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

STUDY SHORT TITLE

PICnIC

FUNDED BY

NIHR | National Institute for Health Research

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (project number: 16/152/01). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA Programme, NIHR, NHS or the Department of Health.

Research reference numbers

Protocol version number and date

Version 2.1, 23 November 2020

IRAS Number

239324

REC Reference

20/WM/0061

NIHR Portfolio CPMS ID

44969

ISRCTN Registry Number

40310490

Sponsor name and reference

University of Cambridge

Cambridge University Hospitals NHS Foundation Trust

Funder name and reference

National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (16/152/01)

Chief Investigator

Dr Nazima Pathan

Sponsor representative

Steven Kelleher

Signature page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to appropriate research governance frameworks and any subsequent amendments of regulations, Good Clinical Practice (GCP) guidelines, the Sponsor's Standard Operating Procedures (SOPs), and other regulatory requirements where relevant.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: **Date**:

..../...../.....

Name: Steven Kelleher

Position: R & D manager, Cambridge University Hospitals NHS Foundation Trust

Chief Investigator:

Signature: **Date**:

..../...../.....

Name: Dr Nazima Pathan

Position: University Lecturer in Paediatric Intensive Care

PICnIC Trial contacts

Chief Investigator	Dr Nazima Pathan *University Lecturer and Consultant in Paediatric Intensive Care* Department of Paediatrics, University of Cambridge, Level 8, Addenbrookes Hospital, Hills Road Cambridge CB2 0QQ Tel: 020 7269 9277 Email: np409@medschl.cam.ac.uk
Clinical Trials Unit	Alanna Brown *Trial Manager* ICNARC CTU Napier House 24 High Holborn London WC1V 6AZ Tel: 020 7269 9277 Fax: 020 7831 6879 Email: picnic@icnarc.org
Sponsor	Cambridge University Hospitals NHS Foundation Trust and The University of Cambridge
Funder	National Institute for Health Research Health Technology Assessment Programme Tel: 02380 595 656 Email: htaoas@southampton.ac.uk

PICnIC Trial Management Group

Name	Role/Expertise	Organisation
Dr Nazima Pathan	Chief Investigator – Paediatric Intensive Care	University of Cambridge
Associate Professor Lyvonne Tume	Co-applicant - Paediatric Intensive Care nursing	Alder Hey Children's Foundation NHS Trust
Theodore Gouliouris	Co-applicant – Infectious diseases and microbiology	University of Cambridge
Dr Kerry Woolfall	Co-applicant – Public health research	University of Liverpool
Dr John Pappachan	Co-applicant - Paediatric Intensive Care	University Hospital Southampton NHS Foundation Trust
Dr Rob Shulman	Co-applicant – Critical Care pharmacy	University College London Hospitals NHS Foundation Trust
Dr Richard Feltbower	Co-applicant – PICANet Data Linkage	University of Leeds
Mr Paul Mouncey	Co-applicant - Health services research	Intensive Care National Audit & Research Centre
Professor Brian Cuthbertson	Co-applicant - Critical Care Medicine	Sunnybrook Health Sciences Centre
Professor David Harrison	Co-applicant - Statistics	Intensive Care National Audit & Research Centre
Professor Kathy Rowan	Co-applicant – Health services research	Intensive Care National Audit & Research Centre
Professor John Myburgh	Scientific advisor – Critical Care Medicine and SDD drug development	The George Institute for Global Health
Ms Alanna Brown	Trial Manager	Intensive Care National Audit & Research Centre
Mr Stefan Sprinckmoller	Data Manager	Intensive Care National Audit & Research Centre
Ms Laura Drikite	Trial Assistant	Intensive Care National Audit & Research Centre
Ms Isobel Sale	N/A	PPI representative

Contents

Abbreviations 8
1. Background 9
2. Aims & Objectives 10
2.1 Aim 10
2.2 Objectives 10
3. Trial Design 11
3.1 Setting 11
3.2 Trial Flow 13
3.3 Outcome Measures 14
3.4 Ecology Surveillance Periods (All sites - Week 1, Week 10, Week 20) 14
3.5 Baseline (All sites – Weeks 2 – 9) 15
3.6 Randomisation 16
3.7 Intervention period (3 sites – Weeks 11 – 19) 16
3.8 Control period (3 sites – Weeks 11 – 19) 18
3.9 Screening 18
3.10 Routine data 18
3.11 Co-enrolment 18
3.12 Informed Consent 19
4. Safety Reporting 20
4.1 Definitions 20
4.2 Assessment 21
4.3 Recording and Reporting procedures 22
4.4 Additional safety monitoring 23
4.5 Notifying the Research Ethics Committee 23
5.Data management guidelines 25
5.1 Case Report Forms and data entry 25
6 Statistics 25
6.1 Sample size calculation 25
7. Mixed method element involving parents/legal representatives and practitioners 26
7.1 Study Design 26
7.3 Parent/legal representative element 26
7.2 Practitioner element 27

7.4 Data Analysis 29
8. Trial monitoring and oversight 29
8.1 Good research practice 29
8.2 Trial management and oversight committees 30
8.3 Role of the ICNARC Clinical Trials Unit 30
8.4 Ethical compliance 30
8.5 Participant confidentiality and data protection 31
9 Trial closure 31
9.1 End of trial 31
9.2 Archiving trial documents 31
9.3 Early discontinuation of the trial 31
10. Sponsorship and Indemnity 32
10.1 Sponsor details 32
10.2 Indemnity 32
10.3. Funding 32
11. Publication policy 32
12. References 33
13. Appendices 35
Appendix 1 – Protocol Version History 35
Appendix 2 – Expected AEs 37

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. Background

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, directly or haematogenously spreading to other organ systems[4,5]. 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 and SuDICCU).

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 cluster randomised trial (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.

2. Aims & Objectives

2.1 Aim

To determine whether it is feasible to conduct a multicentre trial in critically ill children comparing SDD with standard infection control procedures

2.2 Objectives

2.2.1 Pilot cRCT

- To test the ability to randomise PICUs to either control or intervention
- To test the willingness and ability of healthcare professionals to screen and recruit eligible children
- To estimate the recruitment rate of eligible children
- To test adherence to the SDD protocol
- To test the procedures for assessing and collecting selected clinical and ecological outcomes and for adverse event (AE) reporting
- To assess the generalisability of the study results to all PICUs using the Paediatric Intensive Care Audit Network (PICANet)

2.2.2 Mixed-methods study

Perspectives of PICU healthcare professionals:

- To assess the acceptability of implementation of the SDD intervention, recruitment and consent procedures
- To assess the acceptability of collecting data to assess the selected clinical and ecological data
- 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:

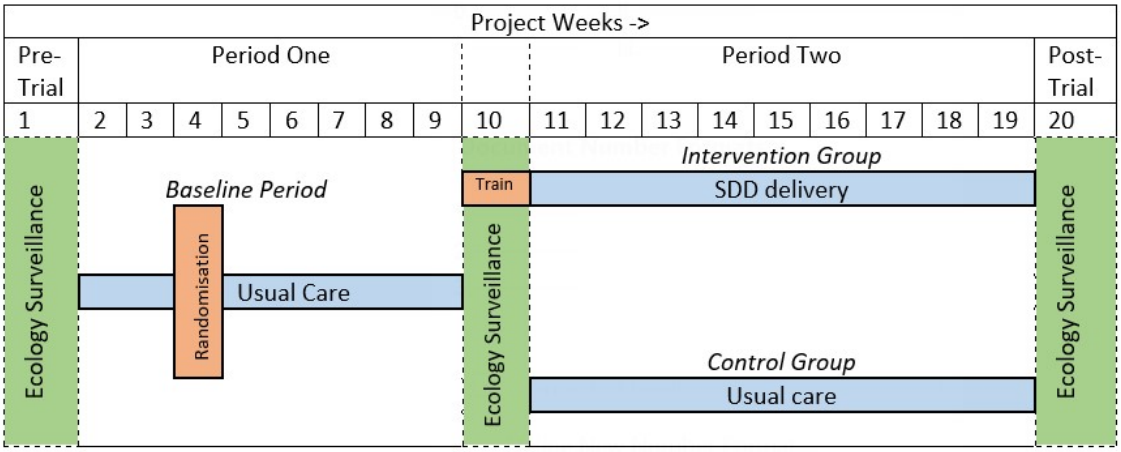
- To review and explore the acceptability of a definitive trial that includes the SDD intervention

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

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

3. Trial Design

External pilot, parallel group cRCT with integrated mixed-methods study. Recruitment will run for a period of 18 weeks, with additional one-week ecological surveillance periods pre- and post-trial. 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.



Week 11 shall be treated as a transition period

3.1 Setting

3.1.1 Sites

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

3.1.2 Site requirements:

- Active participation in PICANet data collection
- Compliance with all responsibilities as stated in the Clinical Trial Site Agreement
- Compliance with all requirements of the trial protocol including study intervention and follow-up
- Compliance with relevant research governance frameworks and the International Conference on Harmonization Guidelines on Good Clinical Practice (ICH-GCP)

3.1.3 Site responsibilities:

- Identify a Principal Investigator who will lead the PICnIC trial locally
- Identify a PICnIC research nurse responsible for day-to-day coordination
- Agree to incorporate the PICnIC trial into routine critical care clinical practice, emphasising the importance of systematic screening for, and recruitment of, eligible patients and ensure sampling procedures are followed
- Ensure adherence with the trial protocol
- Agree to data collection requirements

3.1.4 Site activation:

The following must be in place prior to site activation for recruitment:

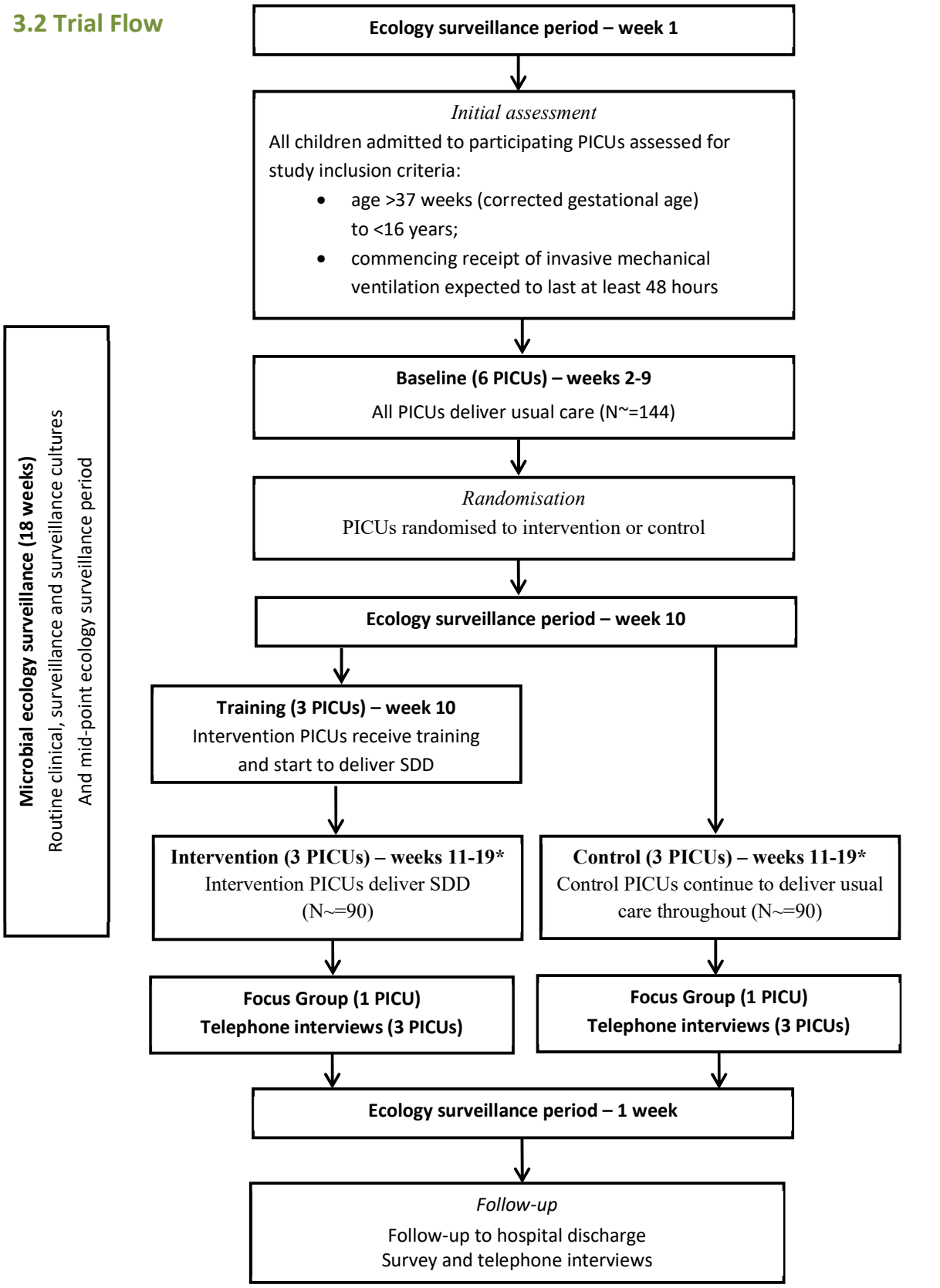
- A completed site initiation
- Confirmation of Capacity and Capability
- Fully-executed Clinical Trial Site Agreement
- A delegation log with adequate staffing to deliver the trial

Once the ICNARC Clinical Trials Unit (CTU) have confirmed all necessary documentation is in place at all sites, a site activation e-mail will be sent to the PI. All sites will commence the 20-week trial period simultaneously.

Throughout the trial, the PI must:

- Maintain familiarity, and ensure the trial is conducted in compliance, with the approved protocol
- Maintain the delegation log, ensuring a copy is sent to the PICnIC trial team at ICNARC when changes are made
- Ensure there are adequate resources (time, staff, facilities) to conduct the trial properly and safely
- Ensure staff are adequately trained to deliver the trial, with adherence to the protocol and Good Clinical Practice (GCP) guidelines
- Ensure appropriate systems are in place to identify and, where applicable, commence treatment in eligible patients, with special consideration to out-of-hours recruitment (i.e. nights and weekends)
- Ensure data collection, validation and entry is accurate, timely and complete
- Ensure reporting of all (Serious) Adverse Events

3.2 Trial Flow



3.3 Outcome Measures

- Acceptability of the intervention to health care professionals and to parents/guardians (assessed by exploring willingness to recruit and acceptability of consent process)
- Adherence to the SDD intervention (assessed by the proportion of eligible children allocated to the intervention that receive SDD)
- Estimation of recruitment rate
- Understanding of potential patient-centered primary and secondary outcome measures for the definitive cRCT

3.4 Ecology Surveillance Periods (All sites - Week 1, Week 10, Week 20)

During the Ecology Surveillance Periods, sites will not be recruiting in to the Intervention or Control groups of the study.

3.4.1 Inclusion criteria

- All patients admitted to the PICU, regardless of ventilation status, during any of the three ecological surveillance periods

3.4.2 Exclusion criteria

- None

3.4.3 Intervention

- None – patients will receive all standard infection control measures (per the site's specific policies) but will receive no study-specific intervention

3.4.4 Samples

During the designated ecology week, samples will be taken on admission and then taken on a Friday, if the patient has not had samples taken in the previous 48 hours.

Samples taken are:

- Nasopharyngeal
- Stool/rectal swabs
- Urine (if clinically indicated)
- Sputum/secretions from the endotracheal tube (If clinically indicated)
- Wound swabs, if present (if clinically indicated)

3.4.5 Data Collection

To include:

- Date of PICU admission
- Date of admission sample collection

- Confirmation of twice-weekly sample collection
- Sample storage details
- Positive microbiological results from samples

3.5 Baseline (All sites – Weeks 2 – 9)

3.5.1 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)

3.5.2 Exclusion criteria

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

3.5.3 Intervention

- None - patients will receive all standard infection control measures (per the site's specific policies) but will receive no study-specific intervention

3.5.4 Samples

Samples will be taken on admission and then twice-weekly until discharge. For patient stays of <7 days, samples should be taken on the day of discharge.

Samples taken are:

- Nasopharyngeal
- Stool/rectal swabs
- Urine (if clinically indicated)
- Sputum/secretions from the endotracheal tube (If clinically indicated)
- Wound swabs, if present (if clinically indicated)

3.5.5 Data Collection

To include:

- Demographics
- Date/time of commencing mechanical ventilation
- Date/time identified as eligible
- Antibiotic usage throughout admission (Route, type, duration, frequency, dose)
- Date/time of final extubation
- Details of Health-care Associated Infection (Confirmed/presumed)
- Date/time of PICU discharge
- Date/time of hospital discharge

3.6 Randomisation

Participating PICUs will be randomised by the trial statistician using computer-based randomisation. Sites will be notified of their randomisation during the 8-week baseline period.

3.7 Intervention period (3 sites – Weeks 11 – 19)

3.7.1 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)

3.7.2 Exclusion criteria

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

3.7.3 Intervention

The intervention will be started in all eligible patients as it will form part of the standard infection control strategy in the participating PICU. In addition to usual care, the following SDD regimen will be adopted:

1. A six-hourly topical, application of a pea-sized (0.5g) SDD paste containing 2% polymyxin E (**colistin)**, 2% tobramycin and 2% nystatin to the buccal mucosa and oropharynx;

2. A six-hourly administration of SDD liquid administered via an existing nasogastric feeding tube into the stomach containing polymyxin E (colistin), tobramycin and nystatin

Dosing of the SDD suspension will be calculated according to age and is listed below:

	0 – 4 years	**5 – 12 years**	**≥13 years**
Polymyxin E (Colistin)	25mg	50mg	100mg
Tobramycin	20mg	40mg	80mg
Nystatin	0.5 x 106 IU	1 x 106 IU	2 x 106 IU
	2.5ml	**5ml**	**10ml**

3.7.4 Duration of treatment

SDD treatment should be started within 6 hours of the patient being identified as eligible and continue for a maximum of 30 days (treatment period).

Treatment will continue until the patient is extubated or no longer mechanically ventilated (in tracheostomised patients).

Patients subsequently re-intubated (either during this PICU admission or readmission to PICU) during the treatment period will restart the intervention.

All other usual care will be provided at the discretion of the treating clinical team.

3.7.5 Provision of product

Polymyxin (colistin), tobramycin and nystatin are licensed antibacterial and antifungal drugs, and are already in common usage. Manufacture of these drugs will be according to Good Manufacturing Practice standards and will be supplied to the PICUs on contract for the trial in individual patient boxes.

The required SDD drug formulation for PICnIC, amenable to paediatric dosing, has been developed by The George Institute for Global Health (TGI). Further, TGI are acting as the Sponsor for SuDDICU (ClinicalTrials.gov NCT02389036), a trial of SDD within the adult population. TGI holds the Intellectual Property for the drug through an exclusive contract with a compounding pharmacy.

To facilitate PICnIC study drug acquisition and distribution, Professor John Myburgh, Director, Division of Critical Care at TGI and SuDDICU Chief Investigator, has agreed to act in a scientific advisory role on the PICnIC Trial Management Group.

Copies of an Investigators Brochure and study drug information sheets will be supplied to participating sites.

3.7.6 Samples

Samples will be taken on admission and then twice-weekly until discharge. For patient stays of <7 days, samples should be taken on the day of discharge.

Samples taken are:

- Nasopharyngeal
- Stool/rectal swabs
- Urine (if clinically indicated)
- Sputum/secretions from the endotracheal tube (If clinically indicated)
- Wound swabs, if present (if clinically indicated)

3.7.7 Data Collection

To include:

- Demographics
- Date/time of commencing mechanical ventilation
- Date/time identified as eligible
- Antibiotic usage throughout admission (Route, type, duration, frequency, dose)
- Date/time of final extubation
- Details of any Healthcare Associated Infection (Confirmed/presumed)
- Date/time of PICU discharge
- Date/time of hospital discharge
- SDD delivery (dose for age, date time first dose, dose per day, change of dose, deviation)

3.8 Control period (3 sites – Weeks 11 – 19)

As per baseline period.

3.9 Screening

Potentially eligible patients presenting to the participating unit will be screened against the inclusion/exclusion criteria by the local clinical team, supported by the site research team. Screening Logs will record the reason patients are eligible but are subsequently not enrolled.

3.10 Routine data

Routine linkage will be made for all patients with the Paediatric Intensive Care Audit Network (PICANet) through the PICANet ID and trial number:

- Baseline demographics and risk factors, including predicted risk of death
- Secondary outcomes of critical care and acute hospital mortality, organ support received

3.11 Co-enrolment

Co-enrolment will be considered onto other interventional studies where there are no conflicts with the PICnIC trial objectives. Consideration must be given to the burden placed upon the child/family of enrolment into multiple trials.

3.12 Informed Consent

3.12.1 Overview/Rationale

Children who are eligible for PICnIC will often become so during a period of life-threatening illness. This is a profoundly stressful time for parents/guardians during which time there are ethical concerns both about the burden placed of trying to understand the trial and their ability to provide informed consent during a time of great distress.

SDD has been shown to influence the rate of HCAIs in all patients within a unit, not just those receiving it. Because of this, it is essential to study both the patient-related direct effects (caused by the delivery of SDD to an individual patient) and the indirect effects of SDD (on all patients due to its impact on the ecology of the unit).

As such, the intervention will be delivered to all eligible patients in participating PICUs as a standard of care for the period of the study, in addition to their standard infection control policies; individual patient consent will not be requested. SDD has been used safely in the UK for many years and is widely adopted in other countries.

3.12.2 Individual patient 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.

Posters will be displayed prominently within the units and information sheets will be provided explaining that a trial is taking place in the PICU. The leaflets will include details of how to obtain further information and clear guidance on how to request their child's data is not included in the data analysis. This is an established method within PICUs and is used to inform patients of data collection for PICANet.

This approach is in line with guidance from the Ottawa Statement on the ethical design and conduct of cRCT. Feedback from proposed guidance on consent in cluster trials from the NHS Health Research Authority, suggests there is broad support for taking different approaches to seeking consent in low-risk trials where the patient is likely to receive the research intervention as part of their standard treatment. The trial falls into this category because the intervention uses non-absorbable antibiotics given as an oropharyngeal paste and nasogastrically-administered solution as part of an enhanced infection control policy and an enhanced microbiological surveillance policy. Clusters not randomised to the intervention will continue to use their standard infection control policies and microbiological surveillance.

3.12.3 Patient Withdrawal

Children may be withdrawn from trial specific data collection by the request of parents who decline participation in the research. If parents opt out from the research before any data has been collected for their child this will be noted on the screening log, which will be held at the unit; the Chief Investigator (CI) and the units Principal Investigator (PI) will be informed.

If at any other stage in the study children are withdrawn, units will inform their PI and the ICNARC CTU. Withdrawal should also be noted by the unit in the patient's medical records. Trial specific and routine data up to the point of withdrawal will be included in the data analysis.

4. Safety Reporting

4.1 Definitions

Adverse event reporting will follow the Health Research Authority guidelines on safety reporting in non-clinical trial investigational medicinal product studies. The following definitions have been adapted from Directive 2001/20/EC of the European Parliament (Clinical Trials Directive) and ICH-GCP guidelines (E6(R1), 1996).

All infants and children eligible for PICnIC are critically ill and, due to the complexity of their condition, are at an increased risk of experiencing AEs. These will not necessarily be reportable to the PICnIC study team, unless they are considered to be possibly, probably or definitely related to the study treatment.

4.1.1 Adverse Event

An Adverse Event (AE) is defined as: any untoward medical occurrence in a patient participating in a study, which does not necessarily have a causal relationship with the treatment.

4.1.2 Serious Adverse Event

A Serious Adverse Event (SAE) is defined as an Adverse Event that:

- results in death;
- is life-threatening ("life-threatening" refers to an event in which the patient was at risk of death at the time of event. It does not refer to an event that hypothetically may have caused death were it more severe);
- requires hospitalisation or prolongation of existing hospitalisation ("hospitalisation" refers to inpatient admission, regardless of length of stay. This

includes admission for continued observation. Any admission for pre-existing conditions that have not worsened, or elective procedures, do not constitute an SAE);
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect

Important adverse events that are not immediately life-threatening, do not result in death or hospitalisation but may jeopardise the subject or require intervention to prevent one or any of the other outcomes listed in the definition above should also be considered as serious.

4.1.3 Unexpected and Related Serious Adverse Event

A suspected Adverse Event related (possibly, probably or definitely) to the treatment that is both unexpected (i.e. not consistent with the expected outcomes of the treatment being offered) and serious.

4.2 Assessment

The PI, or other investigator as listed on the Delegation Log, should make an assessment of relatedness, severity and expectedness, categorised all follows:

4.2.1 Relatedness

- **None**: there is no evidence of any relationship to the study treatment

- **Unlikely:** There is little evidence to suggest a causal relationship (e.g. because the event did not occur within a reasonable time after administration of the trial treatment). There is another reasonable explanation of the event (e.g. the participant's clinical condition, other concomitant medications).

- **Possibly:** There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant medications).

- **Probably:** There is evidence to suggest a causal relationship and the influence of other factors is unlikely

- **Definitely:** There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

4.2.2 Severity

- **None**: indicates no event or complication

- **Mild**: complication results in only temporary harm and does not require clinical treatment.

- **Moderate**: complication requires clinical treatment but does not result in significant prolongation of hospital stay. Does not usually result in permanent harm and where this does occur the harm does not cause functional limitation to the participant.

- **Severe**: complication requires clinical treatment and results in significant prolongation of hospital stay, permanent functional limitation.

- **Life-threatening:** complication that may lead to death.

- **Fatal**: indicates that the participant died as a direct result of the complication/adverse event.

4.2.3 Expectedness

- **Expected**: the event is specified as an expected AE in Appendix 2.
- **Unexpected**: the event is not listed as an expected AE in Appendix 2.

4.3 Recording and Reporting procedures

AEs will be recorded from intervention commencement until PICU discharge. All adverse events will be recorded in the medical notes of the patients. Only AEs deemed possibly, probably or definitely related to the trial intervention should be reported to the ICNARC CTU.

All SAEs must be recorded on the Safety monitoring CRF and if applicable, the PICnIC SAE reporting form should be completed and uploaded to the web-based data entry system within 24 hours of the study team becoming aware of the event. Sites should also email picnic@icnarc.org to inform the trial team the event has been uploaded on the SAE reporting form. Staff should not wait until all information about the event is available before sending SAE notification. Information not available at the time of the initial report must be documented and submitted as it becomes available. However, essential criteria regarding date and time onset, event name, severity and relatedness of the event to the study treatment must be recorded in the first instance.

The following events are exempt for reporting as AEs or SAEs

- Deterioration of condition or death that is not related to the trial intervention
- AEs of other drugs not specified in the protocol.

The process for recording and reporting adverse events and serious adverse events is summarised in Figure 2.

On receipt of the SAE report, a clinical member of the PICnIC Trial Management Group (TMG) will evaluate the site's assessment of the event for severity, relatedness and expectedness to determine whether or not the case qualifies for expedited reporting to the Research Ethics Committee (REC). If the event is evaluated by either the Chief Investigator or a clinical member of the PICnIC TMG as a related and unexpected SAE, the ICNARC CTU will submit a report to the REC within 15 calendar days.

The ICNARC CTU will provide safety information to the Chief Investigator, TMG, Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC) for review on a regular basis (as deemed necessary).

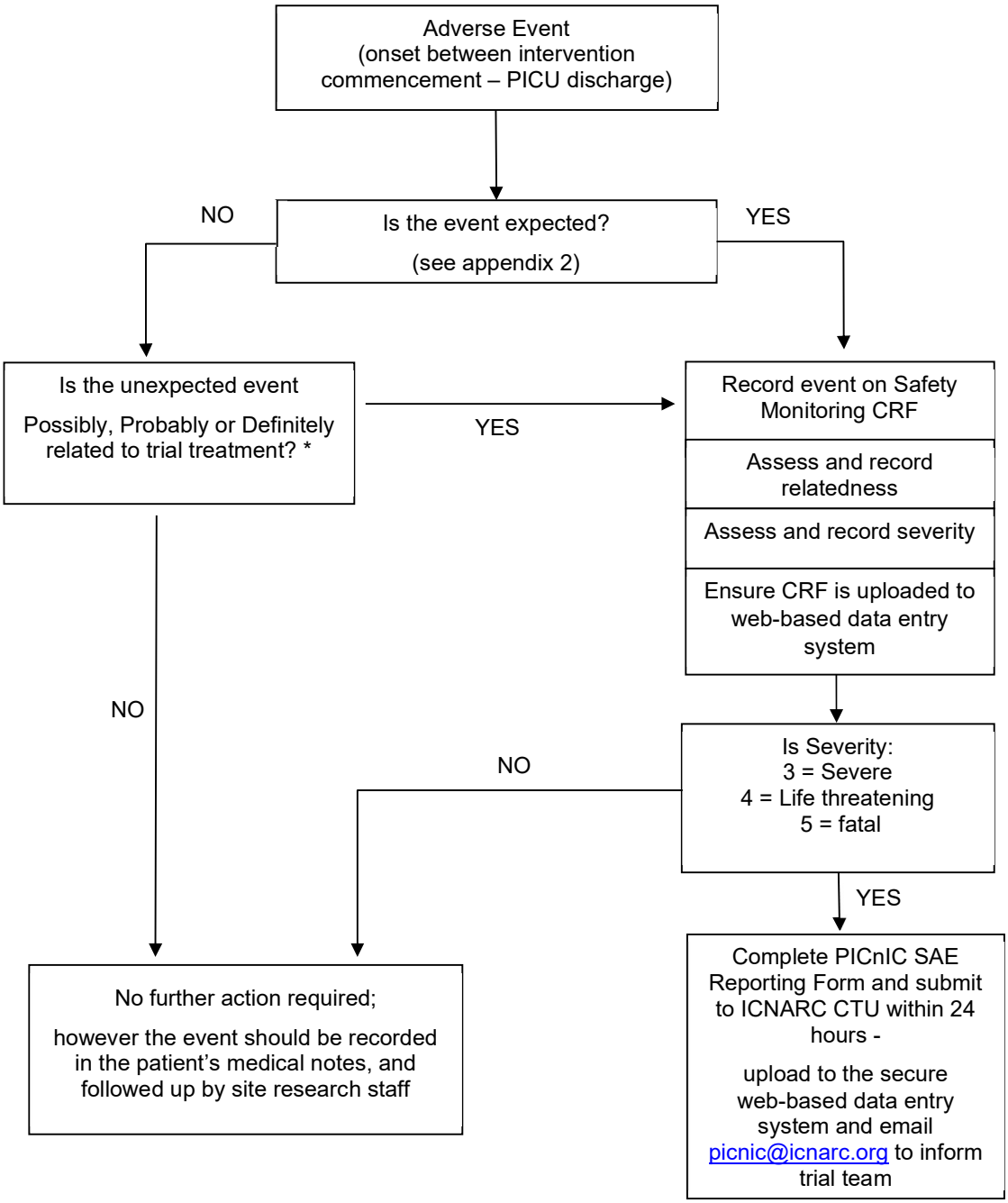
4.4 Additional safety monitoring

The ICNARC CTU will also monitor data for documented AEs that are not considered to be related to the trial treatment. In the event that any trial procedure does appear to be resulting in AEs, the TMG will be contacted for their opinion. If it is declared necessary to review the conduct of the trial, the ICNARC CTU will inform the REC as appropriate.

4.5 Notifying the Research Ethics Committee

AEs leading to treatment failure will be reported in the annual progress report which will be submitted by the ICNARC CTU to the REC annually. This will commence one year from the date of approval for the trial.

Figure 2: Recording and reporting process of Adverse Events



*If there is any uncertainty about whether the AE is associated with trial treatment, then it should be reported.

5.Data management guidelines

5.1 Case Report Forms and data entry

Participant data will be entered onto a secure web-based data entry system. Paper Case Report Forms (CRFs) will be available, however completion of these is not mandatory where it will create a duplication of effort (e.g. sites with electronic medical records). The Site PI will oversee and be responsible for data collection, quality and recording. Collection of data can be delegated by the Site PI to qualified members of the research team and should be recorded on the Delegation Log.

All data will be collected and processed in line with GDPR. Data entered onto the secure trial database will undergo validation checks for completeness, accuracy and consistency of data. Queries on incomplete, inaccurate or inconsistent data will be sent to the research team at participating sites for resolution.

During the conduct of the trial, all electronic participant data will be encrypted and all trial documents stored securely at the site or the ICNARC CTU, as appropriate. On completion of the trial, all participant data (electronic and paper) and other trial documents will be archived securely and retained for 10 years at the site, the sponsor or at the ICNARC CTU, as appropriate.

6 Statistics

6.1 Sample size calculation

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.

7. Mixed method element involving parents/legal representatives and practitioners

7.1 Study Design

The PICnIC pilot cRCT will include an embedded mixed method element. This will involve a questionnaire and interviews with parents/ legal representatives of children involved in the pilot cRCT as well as focus groups, telephone interviews and an online survey with PICU practitioners.

Questionnaires (n=~100) and interviews (until data saturation is reached, n=~15-25 based on previous studies) will be used to explore parents/ legal representatives' views on: the acceptability of conducting a definitive trial; the content and understanding of the information materials; acceptability of the recruitment and consenting procedures; and the selection of important, relevant, patient-centred, primary and secondary outcomes for a definitive trial.

Two focus groups and up to 10 interviews with practitioners involved in the pilot cRCT, as well as an online survey of all UK PICU staff will be used to assess: the acceptability of the implementation of the SDD intervention; interest in participation in a definitive trial in the wider PICU community; the acceptability of the recruitment and consenting procedures for the definitive trial; and the acceptability of collecting data for assessing the selected clinical and ecological outcomes.

7.3 Parent/legal representative element

7.3.1 Eligibility

Inclusion criteria:

- Parents/Legal representatives of children involved in the pilot cRCT, including those who withdraw from data collection

Exclusion criteria:

- Parents/Legal representatives who do not speak English

7.3.2 Enrolment

At participating sites, practitioners will provide parents/legal representatives with information about PICnIC and ask them if they would like to complete the questionnaire and/or provide contact details if they wish to take part in a telephone interview.

7.3.3 Procedures

One of the hospital's local PICnIC team (a member of the healthcare team) will give a copy of the questionnaire to each parent/legal representative to complete. If both parents are present, both will be asked to consent and complete a questionnaire. Completed questionnaires will be placed in a stamped self-addressed envelope and returned the PICnIC team member (e.g. within 12 hours) via post to the University of Liverpool team.

Telephone interviews

The University of Liverpool team will contact parents/legal representatives to arrange an interview within one month of consent. All interviews will be conducted by the team using the parent/legal representative interview topic guide. Consent for audio recording of the interview will be checked verbally before the interview commences. The topic guide has been informed by previous trials conducted in paediatric emergency and critical care in the NHS[15,16] Respondent validation will be used so that previously unanticipated topics will be added to the topic guide and discussed with participants as interviewing and analyses progress.

Any distress during the interviews will be managed with care and compassion. Participants will be free to decline to answer any questions that they do not wish to answer or to stop the interview at any point. Any such families will be supported in obtaining appropriate help.

Interviews will be conducted until data saturation is reached. This is when the major themes identified in new data are reoccurring from the analysis of previous transcripts and no new major themes are being discovered. Based on previous, similar studies[15,16], this is anticipated to involve approximately 15-25 parents/legal representatives.

All families who express an interest in taking part but are not selected for an interview will be contacted via telephone or email to thank them for their interest in the study.

7.2 Practitioner element

7.2.1 Eligibility

Inclusion criteria for focus groups and interviews:

- Practitioners (including doctors, nurses, pharmacists and allied health professionals) working in PICUs that participate in the PICnIC pilot cRCT

Inclusion criteria for questionnaires:

- Practitioners (including doctors, nurses, pharmacists and allied health professionals) working in UK PICUs, including those who participate in the PICnIC pilot cRCT

Exclusion criteria:

- None

7.2.2 Enrolment

Focus groups

The University of Liverpool team will email teams at two of the participating PICUs (e.g. one intervention and one control/one high and one low recruiting site) and invite them to take part in a focus group. Focus groups will involve approximately 8-10 practitioners to ensure adequate opportunity for active participation. Additionally, up to 10 telephone interviews will be conducted with practitioners who cannot attend the focus groups, as well as Principal investigators or lead research nurses at the other four participating sites.

Written consent will be sought from participants before focus group begin. This will include consent for digital audio recording of the group discussion. The team will email or post a copy of the consent form to site research staff who wish to take part in a telephone interview with a request to complete and return the form prior to the arranged telephone interview date.

Online survey

To ensure wider input, the team will send email invitations and use social media to invite UK PICU practitioners to complete the online survey. An overview of the study will be provided in an information sheet for practitioners to read before completing the questionnaire. This will include dissemination through the PICS-SG group and research-active practitioners across all UK PICUs using our database of contacts

7.2.3 Procedures

Focus groups

Focus groups will take place in a meeting room at the selected sites. Both focus groups and telephone interviews will take place towards the end of the pilot cRCT recruitment period. All focus groups and interviews will be conducted by the University of Liverpool team using the practitioner focus group/interview topic guide developed using relevant literature and early findings from parent/legal representative questionnaires and telephone interviews. Consent for audio recording of interviews will be checked verbally before the focus group or interview begins.

Online survey

For staff involved in the pilot cRCT an email outlining the embedded study objectives and invitation to participate in a survey will be sent to the site PI or lead research nurse who will

be asked to disseminate it to all staff involved in the study at their site. The invitation will include a link to the online survey.

For all PICU staff across the UK, a link to the online survey and practitioner information sheet will be included in email invitations and social media advertisements.

Both surveys will include a statement which states that completion of the survey is taken as the participant gives permission for their data to be included in the PICnIC Study.

7.4 Data Analysis

Interviews and focus groups will be transcribed, checked and anonymised as the study progresses. QSR NVivo software will be used to assist in the organisation and indexing of qualitative data. Whilst thematic analysis[18,19] will be informed by the constant comparison approach, the focus will be modified to fit with the criterion of catalytic validity, whereby findings should be relevant to future research and practice (in particular, the design of the definitive cRCT). Quantitative data from parent questionnaires and the online survey will be analysed using SPSS software, descriptive statistics and exact tests will be used, as appropriate. Data from each method will be analysed separately then synthesised through the use of constant comparative analysis.[20]

8. Trial monitoring and oversight

The ICNARC CTU will conduct one monitoring visit to participating sites during the course of the pilot trial. In addition, the REC may request access to source data/documents for audit and review. Trial participants and their parents will be informed of this during the informed consent process.

Following a routine monitoring visit, a report will be sent, which will summarise the visit and the documents reviewed, along with any findings. The Site PI will be responsible for ensuring that all findings are addressed appropriately.

Additional site monitoring visits may be scheduled where there is evidence or suspicion of non-compliance with the PICnIC Protocol.

8.1 Good research practice

PICnIC will be managed according to the Medical Research Council's (MRC) Guidelines for Good Research Practice, Guidelines for Good Clinical Practice in Clinical Trials and Procedure for Inquiring into Allegations of Scientific Misconduct. The ICNARC CTU has developed its own policies and procedures, based on these MRC guidelines, for the conduct of all its research activities. In addition, ICNARC has contractual confidentiality agreements with all

members of staff. Policies regarding alleged scientific misconduct and breach of confidentiality are reinforced by disciplinary procedures.

8.2 Trial management and oversight committees

8.2.1 Trial Management Group

All day-to-day management of PICnIC will be the responsibility of the TMG. Members of the TMG will include the PICnIC Trial Manager, the Chief Investigator, the clinical co-investigators and Scientific Advisor. The TMG will meet regularly to discuss management and progress of the trial and findings from other related research.

8.2.2 Trial Steering Committee

The trial will be supervised by the Trial Steering Committee (TSC), which will be chaired by an independent member. The TSC will be comprised of two additional independent members and a patient and public involvement representative.

8.2.3 Data Monitoring and Ethics Committee

All members of the Data Monitoring and Ethics Committee (DMEC) will be independent of both the PICnIC TMG and the TSC. The DMEC will operate under the DAMOCLES Charter 19-20, and will report to the TSC, making recommendations on the continuation, or not, of the trial. Safety will be monitored by the DMEC through mandatory reporting of SAEs throughout the trial period.

8.3 Role of the ICNARC Clinical Trials Unit

The ICNARC CTU will be responsible for the day-to-day management of the trial and will act as custodian of the data. The ICNARC CTU will ensure that all SAEs are reported, as appropriate, to the REC.

8.4 Ethical compliance

The PICnIC Pilot Study will be conducted in accordance with the approved Trial Protocol, ICH GCP guidelines, the Data Protection Act (2018), the Mental Capacity Act (2005), as well as the ICNARC CTU's research policies and procedures (see section 18.0).

The trial has received Health Research Authority approval on 20 November 2020 a favourable opinion from West Midlands Black country research ethics committee (REC) (Reference: 20/WM/0061). The ICNARC CTU will submit annual progress reports and all amendments to the PICnIC Pilot Study Protocol to the REC for review. The ICNARC CTU will provide relevant approved trial documents and other related materials to participating sites.

It is the responsibility of the Site PI to obtain the necessary local approvals for the PICnIC Pilot Study, including confirmation of capacity and capability from the Trust Research & Development (R&D) Department. The Site PI should submit the site information pack, which will include: current approved version of the Protocol, PIS; Consent Form; and any other written information to be given to participants, to the R&D Department. It is also the responsibility of the Site PI to inform the R&D Department of any subsequent revisions to the Protocol or other trial documents. Evidence of NHS Trust R&D confirmation of capacity and capability must be provided to the ICNARC CTU prior to recruitment of participants.

8.5 Participant confidentiality and data protection

No identifiable participant data will be required by the ICNARC CTU, as all follow-up data will be collected at participating sites. All participant data will be stored securely.

ICNARC is registered under the Data Protection Act (2018) and all ICNARC CTU staff have undergone data protection and ICH GCP training.

9 Trial closure

9.1 End of trial

The end of the trial will be when the last participant has completed their PICU admission.

9.2 Archiving trial documents

At the end of the trial, the ICNARC CTU will archive securely all centrally-held trial-related documents for a minimum 15 years in accordance with ICH GCP guidelines. Arrangements for confidential destruction of all documents will then be made. The Site PI will be responsible for archiving all trial-related documents (including CRFs and other essential documents) held at the participating site for a minimum of 15 years after the end of the trial. Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and to show whether the unit complied with the principles of ICH GCP and other applicable regulatory requirements.

Guidance on archiving will be provided in the trial-specific SOP. All archived documents held centrally and locally, should be available for inspection by appropriate authorities upon request.

9.3 Early discontinuation of the trial

The trial may be stopped early upon recommendation of the TSC. In which case, the ICNARC CTU will inform all relevant staff working on PICnIC and advise on the actions to be taken as

regards the treatment of participants. All randomised participants will continue to be followed up as per the PICnIC Pilot Study Protocol.

10. Sponsorship and Indemnity

10.1 Sponsor details

Sponsor Name:	Cambridge University Hospitals NHS Foundation Trust & The University of Cambridge
Address:	Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital Box 227, Hills Road, Cambridge, CB2 0QQ
Contact:	Adam Loveday
Email:	Adam.Loveday@addenbrookes.nhs.uk

10.2 Indemnity

The NHS Clinical Negligence Scheme for Trusts provides full financial liability for harm caused to participants in the study caused through negligence. The University of Cambridge provides insurance cover for negligent harm caused as a result of the design and management of the study, and for non-negligent harm arising through participation in the study

10.3. Funding

PICnIC is funded National Institute of Health Research Health Technology Assessment Programme (HTA 16/152/01)

11. Publication policy

The final report, including a detailed description of the trial, results and recommendations for future policy and practice and future research, will be submitted to the NIHR HTA Programme. Articles will be prepared for publication in peer-reviewed scientific journals, as well as relevant professional journals. All participant data will be anonymised before publication.

12. References

1. Patrick SW, Kawai AT, Kleinman K, et al. Health care-associated infections among critically ill children in the US, 2007-2012. Pediatrics 2014; 134:705-12.
2. Field-Ridley A, Dharmar M, Steinhorn D, et al. ICU-Acquired weakness is associated with differences in clinical outcomes in critically ill children. Pediatr Crit Care Med 2015; 17:53-7.
3. Choong K, Al-Harbi S, Siu K, et al. Functional recovery following critical illness in children: the "wee-cover" pilot study. Pediatr Crit Care Med 2015; 16:310-8.
4. Heyland DK, Cook DJ, Griffith L, et al. The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. Am J Respir Crit Care Med 1999; 159:1249-56.
5. Bekaert M, Timsit JF, Vansteelandt S, et al. Attributable mortality of ventilator-associated pneumonia: a reappraisal using causal analysis. Am J Respir Crit Care Med 2011; 184:1133-9.
6. Francis JJ, Duncan EM, Prior ME, et al. Selective decontamination of the digestive tract in critically ill patients treated in intensive care units: a mixed-methods feasibility study (the SuDDICU study). Health Technol Assess 2014; 18(25).
7. de Smet AM, Kluytmans JA, Cooper BS, et al. Decontamination of the digestive tract and oropharynx in ICU patients. N Engl J Med 2009; 360:20-31.
8. Canter RR, Harvey SE, Harrison DA, et al. Observational study of current use of selective decontamination of the digestive tract in UK critical care units. Br J Anaesth 2014; 113:610-7.
9. Daneman N, Sarwar S, Fowler RA, Cuthbertson BH. Effect of selective decontamination on antimicrobial resistance in intensive care units: a systematic review and meta-analysis. Lancet Infect Dis 2013; 13:328-41.
10. Liberati A, D'Amico R, Pifferi S, et al. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. Cochrane Database Syst Rev 2009; CD000022.
11. Oostdijk EA, de Smet AM, Blok HE, et al. Ecological effects of selective decontamination on resistant gram-negative bacterial colonization. Am J Respir Crit Care Med 2010; 181:452-7.
12. Plantinga NL, Bonten MJM. Selective decontamination and antibiotic resistance in ICUs. Crit Care 2015; 19:259.
13. Price RJ, Cuthbertson BH. Selective decontamination of the digestive tract and oropharynx: after 30 years of debate is the definitive answer in sight? Curr Opin Crit Care 2016; 22:161-6.
14. Petros A, Silvestri L, Booth R, et al. Selective decontamination of the digestive tract in critically ill children: systematic review and meta-analysis. Pediatr Crit Care Med 2013; 14:89-97.

15. Peters MJ KI, Woolfal K, Deja E, Mouncey PR, Wildd J, et al. Different temperature thresholds for antipyretic intervention in critically ill children with fever due to infection: the FEVER feasibility RCT. Health Technology Assessment 2019;23(5).
16. O'Hara CB CR, Mouncey PR, Carter A, Jones N, Nadel S, et al. . A qualitative feasibility study to inform a randomised controlled trial of fluid bolus therapy in septic shock. Arch Dis Child. 2017;103:28–32.
17. Saunders B, Sim J, Kingstone T, Baker S, Waterfield J, Bartlam B, et al. Saturation in qualitative research: exploring its conceptualization and operationalization. Quality & Quantity. 2018;52(4):1893-907.
18. Transforming qualitative information: Thematic analysis and code development. London Sage Publications; 1998.
19. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative research in psychology. 2006;3(2):77-101.
20. Glaser B. The Constant Comparative Method of Qualitative Analysis. Social Problems. 1965;12(4):436-445.

13. Appendices

Appendix 1 – Protocol Version History

Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1.0	21 November 2019	Daisy Wiley	N/A
1.1	10 March 2020	Daisy Wiley	Section 3 (Trial Design) inclusion criteria changed from >37 weeks to <18yrs to >37 weeks to <16 yrs Section 7.3 (Parent/legal representative element) Removed Amazon vouchers for completion of parent/guardian interview Minor administrative changes
1.2	19 August 2020	Daisy Wiley	Section 3.12.2 (Individual patient consent) update for collection of additional samples Minor administrative changes
2.0	02 October 2020	Alanna Brown	Section 3 (Trial design) trial design chart updated Section 3.2 (Trial Flow) trial flow diagram updated Section 3.4 (Ecology surveillance periods) clarification on Ecology surveillance weeks and the recruitment in to it. Also samples taken updated. Section 3.5 (Baseline) samples taken updated Section 3.7 (Intervention period) update of inclusion criteria. Rewording of duration of treatment information and samples taken updated. Section 3.12.2 (Individual Patient consent) information sheets are to replace leaflets Section 4 (Safety reporting) safety definitions, recording and reporting procedures updated. Including figure 2 updated Section 13 (Appendices) addition of Appendices

			Minor administrative changes
2.1	23 November 2020	Alanna Brown	Section 3.4 (Ecology surveillance). Sampling instructions updated Section 10.2 (Indemnity). Information updated Minor administrative changes

Appendix 2 – Expected AEs

Specified, expected AEs that could be observed in participants from eligibility until discharged from the PICU:

- NG tube blockage
- Choking on paste
- Allergic reaction to SDD

This list is not exhaustive.