A pilot cluster randomised clinical trial of the use of selective gut decontamination in critically ill children (Paediatric Intensive Care and Infection Control)

Statistical Analysis Plan, Version 1.0, 29/04/2022

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Roles and responsibilities

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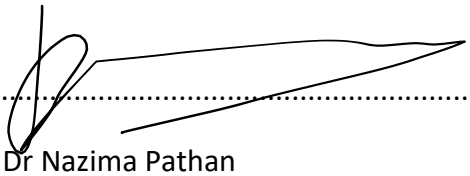

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Version history

Version number	Date	Timing	Summary of main changes from previous versions
1.0	29/04/2022	Following recruitment, prior to data lock	N/A

Contents

Abbreviations

CI	Chief Investigator
DMEC	Data Monitoring and Ethics Committee
ETT	Endotracheal tube
HCAI	Health-care Associated Infection
HTA	Health Technology Assessment
ICNARC	Intensive Care National Audit and Research Centre
ICU	Intensive Care Unit
NIHR	National Institute for Health Research
NHS	National Health Service
PICANet	Paediatric Intensive Care Audit Network
PICU	Paediatric Intensive Care Unit
PICS-SG	Paediatric Intensive Care Society Study Group
PPI	Patient and Public Involvement
PI	Principal Investigator
cRCT	Cluster-randomised Clinical Trial
RCT	Randomised Clinical Trial
SDD	Selective Decontamination of the Digestive Tract
SOP	Standard Operating Procedures
TMG	Trial Management Group
TSC	Trial Steering Committee
VAP	Ventilator Acquired Pneumonia

1. Introduction

1.1 Background and rationale

In critically ill children, healthcare-associated infections (HCAI) are a major cause of morbidity and mortality, with an incidence of 7-14%[1-5]. HCAIs can develop either as a direct result of healthcare interventions such as medical or surgical treatment, or from being in contact with a healthcare setting. HCAIs can be caused by opportunistic microorganisms, residing in the oral cavity and gastrointestinal tract, spreading to other organ systems directly or haematogenously[,5]. Critically ill children are at increased risk due to their relatively immature immune systems, as well as the presence of invasive devices such as urinary catheters, vascular lines and endotracheal tubes.

Evidence from adult intensive care studies suggests that using Selective Decontamination of the Digestive tract (SDD) alongside standard infection control measures reduces mortality and ventilator-associated pneumonia (VAP)[6,7]. It has been shown that the use of SDD influences the microbiological ecology of the unit, thereby reducing incidence of HCAIs in both exposed and non-exposed patients. Despite this, SDD has not been routinely adopted due to concerns that it may promote antimicrobial resistance[6,8]. Recent ecological studies conducted in adult intensive care have found that SDD was associated with a reduction in antibiotic utilisation[9-13]; two large cluster Randomised Controlled Trials (cRCT) are in progress to further evaluate the clinical effects of SDD in adult intensive care (R-GNOSIS , Clinicaltrials.gov Identifier: NCT02208154 and SuDICCU , Clinicaltrials.gov Identifier: NCT02389036).

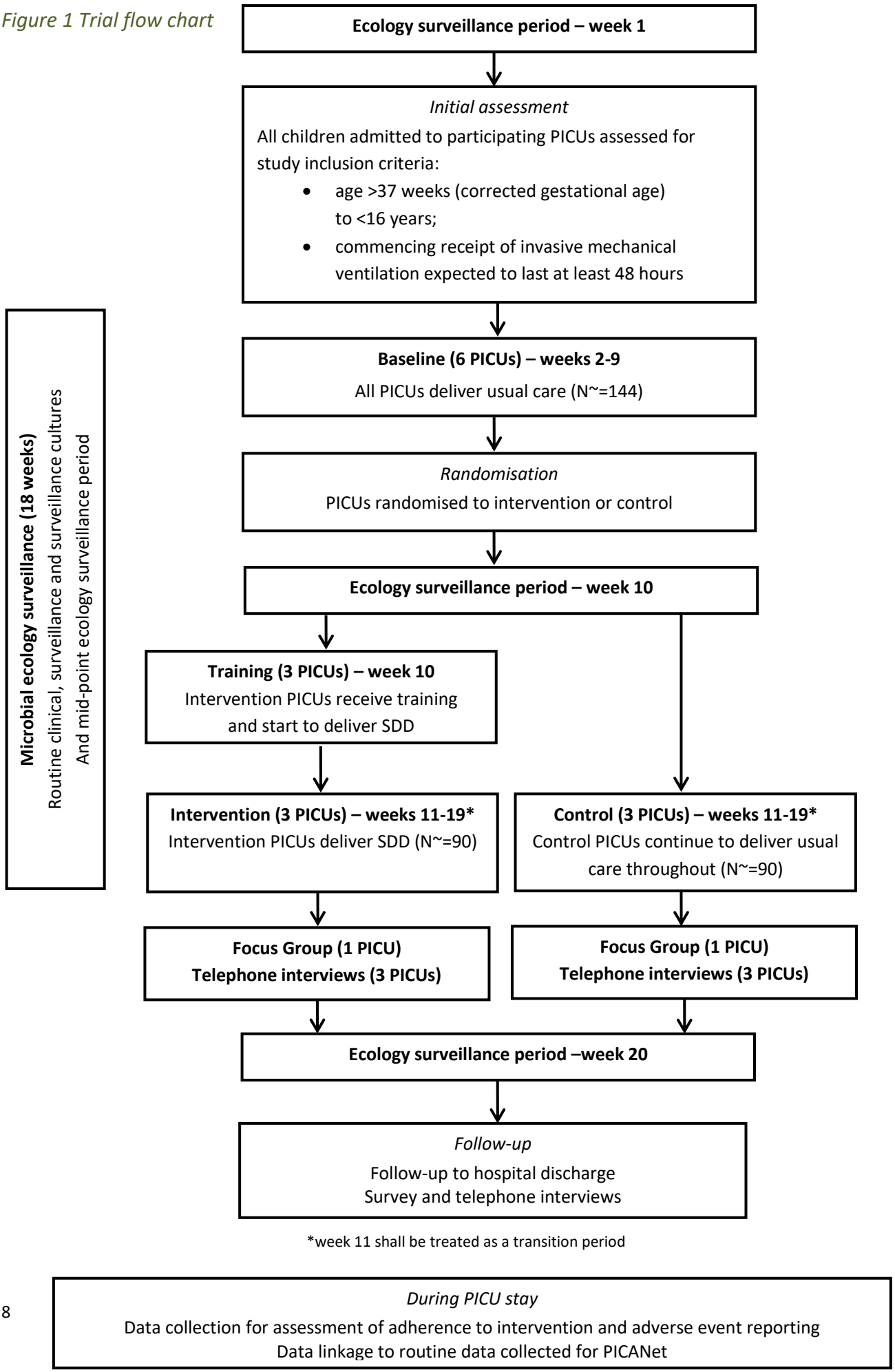
SDD has not been compared directly with modern infection control protocols in the Paediatric Intensive Care (PICU) population. The only trial data suggest a reduction in incidence of VAP but not mortality, however the study was underpowered and the observed mortality was very low[14]. Therefore, a clinical trial comparing SDD with standard infection control methods is required. Before this and given the paucity of data describing the use of SDD in PICU, it is imperative to establish whether a large, multicentre cRCT is feasible.

PICniC is a feasibility study designed to determine whether it is possible to conduct a cRCT of SDD in critically ill children who are likely to be ventilated for $\geq$48 hours, and to explore and test the acceptability of key components of the study to healthcare professionals and families of patients. The flow chart of the study is illustrated in *Figure 1*.

The purpose of this Statistical Analysis Plan (SAP) is to outline the planned analyses to be carried out to support the completion of the trial manuscripts for publication in the scientific literature and to aid the decision as to whether a definitive trial is feasible. Additional exploratory analyses, including in relation to the samples collected, which may not have been identified in this SAP, may also be performed. Any unplanned analyses not identified in this SAP will be clearly outlined as such in the respective report/manuscript.

This SAP has been agreed in advance of inspecting the outcome data for the Trial, so that data-derived decisions in the analyses are avoided. This SAP has been prepared in accordance with published guidelines.[15]

Figure 1 Trial flow chart



1.2 Aim and objectives

The aim of this study is to determine whether it is feasible to conduct a multicentre trial in critically ill children comparing SDD with standard infection control procedures

The objectives are:

Pilot cRCT

i. To test the ability to randomise PICUs to either control or intervention

ii. To test the willingness and ability of healthcare professionals to screen and recruit eligible children

iii. To estimate the recruitment rate of eligible children

iv. To test adherence to the SDD protocol

v. To test the procedures for assessing and collecting selected clinical and ecological outcomes and for adverse event (AE) reporting

vi. To assess the generalisability of the study results to all PICUs using the Paediatric Intensive Care Audit Network (PICANet)

Mixed-methods study

Perspectives of PICU healthcare professionals:

i. To assess the acceptability of implementation of the SDD intervention, recruitment and consent procedures

ii. To assess the acceptability of collecting data to assess the selected clinical and ecological data

iii. To assess the acceptability of the SDD intervention and confirm interest in participation in a definitive trial in the wider PICU community

Perspectives of parents/guardians of recruited patients:

i. To review and explore the acceptability of a definitive trial that includes the SDD intervention

ii. To test the acceptability of the recruitment and consent procedures for the definitive trial, including all proposed information materials

iii. To review and explore selection of important, relevant, patient-centred primary and secondary outcomes for a definitive trial

2. Study methods

2.1 Trial Design

External pilot, parallel group cRCT with integrated mixed-methods study.

2.2 Setting

Six PICUs with a diverse geographical/demographic population representative of national PICU activity and size, which will be referred to as 'site(s)'

2.3 Randomisation

Sites will be randomised by the trial statistician using computer-based randomisation. Sites will be notified of their randomisation during the 8-week baseline period. Sites will be cluster randomised to either usual care or intervention (1:1) during the first 8 weeks of recruitment to allow time for training and transition in the intervention arm, which will occur in weeks 10 and 11.

2.4 Sample size

The PICnIC Pilot Study is set up to test the feasibility of the protocol to recruit eligible patients. Therefore, there is no primary outcome to be compared between the two groups and, hence, a usual power calculation to determine sample size is not appropriate. Instead, the sample size has been determined to be adequate to estimate critical parameters to be tested to a necessary degree of precision. Based on available data from PICANet, it is anticipated that the participating sites will see approximately 4.5 eligible children per week, therefore the anticipated recruitment rate is 3 children per PICU per week providing a total of approximately 324 children in 18 weeks, of which 90 would receive the intervention.

3. Statistical Principles

3.1 Confidence intervals and p-values

Noting that this is a pilot cRCT and not powered to detect differences in outcomes, analyses will be treated as exploratory and will be mainly descriptive. P values will not be calculated or quoted. Effect estimates will be reported with 95% confidence intervals.

3.2 Adherence and protocol deviations

The number and percentage of patients found to have been ineligible will be reported in each treatment group, together with the reasons for ineligibility (inclusion criteria not met or exclusion criteria met).

The number and percentage of patients with at least one protocol deviation in the SDD intervention group will be reported, and the total number of such deviations. A deviation is defined as any of the following:

- SDD treatment starts > 6hrs after being identified as eligible

- SDD treatment starts within 6hrs of being identified as eligible but continues for more than 30 days (treatment period) or finishes before the patient is extubated / no longer mechanically ventilated
- One or both SDD treatments were not given, and patient was mechanically ventilated.
- Dose was wrongly administered (4 per day, every 6 hours while intubated)

3.3 Analysis Population

All patients will be included in the intention to treat (ITT) population. The patients will be analysed according to the group they were randomised to (based on site and date of recruitment), irrespective of whether the treatment allocated was received.

4. Trial Population

4.1 Screening data

Screening logs will be used for all participant sites to record all patients who are admitted or accepted for admittance to critical care. The following summaries will be presented:

- Number and % of patients who did not meet inclusion criteria (see section 4.2), overall and by criteria
- Of the patients who met the inclusion criteria, number and % who met exclusion criteria (see section 4.2), overall and by criteria.
- Of the eligible patients (i.e. met inclusion criteria and did not meet exclusion criteria), number and % not recruited, overall and by reason (if known)

4.2 Eligibility

The eligibility criteria are as follows:

Inclusion criteria

- >37 weeks corrected gestational age to <16 years
- Receiving mechanical ventilation, expected to last at least 48 hours
- Expected to remain on mechanical ventilation until the day after tomorrow (from time of screening)

Exclusion criteria

- Known allergy, sensitivity or interaction to polymyxin E (colistin), tobramycin or nystatin
- Known to be pregnant
- Death perceived as imminent

4.3 Recruitment

A CONSORT flow diagram[i] will be used to summarise the number and % of patients who were:

- assessed for eligibility at screening
- eligible at screening
- ineligible at screening (with reasons)
- eligible and included
- eligible but not included (with reasons)
- lost to follow-up (with reasons)
- included in the primary analysis
- excluded from the primary analysis (with reasons)

4.4 Consent

We will not seek individual patient consent for administration of the intervention. The intervention will be started as part of 'standard practice' in the participating PICUs and initiation of the treatment is time sensitive. We will not seek individual patient consent for routine data collection or for additional, trial specific data. We will seek individual consent for collection of additional samples. We will not seek individual patient consent for samples that are collected on admission to the unit as a part of routine care. A full description of the individual patient consent is given in the trial protocol.

4.5 Withdrawal/follow-up

Data up to the point of withdrawal will be included in the data analysis.

4.6 Baseline patient characteristics

Baseline data is collected at critical care admission via data linkage to PICANet, and directly via trial CRF. The following baseline demographic and clinical data will be summarised overall and by allocated treatment group in each of the two time periods, but not subjected to statistical testing:

- Demographics
    - Age – median (IQR)
    - Age group (< 1 year, 1 year, 2 to 4 years, 5 to 9 years, 10 to 16 years) – number and %
    - Sex (male, female) – number and %
    - Weight– median (IQR)
- Acute severity
    - PIM2r score – median (IQR)
    - Acute diagnosis (main reason for PICU admission) – number and %
    - Physiology in the first 24 hours from admission (raw PIM2r score data)– mean (SD) or median (IQR)

5. Trial analysis

5.1 Outcome measures

The outcomes of this study measure the respective objectives stated in section 1.2.1.1 and will be focused on assessing the feasibility of a larger scale definitive study.

The ability to randomise PICUs to either control or intervention will be assessed by the successful random assignment of three PICUs to the intervention without delay to subsequent phases of the trial.

The willingness and ability of healthcare professionals to screen and recruit eligible children will be assessed by the proportion of eligible children recorded on study screening logs successfully recruited to the pilot cRCT and the reported reasons for non-recruitment.

The potential recruitment rate for a future definitive cRCT trial of SDD-enhanced infection control in eligible children will be estimated by combining the proportion of eligible children recruited to the pilot cRCT with the size of the potentially eligible population (estimated from nesting the screening log data from participating PICUs within the national UK PICU data from PICANet).

Adherence to the SDD protocol will be assessed by the proportion of eligible children allocated to the intervention receiving (1) both elements and (2) each individual element of the SDD intervention, the number of days on which these elements were received relative to days eligible for the SDD intervention and the reported reasons for nonadherence.

Procedures for assessing and collecting selected clinical and ecological outcomes and for AE reporting will be assessed by the proportion of children with complete data for these outcomes including, for ecological outcomes, the proportion consenting to additional study specific sample collection.

Generalisability of the study results to all UK PICUs will be assessed by comparing baseline characteristics and outcomes for children recruited to the pilot cRCT with data from all potentially eligible children (receiving invasive mechanical ventilation for at least three calendar days) within participating PICUs and within all UK PICUs (from PICANet).

With the aim of understanding potential patient-centred primary and secondary outcome measures for the definitive cRCT, the following potential outcome measures will be reported:

- Healthcare associated infection (confirmed/presumed) – number and %;
- Any positive microbiology result – number and %;
- Antibiotic use (patient received any antibiotics during this admission to PICU) – number and %;
- Percentage of days antibiotic free (from confirming eligibility to PICU discharge) – median (IQR);
- PICU mortality: death before PICU discharge – number and %;
- Hospital mortality: death before hospital discharge – number and %;

- Mortality within 30 days post enrolment: from the patients' survival status as of 30 days post enrolment on the CRF– number and %;
- Length of hospital stay: days from confirming eligibility to hospital discharge – mean (SD) and median (IQR);
- Length of stay in PICU: hours from confirming eligibility to PICU discharge – mean (SD) and median (IQR);
- Duration of mechanical ventilation: days from confirming eligibility to date of first successful extubation – mean (SD) and median (IQR).

5.2 Analysis methods

Recruitment to the pilot cRCT will be presented as a rate (see section 4.5) over the two recruitment periods and per week, overall and per site. Potential reasons for variation in recruitment rates will be explored.

Baseline demographic and clinical data will be summarised for the ITT population overall and for each of the two treatment groups as described in section 4.5. In addition, patients' characteristics for children recruited to the pilot cRCT will be compared with those for potentially eligible children within participating PICUs and within all UK PICUs. There will be no statistical testing for any of the summary measures whilst comparing the baseline variables. Outcomes measures will be reported as indicated above by period, by treatment group when applicable, and by site.

Data completeness of clinical and ecological outcomes and for AE reporting will be summarised.

The characteristics (proportion or mean and standard deviation, and ICC) of potential outcome measures will be estimated and reported from the observed data from control PICUs and from the pre-intervention period for intervention PICUs. As a pilot cRCT, there will be no statistical testing for any of the summary measures. Comparisons between groups will be used to estimate the potential magnitude of the treatment effect but p values will not be calculated or quoted. To account for cluster randomisation, we will use multilevel logistic or generalised linear regressions in the above analyses. Patients who withdrew or withheld consent from data collection will not be included in these analyses.

To determine the most appropriate primary outcome for a definitive trial, for all potential outcome measures the number of patients with complete data in each treatment group will be reported. For measures requiring data linkage with routine data sources (PICANet), the proportion of successfully linked records will be reported.

6. Handling of missing data

The proportion of variables included in the analyses that are missing will be reported.

7. Safety

The numbers of serious adverse events and number and percentage of patients experiencing each serious adverse event following enrolment until critical care discharge will be reported in each treatment group and time period and by site.

8. Statistical software

The analyses will be conducted in Stata/SE version 16.0.

9. Mixed methods study

Details of analysis and reporting for the mixed methods study will be documented separately.

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11. Appendix – proposed tables and figures

Table 1 Number of patients screened, eligible, recruited, consented, withdrawn, and analysed, by treatment group and time period

Variables	Intervention sites		Control sites		Total
	Period One	Period Two	Period One	Period Two	
Number screened, N	XX	XX	XX	XX	XX
Number of eligible patients, n (% of screened)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Number of recruited patients, n (% of eligible)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Consent obtained, n (% of recruited)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Refused consent, n (% of recruited)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Withdrawal, n (% of consented)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Number of patients analysed n (% of recruited)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)

n: Number of patients; %: Percentage; N: Total number of patients

Table2a: Number of patients screened and recruited per week and by site (period 1)

Site	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Overall	Average enrolment per week
Site A										
Site B										
Site C										
Site D										
Site E										
Site F										

Table 2b: Number of patients screened and recruited per week and by site (period 2)

Site	Week 11	Week 12	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Overall	Average enrolment per week
Site A											
Site B											
Site C											
Site D											
Site E											
Site F											

Table 3: Baseline demographic and clinical variables by treatment group and time period

Variables	Intervention sites		Control sites		Total
	Period One	Period Two	Period One	Period Two	
	N = XX	N = XX	N = XX	N = XX	N = XXX
Age (years), median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)
Age group, n (%)					
< 1 year	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
1 year	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
2 to 4 years	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
5 to 9 years	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
10 to 16 years	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Sex, n (%)					
Female	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Male	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Weight (kg), median (IQR)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)
PIM3 score, median (IQR)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)
Main reason for PICU admission, n (%)					
Apnoea	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Asthma/wheeze	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Bronchiolitis	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Cardiac	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Lung disease	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Neurological	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Neuromuscular disorder	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Sepsis	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Upper airway obstruction	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Baseline physiology, median (IQR)					
Systolic blood pressure (mmHg)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)
PaO_2/FiO_2 (kPa)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)
Base excess (mmol/L)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)

n: Number of patients; %: Percentage of patients; N: Total number of patients;
SD: Standard deviation; IQR: Inter-quartile range

Table 4: Samples by time period

	Ecology Surveillance (week 1)	Ecology Surveillance (week 10)	Ecology Surveillance (week 20)	Period 1	Period 2
Week 1					
Sample 1 (admission)					
Pt eligible for sample, n					
Sample taken, n (%)					
Sample not taken, n (%)					
Sample taken on day of admission, n (%)					
Sample 2					
Pt consented for sample 2 with data, n					
Sample 2 taken, n (%)					
Sample 2 not taken, n (%)					
Reasons for sample 2 not taken					
- NA					
- Missed					
- Clinical					
Pt refused consent for samples but stayed in PICU more than 4 days since admission sample, n					
Of those refused, additional sample 2 taken as part of routine care, n					
Week 2					
Sample 1					
Pt consented for sample 1 with data, n					
Sample 1 taken, n (%)					
Sample 1 not taken, n (%)					
Reasons for sample not taken					
- NA					

- Missed					
- Clinical					
Pt refused consent for samples but stayed in PICU more than 8 days since admission, n					
Of those refused consent, additional sample 1 taken as part of routine care, n					
Sample 2					
Pt consented for sample 2 with data, n					
Sample 2 taken, n (%)					
Sample 2 not taken, n (%)					
Reasons for sample 2 not taken					
- NA					
- Missed					
- Clinical					
Pt refused consent for samples but stayed in PICU more than 12 days since admission, n					
Of those refused consent, additional sample 2 taken as part of routine care, n					

Table 5: Adherence to protocol

	SDD	SDD Oral paste	SDD Gastric Suspension
Eligible children treated	XX		
Number of children receiving SDD any, n (% of recruited)	XX (XX.X)		
Number of children started treatment within 6 hrs of being identified as eligible, n (% of recruited)	XX (XX.X)		
Number of children started treatment within 6 hrs of being identified as eligible but continue for more than 30 days (treatment period), n (% of recruited)	XX (XX.X)		
Number of children finished treatment before the patient is extubated / no longer mechanically ventilated, n (% of recruited)	XX (XX.X)		
Number of children with at least one episode of non-adherence[1], n (% of recruited)	XX (XX.X)		
Number of doses administered		XX	XX
Number of doses administered per patient, median (IQR)		XX (XX, XX)	XX (XX, XX)
Doses expected to be given[2], n		XX	XX
Expected doses not given, n (%)		XX (XX.X)	XX (XX.X)
Reasons for doses not given, n (%)			
Reason 1		XX (XX.X)	XX (XX.X)
Reason 2 etc		XX (XX.X)	XX (XX.X)

n: Number of patients; %: Percentage of patients.[1] At least one dose per day not given; [2] Patient ventilated (based on CRF data).

Table 6: Adverse events (during Period Two) by treatment group

	Intervention sites	Control sites
Number of patients	**XX**	**XX**
Total number of adverse events (AEs)	XXX	XXX
Number (%) of patients experiencing one or more AEs	XX (XX.X)	XX (XX.X)
Specified AEs, n (%)		
NG tube blockage	XX (XX.X)	XX (XX.X)
Choking on paste	XX (XX.X)	XX (XX.X)
Allergic reaction to SDD	XX (XX.X)	XX (XX.X)
Total number of serious adverse events (SAEs)	XXX	XXX
Number (%) of patients experiencing one or more SAEs	XX (XX.X)	XX (XX.X)

n: Number of patients; %: Percentage of patients

Table 7: Generalisability of study data – baseline characteristics and outcomes

Variables	Recruited patients	Potentially eligible patients in study PICUs	Potentially eligible patients in all UK PICUs
	N = XX	N = XX	N = XXX
Age (years), median (IQR)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)
Age group, n (%)			
< 1 year	XX (XX.X)	XX (XX.X)	XX (XX.X)
1 year	XX (XX.X)	XX (XX.X)	XX (XX.X)
2 to 4 years	XX (XX.X)	XX (XX.X)	XX (XX.X)
5 to 9 years	XX (XX.X)	XX (XX.X)	XX (XX.X)
10 to 16 years	XX (XX.X)	XX (XX.X)	XX (XX.X)
Sex, n (%)			
Female	XX (XX.X)	XX (XX.X)	XX (XX.X)
Male	XX (XX.X)	XX (XX.X)	XX (XX.X)
Weight (kg), median (IQR)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)
PIM2r score, median (IQR)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)
Primary reason for PICU admission, n (%)			
Apnoea	XX (XX.X)	XX (XX.X)	XX (XX.X)
Asthma/wheeze	XX (XX.X)	XX (XX.X)	XX (XX.X)
Bronchiolitis	XX (XX.X)	XX (XX.X)	XX (XX.X)
Cardiac	XX (XX.X)	XX (XX.X)	XX (XX.X)
Lung disease	XX (XX.X)	XX (XX.X)	XX (XX.X)
Neurological	XX (XX.X)	XX (XX.X)	XX (XX.X)
Neuromuscular disorder	XX (XX.X)	XX (XX.X)	XX (XX.X)
Sepsis	XX (XX.X)	XX (XX.X)	XX (XX.X)
Upper airway obstruction	XX (XX.X)	XX (XX.X)	XX (XX.X)
Baseline physiology, median (IQR)			
Systolic blood pressure (mmHg)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)
PaO_2/FiO_2 (kPa)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)
Base excess (mmol/L)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)
Outcomes			
PICU mortality, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Length of PICU stay (days), median (IQR):	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)
Duration of mechanical ventilation, median (IQR):	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)
Days alive and free from mechanical ventilation, median (IQR)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)

n: Number of patients; %: Percentage of patients; N: Total number of patients;
SD: Standard deviation; IQR: Inter-quartile range

Table 8a: Number of patients with complete outcome data by ecology week

Outcome measure	Intervention sites			Control sites		
	Week 1	Week 10	Week 20	Week 1	Week 10	Week 20
Number of patients	XX	XX	XX	XX	XX	XX
Patients with complete data, n (%)						
Any microbiology positive result	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Site of positive sample	XX/XX (XX.X)	XX/XX (XX.X)	XX/XX (XX.X)	XX/XX (XX.X)	XX/XX (XX.X)	XX/XX (XX.X)
Organism	XX/XX (XX.X)	XX/XX (XX.X)	XX/XX (XX.X)	XX/XX (XX.X)	XX/XX (XX.X)	XX/XX (XX.X)

Table 8b: Outcome data by ecology week

Outcome measure	Intervention sites			Control sites		
	Week 1	Week 10	Week 20	Week 1	Week 10	Week 20
Number of patients	XX	XX	XX	XX	XX	XX
Any microbiology positive result	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Total number of microbiology positive results	XX	XX	XX	XX	XX	XX
Site of positive sample						
Nasopharyngeal	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Stool/Rectal	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Urine	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
ETT Secretions	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Wound	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Blood	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Organism						
Gram Negative Bacteria	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Gram Positive Bacteria	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Virology	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Fungal	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)

Table 9: Characteristics of potential outcome measures among all patients receiving usual care (control PICUs throughout and intervention PICUs in Period One)

Outcome measure	Completeness, n (%)	Number with outcome (%) or mean (SD)	ICC
Healthcare associated infection	XX (XX.X)	XX (XX.X)	X.XXX
Any positive microbiology result	XX (XX.X)	XX (XX.X)	X.XXX
Antibiotic use	XX (XX.X)	XX (XX.X)	X.XXX
Percentage of days antibiotic free	XX (XX.X)	XX (XX.X)	X.XXX
PICU mortality	XX (XX.X)	XX (XX.X)	X.XXX
Hospital mortality	XX (XX.X)	XX (XX.X)	X.XXX
30-day mortality	XX (XX.X)	XX (XX.X)	X.XXX
Length of PICU stay (days)	XX (XX.X)	XX.X (XX.X)	X.XXX
Length of hospital stay (days)	XX (XX.X)	XX.X (XX.X)	X.XXX
Duration of invasive ventilation (days)	XX (XX.X)	XX.X (XX.X)	X.XXX

n: Number of patients; %: Percentage of patients; N: Total number of patients; SD: Standard deviation

Table 10: Effect estimates with 95% confidence intervals for potential outcome measures

Outcome measure	Intervention sites		Control sites		Effect estimate (95% CI)
	Period One	Period Two	Period One	Period Two	
Healthcare associated infection, n/N (%)	XX/XX (XX.X)	XX/XX (XX.X)	XX/XX (XX.X)	XX/XX (XX.X)	X.XX (X.XX, X.XX)
Any positive microbiology result, n/N (%)	XX/XX (XX.X)	XX/XX (XX.X)	XX/XX (XX.X)	XX/XX (XX.X)	X.XX (X.XX, X.XX)
Antibiotic use, n/N (%)	XX/XX (XX.X)	XX/XX (XX.X)	XX/XX (XX.X)	XX/XX (XX.X)	X.XX (X.XX, X.XX)
Percentage of days antibiotic free, median (IQR) [N]	XX (XX, XX) [XX]	XX (XX, XX) [XX]	XX (XX, XX) [XX]	XX (XX, XX) [XX]	X.XX (X.XX, X.XX)
PICU mortality, n/N (%)	XX/XX (XX.X)	XX/XX (XX.X)	XX/XX (XX.X)	XX/XX (XX.X)	X.XX (X.XX, X.XX)
Hospital mortality, n/N (%)	XX/XX (XX.X)	XX/XX (XX.X)	XX/XX (XX.X)	XX/XX (XX.X)	X.XX (X.XX, X.XX)
30-day mortality, n/N (%)	XX/XX (XX.X)	XX/XX (XX.X)	XX/XX (XX.X)	XX/XX (XX.X)	X.XX (X.XX, X.XX)
Length of PICU stay (days), [N]	[XX]	[XX]	[XX]	[XX]	
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	X.XX (X.XX, X.XX)
Median (IQR)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)	X.XX (X.XX, X.XX)
Length of hospital stay (days), [N]	[XX]	[XX]	[XX]	[XX]	
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	X.XX (X.XX, X.XX)
Median (IQR)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)	X.XX (X.XX, X.XX)
Duration of invasive ventilation (days), [N]	[XX]	[XX]	[XX]	[XX]	
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	X.XX (X.XX, X.XX)
Median (IQR)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)	X.XX (X.XX, X.XX)

n: Number of patients; %: Percentage of patients; N: Total number of patients; SD: Standard deviation

Figure 1: Study flow diagram
CONSORT flow diagram

Figure 2: Patients screened and recruited over time

Plots of number of patients screened and recruited per week and by site will be developed

Figure 3: Cumulative recruitment over time compared with pre-trial expected recruitment

Figure 4: Proportion of patients who received any antibiotic during PICU stay