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

Statistical Analysis Plan

Version: 1.0 (final)

Date: 18 September 2020

Authors:

Laurent Billot^{ID}, John Myburgh^{ID}, Fiona Goodman, Simon Finfer^{ID}, Ian Seppelt^{ID}, Anthony Gordon^{ID},
Brian Cuthbertson^{ID}, on behalf of the SuDDICU Australia Management Committee

Corresponding author:

Laurent Billot

The George Institute for Global Health

Faculty of Medicine, UNSW Sydney

lbilot@georgeinstitute.org

The George Institute
for Global Health Australia

1 Administrative information

1.1 Study identifiers

- Protocol Number: GI-CCT070115, Version: 3.0, Date: 14th March 2018.
- Australian New Zealand Clinical Trials Registry, Number: [ACTRN12615000411549](https://www.anzctr.org.au/Trial/Registration/TrialRegistration.aspx?ACTRN12615000411549).
- ClinicalTrials.gov register Identifier: [NCT02389036](https://clinicaltrials.gov/ct2/show/study?term=NCT02389036).

1.2 Revision history

Version	Date	Details
0.1 (draft)	19 September 2019	First (internal) draft by Laurent Billot (LB), not circulated
0.2 (draft)	13 January 2020	First version created by LB and circulated to Fiona Goodman (FG) and John Myburgh (JM)
0.3 (draft)	12 February 2020	Updated by LB after receiving comments from FG and JM
0.4 (draft)	19 March 2020	Updated by LB
0.5 (draft)	27 May 2020	Edits by JM, Simon Finfer (SF) and Ian Seppelt (IS)
0.6 (draft)	12 June 2020	Updated ecology analysis and analysis of secondary outcomes. Updated mock tables
0.7 (draft)	18 August 2020	Edits by Brian Cuthbertson
1.0 (final)	18 September 2020	Final version

1.3 Contributors to the statistical analysis plan

1.3.1 Roles and responsibilities

Name and ORCID	Affiliation	Role on study	SAP contribution
A/Prof Laurent Billot	The George Institute for Global Health, UNSW Sydney	Study statistician	Prepared initial draft and revisions
Prof John Myburgh	The George Institute for Global Health, UNSW Sydney	Chair SuDDICU Australia Management Committee, Director George Institute, International Steering Committee representative	Revisions and liaison with study Management Committees
Ms Fiona Goodman	The George Institute for Global Health	Project manager SuDDICU Australia	Revisions and liaison with study Management Committees
Prof Simon Finfer	The George Institute for Global Health, UNSW Sydney	Chief investigator SuDDICU Australia	Revisions
Clinical Prof Ian Seppelt	The George Institute for Global Health; Macquarie	Chief investigator, SuDDICU Australia	Revisions and liaison with study

Name and ORCID	Affiliation	Role on study	SAP contribution
	University and University of Sydney		Management Committees
Prof Anthony Gordon	Imperial College London	Chief Investigator UK	Reviewed draft
Prof Brian Cuthbertson	Sunnybrook Health Science Centre	Chief Investigator Canada	Reviewed draft

1.3.2 Approvals

The undersigned have reviewed this plan and approve it as final. They find it to be consistent with the requirements of the protocol as it applies to their respective areas. They also find it to be compliant with ICH-E9 principles and, in particular, confirm that this analysis plan was developed in a completely blinded manner, i.e. without knowledge of the effect of the intervention(s) being assessed.

Associate Professor Laurent Billot

signature

18/09/2020

date

Professor John Myburgh

signature

18/09/2020

date

Ms Fiona Goodman

signature

18/09/2020

date

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2 Introduction

2.1 Study synopsis

Selective decontamination of the digestive tract (SDD) is an infection-control strategy designed to reduce mortality by preventing hospital-acquired infection in ventilated critically ill patients. The SDD in Intensive Care (SuDDICU) study 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.

SuDDICU is an international, multicentre, cross-over, cluster randomised controlled trial (x-cRCT) of eligible patients in participating ICUs using two 12-month interventional trial periods separated by a 3-month inter-period gap. An observational ecological assessment will be conducted in all 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; in all ICU patients during one week of each month during the 3-month inter-period and post-trial periods.

2.2 Study population

2.2.1 Site eligibility criteria

- **Inclusion**
 - A general ICU or complex of ICUs (medical, surgical, mixed) capable of treating mechanically ventilated critically ill patients.
- **Exclusions**
 - Unwilling or unable to follow trial protocols
 - Unable to capture the minimum data set required for the study

- 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
- Specialty paediatric ICUs.

2.2.2 Patient eligibility criteria

- **Inclusion**

- 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
- 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
- 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.

- **Exclusions**

- Patients enrolled in a trial that would interact with the intervention
- Patients with a known allergy, sensitivity or interaction to trial intervention preparation
- Patients who are known or suspected to be pregnant
- Patients who are moribund and not expected to survive the next 12 hours
- 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.

2.2.3 Ecology surveillance period eligibility criteria

- **Inclusion**

- 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.

- **Exclusion**

- None

2.3 Interventions

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

2.3.1 SDD arm

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 0.5 g paste containing colistin 10 mg, tobramycin 10 mg 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 x 10⁶ IU nystatin, to the gastrointestinal tract via a gastric/post-pyloric tube
3. A four-day course of an intravenous (IV) antibiotic. Patients not already receiving a therapeutic antibiotic will be prescribed cefotaxime 1 g six-hourly or ceftriaxone 1 g daily, with dose adjusted as appropriate for organ dysfunction. Ciprofloxacin (400 mg 12-hourly) may be used as an alternative if there is a contraindication to cephalosporins, such as allergy. Patients already receiving an appropriate alternative IV antibiotic as clinically indicated will not receive an additional IV antibiotic but will continue the prescribed antibiotic for the usual duration of therapy.

2.3.2 Control arm

In ICUs allocated to the control arm, patients will receive all usual infection control measures but will receive no study-specific interventions.

2.4 Outcomes

The study outcomes are:

2.4.1 Primary outcome:

- All-cause hospital mortality related to ICU index admission

2.4.2 Secondary outcomes:

- Ecology assessments:
 - The incidence of antibiotic resistant organisms (ARO) isolated from all clinical and surveillance specimens
 - Changes in ARO rates between surveillance, intervention and post intervention periods
 - The incidence of *Clostridioides difficile* infections
 - Total antibiotic usage (as daily defined doses)
- Clinical assessments:
 - Duration of mechanical ventilation

- ICU length of stay
- ICU mortality
- Hospital length of stay
- Health economic assessment:
 - Health economic analysis from a healthcare system perspective.

2.5 Randomisation and blinding

ICUs are randomised in the pre-trial period to either deliver SDD in the first 12-month period and to be a control ICU in the second 12-month period, or to be a control ICU first and deliver SDD in the second period. This is an unblinded study where SDD becomes usual practice for participating ICUs when allocated to the intervention arms.

2.6 Statistical hypotheses

The primary statistical hypotheses are as follows:

- **Null hypothesis:** no difference in the proportion of patient's dead at 90-days between those randomised to SDD (p_1) and Usual Care (p_0) i.e. $p_1 = p_0$
- **Alternative hypothesis (2-sided):** $p_1 \neq p_0$, with the expectation that the proportion would be lower in those randomised to SDD.

2.7 Sample size

SuDDICU is aiming to recruit patients from about 30 ICUs in Australia, UK and Canada each recruiting an average of at least 150 patients per period (i.e. at least 300 patients per ICU). Assuming an intra-cluster correlation coefficient (ICC) of 0.01 and inter-period correlation (IPC) of 0.005, this will provide at least 80% power to detect a 3.5% absolute reduction in hospital mortality from a baseline mortality of 29% with a 2-sided $\alpha = 0.05$.

An analysis consisting of Australian clusters only would have at least 80% power to detect an absolute reduction in mortality of 4.2%. The table below shows the detectable absolute risk reduction according to the number of clusters and number of patients recruited per period.

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

3 Statistical analysis

3.1 Statistical principles

3.1.1 *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 [1].

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

3.1.2 *Statistical software*

Analyses will be conducted primarily using SAS software (version 9.3 or above).

3.2 Analysis 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. The flow of patients through the study will be displayed in a CONSORT diagram.

3.2.1 *Analysis by region*

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

As completion of recruitment in Australia will precede Canadian/UK by more than six months, a two-staged statistical analysis will be conducted.

1. The Australian database will be analysed as soon as the database is locked and reported as a separate analysis in accordance with this statistical analysis plan.

2. The Canada/UK database will be merged with the Australian database following database transfer from Sunnybrook Health Sciences Centre to the George Institute. A separate Canada/UK analysis will be conducted followed by a combined analysis of the merged databases.

3.3 Baseline analyses

3.3.1 Cluster characteristics

Description of the cluster characteristics (e.g. location, size of ICU, baseline rates of antibiotic resistance) will be presented by treatment group. Discrete variables will be summarised by frequencies and percentages. Percentages will be calculated according to the number of clusters with available data. Continuous variables will be summarised by using mean and standard deviation (SD), and median and interquartile range (Q1-Q3).

3.3.2 Patient characteristics

Description of the baseline characteristics will be presented by treatment group and by centre. Discrete variables will be summarised by frequencies and percentages. Percentages will be calculated according to the number of patients in whom data are available. Continuous variables will be summarised by using mean and SD, and median and interquartile range (Q1-Q3). No adjustment for clustering will be applied when summarising baseline characteristics.

Baseline measures for all patients will be tabulated for the variables listed below:

- Age
- Sex
- ICU admission source
- Time between ICU admission and enrolment (hours)
- Severity of illness score (APACHE / MODS)
- APACHE III Diagnosis codes
- Diabetes (Yes/No)
- Immunosuppressed (Yes/No)
- Systemic steroids (Yes/No)
- Oral chlorhexidine (Yes/No)
- IV antibiotics (Yes/No) (at time of enrolment and >48 hours prior)

3.4 Analysis of compliance and concomitant therapies

3.4.1 Compliance and concomitant therapies

For patients in the SDD arm, we will report the type of study antibiotic received and the number of doses received each day between days 1-5. In addition, we will report 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. In addition, for SDD intervention antibiotics, we will report 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 for the following antibiotic groups

- Penicillins
- Carbapenems
- Cephalosporins
- Quinolones
- Aminoglycosides
- Lincosamides
- Anti-fungals
- Others

3.4.2 Protocol deviations

Protocol deviations will be categorised and reported as the number and proportion of subjects experiencing a deviation. A listing of all protocol deviations will be provided.

3.5 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 (defined below). Other analyses of hospital mortality will include a survival analysis of time to death obtained via a Cox model.

3.5.1 Main analysis

The primary analysis of hospital mortality will be conducted using a hierarchical logistic regression which allows us to directly model all levels of clustering. To account for clustering of participants within sites as well as the cross-over design, the model will include both a random cluster effect and a random cluster-period effect (see “random-random” model (equation 11) in Morgan et al [2]). The corresponding logistic model can be written as follows:

$$\text{logit}(P\{Y_{ijk}=1\}) = \mu + \beta_{\tau}\tau_{ij} + \beta_{\pi}\pi_j + c_i + p_{ij} + e_{ijk} \quad (1)$$

where:

- Y_{ijk} denotes the outcome (0 or 1) of subject k ($k=1, \dots, m_{ij}$) in period j ($j=1, 2$) within cluster i ($i=1, \dots, N$) where m_{ij} indicates the number of subjects in period j within cluster i
- μ is the overall intercept
- τ_{ij} is a dummy variable indicating group allocation during period j for cluster i with $\tau_{ij} = 1$ for intervention and $\tau_{ij} = 0$ for control
- β_τ is the parameter of interest estimating the fixed effect of the SDD intervention and where $\exp(\beta_\tau)$ is the odds ratio (OR)
- π_j is a dummy variable indicating the period with $\pi_j = 1$ for the second period and $\pi_j = 0$ for the first period
- β_π is a fixed period effect
- c_i is a random cluster effect with $c_i \sim N(0, \sigma_c^2)$
- p_{ij} is a random cluster-period effect with $p_{ij} \sim N(0, \sigma_p^2)$
- e_{ijk} are individual-level errors following a binomial distribution

The effect of the intervention will be presented as the OR of death and its 95% confidence interval (CI) using the control arm as the reference (i.e. where an OR greater than unity corresponds to an increase in hospital mortality in the SDD arm compared to the control arm). The Kenward-Rodger [3] correction will be applied to estimate the number of degrees of freedom as it has been shown to improve estimation with a small number of clusters [4]. Samples of SAS code for both models are provided in the Appendix (Table 8).

Based on this model, two intra-cluster correlation coefficients (ICC) will be estimated, the first one (ρ_c) corresponding to the correlation between two outcomes from the same cluster-period, the second one (ρ_p) corresponding to the additional correlation between two outcomes from the same cluster-period compared to two outcomes from the same cluster but different periods. The two ICCs, ρ_c and ρ_p , will be estimated as follow:

$$\rho_c = \{ \sigma_c^2 + \sigma_p^2 \} / \{ \sigma_c^2 + \sigma_p^2 + \pi^2/3 \}$$

$$\rho_p = \{ \sigma_p^2 \} / \{ \sigma_c^2 + \sigma_p^2 + \pi^2/3 \}$$

where:

- σ_c^2 is the variance between the cluster means
- σ_p^2 is the variance between the cluster-period means conditional on the cluster mean
- π is the mathematical constant (3.1415...).

The inter-period correlation (IPC), that is the correlation between two outcomes from the same cluster but different periods will be estimated as:

$$\eta = \{ \sigma_c^2 \} / \{ \sigma_c^2 + \sigma_p^2 + \pi^2/3 \}$$

In our sample size calculations, we assumed values of 0.01 for p_c and 0.005 for η ($p_p = 0.005$). With 19 sites recruited in Australia and a total of about 30 sites, we expect the random-random model described above to provide reasonable control of the type-I error rate; however, to assess the robustness to potential departures from our assumptions, especially around the two ICCs, we will be conducting the following sensitivity analyses:

1. Re-running the same model as model (1) but without using the Kenward-Roger correction
2. Linear regression on summary measures: we will fit a linear regression to model the proportion of events in each cluster-period using the following model (see equation 13 in Morgan et al [2]):

$$P_{ij} = \alpha + \beta_{\tau}\tau_{ij} + \beta_{\pi}\pi_j + \gamma_i + e_{ij} \quad (2)$$

where:

P_{ij} is the proportion of events in period j of cluster i (Y_{ij}/n_{ij})

α is the overall intercept

β_{τ} is the treatment effect corresponding to the average difference in proportions and τ_{ij} is an indicator variable for treatment of interest

β_{π} is a fixed period effect and π_j is an indicator variable for period

γ_i is a fixed effect of cluster

e_{ij} is a normally distributed residual error term with mean zero and variance σ^2_e

The regression will be weighted proportionally to the inverse of the binomial variance for each cluster-period with each weight calculated as $\{ n_{ij} / [p_{ij} (1 - p_{ij})] \}$ (i.e. using the third set of weights in Morgan et al [2]).

3.5.2 Adjusted analyses

The logistic regression model described in Section 3.5.1 will be re-run after adjustment for the following individual baseline covariates:

- Age (continuous)
- Sex (male vs female)
- Admission diagnosis (medical vs surgical)
- APACHE / MODS score (continuous)

3.5.3 Subgroup analyses

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

- Nature of admission

- Operative versus non-operative
 - Trauma versus non-trauma
- Above versus below median ICU admission APACHE II / III score
- Above versus below median age
- Sex (Male vs Female)

Each subgroup analysis will be performed by adding the subgroup variable as well as its interaction with the intervention as fixed effects to the logistic regression model used for the primary analysis (see Section 3.5.1). Within each subgroup, summary measures will include raw counts and percentages within each treatment arm, as well as the OR for treatment effect with 95% CI. 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.

3.5.4 Treatment of missing data

The primary analysis will use all available data with no imputation. In addition, we will perform sensitivity analyses to assess the potential impact of missing data on the study conclusions. We will start by rerunning Model (1) under the two following most extreme scenarios:

- Extreme scenario 1 ('worst' case): all patients with missing data assumed as dead in the SDD arm and alive in the control arm
- Extreme scenario 2 ('best' case): all patients with missing data assumed as alive in the SDD arm and dead in the control arm

We will check whether the study conclusion changes as indicated by the resulting p-values. In the case where both extremes result in the same statistical significance as the main analysis, no further tipping point analysis will be performed. In case the conclusions disagree, we will perform a tipping point search by identifying combinations where the level of significance switches from significant to non-significant (or vice versa) as described by Yan et al. [5].

3.6 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. Outcomes will be analysed using a model similar to Model 1 but using a linear model (normal distribution and identity link) instead of a logistic one (binomial distribution and logit link). The effect of the intervention will be reported as the adjusted mean difference and its 95% confidence interval. Only the main version of Model 1 using the Kenward-Roger

correction will be applied to these outcomes. We are not planning adjusted or subgroup analyses of these outcomes.

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. While in ICU, a missing daily mechanical ventilation status will be handled as follows:

1. For intermittent missing values i.e., missing values surrounded by non-missing values both before and after, we will replace the missing value with the closest (in time) non-missing value. In case the time-interval before and after are the same, the missing value will be replaced with the most pessimistic value of the two.
For missing values following the baseline assessment i.e. occurring on Day 1 onwards, the mechanical ventilation status at the time of randomisation will be used to guide the imputation. In case of a missing baseline value, the patient will be assumed to be free of mechanical ventilation at baseline. After imputation of the baseline value, missing values will be imputed by following Step 1 above.
2. For missing values preceding ICU discharge, the patient will be assumed to be free of mechanical ventilation on the day of discharge if discharged alive and not if she/he died within a day of ICU discharge. After imputation of the value on the day of discharge, missing values will be imputed by following Step 1 above.

As a sensitivity analysis, we will allocate zero 'free days' to patients who die by Day 90.

Time to alive discharge from index ICU and time to alive discharge from index hospital admission will be summarized using cumulative incidence functions treating mortality as a competing risk and with censoring at Day 90. Medians and quartiles of time to discharge will be obtained from the cumulative incidence functions. The effect of the intervention will be estimated as the hazard ratio (SDD divided by Usual care) and its 95% confidence interval obtained from a Cox model of the cause-specific hazard which estimates the risk of discharge in subjects who are still alive and have not yet been discharged [6]. To model potential within-site correlations due to stratification, we will use a shared-parameter frailty Cox model with a fixed effect of treatment and a random site effect [7].

ICU mortality will be analysed in the same way as hospital mortality using Model 1.

3.7 Analysis of microbiology and safety outcomes

3.7.1 Microbiology outcomes

Microbiology outcomes include the presence of 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 as in the second sensitivity analysis of the primary outcome (see Model (2)) and using the same weighting method.

3.7.2 Adverse events

Expected SAEs will be summarised as the number and proportion of patients experiencing at least one event. This will be done overall and by category. In addition, 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. Linear regression will be used to model the proportion of events in each cluster-period, both overall and by category as in the second sensitivity analysis of the primary outcome (see Model (2)) and using the same weighting method. A listing of all adverse events will be provided.

3.8 Analysis of unit level ecology surveillance data

The study includes five unit-level ecology surveillance periods as shown on the diagram below. During these periods, data on ecology outcomes are collected on all patients admitted to the ICU for one full week during each calendar month, regardless of the patient's ventilation status.

Pre-trial	Study Period 1		Washout	Study Period 2		Post-trial
Ecology 1		Ecology 2	Ecology 3		Ecology 4	Ecology 5

Data collected during these periods will be used to evaluate the effect of the SDD intervention on the following outcomes:

- The incidence of antibiotic resistant organisms isolated from sterile or non-sterile sites
- The incidence of all new positive blood cultures
- The incidence of new *Clostridioides difficile* infections

A flow chart will include details of subjects included in the ecology surveillance in each period (pre-trial, Study Period 1, washout, Study Period 2, and post-trial). Baseline characteristics including sex, age, time since admission and APACHE score will be described together with their vital status at discharge.

Incidence of AROs, bloodstream infections and *Clostridioides difficile* infections 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%.

- *Null hypothesis*: The proportion of patients with the *outcome* is higher with the SDD intervention than with usual care
- *Alternative hypothesis*: The proportion of patients with the *outcome* with the SDD intervention is not inferior to the one with usual care

To reject the null hypothesis and ‘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 as in the second sensitivity analysis of the primary outcome (see Model (2)) and using the same weighting method. 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. Other exploratory tests may be conducted depending on the results of these two pre-specified comparisons.

4 References

1. Holm S. A Simple Sequentially Rejective Multiple Test Procedure. *Scandinavian Journal of Statistics* 1979;6:65-70.
2. Morgan KE, Forbes AB, Keogh RH, Jairath V, Kahan BC. Choosing appropriate analysis methods for cluster randomised cross-over trials with a binary outcome. *Stat Med*. 2016 Sep 28.
3. Kenward MG, Roger JH. An improved approximation to the precision of fixed effects from restricted maximum likelihood. *Computational Statistics & Data Analysis*. 2009;53 (7):2583–2595.
4. McNeish D. Estimation Methods for Mixed Logistic Models with Few Clusters. *Multivariate Behavioral Research*. 2016; 51:6, 790-804,
5. Yan X, Lee S, Li N. Missing data handling methods in medical device clinical trials. *Journal of Biopharmaceutical Statistics*. 2009;19(6):1085–1098.
6. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. *Circulation* 2016 Feb 9;133(6):601-9
7. Ripatti S, Palmgren J. Estimation of multivariate frailty models using penalized partial likelihood. *Biometrics* 2002; 56: 1016-22

5 Proposed outputs

5.1 Tables

Table 1. Randomised patients by country and study site

Country / Site	Period 1			Period 2			Total		
	Screened	Enrolled	Discharged alive from hospital	Screened	Enrolled	Discharged alive from hospital	Screened	Enrolled	Discharged alive from hospital
Total	xxx	xxx (xx.x%)	xxx (xx.x%)	xxx	xxx (xx.x%)	xxx (xx.x%)	xxx	xxx (xx.x%)	xxx (xx.x%)
Australia	xxx	xxx (xx.x%)	xxx (xx.x%)	xxx	xxx (xx.x%)	xxx (xx.x%)	xxx	xxx (xx.x%)	xxx (xx.x%)
Site 1	xxx	xxx (xx.x%)	xxx (xx.x%)	xxx	xxx (xx.x%)	xxx (xx.x%)	xxx	xxx (xx.x%)	xxx (xx.x%)
Site 2	xxx	xxx (xx.x%)	xxx (xx.x%)	xxx	xxx (xx.x%)	xxx (xx.x%)	xxx	xxx (xx.x%)	xxx (xx.x%)
Etc.	xxx	xxx (xx.x%)	xxx (xx.x%)	xxx	xxx (xx.x%)	xxx (xx.x%)	xxx	xxx (xx.x%)	xxx (xx.x%)

Table 2. Patients included in the ecology surveillance analysis by country and study site

Country / Centre	Pre-trial	Period 1	Washout	Period 2	Post-trial	Total
Total	xxx	xxx	xxx	xxx	xxx	xxx
Australia	xxx	xxx	xxx	xxx	xxx	xxx
Site 1	xxx	xxx	xxx	xxx	xxx	xxx
Site 2	xxx	xxx	xxx	xxx	xxx	xxx
Etc.	xxx	xxx	xxx	xxx	xxx	xxx

Table 3. Baseline characteristics

Characteristics	SDD (N =)	Usual Care (N =)	Total (N =)
Age (years)	N=xxx	N=xxx	N=xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median [Q1 – Q2]	xx.x [xx.x - xx.x]	xx.x [xx.x - xx.x]	xx.x [xx.x - xx.x]
Sex	N=xxx	N=xxx	N=xxx
Male	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Female	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Admission source	N=xxx	N=xxx	N=xxx
Emergency Department	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Hospital Floor (i.e. wards)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Transfer from another ICU	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Transfer from another hospital	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
From OT following emergency surgery	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
From OT following elective surgery	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
APACHE III Diagnosis	N=xxx	N=xxx	N=xxx
Non-operative diagnoses			
Diagnosis 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Diagnosis 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Diagnosis 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
...	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Operative diagnoses			
Diagnosis 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Diagnosis 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Diagnosis 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
...	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
APACHE II/III score	N=xxx	N=xxx	N=xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median [Q1 – Q2]	xx.x [xx.x - xx.x]	xx.x [xx.x - xx.x]	xx.x [xx.x - xx.x]
Time between ICU admission and enrolment (hours)	N=xxx	N=xxx	N=xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median [Q1 – Q2]	xx.x [xx.x - xx.x]	xx.x [xx.x - xx.x]	xx.x [xx.x - xx.x]
Diabetes	N=xxx	N=xxx	N=xxx
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Immunosuppressed	N=xxx	N=xxx	N=xxx
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Systemic steroids	N=xxx	N=xxx	N=xxx
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Oral chlorhexidine	N=xxx	N=xxx	N=xxx
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
On IV antibiotics at time of enrolment	N=xxx	N=xxx	N=xxx
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
IV antibiotics received >48 hours prior enrolment	N=xxx	N=xxx	N=xxx
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Programming note: refer to data completion manual for list of operative and non-operative diagnoses

Table 4. SDD antibiotics summary

Study day	SDD Oral Paste # doses	SDD Gastric Suspension # doses	SDD Intervention Antibiotic # doses
4-day SDD course received (Y/N)	xx/xxx (xx.x%)	xx/xxx (xx.x%)	xx/xxx (xx.x%)
Number of days with at least one dose (days 1-90)	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)
Total number of doses (days 1-90)	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)
Day 1	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)
Day 2	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)
Day 3	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)
Day 4	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)
Day 5	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)
Day 6	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)
Day 7	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)

Programming note: for daily data, only count patients in ICU on the corresponding day

Table 5. Cumulative defined daily doses of antibiotics (days 1-90)

Study day	SDD (N=)	Usual Care (N=)
Any antibiotic	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)
Penicillins	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)
Carbapenems	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)
Cephalosporins	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)
Quinolones	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)
Aminoglycosides	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)
Lincosamides	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)
Anti-fungals	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)
Others	N mean (SD) Q1 (Q2-Q3)	N mean (SD) Q1 (Q2-Q3)

Table 6. Microbiology outcomes

	SDD arm (N =)	Usual Care (N =)	p-value
New antibiotic resistant organism	xxx/XXX (xx%)	xxx/XXX (xx%)	0.xxx
New bloodstream infection	xxx/XXX (xx%)	xxx/XXX (xx%)	0.xxx
Positive for <i>Clostridioides difficile</i> whilst in ICU	xxx/XXX (xx%)	xxx/XXX (xx%)	0.xxx
Blood cultures obtained	xxx/XXX (xx%)	xxx/XXX (xx%)	
Organism 1	xxx (xx%)	xxx (xx%)	
Organism 2	xxx (xx%)	xxx (xx%)	
Organism 3	xxx (xx%)	xxx (xx%)	
Etc. (up to 10 th most frequent)	xxx (xx%)	xxx (xx%)	
Non-blood ARO cultures obtained	xxx/XXX (xx%)	xxx/XXX (xx%)	
Organism 1	xxx (xx%)	xxx (xx%)	
Organism 2	xxx (xx%)	xxx (xx%)	
Organism 3	xxx (xx%)	xxx (xx%)	
Etc. (up to 10 th most frequent)	xxx (xx%)	xxx (xx%)	

Programming note: under each category (blood and non-blood), list the 10 most commonly identified organisms in decreasing order of frequency then group all remaining ones into the “other” category. See Section 3.7.1 for statistical details.

Table 7. Protocol deviations

Protocol violations	SDD (N =)	Usual Care (N =)
Enrolment of ineligible patient	nVIOL nPT (xx.x%)	nVIOL nPT (xx.x%)
SDD intervention not started within 6 hours post enrolment	nVIOL nPT (xx.x%)	nVIOL nPT (xx.x%)
SDD IV AB not administered	nVIOL nPT (xx.x%)	nVIOL nPT (xx.x%)
SDD oral paste not administered	nVIOL nPT (xx.x%)	nVIOL nPT (xx.x%)
SDD gastric suspension not administered	nVIOL nPT (xx.x%)	nVIOL nPT (xx.x%)
Additional dose of SDD oral paste administered	nVIOL nPT (xx.x%)	nVIOL nPT (xx.x%)
Additional dose of SDD gastric suspension administered	nVIOL nPT (xx.x%)	nVIOL nPT (xx.x%)
Incomplete dose of SDD oral paste administered	nVIOL nPT (xx.x%)	nVIOL nPT (xx.x%)
Incomplete dose of SDD gastric suspension administered	nVIOL nPT (xx.x%)	nVIOL nPT (xx.x%)
Inappropriate stopping of intervention prior to extubation	nVIOL nPT (xx.x%)	nVIOL nPT (xx.x%)
Other	nVIOL nPT (xx.x%)	nVIOL nPT (xx.x%)

Table 8. Clinical outcomes

Outcome	Raw estimates ¹			Model estimates		Model estimates	
	SDD (N =)	Usual Care (N =)	Total (N =)	(unadjusted)		(adjusted ²)	
				OR or MD (95% CI)	P-value	OR or MD (95% CI)	P-value
All cause hospital mortality							
Hierarchical model with KR	xx/xxx (xx.x%)	xx/xxx (xx.x%)	xx/xxx (xx.x%)	xx.x (xx.x to xx.x)	0.xxx	xx.x (xx.x to xx.x)	0.xxx
<i>Worst-best imputation</i>	xx/xxx (xx.x%)	xx/xxx (xx.x%)	xx/xxx (xx.x%)	xx.x (xx.x to xx.x)	0.xxx		
<i>Best-worst imputation</i>	xx/xxx (xx.x%)	xx/xxx (xx.x%)	xx/xxx (xx.x%)	xx.x (xx.x to xx.x)	0.xxx		
Hierarchical model without KR	xx/xxx (xx.x%)	xx/xxx (xx.x%)	xx/xxx (xx.x%)	xx.x (xx.x to xx.x)	0.xxx	xx.x (xx.x to xx.x)	0.xxx
Cluster-level linear regression	N Mean (SD)	N Mean (SD)	N Mean (SD)	xx.x (xx.x to xx.x)	0.xxx		
Secondary outcomes							
Death within ICU	xx/xxx (xx.x%)	xx/xxx (xx.x%)	xx/xxx (xx.x%)	xx.x (xx.x to xx.x)	0.xxx		
Days alive and free of MV	N Mean (SD)	N Mean (SD)	N Mean (SD)	xx.x (xx.x to xx.x)	0.xxx		
<i>With death = 0 days</i>	N Mean (SD)	N Mean (SD)	N Mean (SD)	xx.x (xx.x to xx.x)	0.xxx		
Days alive and out of ICU	N Mean (SD)	N Mean (SD)	N Mean (SD)	xx.x (xx.x to xx.x)	0.xxx		
<i>With death = 0 days</i>	N Mean (SD)	N Mean (SD)	N Mean (SD)	xx.x (xx.x to xx.x)	0.xxx		
Days alive and out of hospital	N Mean (SD)	N Mean (SD)	N Mean (SD)	xx.x (xx.x to xx.x)	0.xxx		
<i>With death = 0 days</i>	N Mean (SD)	N Mean (SD)	N Mean (SD)	xx.x (xx.x to xx.x)	0.xxx		

1) Raw estimates: numerator/denominator and % for binary outcomes ; n mean (SD) Median (Q1 – Q3) for continuous outcomes

2) Model estimates: obtained using a hierarchical logistic (linear for continuous outcomes) regression with a fixed effect indicating the group allocation during the period, a random cluster effect and a random cluster-period effect

Example of SAS code for logistic model with random cluster effect and random cluster-period effect:

```
proc glimmix data=SUDDICU;
class      CENTRE PATIENT PERIOD TREATMENT;
model      DEATH = TREATMENT PERIOD      / dist=binomial link=logit solution covb oddsratio DDFM=KENWARDROGER2;
random     CENTRE                        / g;
random     PERIOD(CENTRE)                / g;
run;
```

Table 9. Summary of adverse events

Adverse Events	SDD (N =)	Usual Care (N =)	P-value
Adverse Drug Reactions	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	0.xx
Serious Adverse Drug Reactions	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	0.xx
Suspected Unexpected Serious Adverse Reactions	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	0.xx
Serious adverse events	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	0.xx
Serious events			
Resulted in death	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Life threatening	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Requires prolonged hospitalisation	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Results in persistent or severe disability/incapacity	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Results in congenital anomaly/birth defect	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Medically significant	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Relationship to study treatment			
Not related	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Unlikely related	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Possibly related	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Probably related	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	
Definitely related	nEVT nPT(xx.x%)	nEVT nPT(xx.x%)	

Programming note:

AEs will be summarised as the number and proportion of patients experiencing at least one event. In addition, except for deaths, the total number of events will be reported. Proportions of patients with at least one SAEs 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, both overall and by category. The regression will be weighted proportionally to the inverse of the binomial variance for each cluster-period.

Table 10. Causes of death

Cause	SDD (N =)	Usual Care (N =)
Proximate cause of death	N=XXX	N=XXX
Most common cause #1	nnn xx%	nnn xx%
Most common cause #2	nnn xx%	nnn xx%
Etc.		
Most common cause #10	nnn xx%	nnn xx%
All other causes	nnn xx%	nnn xx%
Underlying causes of death	N=XXX	N=XXX
Most common cause #1	nnn xx%	nnn xx%
Most common cause #2	nnn xx%	nnn xx%
Etc.		
Most common cause #10	nnn xx%	nnn xx%
All other causes	nnn xx%	nnn xx%

Programming notes:

- Refer to data completion manual to retrieve categories.
- Order causes of death by descending frequency.
- Do not list categories with 0 deaths.
- Use number who died
- Depending on the distribution of deaths, we may choose to only report the x (e.g. 10) most common in the publication; however, the original table should include all causes with at least one patient.

Table 11. AEs by categories

Cause	SDD (N =)	Usual Care (N =)
SAE category 1		
AE subcategory #1	nnn xx%	nnn xx%
AE subcategory #2	nnn xx%	nnn xx%
Etc.		
SAE category 2		
AE subcategory #1	nnn xx%	nnn xx%
AE subcategory #2	nnn xx%	nnn xx%
Etc.		

Programming notes:

- Order categories and subcategories by descending frequency.
- Do not list categories with 0 patients.
- Use all patients enrolled as the denominator

Table 12. Ecology results

Mean proportion (SE)				
Outcome / Period	SDD → Usual Care	Usual Care → SDD	Mean difference (95% CI)	P-value
Antibiotic resistant organisms				
Period 1	0.xx (0.xx)	0.xx (0.xx)		
Period 2/3	0.xx (0.xx)	0.xx (0.xx)		
Change	0.xx (0.xx)	0.xx (0.xx)	0.xxx (0.xxx to 0.xxx)	0.xxxx
Period 3	0.xx (0.xx)	0.xx (0.xx)		
Period 4/5	0.xx (0.xx)	0.xx (0.xx)		
Change	0.xx (0.xx)	0.xx (0.xx)	0.xxx (0.xxx to 0.xxx)	0.xxxx
Bloodstream infections				
Period 1	0.xx (0.xx)	0.xx (0.xx)		
Period 2/3	0.xx (0.xx)	0.xx (0.xx)		
Change	0.xx (0.xx)	0.xx (0.xx)	0.xxx (0.xxx to 0.xxx)	0.xxxx
Period 3	0.xx (0.xx)	0.xx (0.xx)		
Period 4/5	0.xx (0.xx)	0.xx (0.xx)		
Change	0.xx (0.xx)	0.xx (0.xx)	0.xxx (0.xxx to 0.xxx)	0.xxxx
Clostridioides difficile infections				
Period 1	0.xx (0.xx)	0.xx (0.xx)		
Period 2/3	0.xx (0.xx)	0.xx (0.xx)		
Change	0.xx (0.xx)	0.xx (0.xx)	0.xxx (0.xxx to 0.xxx)	0.xxxx
Period 3	0.xx (0.xx)	0.xx (0.xx)		
Period 4/5	0.xx (0.xx)	0.xx (0.xx)		
Change	0.xx (0.xx)	0.xx (0.xx)	0.xxx (0.xxx to 0.xxx)	0.xxxx

Programming note: all numbers in this table to be estimated from model described in Section 3.8

5.2 Figures

Figure 1. CONSORT diagram

Figure 2. Subject disposition

Stacked bar graph showing, for each day (up to Day 90), the proportion of patients according to the 6 following mutually exclusive categories:

- 1) In ICU and receiving antibiotics
- 2) In ICU and alive but not receiving antibiotics
- 3) Discharged alive from ICU, but still in hospital
- 4) Discharged alive from hospital (assumed to remain alive until Day 90),
- 5) Dead
- 6) Unknown status

The figure will consist a stacked bar chart with one bar per day and, within each bar, the proportion of patients in each category (summing to 100%). It will include 4 panels: (1. top-left) Period 1 for sites under SDD, (2. bottom left) Period 1 for sites under Usual Care, (3. top-right) Period 2 for sites under Usual Care, (4. bottom-right) Period 2 for sites under SDD.

Figure 3. Overall antibiotic use in Daily Defined Doses (days 1-90)

Programming note: show mean number of DDDs and 95% CI for each day by intervention arm. Show denominators every 10 days. Do for overall antibiotic use (combining any SDD and non-SDD antibiotics).

Figure 4. Kaplan–Meier plot of time to death

Programming note: add number at risk every 10 days, median, quartiles, hazard ratio, 95% CI and P value from the Cox model.

Figure 5. Cumulative incidence function of time to ICU discharge

Programming note: add number at risk every 10 days, median, quartiles, hazard ratio, 95% CI and P value from the Cox model.

Figure 6. Cumulative incidence function of time to hospital discharge

Programming note: add number at risk every 10 days, median, quartiles, hazard ratio, 95% CI and P value from the Cox model.

Figure 7. Forest plot for subgroup analysis of hospital mortality

Figure 8. Incidence of AROs during each ecology surveillance period

Programming note: One plot reporting the proportion of patients with ARO with once cell per ecology period (pre-trial, x-cRCT Period 1, inter-period gap, x-cRCT Period 2, post-trial) and per group (2 groups of clusters

according to the randomisation sequence) and period. It would be good to use colors to indicate the incidence level. See dummy example below:

	Pre-trial (baseline)	Period 1	Washout	Period 2	Post-trial
Group 1 (N=10)	10%	20%	17%	12%	10%
Group 2 (N=10)	11%	10%	11%	21%	16%

Group 1: clusters randomised to SDD (Period 1) → Control (Period 2)

Group 2: clusters randomised to Control (Period 1) → SDD (Period 2)

Figure 9. Incidence of bloodstream infections during each ecology surveillance period

Programming note: similar format as Figure 8

Figure 10. Incidence of *Clostridioides difficile* infections during each ecology surveillance period

Programming note: similar format as Figure 8

5.3 Listings

Listing 1. Listing of adverse drug reactions

Site ID	Patient ID	Onset date	Event description	Type of Event	Serious category	Relation to study drug	Outcome
6	6001	27-Sep-10	xxx	ADR		Possibly related	Other
	6008	20-Sep-10	yyyy	SADR	Resulted in death	Possibly related	Resolved with treatment
	6052	26-Jun-11	zzzzzzzz	SUSAR	Life threatening	Possibly related	Resolved with treatment
	6054	21-Jun-11	hhhhhhhhhh	SUSAR	Results in congenital anomaly/birth defect	Probably related	Resolved with treatment

Listing 2. Protocol deviations

Site ID	Patient ID	Date	Type of deviation	Description	Corrective action taken
6	6001	27-Sep-10			
	6008	20-Sep-10			
	6052	26-Jun-11			
	6054	21-Jun-11			