance, intervention and post intervention periods 1.3 The incidence of <i>Clostridioides difficile</i> infections 1.4 Total antibiotic usage (as daily defined doses) 2. Duration of mechanical ventilation 3. ICU length of stay 4. ICU mortality 5. Hospital length of stay 6. Health economic analysis from a healthcare system perspective.
Statistical considerations and sample size	SuDDICU will recruit 10 000-15 000 patients from 19 ICUs in Australia, 7 in Canada and 3 in the UK that will detect between a 3-5% absolute reduction in hospital mortality from a baseline mortality of 29%, using 80% power, $\alpha < 0.05$.

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Associate Professor Craig French, Past-Chair ANZICS-CTG, University of Melbourne
Professor Rob Fowler, Chair CCCTG, Sunnybrook Health Sciences Centre
Professor Natalie Pattison, Chair UKCCRG, University of Hertfordshire
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Dr Srin Murthy, SuDDICU Canada PI, University of British Columbia (ex officio)
Clinical Professor Ian Seppelt, Australian Lead Investigator (ex officio)

2.2.2 Australian Management Committee

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Ms Fiona Goodman (Project Manager), The George Institute for Global Health
Dr Naomi Hammond, The George Institute for Global Health
Clinical Professor Ian Seppelt, The George Institute for Global Health
Professor Simon Finfer AO, The George Institute for Global Health
Associate Professor Laurent Billot, The George Institute for Global Health
Professor Jon Iredell, Westmead Hospital
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Dr Colman Taylor, The George Institute for Global Health
Ms Jennene Miller, St George Hospital
Professor Brian Cuthbertson, Sunnybrook Health Sciences Centre
(Other experts/members as appointed/delegated)

2.2.3 Canadian Management Committee

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Dr Srinivas Murthy, British Columbia Children's Hospital and the University of British Columbia
Dr Louise Rose, University of Toronto
Ms Gail Klein, Sunnybrook Research Institute
Ms Mariam Saleem, Sunnybrook Research Institute
Ms Chandni Patel, Sunnybrook Research Institute
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Professor Alison McGeer (Infectious Disease Physician, University Hospital Network, Toronto)
Professor Cheryl Misak (Professor, Department of Philosophy, University of Toronto)
Dr Caroline Quach (Associate Infection Control Physician for Child and Adolescent Services of the McGill University Health Centre and is the president of the Association of Medical Microbiology and Infectious Disease (AMMI) Canada)
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(Other experts/members as appointed/delegated)

2.2.4 UK Management Committee

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2.2.5 Data Safety and Monitoring Committee

Professor Duncan Young (Chair), University of Oxford
Professor Ian Roberts, London School of Hygiene and Tropical Medicine
Professor Tom van der Poll, University of Amsterdam
Dr Qiang Li, The George Institute for Global Health (unblinded statistician)

2.3 Funding

Project Grant from the Australian National Health and Medical Research Council (NHMRC) - Project Grant ID 1084244.

Strategy for Patient Orientated Research (SPOR) grant from Canadian Institutes of Health Research (CIHR) in Canada- Project Grant ID 381434;
CIHR Project Grant funding- Project Grant ID 378431.

2.4 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.

3 Introduction

3.1 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.¹ 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.² 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 Intensive Care Unit (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.² Hospital-acquired infection is also associated with increased hospital length of stay and associated healthcare costs.³ The prevention of ICU-acquired sepsis is critical and therefore the subject of several 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.⁴

Selective Decontamination of the Digestive Tract (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.⁵

"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 intravenous antibiotics, in addition to strict hand hygiene and other infection control measures.^{6,7} 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.⁸ The first trial of SDD in intensive care was in trauma patients in the early 1980s.⁶ In the subsequent 25 years, over 40 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.^{6,9-11}

Our group published a systematic review and updated meta-analysis of all SDD trials on the effect on mortality among other endpoints.¹² 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)¹¹. There was marked statistical heterogeneity due to the long historical inception period, small sample sizes, and methodological limitations.

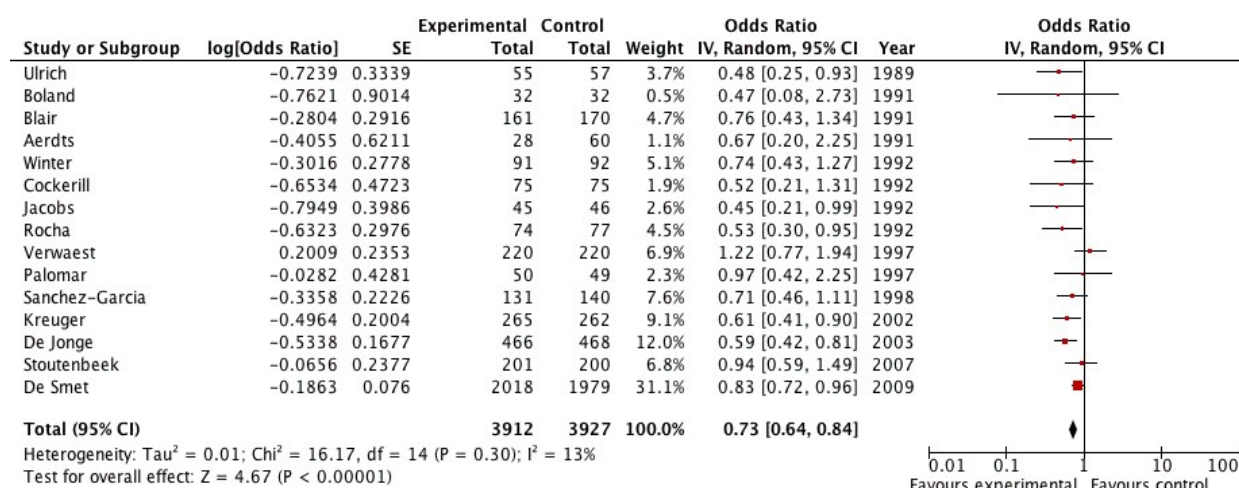


Figure 1: Effect of SDD on mortality¹¹

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. 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’.¹³

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.¹⁴ Broad-spectrum antibiotics are also associated with an increased prevalence of *Clostridioides 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.⁹

While many SDD trials report antibiotic resistance in study patients or short-term studies of ICU ecology,¹⁴ 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.

3.2 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 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)

3.2.1 Systematic review of antibiotic resistance

In addition to the updated systematic review looking at the effect of SDD on mortality¹² we conducted a meta-analysis of all available trials that looked at the development of antibiotic resistance with SDD.¹⁵

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.^{9,14}

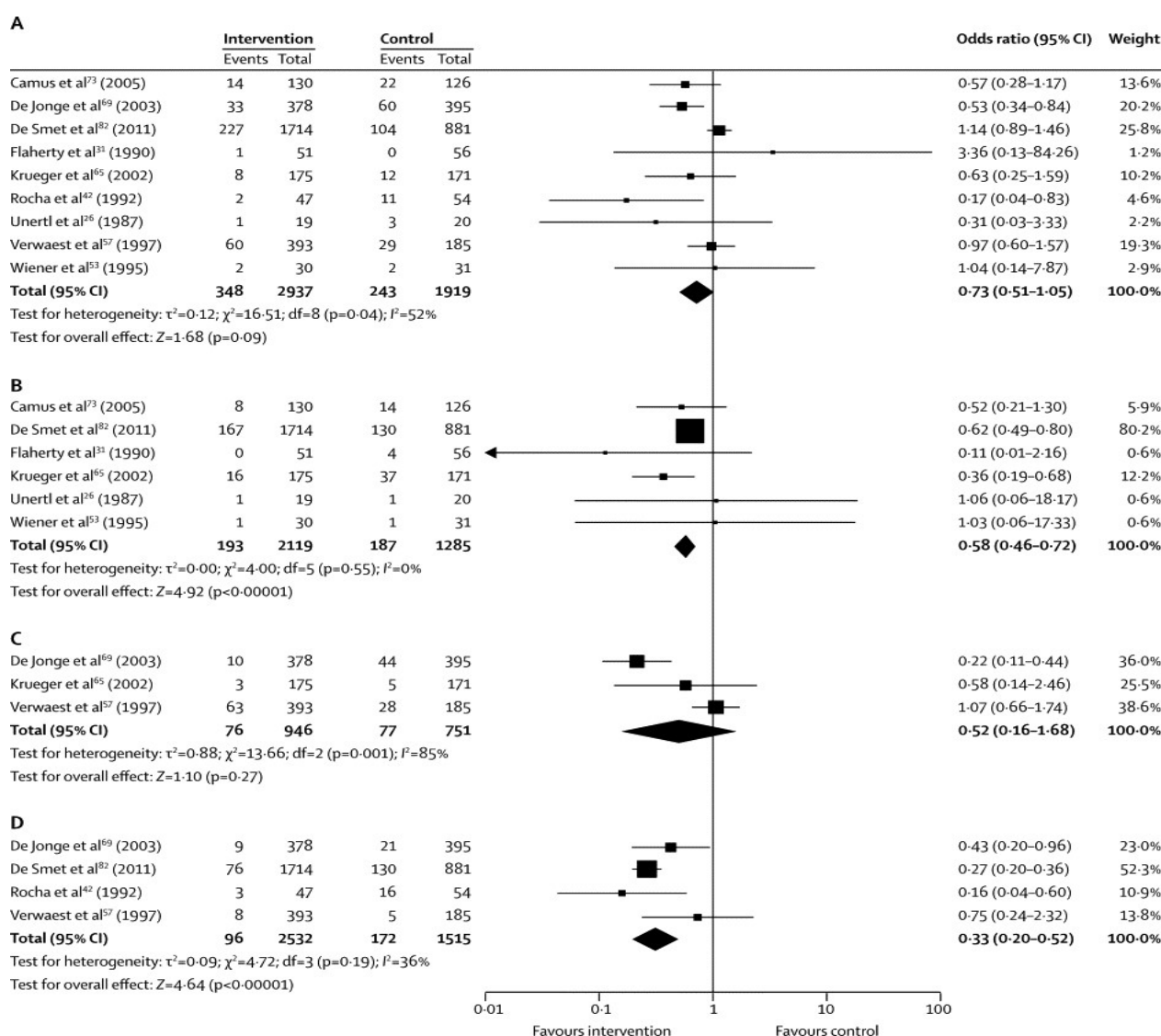


Figure 2: The prevalence of Gram-negative organisms resistant to (A) aminoglycosides, (B) polymyxin E or B, (C) fluoroquinolones, or (D) third generation cephalosporins¹⁵

3.2.2 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%).¹⁶

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.^{17,18}

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.

3.2.3 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 intravenous and oral/gastric intervention (>90%) and concluded the intervention delivery for a cluster-RCT (cRCT) was feasible.

To address the question of whether or not to include the intravenous 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, $p=0.015$).

3.2.4 A cluster-RCT 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, cluster RCT 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 clusters (ICUs) was projected. This international trial was dependent on success in simultaneous applications to national research funding agencies in the four countries.

Only the Australian NHMRC grant application was successful and in 2014 a decision was made to modify the original cluster RCT to a crossover-cRCT (x-cRCT) with the George Institute for Global Health acting as Principal Sponsor in 2014. The x-cRCT design is consistent with the aims of the original cRCT and allows each ICU to serve as its own control, minimising the risk of imbalance between participating ICUs, and significantly increasing statistical power compared to a parallel group cRCT.¹⁹

The ecological assessment was modified to an observational study to determine secular trends in antibiotic resistance patterns before, during, in between and after the intervention periods.

Following successful applications to the Canadian Institute of Health Research in 2017, the trial included patients from 7 ICUs in Canada and 3 ICUs in the UK to increase the overall study population, with Sunnybrook Health Sciences Centre acting as Sponsor for Canada/UK.

Due to initial time desynchronies in study timelines and the subsequent impact of the COVID-19 pandemic on trial recruitment in Canada and UK, a decision was made to publish the Australian data first followed by a second publication of the Canadian/UK data. A third publication of the analysis of all combined data will follow the second paper. The statistical power for differing models presented in section 15.1.

4 Study design

4.1 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.

4.2 Design

The SuDDICU trial is an international, 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 (microbiological) assessment will be conducted in all ICU patients during one week of each month during the 3-month surveillance period before the first intervention period; in all trial eligible patients during the two 12-month intervention periods; in all ICU patients during one week of each month of the final 3-months of the two intervention periods; in all ICU patients during one week of each month during the 3-month inter-period and post-trial periods.

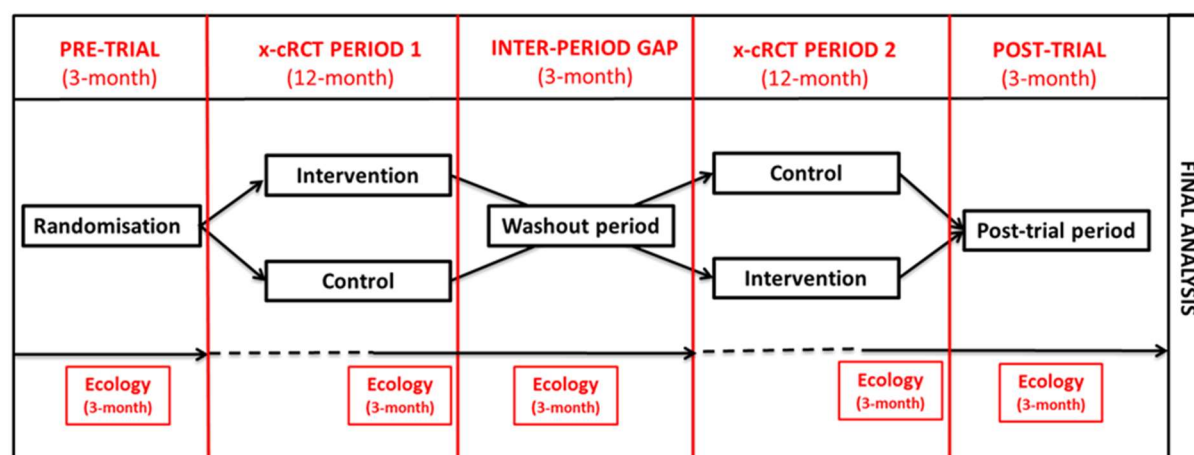


Figure 3: The elements of the trial design

5 Study outcomes

5.1 Primary outcomes

All-cause hospital mortality related to ICU index admission.

5.2 Secondary outcomes

5.2.1 Microbiological assessments

1. The incidence of antibiotic resistant organisms (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. Changes in ARO rates between surveillance, intervention and post intervention periods
3. The incidence of *Clostridioides difficile* infections
4. Total antibiotic usage (as daily defined doses)

5.2.2 Clinical assessments

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

5.2.3 Health economic assessment

1. Health economic analysis from a healthcare system perspective

6 Study population

6.1 Study setting

SuDDICU will be conducted in 19 general ICUs in Australia, 7 in Canada and 3 in the UK.

6.2 Site eligibility criteria

6.2.1 Inclusion

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

6.2.2 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.

6.3 Patient eligibility criteria

6.3.1 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.

6.3.2 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 the UK

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.

6.4 Ecology surveillance period eligibility criteria

6.4.1 Inclusion

1. All patients admitted to the ICUs regardless of ventilation status, during one full week of every calendar month for 3-months during the pre-trial period, during one week of each

month of the final 3-months of the two interventional periods, the inter-period gap and post-trial periods for the duration of their ICU admissions.

6.4.2 Exclusion

1. None

7 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.

7.1 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.

7.2 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 10mg, tobramycin 10mg and nystatin 125,000 IU, 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 2×10^6 IU nystatin, to the gastrointestinal tract via a gastric/post-pyloric tube
3. A four-day course of an intravenous 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 intravenous antibiotic, but will continue the prescribed antibiotic for the usual duration of therapy.

7.2.1 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 intravenous 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.

7.2.2 Provision of study drug

The George Institute for Global Health holds all intellectual property for the acquisition, manufacturing and distribution of the SuDDICU drug preparation for the conduct of the x-cRCT in Australia, Canada and the UK.

Under a legal agreement, the George Institute has contracted Verita Pharma®, Sydney, Australia to acquire, manufacture, test and package the SuDDICU drug preparation according to Good Manufacturing Practice (GMP) standards, supplied in numbered patient-specific boxes to the ICUs / hospital pharmacies from a central store to sites in Australia.

Drug acquisition and distribution to Canada/UK will be provided by Verita Pharma® under licence from the George Institute.

The study paste and suspension will be constituted from GMP-certified suppliers of colistin, tobramycin and nystatin that are licensed antibacterial and antifungal drugs used in critically ill patients when indicated.

The study paste and suspension will be registered with the Australian Therapeutic Goods Administration, via the Clinical Trial Notification (CTN) process, Health Canada in Canada and the Medicines and Healthcare products Regulatory Agency (UK).

Copies of an Investigator's Brochure and study drug information sheets will be supplied to participating sites and updated as required.

Most of the intravenous antibiotics are considered standard practice and the only study specific intervention is an intravenous antibiotic (ceftriaxone/cefotaxime or ciprofloxacin) administered to the subset of patients not already treated with antibiotics for clinical purposes.

7.3 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.

7.4 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.

7.5 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.

7.6 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.

7.7 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.

In Canada, sites will collect additional surveillance swabs (rectal and nasal swabs) in one in four patients on study days 2 and 7.

7.8 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 deleted and no further analysis undertaken.

8 Data collection

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

8.1 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.

8.2 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.

8.3 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 up to 48 hours prior to enrolment.

8.4 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 *Clostridioides 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.

8.5 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.

8.6 Ecology (microbiology) surveillance periods

During the fifteen discrete ecology (microbiology) surveillance periods (three pre-trial, three during the last 3-months of each intervention period, three during the inter-period gap and three post-trial), data will be collected on all patients admitted to the ICU during one 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 *Clostridioides difficile*, the results of all blood cultures and any positive AROs in sterile or non-sterile sites.

9 Study timelines

9.1 Australia (actual timelines)

Date	Project Milestone
July 2015 – December 2016	Start-up phase, including site feasibility and selection, and agreement by sites to follow study protocols (intensive care and infectious diseases)
August 2016	Protocol finalised
August - October 2016	Case Report Form (CRF) and other study documents finalised
November 2016	All ethics and other regulatory requirements met
May 2017	3-month pre-trial data collection period commenced (surveillance ecology); site randomisation and initiation
March 2018	Completion of SDD study drug acquisition and commencement of distribution to sites
April 2018	First trial recruitment period (SDD or control) and 3-month surveillance ecology data collection period during recruitment period commenced
April 2019	3-month inter-period data collection (surveillance ecology) and site initiation for crossover commenced
July 2020	Second trial recruitment period (control or SDD after crossover) and 3-month surveillance ecology data collection period during recruitment period commenced
August 2020	3-month post-trial data collection period (surveillance ecology) commenced
August 2021	Completion of post-trial collection period (surveillance ecology) final site

October - December 2021	Database lock, analysis and publication of primary (mortality) and secondary (ecology) endpoints of Australian dataset.
June - December 2023	Merger with Canada/UK database, analysis and publication of primary (mortality) and secondary (ecology) endpoints of combined dataset, subject to funding

9.2 Canada/UK (actual/indicative timelines)

Date	Project Milestone
July 2015 – December 2018	Start-up phase; including site feasibility and selection, and agreement by sites to follow study protocols (intensive care and infectious diseases)
August 2016	Protocol finalised
June 2019	Case Report Form (CRF) and other study documents finalised
May 2019	All ethics and other regulatory requirements met
May 2019	3-month pre-trial data collection period (surveillance ecology); site randomisation and initiation commenced
September 2019	First trial recruitment period (SDD or control) and 3-month surveillance ecology data collection period during recruitment period commenced
March 2020	Suspension of recruitment due to COVID-19 at all sites
May 2020	Potential restart after COVID-19 commenced
March 2021	Start of 3-month inter-period data collection (surveillance ecology) and site initiation for crossover
June 2021	Start of second trial recruitment period (control or SDD after crossover) and 3-month surveillance ecology data collection period during recruitment period
July 2022	Start of 3-month post-trial data collection period (surveillance ecology)
December 2022	Potential completion of post-trial collection period (surveillance ecology) final site

June - December 2023

Database lock, analysis and publication of Canada/UK dataset.
This will be followed by merger with Australian database,
analysis and publication of combined primary (mortality) and
secondary (ecology) endpoints of combined dataset, subject to
funding

10 Safety monitoring and reporting : Australia

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).

10.1 Adverse Drug Reactions (ADR)

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

'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.

10.2 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.

10.3 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.

10.4 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 a SADR or SUSAR and reporting to the regulatory authorities within required time frames.

In Australia, 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.

10.5 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 analyses of safety and outcome data and to recommend to the International Steering 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.

10.6 Antibiotic Resistant Organism (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 *Clostridioides difficile* infection will be reported as serious adverse events.

10.7 Study termination

The study may be terminated at any time at the request of the International Steering Committee in consultation with the DSMC, 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.

11 Safety Monitoring and Reporting : Canada / UK

11.1 Assessment of safety

The safety of research participants is foremost and should always be considered throughout the conduct of research.

11.2 Adverse Events

An adverse event (AE) means any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not

necessarily have to have a causal relationship with this treatment and includes an adverse drug reaction.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.

11.3 Adverse Drug Reaction (ADR)

An adverse drug reaction is a response to an investigational product which is noxious and unintended that which occurs in doses normally used in humans for prophylaxis, diagnosis or therapy of disease or for modification of physiological function.

The phrase "responses to an investigational product" means that a causal relationship between an investigational product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

The expression "causal relationship" is meant to convey that in general there are facts, evidence or arguments to suggest a reasonable causal relationship.

11.4 Serious Adverse Events (SAE)

A serious adverse event or reaction is any untoward occurrence that at any dose:

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

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

11.5 Serious Adverse Drug Reaction (SADR)

SADRs are any adverse events that have a causal relationship (i.e. possibly, probably, or definitely related) with the investigational product which are serious.

11.6 Serious and Unexpected Adverse Drug Reaction (SUADR)

SUADRs are SADR that are unexpected, where severity of which is not consistent with the applicable product information of each component of the paste and suspension.

All SUADRs will have expedited reporting to regulatory agencies following ICH-GCP and local regulatory requirements.

11.7 Assessment of all Adverse Events (including Serious Adverse Events)

11.7.1 Relationship (Causality/Relatedness)

The causality assessment is the determination, according to the site investigator's clinical judgment, of the existence of a reasonable possibility that the study drug (Investigational Product) caused or contributed to an adverse event.

If the site investigator or delegated sub-investigator is unsure about whether or not the study drug caused or is related to the event, then the event will be handled as "related" to the study drug for reporting purposes of the trial. If the causality assessment is "unknown but not related" to the study drug, this should be clearly documented in the source documents.

11.7.2 Expectedness

Events are classified as unforeseen or unexpected if the nature, severity or frequency is not consistent with the risk information set out in the product information or label of each component of the paste and suspension.

11.7.3 Seriousness

Events are classified as serious if associated with effects threatening the life or physiological functions of a participant. Refer to the definition above for "Serious Adverse Events".

11.7.4 Severity

The term "severe" is often used to describe the intensity (severity) of a specific event (e.g. mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache).

This is not the same as "serious," which is based on participant/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. The terms "serious" and "severe" are not synonymous. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

11.7.5 Adverse Event Recording

Adverse events that are assessed and determined **not** to be related to the investigational product will not be recorded and reported.

In this study, recording and reporting of adverse events will be restricted to events that are assessed by the site investigator or delegated sub-investigators to be related to investigational product (i.e. possibly, probably or definitely related).

Investigations into potential adverse events should be done during each contact with a participant. Investigations may be done through specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded promptly in the source document e.g. medical chart, progress notes, and assessed by the site investigator or delegated sub-investigators in a timely manner allowing sufficient time to meet required reporting timelines for AEs if needed. Only AEs that are related to the investigational product, regardless of seriousness, will be recorded on the study CRFs (e.g. adverse event

CRFs). Adverse event CRFs should be completed using source documents by a delegated research team member in a timely manner/within 15 days of site awareness. All clearly related signs, symptoms, and abnormal diagnostic procedures should be recorded in the source document, though should be grouped under one diagnosis. Each diagnosed adverse event should then be categorized in accordance with Medical Dictionary for Regulatory Activities (MedDRA) classifications.

If the site investigator or delegated sub-investigator is unsure about whether the event is caused by or related to the investigational product, then the event will be handled as “related” to the study drug for reporting purposes of the trial. If the causality assessment is “unknown but not related” to the investigational product, this should be clearly documented in the source documents.

The following are not considered AEs and therefore do not require recording:

1. Pre-existing diseases or conditions identified and recorded at screening/baseline unless, at the discretion of the site investigator, the disease or condition worsens in severity or frequency
2. At the discretion of the site investigator, events considered likely manifestations of the underlying disease or that commonly occur in the study population independent of investigational product exposure
3. Elective medical or surgical procedures.

11.8 Reporting of SAEs and Unanticipated Events

Serious adverse events and unanticipated events that are assessed and determined **not** to be related to the investigational product **will not** be recorded and reported.

11.9 Investigator reporting: Notifying the REB

Serious adverse events and unanticipated events should be recorded and reported to the REB by the site investigator in accordance with local reporting requirements and timelines.

11.10 Investigator reporting: Notifying the Canadian Sponsor

The site investigator is responsible for reporting SAEs and SUADRs to the sponsor in accordance with applicable regulations and reporting requirements and timelines.

Serious and unexpected events that are related or cannot be ruled out as related to the investigational product are considered SUADRs. Reporting for SUADRs should include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. The minimum information required includes at least one identifiable participant, one identifiable reporter, one serious reaction, and one suspect product.

Additionally, serious adverse events that are both related and unexpected, CIOMS I Form must be completed by the site investigator and forwarded to the Sponsor at SuDDICU@sunnybrook.ca within 24 hours of site awareness. Information on other possible causes of the event, such as concomitant medications and illnesses should also be provided as soon as it is made available.

Information on all serious adverse events should be recorded promptly in the source document e.g. medical chart, progress notes, and assessed by an investigator in a timely manner allowing sufficient time to meet required reporting timelines for SAEs and serious and unexpected adverse drug reaction (SUADRs) if needed (see below).

All cases of *Clostridioides Difficile* infections will be recorded on the study CRFs and reported to the Sponsor as a SAE within 72 hours.

11.11 Sponsor Reporting of SUADRs: Notifying Health Canada

The regulatory sponsor is responsible for reporting SUADRs to regulatory authorities in accordance with local expedited reporting requirements and timelines. In addition, the Sponsor will complete the ADR Expedited Reporting Summary Form and submit this form in conjunction with the completed CIOMS Form to the appropriate Health Canada directorate.

11.12 Sponsor Reporting of SUADRs: Notifying Sites

The regulatory sponsor is responsible for distributing blinded expedited reports of SUADRs to each investigator within 15 days of sponsor awareness.

11.13 Reporting and Entry Timelines

The site investigator will report SAEs to the sponsor within the following timelines:

1. All deaths and immediately life-threatening events, related, will be recorded on the CRF and reported to the sponsor within 24 hours of site awareness.
2. Serious adverse events other than death and immediately life-threatening events will be reported to the sponsor within 72 hours of site awareness.
3. All cases of *Clostridioides Difficile* infections will be reported to the sponsor within 72 hours of site awareness.

SADR and SUADR information and all cases of *Clostridioides Difficile* infections will be entered into the CRF in a timely manner/within 72 hours from the time the site investigator becomes aware of the event.

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 : Australia

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/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.

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 Research and the Ottawa Statement on the Ethical Design and Conduct of cRCTs.

12.3 Individual patient consent

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

In Australia, individual patient consent for the period of the study up to hospital discharge (the primary outcome) will not be required as a waiver of consent has been approved in Australia, subject to variation in state and institutional laws. 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.

12.5 Canadian / UK Ethics and Dissemination

12.5.1 Ethical Standard

The investigator will ensure that this study is conducted in accordance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Participants of Research and codified in the Tri-Council Policy Statement and/or the ICH E6.

12.5.2 Research Ethics Board (REB)

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the REB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the REB before the changes are implemented in the study, unless to eliminate an immediate hazard.

In the UK ethical approval has been awarded by an independent ethics committee according to the guidance from the NHS Health Research Authority.

12.5.3 Consent

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

In Canada, the laws of the jurisdiction do not allow a waiver of consent for this trial, so a delayed model consent by the substitute decision maker will be sought as soon as possible for after intervention commencement in all patients recruited into the intervention arm of the trial.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the RCT and continues throughout the study participation. Given that the study intervention is time sensitive and the participant does not have capacity to provide consent, deferred consent will be used for participating sites in Canada. Deferred consent will be sought from the substitute decision maker (SDM) after the participant has been enrolled into the study and has started to receive the intervention.

Participants in both the intervention and control arms will receive an information sheet after being enrolled into the study. Initial data collection will be conducted under a waiver of consent. A member of the study staff will deliver an Information Sheet informing the SDM of the participant's enrolment into the study. The information sheet will include contact information for the SDM to reach a member of the study staff if they have any questions or do not want to participate in ongoing data collection for the study.

For participants in the intervention arm, deferred consent will be sought once an SDM has been identified. Continuous attempts (see Consent Process) will be made to approach the SDM to provide them with an informed consent form (ICF) describing in detail the study procedures and associated risks. A member of the study staff will explain the research study to the SDM and answer any questions that may arise. The SDM will sign the ICF to allow the participant to continue with the treatment. The original ICF in its entirety will be maintained by the site, and a copy of the signed ICF will be provided to the SDM. The rights and welfare of the participants will be protected by emphasizing to the SDM that the quality of the participant's clinical care will not be adversely affected if they decline to participate in this study.

If attempts to contact the SDM continue to be unsuccessful and the participant has been discharged from the ICU, or if the participant dies within 48 hours of being enrolled into the

study information recorded for the participant, along with outcome data, will be used for the study.

12.5.4 Consent Process:

1. As patients are enrolled into the study, an information sheet informing SDM of patient's enrolment into the study and collection of their study data will be provided.
 - a. This information sheet will also provide the SDM with information on how they can contact a member of the study team to discuss consent.
2. A member of the study team will review the patient enrolment log to see which patients have been enrolled/started treatment and therefore requires consent.
3. A member of the study team, designated on the task delegation log to obtain consent, will approach the patient's nurse to confirm if the information sheet was provided to the patient and if an SDM has been identified to be approached for consent. Alternatively, the study team member will check the patient records to identify the SDM.
4. The study team member will conduct regular bedside checks to find and gain consent from the SDM.
5. The study team member will make a minimum of 3 phone calls to the SDM if they cannot be identified at the bedside.
6. The study team member will document all attempts to obtain consent.

Ecology study- The requirement for consent has been waived by the REB for the ecology data collection.

In the UK, individual consent for participation in the study will be sought. However, as patients who are eligible for inclusion in the trial will lack capacity to consent, then advice about their participation will be sought from a consultee (personal or nominated) according to the Mental Capacity Act (2005). However, as initiation of the intervention is time sensitive, the intervention will be started within six hours in all eligible patients if a consultee is not available to advise. In this situation, a consultee will be approached as soon as practically possible to seek retrospective advice. Once the patient regains capacity while in hospital, s/he will be approached to seek their consent for continued participation in the study. For routinely collected anonymised clinical data (including hospital outcome data) we will not seek individual patient consent.

13 Data collection, management, and analysis

The George Institute for Global Health and Sunnybrook Research Institute are the joint trial sponsors with the George institute acting as the Principal trial co-ordination centre for the SuDDICU x-cRCT.

The George Institute 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 for Australia. These roles will be undertaken by Sunnybrook for Canada and the UK.

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 case report form 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.

13.1 Canadian Data Collection and retention

It is the responsibility of the REB, investigator and regulatory sponsor to retain study essential documents as per local regulatory requirements and GCP Guidelines.

Study essential documents must be maintained in a secure and confidential manner for participating Canadian sites for a period of 25 years. For the purposes of this study, the start date of the retention period is the date of the final report of the trial. Exceptions may be made for sites which close prematurely, wherein the start date for the retention period will be the date of notification to Health Canada of the sites closure.

Sites conducting this study outside of Canada must maintain study records for the required retention period as stipulated by local regulatory authorities. All study records are then to be destroyed according to local and national policy and requirements. It is the investigator's responsibility to request authorization for destruction at the completion of the retention period and/or for the sponsor to inform the investigator/institution when these documents may be destroyed.

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 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 case report forms 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 : Australia

According to the International Conference on Harmonisation guidelines for Good Clinical Practice, the monitoring team must check the case report form 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. 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.

14.6 Quality Control and Assurance: Canada

14.6.1 Site monitoring, audit and inspection

Site monitoring is conducted to ensure the safety of human study participants and the protection of their rights and well-being. Monitoring also verifies that collected study data is accurate, complete and verifiable by source documentation and that the study is conducted in accordance with the protocol and operating procedures.

Monitoring for this study is the responsibility of the sponsor. The delegated monitor will evaluate study processes and documentation based on the approved protocol/amendment(s), Part C, Division 5 of the Food and Drug Regulations, the International Conference on Harmonisation (ICH), E6: Good Clinical Practice guidelines (GCP) and institutional policies.

The extent and nature of monitoring is outlined in the Monitoring Plan. The monitoring plan specifies the frequency of monitoring, monitoring procedures, the level of site monitoring activities (e.g., the percentage of participant data to be reviewed), and the distribution of monitoring reports. Monitoring activities will be performed both in person and remotely. Reports of findings identified during monitoring activities will be provided to sites detailing any required actions. Documentation of monitoring activities and findings will be provided to the

site study team and the study QI. The institution and/or local REB reserves the right to conduct independent audits as necessary.

The Investigator is responsible for ensuring monitors and/or quality assurance reviewers are given access to all study-related documents noted above and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and have adequate space to conduct the monitoring visit or audit.

14.6.2 Auditing and Inspecting

The investigator will provide direct access to source data/documents for the purposes of study-related monitoring, audits, and inspections by the REB, the sponsor, and applicable regulatory bodies. The investigator will permit the review of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.) and will ensure access to applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

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 arm¹⁰. 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 SuDDICU cRCT was originally 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-analyses¹⁰ and the mortality difference observed in the most recent European SDD trial⁸. This absolute risk reduction is biologically plausible and consistent with the mortality difference seen in other large high-quality intensive care trials. 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.⁷ An ICC of 0.01 has been calculated from the UK national Intensive Care National Audit and Research Centre and Australian and New Zealand Intensive Care Society Centre for Outcome Research databases.

Due to restrictions in funding in New Zealand, Canada and the UK, the original cRCT was modified to a x-cRCT conducted in Australia, assuming the same baseline mortality rate of 29% with 80% power and based on the inter-period correlation (IPC) coefficient estimated at 0.005 and sample size calculations are conservatively based on these assumptions. These assumptions are supported by data from the Australian and New Zealand Intensive Care Society ANZICS Clinical Trials Group x-cRCT PEPTIC study that reported an ICC 0.0093 and IPC 0.0072.²²

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.

The current SuDDICU x-cRCT will recruit 10 000 to 15 000 patients from 19 ICUs in Australia, 7 in Canada and 3 in the UK, each recruiting at least 150 patients per period (i.e. at least 300 patients per ICU).

An analysis consisting of Australian clusters only will have at least 80% power to detect an absolute reduction in mortality of 4.2%.

An analysis consisting of Canadian and UK clusters only will have at least 80% power to detect an absolute reduction in mortality of 5.5%.

The table below shows the detectable absolute risk reduction according to the number of clusters (ICUs) and numbers of patients recruited per period.

	Average number of patients recruited per cluster per period		
	150 patients	200 patients	250 patients
Australia only (20 clusters)	4.2%	4.0%	3.8%
Australia, Canada, UK (30 clusters)	3.5%	3.3%	3.1%
Canada and UK only (10 clusters)		5.5%	

Assuming that the main ecology analyses will be performed similarly to the mortality analysis, i.e. by comparing outcome data between groups during both intervention periods, the power can be calculated assuming a cross-over design.

15.2 Statistical analysis plan

A separate statistical plan including additional details about the statistical models, sensitivity analyses and mock tables will be finalised before unblinding and database lock.

15.2.1 Level of statistical significance

One interim analysis is planned once 100% of Australian sites have finished recruitment to the first 12-month intervention period.

Haybittle-Peto stopping rules will be used at the interim analysis using a difference of 3 standard-deviations on hospital mortality (or a p-value of 0.0027).

Given the conservative rule used and the negligible amount of type-I error rate spent at the interim analysis, the significance threshold will remain at 5% for the final analysis.

Final analyses of the primary outcome including sensitivity analyses will all be conducted using a two-sided significance level of 5%.

For the four secondary clinical outcomes, we will control the family-wise error rate by applying a Holm-Bonferroni correction.

No multiplicity correction will be applied to the ecology analyses or other statistical tests.

15.2.2 Timelines for analysis

The main primary analysis will be completed immediately after completion of the two intervention periods and the 3-month post-trial period when all RCT data and outcomes are available. This analysis will evaluate the primary outcome and clinical 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.

15.2.3 Analysis of populations

Due to the cluster-crossover design, the group allocation for a patient is determined by the site and by the period during which they participated, regardless of treatment adherence.

The intention-to-treat analysis set will be used to assess both effectiveness and safety.

15.2.4 Analysis by region

SuDDICU is an international study conducted in two separate geographical regions – Australia and Canada/UK (as a combined region).

Due to an extended gap in recruitment timelines between Australia and Canada/UK due to operational and funding delays and interruption to recruitment caused by the SARS-coV-2 (COVID-19) pandemic in Canada/UK in 2020, a two-stage analysis of the dataset will be conducted:

1. The Australian database will be analysed as soon as the database is locked and reported as a separate analysis.
2. The Canadian / UK database will be analysed as soon as the database is locked and reported as a separate analysis
3. The Canada/UK database will be merged with the Australian database following database transfer from Sunnybrook Health Sciences Centre to the George Institute.
4. Indicative timelines for these analyses are 2021 and 2023 respectively.

15.2.5 Baseline analyses

Description of the cluster characteristics (e.g. location, size of ICU, baseline rates of antibiotic resistance) will be presented by treatment group.

Description of the baseline characteristics will be presented by treatment group.

15.2.6 Analysis of compliance and concomitant therapies

For patients in the SDD arm, the type of study antibiotic received, and the number of doses received each day between days 1-5.

The total number of doses received, the proportion of eligible doses delivered, as well as the number of days with at least one dose. This will be done separately for the SDD oral paste, SDD gastric suspension, SDD intervention intravenous antibiotics as well as non-SDD antibiotics.

For SDD intervention intravenous antibiotics the proportion of patients who received the full 4-day SDD course. We will report the number of daily defined doses of non- SDD antibiotics, and total antibiotics, received in the ICU between days 1-28 in the SDD and control arms in total and separately

15.3 Analysis of the Primary Outcome

The primary outcome is hospital mortality analysed as the proportion of patients who died during the index hospital admission (up to day 90).

The primary intervention effect will be estimated as the odds ratio (OR) of mortality between the SDD arm and the control arm obtained from a hierarchical logistic model including a random cluster effect and a random cluster-period effect.

Other analyses of hospital mortality will include a survival analysis of time to death obtained via a Cox model.

15.3.1 Adjusted analyses

The logistic regression model will be re-run after adjustment for the following individual baseline covariates:

1. Age (continuous)
2. Sex (male vs female)
3. Admission diagnosis (medical vs surgical)
4. Severity of illness (APACHE or MODS score) (continuous)

15.4 Planned subgroup analyses

1. Nature of admission
 - i. Operative vs. non-operative
 - ii. Trauma vs. non-trauma

2. Severity of illness as determined by above vs. below median ICU admission APACHE II or MODS score
3. Sex: male vs. female

15.5 Treatment of missing data

The primary analysis will use all available data with no imputation for missing data.

Sensitivity analyses to assess the potential impact of missing data on the study conclusions will be conducted.

15.6 Analysis of secondary clinical outcomes

Secondary clinical outcomes include duration of mechanical ventilation, ICU length of stay, hospital length of stay and ICU mortality.

Duration outcomes will be analysed as the number of days alive and free of outcome (e.g. days alive and free of mechanical ventilation or days alive and out of ICU) up to Day 90.

No adjusted or subgroup analyses of these outcomes will be performed.

Mechanical ventilation is only expected to occur while in ICU. Therefore, once discharged from ICU, patients will be assumed to be free of mechanical ventilation. Similarly, once discharged from hospital, patients will be assumed to be alive up to Day 90.

ICU mortality will be analysed in the same way as hospital mortality.

15.7 Analysis of microbiology and safety outcomes

15.7.1 Microbiology outcomes

1. new antibiotic resistant organism,
2. new bloodstream infections and
3. new *Clostridioides difficile* infections.

Proportions of patients with at least one event (e.g. one new bloodstream infection) will be compared between treatment arms using an analysis at the cluster-period level.

Linear regression will be used to model the proportion of events in each cluster-period.

15.8 Adverse events

Expected SAEs will be summarised as the number and proportion of patients experiencing at least one event, overall and by category the total number of events will be reported.

Proportions of patients with at least one SAEs and proportion of patients' dead will be compared between treatment arms using an analysis at the cluster-period level.

15.9 Analysis of unit level microbiological data

Incidence of microbiological outcomes will first be described as the number and proportion of patients within each of the five ecology periods (pre-trial, period 1, washout, period 2 and post-trial).

This will be done according to the randomisation sequence, that is, separately for sites randomised to control →SDD and sites randomised to SDD→Control.

The main hypothesis to be tested is whether rates are the same with and without the SDD intervention. This will be assessed using a non-inferiority comparison and with a non-inferiority margin set at 2%.

To 'declare' non-inferiority of SDD compared to usual care, the upper bound of the 95% confidence interval around the absolute risk difference (SDD - usual care) will need to be lower than 2%.

We will analyse data from all 5 periods using linear regression to model the proportion of events in each cluster and each period.

To test whether the proportion of patients with the SDD intervention is non-inferior to the one with usual care, we will group periods 2 and 3 and, within each arm (SDD or usual care), will estimate the change between period 1 (baseline) and periods 2/3 combined.

We will then estimate the difference (SDD – Usual care) in change from baseline to assess whether the change with SDD is similar (non-inferior) to the change with usual care.

Using the same model, to further assess the effect of SDD over time including potential withdrawal effects (i.e. whether rates change after withdrawing SDD), we will compare the change between period 3 and periods 4/5 combined in units randomised to use SDD in the first intervention period.

16 Health economics evaluation: Australia

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). 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 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

Results from the SuDDICU RCT will be published as discrete manuscripts in accordance with a pre-specified authorship policy and presented at professional conferences.

18.1 Public access

The protocol and statistical analysis plan will be placed on the study website housed at the George Institute and published in an open-access journal prior to database lock.

The participant level dataset will not be publicly available immediately but will be available to collaborative researchers after consultation and negotiation with the SuDDICU Investigators.

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