# Protocol summary and statistical analysis plan for the Selective Decontamination of the Digestive Tract in Intensive Care Unit Patients (SuDDICU) crossover, cluster randomised controlled trial

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## ABSTRACT

**Background:** It is unclear whether the use of selective decontamination of the digestive tract (SDD) improves outcomes in ventilated patients in intensive care units (ICUs) and whether SDD is associated with the development of antibiotic resistance.
**Objective:** To describe the study protocol and statistical analysis plan for the Selective Decontamination of the Digestive Tract in Intensive Care Unit Patients (SuDDICU) trial.
**Design, setting, participants and intervention:** SuDDICU is an international, crossover, cluster randomised controlled trial of mechanically ventilated patients in ICUs using two 12-month trial periods. For each period, participating ICUs will implement SDD plus standard care or standard care alone. The SuDDICU drug intervention is an oral paste and gastric suspension of three antibiotics combined with a 4-day course of intravenous antibiotics. Observational ecological assessments will be conducted during five surveillance periods. The trial will be conducted in 19 ICUs in Australia and ten ICUs in Canada and the United Kingdom, and will recruit 15 000–17 000 patients. Recruitment commenced in Australia in 2017.
**Main outcome measures:** The primary outcome is all-cause hospital mortality. Secondary outcomes include: duration of ventilation, ICU stay and hospital stay; incidence of new antibiotic-resistant organisms during the index ICU admission; changes in antibiotic-resistant organism rates; incidence of new *Clostridioides difficile* infections; and total use of antibiotics.
**Results and conclusions:** SuDDICU will determine whether the use of SDD plus standard care is associated with a reduction in hospital mortality in ventilated ICU patients compared with standard care alone. It will also quantify the impact of the use of SDD on the development of antibiotic resistance.
**Trial registration:** Australian New Zealand Clinical Trials Registry (ACTRN12615000411549) and ClinicalTrials.gov (NCT02389036).


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Selective decontamination of the digestive tract (SDD) is not a new concept. It was first described in immunocompromised patients with haematological conditions, in the 1980s, and later extended to critically ill patients in intensive care units (ICUs).[1,2] The digestive tract is selectively decontaminated by application of topical non-absorbable antibiotics and antifungals to the oropharynx and gastrointestinal tract in combination with a short course of intravenous antibiotics. The primary aims of this strategy are to prevent the development of nosocomial pneumonia caused by proliferation of potentially pathogenic Gram-negative bacteria and to prevent secondary overgrowth of yeasts in the upper gastrointestinal tract, particularly in mechanically ventilated patients.[3-7] SDD usually involves use of an oral paste and gastric suspension of three non-absorbed antimicrobial agents (an aminoglycoside, a peptide antibiotic and an antifungal) combined with a short course of intravenous third-generation cephalosporin or fluoroquinolone.[2]

While systematic reviews of more than 40 published randomised controlled trials (RCTs) have consistently reported statistically significant and clinically important reductions in hospital mortality and hospital-acquired pneumonia,[8-12] widespread international use of SDD as a standard of care remains low, with weak recommendations about the role and use of SDD published in international consensus guidelines on managing sepsis.[13,14] There are two main reasons for the substantive uncertainty regarding SDD use. First, there are concerns about the generalisability of RCTs from centres with limited internal and external validity. Second, there are increasing, yet unsubstantiated concerns about development of antibiotic resistance associated with SDD use, particularly resistance to colistin and cephalosporins.[6,15]

The Selective Decontamination of the Digestive Tract in Intensive Care Unit Patients Collaboration was

established through critical care clinical trial networks in Australia, New Zealand, Canada and the United Kingdom in 2009. The aim of this international collaboration is to design and conduct an integrated research program to address this fundamental knowledge and implementation gap that has concerned intensive care clinicians for more than 40 years. The program commenced with the publication of systematic reviews about the effects of SDD on mortality and antibiotic resistance,[16,17] descriptive studies of barriers to global implementation of SDD,[18,19] and feasibility studies.[20] These initiatives informed the design of a large scale RCT aimed at determining whether SDD improves patient-centred outcomes without the development of antibiotic resistance.

In this article, we describe the study protocol and statistical analysis plan for the Selective Decontamination of the Digestive Tract in Intensive Care Unit Patients (SuDDICU) crossover, cluster RCT.

## Methods

### Trial management

The SuDDICU study is an investigator-initiated, international, crossover, cluster RCT (x-cRCT) that is an endorsed collaboration between the SuDDICU investigators and the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group, the Canadian Critical Care Trials Group and the UK Critical Care Research Group.

The principal sponsor of the SuDDICU x-cRCT is the George Institute for Global Health, Sydney, Australia, which will undertake the following roles for operations in Australia: providing oversight and monitoring of data collection; coordinating ethics, regulatory and legal approvals; conducting statistical analysis of study data; and taking responsibility for study drug distribution. For operations in Canada and the UK, these roles will be undertaken by co-sponsor Sunnybrook Health Sciences Centre, Toronto, Canada.

The study is funded by the National Health and Medical Research Council (NHMRC) of Australia (Project Grant 1084244) and the Canadian Institutes of Health Research (Strategy for Patient Orientated Research Project Grant 381434 and Project Grant 378431). These agencies had no input into the study design, and will have no input into study conduct, data analysis, or presentation and publication of the trial results.

The study sponsors and study management committees are responsible for the trial conduct and integrity. Full details of all study committee members, study site investigators and study collaborators are available online (Supporting Information, section 2).

The trial is registered on the Australian New Zealand Clinical Trials Registry (ACTRN12615000411549) and on ClinicalTrials.gov (NCT02389036).

### Trial design

The SuDDICU x-cRCT has been designed to determine whether the use of SDD plus standard care reduces hospital mortality in mechanically ventilated ICU patients without increasing antibiotic resistance compared with standard care alone. Its design consists of: a 3-month pre-trial observational period; two 12-month x-cRCT periods (SDD plus standard care, or standard care alone) separated by a 3-month observational inter-period gap; and a 3-month post-trial observational period. Ecological (microbiological) assessments will be conducted during the three observational periods and the last 3 months of each x-cRCT period to determine secular changes in antibiotic resistance patterns associated with the implementation of SDD in participating ICUs (Figure 1).

### Rationale for study design

For SDD prophylaxis to be maximally effective, it needs to be used in every eligible patient as soon as possible after ICU admission. This requires SDD to become standard practice at each participating site for the duration of the SDD plus standard care intervention period.

A cluster RCT where the participating ICU (cluster) is randomised to either SDD plus standard care (intervention) or standard care alone (control) for the two x-cRCT periods is the only feasible trial design for comparing SDD to standard care on patient-centred outcomes and to evaluate the impact of using SDD on antibiotic resistance at each site. By adding a crossover design to the cluster RCT, the effects of site imbalances are mitigated, which increases statistical power.[21]

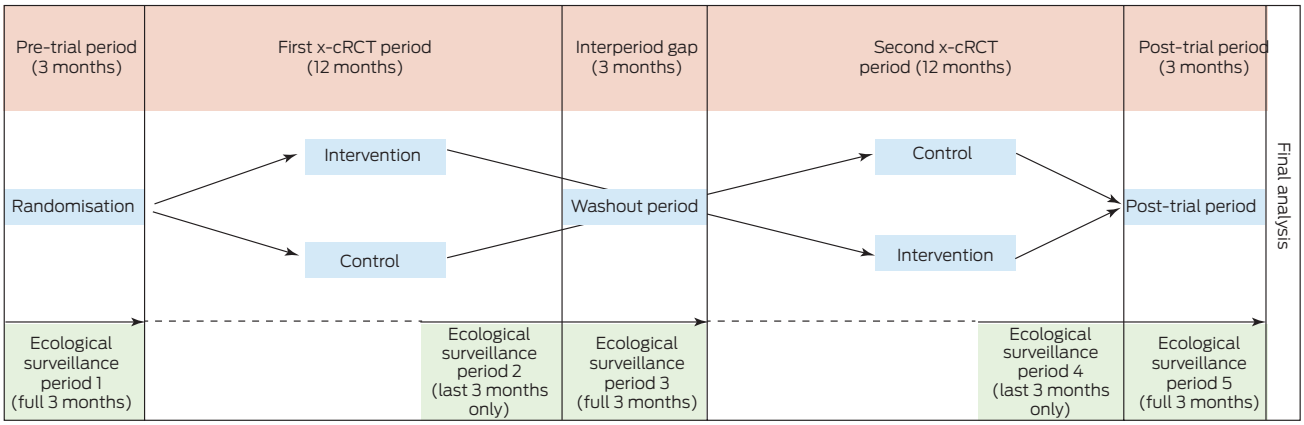
### Setting and population

Sites are eligible for inclusion if they are a general ICU or a complex of ICUs (medical, surgical, mixed) capable of treating mechanically ventilated critically ill patients. Eligible patients are all those who require mechanical ventilation via an endotracheal tube on admission to the ICU or during their index ICU admission, and who are predicted to remain ventilated beyond the end of the calendar day after the day of ICU admission. Patients eligible for ecological surveillance are all those admitted to the ICU regardless of ventilation status. Site, patient and ecological surveillance eligibility criteria are shown in Table 1.

### Randomisation

Participating ICUs will be randomly assigned by an independent statistician using a computer-based

**Figure 1. Trial design**




randomisation program during the 3-month pre-trial period to either deliver SDD or to be a control ICU in the first 12-month x-cRCT period and vice versa in the second 12-month x-cRCT period.

### SDD plus standard care (intervention group)

Patients in the SDD plus standard care group will receive all usual infection control measures according to existing protocols in each participating ICU, with no restrictions on the use of specific mouth-care preparations, including oral chlorhexidine or other antibiotic use for clinical reasons. Within 6 hours of meeting eligibility criteria, they will receive two open-label SuDDICU study drug preparations that have been specifically manufactured for this trial according to Good Medical Practice standards in a facility approved by the Australian Therapeutic Goods Administration (Verita Pharma, Sydney, Australia) under licence from the George Institute for Global Health. One of these is a topical application of 0.5 g paste containing colistin 10 mg, tobramycin 10 mg and 125 000 IU nystatin, which is applied 6-hourly to the buccal mucosa and oropharynx. The other is a 10 mL suspension containing 100 mg colistin, 80 mg tobramycin and $2 \times 10^6$ IU nystatin, which is applied 6-hourly to the gastrointestinal tract via a gastric or post-pyloric tube. More detail on both preparations is available online (Supporting Information, section 3). Study preparations will be distributed by the manufacturer in numbered, temperature-controlled, patient-specific boxes, and delivered to ICUs and hospital pharmacies from central repositories in Australia, Canada and the UK.

Both topical study drug preparations will continue to be given until tracheal extubation, removal of the enteral feeding tube, 24 hours of unsupported spontaneous ventilation via tracheostomy or ICU discharge (whichever comes first) for a maximum of 90 days. 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 inter-period gap and post-trial period.

In addition, all eligible patients in the SDD arm will receive intravenous antibiotic therapy. Patients not already receiving a therapeutic antibiotic will be prescribed a 4-day course of cefotaxime 1 g 6-hourly or ceftriaxone 1 g daily, with dose adjusted as appropriate for organ dysfunction. A 4-day course of ciprofloxacin (400 mg 12-hourly) will be prescribed as an alternative for these patients if there is a contraindication to cephalosporins such as allergy. The intravenous antibiotic will be continued for 4 days or until ICU discharge, whichever comes first. Patients already receiving an alternative intravenous antibiotic as clinically indicated will not receive an additional intravenous antibiotic but will continue receiving the prescribed antibiotic for the usual duration of therapy. For all patients, if there is a clinical indication to continue systemic antibiotics for a longer period, 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.

### Standard care alone (control group)

Patients in the standard care alone group will receive all usual infection control measures according to existing protocols in each participating ICU, with no restrictions on the use of specific mouth-care preparations, including oral chlorhexidine, or other antibiotic use for clinical reasons.

**Table 1. Eligibility criteria for sites, patients and ecological surveillance**

| | |
|---|---|
| **Site eligibility criteria for inclusion in study** | |
| Inclusion criterion | • A general ICU or complex of ICUs (medical, surgical, mixed) capable of treating mechanically ventilated patients |
| Exclusion criteria | • Unwilling or unable to follow trial protocols |
| | • Unable to capture the minimum dataset required for the study |
| | • Isolated specialty ICU not co-located with a general ICU (eg, ICUs that only admit cardiac, neurological/ neurosurgical or burns patients*) |
| | • Specialty paediatric ICU |
| **Patient eligibility criteria for inclusion in study** | |
| Inclusion criteria† | • Mechanically ventilated via an endotracheal tube on admission to ICU and predicted to remain ventilated beyond the end of the calendar day after the day of ICU admission |
| | • Became mechanically ventilated via an endotracheal tube during their ICU stay, and predicted to remain ventilated beyond the end of the calendar day after the day they are first ventilated |
| | • Not already recruited but receiving mechanical ventilation via an endotracheal tube and expected to receive ongoing ventilation for a further 48 hours or more despite an earlier prediction that ventilation would be discontinued earlier |
| Exclusion criteria | • Enrolled in a trial that would interact with the intervention |
| | • Known allergy, sensitivity or interaction to trial topical intervention drugs |
| | • Known or suspected to be pregnant |
| | • Moribund and not expected to survive the next 12 hours |
| | • Younger than 16 years and in the United Kingdom |
| **Patient eligilibity criterion for inclusion in ecological surveillance‡** | |
| Inclusion criterion | • Admitted to the ICU regardless of ventilation status during one full week of any of the following periods: each calendar month during the pre-trial period; each calendar month during the final 3 months of the two x-cRCT periods; each calendar month during the inter-period gap; each calendar month during the post-trial period |

ICU = intensive care unit. x-cRCT = crossover, cluster randomised controlled trial. * Specialty patients cared for in general ICUs will be included. † To be eligible, patients must meet one of the inclusion criteria. ‡ For all patients included in the ecological surveillance, this will be for the duration of their admission, and no exclusion criteria will be used for the ecological surveillance.

## Study outcomes

The primary outcome is all-cause hospital mortality related to the index ICU admission. Secondary outcomes relate to clinical, microbiological and health economic assessments. All outcome definitions are shown in Table 2.

## Data collection and management

Details on data to be collected — patient screening data, baseline patient characteristics, details on study drug compliance and concomitant therapies (including defined daily doses of study and non-study antibiotics), microbiological data, patient outcomes, adverse events and protocol violations — are shown in Table 3. Data monitoring at each site will be conducted by independent clinical research associates from each sponsor in accordance with a pre-specified source data verification plan. Process measures and outcomes data will be collected in the same manner for patients in both treatment groups.

Microbiological data will be collected during five discrete ecological surveillance periods, including during the two x-cRCT periods (Figure 1), according to standard clinical practice in the participating ICU. It will be recommended that oral or endotracheal swabs and perineal or rectal swabs be routinely collected for all patients on admission, at least weekly during their admission and on discharge, or as mandated in each ICU or jurisdiction. Microbiological data will be captured on a study-specific case report form and entered into an electronic password-protected website housed at the George Institute for Global Health (Australia) and Sunnybrook Health Sciences Centre (Canada and UK). The databases will be amalgamated at the end of the completed study in each country and housed at the George Institute for Global Health.

**Table 2. Primary and secondary study outcomes**

**Primary outcome**

- All-cause hospital mortality related to the index ICU admission, censored at Day 90

**Secondary outcomes**

- Clinical assessments
  - ► Duration of mechanical ventilation
  - ► ICU length of stay
  - ► ICU mortality
  - ► Hospital length of stay
- Microbiological assessments
  - ► The incidence of AROs isolated from all clinical and surveillance specimens, including the incidence of AROs in cultures from blood or other sterile sites, the incidence of AROs in non-sterile clinical and surveillance specimens, and the incidence of bacteraemia in all blood culture specimens
  - ► Changes in ARO rates between pre-trial, intervention and post-trial periods
  - ► Incidence of *Clostridioides difficile* infections
  - ► Total antibiotic use (as daily defined doses)
- Health economic assessment
  - ► Health economics analysis from a health care system perspective

ICU = intensive care unit. ARO = antibiotic-resistant organism.

## Adverse events

Reporting of adverse events will be restricted to events related to study treatment (possibly, probably or definitely), as determined by the principal investigator at each site. All new cases of *Clostridioides difficile* infection acquired during the index ICU admission will be reported as serious adverse events. All adverse reactions will be reviewed by the coordinating centre staff and recorded in a safety database, which will be monitored by the respective study management committees. Reports of suspected severe adverse drug reactions that are unexpected will be reported to the coordinating centre and respective ethics and research governance officer as required in each jurisdiction.

## Antibiotic-resistant organism outbreaks

An antibiotic-resistant organism outbreak is defined by the need for any new infection control interventions that are deemed by the site investigator to be directed specifically to contain an outbreak of an antibiotic-resistant organism. Outbreaks will be reported to study management committees and assessed by the data safety and monitoring committee (DSMC). Usual study procedures should continue while any outbreak is being assessed. Appropriate clinical management at each study site will be determined by the clinical team and infection control staff. Study sites will be actively encouraged to resume normal trial conduct after control of the situation.

## Withdrawal of study treatment

The study intervention can be stopped if:

• a serious adverse reaction to the study intervention occurs;

• a definite contraindication to the study intervention becomes apparent; or

• a request to withdraw is made by the patient or their substitute (ie, person responsible), if applicable.

In the case of a request to withdraw, the patient or substitute will be asked whether previously collected data can be used, and whether the trial primary outcome can be collected and analysed for the study. If consent for this is not provided, then the patient's data will be deleted and not analysed any further.

## Ethics approval

The study will be performed in accordance with ethics principles consistent with the Declaration of Helsinki and all relevant national and local guidelines on the ethical conduct of research. The trial has been approved by the Human Research Ethics Committee (HREC) of Royal Brisbane and Women's Hospital, Brisbane, Australia (the lead HREC for the study) (Protocol GI-CCT070115; HREC/15/ORBW/241) for Australian sites except those in New South Wales, and the HREC of Royal Prince Alfred Hospital (Protocol X15-0076; HREC/15/RPAH/110) for sites in NSW. Additional reviews and approvals were conducted by the NSW Civil and Administrative Tribunal (Trial 1/2016) and by research governance officers at each participating site. In Canada, the trial was approved by the Clinical Trials Ontario Research Ethics Board. In the UK, the trial has received a favourable opinion from the London – Queen Square Research Ethics Committee. All protocol amendments will be submitted to the lead ethics committees and site research governance officers for approval, and updated on clinical trial registries as required.

## Consent

In Australia, the intervention will be offered to all eligible patients in participating ICUs as part of standard practice for those ICUs, and individual patient consent for the period of the study up to hospital discharge (the primary outcome) will not be required. A waiver of consent has been approved in Australia, subject to variations in state law. This is consistent with the *NHMRC national statement on ethical conduct in human research*.

**Table 3. Summary of data to be collected**

| Time of collection | Data collected |
|---|---|
| Patient screening | • Site name and number |
| | • Patient initials |
| | • Date of ICU admission |
| | • Date of hospital admission |
| | • Reason(s) for exclusion, if applicable |
| Patient characteristics at baseline | • Age |
| | • Sex |
| | • Admission source |
| | • APACHE III diagnosis |
| | • APACHE II or III score or MODS |
| | • Time from ICU admission to enrolment |
| | • Diabetes (yes or no) |
| | • Immunosuppressed (yes or no) |
| | • Systemic steroids (yes or no) |
| | • Oral chlorhexidine (yes or no) |
| | • On intravenous antibiotics at time of enrolment (yes or no) |
| | • Intravenous antibiotics received > 48 hours before enrolment (yes or no) |
| Day 1 to Day 90: SDD antibiotics | • 4-day intravenous course received (yes or no) |
| | • Number of days with at least one dose (oral and gastric) |
| | • Total number of doses (oral and gastric) |
| Day 1 to Day 90: cumulative defined daily doses of antibiotics (intervention and control) | • Any antibiotics |
| | ▪ Penicillins |
| | • Carbapenems |
| | • Cephalosporins |
| | • Quinolones |
| | • Aminoglycosides |
| | • Lincosamides |
| | • Antifungals |
| | • Others |
| Microbiological data | • New AROs |
| | • New positive blood culture result |
| | • Positive *Clostridioides difficile* test result while in ICU |
| | • Organisms obtained from blood cultures |
| | • Organisms obtained from non-blood cultures |
| Patient outcomes | • Vital status at hospital discharge |
| | • Vital status at ICU discharge |
| | • Cause of death |
| | • Duration of mechanical ventilation, all episodes |
| | • Duration of ICU admission, including re-admissions |

(*Continues*)

In Canada, laws of the jurisdiction do not allow a waiver of consent for this trial, so a delayed consent model will be used. Consent from substitute decision makers will be sought as soon as possible after the intervention begins for all patients recruited into the intervention arm. Full details of the Canadian consent process are provided online (Supporting Information, section 4).

In the UK, consent for participation in the study will be sought for all included patients. As patients who are eligible for inclusion in the trial will lack the capacity to provide consent, advice about their participation will be sought from a consultee (personal or nominated) according to the *Mental Capacity Act (2005)*. As initiation of the intervention is time sensitive, the intervention will be started within 6 hours in all eligible patients if a consultee is not available to advise. In these situations, a consultee will be approached as soon as it is practically possible to seek retrospective advice. Once patients regain capacity while in hospital, they will be approached to seek their consent for continued participation in the study.

In all jurisdictions, patients in the control arm of the trial, and the ecological surveillance periods, will be recruited without consent as no intervention is being offered.

### Data safety and monitoring committee

An independent DSMC will review analyses of safety and outcomes data and all adverse reactions at pre-determined intervals during the study, or as they deem appropriate. One pre-determined interim analysis will be conducted by the DSMC on completion of the first x-cRCT period in Australia, according to a pre-specified statistical analysis plan provided by the George Institute for Global Health statistical team. Members of the DSMC are listed online (Supporting Information, section 2).

### Study timelines and modifications

SuDDICU was originally planned as an international, multicentred, parallel-arm cluster RCT that was to be simultaneously conducted in Canada, the UK, Australia and New Zealand, with a projected study population of 22 500 patients from 100 ICUs. This international trial was dependent on the success of simultaneous applications to national research funding agencies in the four countries.

**Table 3. Summary of data to be collected (*continued*)**

| Time of collection | Data collected |
|---|---|
| Adverse events | • Description, timing and grading |
| | • Causality and resolution |
| | • Positive *Clostridioides difficile* test result while in ICU |
| Protocol violations | • Enrolment of ineligible patient |
| | • SDD intervention not started within 6 hours |
| | • SDD paste or suspension not administered, incompletely administered or additional dose given |
| | • Early cessation of SDD (before extubation) |
| | • SDD intravenous antibiotics not administered |

APACHE = Acute Physiology and Chronic Health Evaluation. ARO = antibiotic-resistant organism. ICU = intensive care unit. MODS = Multiple Organ Dysfunction Score. SDD = selective decontamination of the digestive tract.

Initially, only the Health Research Council of New Zealand and Australian NHMRC grant applications were successful. Following withdrawal of the New Zealand grant, the trial design was modified to an x-cRCT in 2014, to be conducted in up to 20 Australian ICUs and funded by the NHMRC. Then, following funding from the Canadian Institutes of Health Research in 2017, the trial was expanded to include patients from seven ICUs in Canada and three ICUs in the UK.

Given the dyssynchrony due to funding and operational delays, and the subsequent impact of the coronavirus disease 2019 (COVID-19) pandemic on trial recruitment in Canada and the UK, a decision was made to publish the Australian data following completion of recruitment in Australia in 2021, publish the Canadian and UK data in 2022 or 2023, and publish an analysis of combined data in 2023 or 2024. A summary table of actual and indicative study timelines is available online (Supporting Information, section 5).

## Statistical analysis plan

A detailed statistical analysis plan was completed by statisticians from the George Institute for Global Health and published as a preprint on an open access website before recruitment of the index trial was completed (https://osf.io/bd7t4), and a summary of planned tables and figure for publication is shown in Table 4. Analyses will be conducted primarily using SAS software, version 9.3 or higher (SAS Institute).

### Sample size

For the SuDDICU x-cRCT, we aim to recruit between 15 000 and 17 000 patients from 19 ICUs in Australia, seven in Canada and three in the UK, and at least 150 patients per period at each ICU (ie, ≥ 300 patients per ICU). Assuming an intracluster correlation coefficient (ICC) of 0.01 and an inter-period correlation (IPC) of 0.005, this will provide at least 80% power to detect a 3.5% absolute risk reduction (ARR) in hospital mortality from a baseline mortality of 29% with a two-sided significance level of 5%. The initial global (and regional) effect size of an ARR of 3.5% was informed by large scale pragmatic comparative effectiveness RCTs conducted by our group at the time (SAFE[22,23] and NICE-SUGAR[24]), which reported biologically plausible effect sizes of 3.5–5.0%. An effect size in this range accords with more recent RCTs published by our group, including the CHEST[25] and ADRENAL[26] trials. The baseline mortality rate was informed by pilot trials conducted in Australia, New Zealand, Canada and the UK from 2012 to 2014. We initially selected the ICC and IPC using the best available metrics from similar and equivalent RCTs at the time of designing the trial. These assumptions are appropriately conservative and accord with data from the ANZICS Clinical Trials Group x-cRCT PEPTIC study, which reported an ICC of 0.0093 and an IPC of 0.0072.[27]

Revised power calculations from the original cRCT to the x-cRCT, and justification for these, are available online (Supporting Information, section 6). In summary:

- the analysis of Australian sites only will have at least 80% power to detect an absolute reduction in mortality of 4.2%;
- the analysis of Canadian and UK sites only will have at least 80% power to detect an absolute reduction in mortality of 5.5%; and
- the revised design has statistical power to detect a plausible effect size for the primary outcome (hospital mortality) for the combined analysis and each regional cohort.

### Level of statistical significance

All analyses of the primary outcome, including sensitivity analyses, will be conducted using a two-sided significance level of 5%. Analyses of secondary clinical outcomes will have a Holm–Bonferroni correction to control the family-wise error rate. No multiplicity correction will be applied to the ecology analyses or other statistical tests.

### Analyses of populations

Owing to the crossover cluster design, the group allocation for a patient is determined by the site and by the period during which they are included, regardless of treatment adherence. The intention-to-treat analysis

**Table 4. Planned tables and figures for publication**

**Planned tables and figures for the main manuscript**

- Table 1: Baseline patient characteristics
- Table 2: Primary and secondary outcomes
- Table 3: Ecological surveillance results
- Figure 1: Flow of participants through the trial
- Figure 2: Kaplan–Meier plot of time to death
- Figure 3: Forest plot for subgroup analysis of hospital mortality

**Planned tables and figures for the supplementary appendix**

- Table S1: SDD antibiotics summary
- Table S2: Cumulative defined daily doses of antibiotics
- Table S3: Causes of death
- Table S4: Protocol deviations
- Table S4: Adverse events
- Figure S1: Patient disposition
- Figure S2: Overall antibiotics use in defined daily doses
- Figure S3: Cumulative index function of time to ICU discharge
- Figure S3: Cumulative index function of time to hospital discharge
- Figure S4: Incidence of AROs during each ecological surveillance period
- Figure S5: Incidence of bloodstream infections during each ecological surveillance period
- Figure S6: Incidence of *Clostridioides difficile* during each ecological surveillance period

ARO = antibiotic-resistant organism. ICU = intensive care unit. SDD = selective decontamination of the digestive tract.

set will be used to assess effectiveness and safety, and the primary analysis will use all available data with no imputation for missing data.

### Analyses of baseline data

**Cluster characteristics.** Description of cluster characteristics will be presented by treatment group. Discrete variables will be summarised as frequencies and percentages, and percentages will be calculated according to the number of clusters with available data. Continuous variables will be summarised a mean (standard deviation [SD]), and median (interquartile range [IQR]).

**Patient characteristics.** Description of patient baseline characteristics will be presented by treatment group and by centre. Discrete variables will be summarised as frequencies and percentages, and percentages will be calculated according to the number of patients for whom data are available. Continuous variables will be summarised as mean (SD) and median (IQR). No adjustment for clustering will be applied when summarising baseline characteristics.

### Analyses of compliance and concomitant therapies

For patients in the SDD plus standard care group, separate analyses will be done for the SDD oral paste, SDD gastric suspension and SDD intravenous antibiotics. These analyses will include:

- type and number of doses received each day;
- total number of daily doses received;
- proportion of eligible doses received;
- number of days with at least one dose; and
- proportion of patients who received the full 4-day course of SDD intravenous antibiotics.

For patients who received non-SDD antibiotics, the number of daily defined doses in the ICU between Day 1 and Day 28 day will be collected in total, and separately for the two treatment groups.

### Analysis of the primary outcome

The primary outcome is hospital mortality, defined 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 of mortality between the SDD plus standard care group and the control group obtained from a hierarchical logistic regression model including a random cluster effect and a random cluster-period effect. The hierarchical model is presented online (Supporting Information, section 6). The logistic regression model will be re-run after adjustment for the following individual baseline covariates:

- age (continuous);
- sex (male versus female);
- admission diagnosis (medical versus surgical); and
- severity of illness (Acute Physiology and Chronic Health Evaluation [APACHE] II or III score or Multiple Organ Dysfunction Score [MODS]) (continuous).

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

### Subgroup analyses

The following subgroup analyses are planned for the primary outcome only, regardless of the statistical significance in the primary analysis:

- ICU admission diagnosis (operative versus non-operative, and trauma versus non-trauma);
- severity of illness (above versus below median ICU admission APACHE II or III score or MODS);
- age (above versus below median age); and
- sex (male versus female).

Each subgroup analysis will be performed by adding the subgroup variable and its interaction with the intervention as fixed effects to the logistic regression model used for the primary analysis. In each subgroup, summary measures will include raw counts and percentages in each treatment group, and the odds ratio (95% confidence interval [CI]) for treatment effect. The results will be displayed on a forest plot including the *P* value for heterogeneity corresponding to the interaction term between the intervention and the subgroup variable. Handling of missing data for the primary outcome is presented online (Supporting Information, section 6).

### Analysis of secondary 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 (eg, days alive and free of mechanical ventilation, or days alive and out of ICU) up to Day 90. Outcomes will be analysed using a hierarchical linear model instead of a logistic model. The effect of the intervention will be reported as adjusted mean difference (95% CI). No adjusted or subgroup analyses of these outcomes will be performed. ICU mortality will be analysed in the same way as hospital mortality.

Mechanical ventilation is only expected to be used in the ICU setting. Therefore, once discharged from the 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. As a sensitivity analysis, we will allocate zero "free days" to patients who die by Day 90. Further sensitivity analyses are presented online (Supporting Information, section 6).

Time to alive discharge from index ICU and time to alive discharge from index hospital admission will be summarised using cumulative incidence functions (medians and quartiles of time) treating mortality as a competing risk and with censoring at Day 90. The effect of the intervention will be estimated as the hazard ratio (SDD divided by control) and its 95% CI obtained from a Cox model of the cause-specific hazard that estimates the risk of discharge in patients who are still alive but have not yet been discharged.

### Analysis of ecological outcomes

The following microbiology outcome data will be collected for all trial-eligible patients (both intervention and control) during the two 12-month x-cRCT periods:

- new antibiotic-resistant organism from sterile and non-sterile sites;
- new positive test result for bloodstream infections; and
- new *Clostridioides difficile* infections.

Proportions of patients with at least one event 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 as done in the second sensitivity analysis of the primary outcome and using the same weighting method.

### Analysis of unit-level ecological surveillance data

Observational data for microbiological outcomes (ie, those used for the analysis of ecological outcomes) will be collected for all ICU patients, regardless of ventilation status, during one full week of each month in the following periods: the 3-month pre-trial (period 1), the final 3 months of the first x-cRCT period (period 2), the 3-month inter-period gap (period 3), the final 3 months of the second x-cRCT period (period 4) and the post-trial period (period 5) (Figure 1). Analyses of these observational data will include:

- baseline characteristics (age, sex, time since admission, severity of illness);
- vital status at discharge; and
- numbers and proportions of microbiological outcomes in each period according to randomisation sequence (ie, SDD followed by control or control followed by SDD).

To reject the null hypothesis and declare non-inferiority of SDD plus standard care (intervention) compared with standard care alone (control), the upper boundary of the 95% CI around the absolute mean difference between intervention and control will need to be lower than 2%. Data will be analysed from all periods using linear regression to model the proportion of events in each cluster and each period. To test whether the proportion of events in the intervention group is non-inferior to that in the control group, we will group periods 2 and 3 within each arm and estimate the change from baseline (period 1). To test whether the change from baseline with intervention is non-inferior to the change from baseline with control, we will then estimate the difference between intervention and control from baseline. Using the same model, to further assess the effect of SDD over time, including potential withdrawal effects (ie, whether rates change after withdrawing SDD), we will compare the change between period 3 and periods 4 and 5 combined in units randomised to use SDD in the first x-cRCT period. Further details of the ecological surveillance analyses are presented online (Supporting Information, section 6).

### Health economic analysis

A separate cost-effectiveness and cost-utility analysis that will use the most appropriate data collected across all settings will be conducted but will use parameters that are judged context-specific (eg, unit costs) and taken from local sources. In Australia and Canada, health economic analyses

will be undertaken from the perspective of the "idealised insurer" or third party payer (ie, the provincial, state and federal government payer perspective). Data for these analyses will be obtained via routine patient follow-up and augmented by data linkage to capture pharmaceutical and medical service use.

## Pre-specified substudies

Two pre-specified, independently funded substudies will run concurrently with the SuDDICU x-cRCT. First, an ecological substudy will be conducted in selected Australian ICUs to determine rates of colonisation by antibiotic-resistant organisms in patients treated with SDD and non-SDD antibiotics. This will involve characterisation of microflora and microbiome genomics, metagenomic changes over time, and associations between these changes and clinical outcomes. This substudy is funded by the NHMRC (Project Grant APP1127292). Second, a process evaluation exploring context and process of trial implementation will be conducted in Canadian and UK ICUs. This substudy is funded by the Canadian Institutes of Health Research (Grant 171478).

## Summary

The SuDDICU study is an international, crossover, cluster randomised controlled trial that will determine whether the application of SDD to standard care for mechanically ventilated patients in the ICU setting is associated with reduced hospital mortality compared with standard care alone. An assessment of the use of SDD on the development of antibiotic resistance will also be conducted. This protocol summary and statistical analysis plan was submitted for publication before recruitment of the Australian cohort was completed.

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## Competing interests

The George Institute for Global Health holds all intellectual property rights related to the SuDDICU study drug, including component drug acquisition, manufacturing, packaging and distribution. None of the SuDDICU investigators have direct or indirect financial or commercial interests relating to the development of the SuDDICU study drug.

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