Full Title:	A randomised controlled trial of **SHORT** duration antibiotic th**ER**apy for critically ill patients with sepsis
Short Title/Acronym:	SHORTER trial
Protocol Version Number & Date:	Version 4.0, 12 March 2024

Statement: This protocol has regard for the HRA guidance.

RESEARCH REFERENCE NUMBERS

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted. The Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the Research Governance Framework, Good Clinical Practice (GCP) guidelines, the relevant Standard Operating Procedures and other regulatory requirements as applicable.

The undersigned 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 investigation without the prior written consent of the Sponsor.

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PROTOCOL ACCEPTANCE SIGNATURE PAGE

Short Trial Title: SHORTER

Site Name:

Principal Investigator

I have carefully read and understood protocol version 4.0 dated 12 March 2024. I agree to conduct the trial in compliance with Good Clinical Practice and all regulatory requirements.

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TRIAL SUMMARY

Trial Title	A randomised controlled trial of **SHORT** duration antibiotic th**ER**apy for critically ill patients with sepsis	
Acronym	SHORTER trial	
Summary of Trial Design	A pragmatic, open-label, multi-centre, parallel arm, randomised controlled trial with an embedded process evaluation	
Summary of Participant Population	Adult patients (≥ 18 years) with suspected or confirmed sepsis who require admission to a critical care unit	
Planned Sample Size	A sample size of 2244 patients will have 90% power, with a one-sided alpha of 2.5%, to demonstrate non-inferiority with a margin of 6% for 28-day mortality and detect superiority of 1.1 days of total antibiotic treatment at 28 days, allowing for a 5% dropout.	
Planned Number of Sites	50 UK Critical Care Units	
Intervention	5-day fixed course of initial antibiotic treatment for sepsis	
Comparator	Standard of care	
Follow Up Duration	90 days	
Planned Trial Period	Trial set-up = 6 months Recruitment and follow-up (including data collection) = 29 months Final data cleaning, data lock, analysis and reporting = 8 months Total trial period = 43 months	
	Objectives	**Outcome Measures**
Co-primary	To determine whether short duration antibiotic therapy is non-inferior to standard of care in terms of mortality and reduces overall antibiotic exposure.	• 28-day all-cause mortality (non-inferiority safety outcome) • Total antibiotic treatment days measured at 28 days (superiority clinical effectiveness outcome)
Secondary	*To assess the effect of short duration antibiotic therapy on:*	
	90-day mortality	All-cause mortality at 90 days
	Suspected clinically relevant antibiotic-associated adverse events	Suspected clinically relevant antibiotic-associated adverse events during index hospital

		admission occurring from randomisation up to discharge
	Length of critical care unit stay	Length (number of days) of critical care unit stay up to 90 days
	Length of hospital-stay	Length (number of days) of hospital stay up to 90 days
	Rate of further/recurrence of infections	Number of further/recurrence of infections requiring additional antibiotic courses following index sepsis episode up to 28 days
	Readmission to critical care or hospital	Occurrence of readmission to critical care or hospital during the 90 day follow up period
	Health Economic: *Is the intervention cost effective compared to usual care at 90 days follow-up?*	• Incremental cost per death avoided • Incremental cost per Quality Adjusted Life Year (QALY) gained at 90 days • Cost-effectiveness acceptability curves (CEACs) to assess the probability of the intervention being considered cost-effective at different willingness-to-pay (WTP) thresholds for a gained QALY at 90 days • Average healthcare costs per participant over 90 days following the initiation of antibiotic treatment for each area of resource use • Utility scores derived from responses to the EQ-5D-5L

		questionnaire at 90 days following the initiation of antibiotic treatment • Average QALYs per participant at 90 days following the initiation of antibiotic treatment
	Health Economic: *Is the intervention cost effective compared to usual care over the participants lifetime?*	• Incremental cost per QALY gained over the patient's lifetime • Cost-effectiveness acceptability curves (CEACs) to assess the probability of the intervention being considered cost-effective at different willingness-to-pay (WTP) thresholds for a gained QALY over the participants lifetime
Process Evaluation	To understand the implementation of the trial protocol and willingness of clinicians to follow a fixed short-duration intervention	

CONTENTS

GLOSSARY OF ABREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
AMR	Antimicrobial Resistance
APACHE	Acute Physiology And Chronic Health Evaluation
ABG	Arterial Blood Gas
CAP	Community-Acquired Pneumonia
CAPA	Corrective And Preventive Actions
CDMS	Clinical Data Management System
CHI	Community Health Index
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
CMP	Case Mixed Programme
COPD	Chronic Obstructive Pulmonary Disease
CREST	Council of Registered Ethical Security Testers
CRP	C-Reactive Protein
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
FCI	Functional Comorbidity Index
FDA	Food And Drug Administration
GCP	Good Clinical Practice
GCS	Glasgow Coma Score
GP	General Practitioner
H&C	Health & Care Number
HCUQ	Health Care Utilisation Questionnaire
HDU	High Dependency Unit
HRA	Health Research Authority
HTA	Health Technology Assessment
ICF	Informed Consent Form
ICNARC	Intensive Care National Audit & Research Centre
ICO	Information Commissioner's Office
ICU	Intensive Care Unit
ISF	Investigator Site File

ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention-To-Treat
MAP	Mean Arterial Pressure
MHRA	Medicines and Healthcare Products Regulatory Agency
NCTU	Newcastle Clinical Trials Unit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NoMAD-23 item	Normalisation Measure Development Survey Instrument
NPT	Normalisation Process Theory
PCT	Procalcitonin
PE	Process Evaluation
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PSS	Personal Social Services
QALY	Quality Adjusted Life Years
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SACE	Survivor Average Causal Effect
SAE	Serious Adverse Event
SICSAG	Scottish Intensive Care Society Audit Group
SOFA	Sequential Organ Failure Assessment
SOP	Standard Operating Procedure
SSC	Surviving Sepsis Campaign
TIA	Transient Ischaemic Attack
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File
T&T Questionnaire	Time And Travel Questionnaire
UKHSA	UK Health Security Agency
USM	Urgent Safety Measure
VAP	Ventilator-Associated Pneumonia
WBC	White Blood Cells

1 BACKGROUND

1.1 Sepsis

Sepsis is a syndrome of life-threatening organ dysfunction secondary to infection and is a leading cause of death worldwide. A third of patients with sepsis die in hospital and sepsis is estimated to cost the UK National Health Service (NHS) £15 billion per year (1,2). Sepsis is characterised by organ dysfunction, frequently resulting in a requirement for advanced organ support including mechanical ventilation, dialysis, or vasopressor support in a critical care setting (intensive care unit (ICU) or high dependency unit (HDU)). Sepsis is therefore a common reason for admission to a critical care unit, accounting for one third of general adult critical care admissions, equating to approximately 40,000 patients per year in the UK (1).

Antibiotics are lifesaving in sepsis and current international and National Institute for Health and Care Excellence (NICE) guidelines recommend the initiation of antibiotics within one hour of recognition of more severe forms of suspected sepsis (3,4). Central to decision-making at the point of antibiotic initiation is the severity of illness. Patients presenting with life-threatening suspected sepsis have broad-spectrum antibiotics initiated in a 'hard-and-fast' approach due to the perceived risk of under-treating a severe infection. This has been highlighted during the COVID pandemic with high levels of antibiotic prescribing despite low rates of bacterial co-infection (5).

Once antibiotics are initiated, the optimal duration is unknown. Previous sepsis guidelines recommended 7-10 days of antibiotics (6). Updated guidelines encourage shorter duration antibiotics, although this is a weak recommendation based on very low quality of evidence (3). UK Health Security Agency (UKHSA) (previously Public Health England) and NICE both promote antibiotic stewardship, encouraging the shortest duration of antibiotics needed and discontinuation of antibiotics if there is no evidence of infection. Antibiotic stewardship teams are regularly present in critical care settings, encouraging a multi-disciplinary approach to antibiotic prescribing involving critical care specialists, microbiologists and pharmacists. However, in practice, discontinuing antibiotics in critically ill patients is challenging since there are no accurate measures to inform clinicians that an infection has cleared. Laboratory markers such as white blood cell count (WBC), C-reactive protein (CRP) and procalcitonin (PCT), or the absence of pyrexia, are often considered but are not specific to infection. Our survey of clinicians' practice in the UK showed that antibiotic duration is based on patient response through clinical or biomarker improvement, based on local protocols and fixed courses. The minimum safe treatment duration required is unknown and it is likely that overtreatment occurs commonly.

1.2 Need for antibiotic stewardship in critically ill patients

UKHSA data show that antibiotic use in critical care far exceeds any other hospital setting (7). This high antibiotic use reflects the proportion of patients admitted to critical care with severe infections and the vulnerability of critically ill patients to healthcare-associated infections that require further courses of antibiotics.

Antimicrobial resistance (AMR) continues to rise in the UK and antibiotic use drives the emergence of AMR. There were an estimated 65,000 antibiotic-resistant infections in England in 2019 (7). The burden of harm from AMR is associated with hospital care, where there is greatest use of broad-spectrum antibiotics. Indeed, 72% of deaths attributable to AMR occur in hospital (8).

The harms associated with antibiotics and AMR are concentrated in critical care due to the very high antibiotic use in this setting. Patients in critical care units are at risk of infections from resistant pathogens, which increases the risk of poor outcomes (9) and promotes the spread of antibiotic-resistant infection to patients in other areas of the hospital. An aggressive approach to antibiotic prescribing, which is often used in critically ill patients, has been shown to have adverse consequences including deterioration in renal function from drug toxicity (10), antibiotic-associated infections such as *Clostridium difficile* (11), prolonged stay in intensive care, prolonged organ support (12) and increased mortality (10).

Optimal use of antibiotics would mean that only patients with a true bacterial infection are treated with antibiotics and for the minimum safe duration. Optimising antibiotic duration is an attractive approach when the pressures to initiate antibiotics are so high. The duration of antibiotic courses is often based on historical practice with little evidence to support the duration. A review of the evidence for antibiotic duration in sepsis found that there were no trials of fixed antibiotic duration in critical care patients with sepsis (13). Trials of antibiotic duration have been carried out in patients with specific sources of infection and generally excluded patients admitted to critical care.

1.3 Review of literature

Short duration antibiotics courses have been trialled in mild-moderate severity community-acquired pneumonia (CAP), demonstrating that short courses (3 or 5 days) achieved similar rates of clinical cure compared to longer durations (14). In a trial of 312 patients hospitalised with CAP, including those with severe CAP but not requiring admission to ICU, patients who reached criteria of clinical stability

were randomised to 5 days of antibiotics or standard of care (average 10 days) (15). Clinical cure rates were similar in the two trial arms. Current CAP guidelines acknowledge the limited evidence in patients with severe CAP when recommending short treatment duration (16). Central to these recommendations is that patients should achieve 'clinical stability' prior to antibiotics being stopped. Clinical criteria for stability after CAP, such as normal vital signs, normal mentation, and ability to eat, are of little value in critically ill patients, in whom delirium or nasogastric tube feeding may extend long after an antibiotic course has completed.

For intra-abdominal infections, guidelines recommend an antibiotic duration of 4-7 days if adequate source control can be achieved (17). This approach was tested in a non-inferiority trial of 518 patients with intra-abdominal infection who had undergone either surgical or radiological source control (18). Patients in the intervention arm received a 4-day fixed course of antibiotics and the comparator group had up to 10 days of antibiotics. Short-course antibiotics were non-inferior to longer durations in the composite primary outcome measure of surgical-site infection, recurrent intra-abdominal infection or death. This trial did not prospectively identify patients with sepsis but a retrospective analysis found no difference in outcomes between short- and long-course antibiotics in patients meeting suspected sepsis criteria (19).

Current guidelines recommend short course antibiotics (3 days) for simple urinary tract infections but longer durations (7 days) for complicated urinary tract infections (20). The recommended 7-day duration is to ensure 'complete cure' to avoid complications. The evidence for antibiotic duration in complicated urinary tract infections is limited. In a meta-analysis of eight RCTs of antibiotic duration for pyelonephritis and urinary tract sepsis, the short duration was 5 days in 2 trials and 7 days in the remaining trials (21). This systematic review found that antibiotic courses of 7 days or less were equivalent to longer duration in preventing treatment failure, although findings suggested longer durations might be necessary for patients with urogenital tract abnormalities.

Fixed duration antibiotics have been trialled in an ICU setting. In a trial of 401 patients with ventilator-associated pneumonia (VAP), patients were randomised to 8 or 15 days of antibiotics (22). The investigators found that the 8-day course was not associated with an increase in mortality or recurrence of infection and resulted in a significant increase in antibiotic-free days at 28-days. This trial excluded patients with early-onset VAP and no recent antibiotics, so as to exclude infections with highly sensitive pathogens. Many patients with sepsis, despite the severity of illness, will have a highly sensitive pathogen and so it is likely that shorter durations could be sufficient for these patients.

Overall, the current evidence for antibiotic duration from specific source infections provides proof of concept that short durations may be applied safely in critically ill patients with sepsis.

2 RATIONALE

Critically ill patients with sepsis have not previously been included in trials of short duration antibiotics. This group of patients is particularly vulnerable to antibiotic overuse and associated harms. Severity of illness has often been an exclusion criterion for trials. As our understanding of the pathobiology of sepsis has advanced, we recognise that the organ dysfunction for which patients are admitted to critical care is a consequence of a dysregulated immune response (23). Critical illness does not necessarily imply failure of antibiotics or that prolonged antibiotics are necessary.

Although national guidelines recommend the shortest necessary duration of antibiotics, these fail to consider the individual and system-level factors that influence decision-making (24). Evidence to date suggests that clinicians are reluctant to discontinue antibiotics when presented with negative results (25,26).

A fixed short duration would provide a standardised, simple approach to antibiotic stewardship that could be widely implemented. If we demonstrate clear evidence of effectiveness and safety, this approach could form the basis of prescribing protocols and remove elements of individual prescribing behaviours. This approach to antibiotic stewardship accounts for challenges in reducing antibiotics in patients with life-threatening infections, such as the pressure to initiate antibiotics at the time of recognition of suspected sepsis. This intervention would be applicable to the range of source infections that lead to sepsis and provide an opportunity to reduce antibiotic exposure in patients who receive antibiotics for non-bacterial infections.

If we demonstrate that short duration antibiotic treatment is safe and effectively reduces antibiotic use in sepsis, this is likely to have major implications for patient care in the NHS and worldwide. If antibiotic durations were reduced from an average of 8 days to 5 days, this could avoid 120,000 antibiotic days per year in critically ill patients with sepsis in the UK.

2.1 Risk assessment

The main risk relates to the short course antibiotic intervention. The trial will test this short course of antibiotics because there is increasing evidence of the harms associated with antibiotics overuse. We believe that patients will benefit from the short course of antibiotics. However there remains a risk of undertreatment and the short course may not be suitable to some patients. We have mitigated this risk in a number of ways. Firstly, the trial excludes patients who would be at risk of under-treatment. These are patients with pre-existing immunosuppression or patients with an infection where a longer course of antibiotics is an established treatment. Secondly, due to the severity of illness, the intervention is not blinded. This means that the treating clinician will know if the patient is receiving short course antibiotics. Compliance with the short-course intervention will be strongly encouraged. However, if additional antibiotics are required beyond the initial course, clinical teams will be able to prescribe these. The trial is pragmatic and embeds the intervention in usual antibiotic stewardship practice. The clinical team will continue to have oversight of patient care and can make decisions necessary to maintain patient safety.

There is a burden associated with approaching patients and families during such a stressful time as critical illness. However, carrying out research in this patient group is important to continue to strive for better outcomes for critically ill patients. This research team and the critical care research teams at sites have considerable experience of obtaining consent (or assent) during such a difficult time. In this trial patients can be identified, consent and be randomised during the first 4 days of the course of antibiotics. This time interval was suggested by our lay team members as giving sufficient time for patients and families to consider participation in the trial.

3 OBJECTIVES AND OUTCOME MEASURES

3.1 Primary objective

To determine whether short duration antibiotic therapy (5 days) is non-inferior to standard of care antibiotic duration, in terms of 28-day mortality, and reduces overall antibiotic exposure in adult patients requiring admission to critical care with confirmed or suspected sepsis.

3.2 Secondary objectives

To assess the effect of short duration antibiotic therapy on:

- 90-day all-cause mortality

- Suspected clinically relevant antibiotic-associated adverse events
- Length of critical care unit stay
- Length of hospital stay
- Rate of further/recurrence of infections
- Readmission to critical care or hospital
- Cost-effectiveness compared to usual care at 90 days follow-up post intervention
- Cost-effectiveness compared to usual care over the patient's lifetime
- An embedded process evaluation will aim to understand the implementation of the trial protocol and willingness of clinicians to follow a fixed short-duration intervention.

3.3 Measurement of outcome measures

3.3.1 Defining the index course of antibiotics for sepsis

All outcomes will be measured from the start of the antibiotic course for sepsis, defined as trial day 1 (see 7.6.1 Schedule of Events). The index course of antibiotics are the antibiotics the patient is receiving for sepsis at the point of randomisation. Trial day 1 is the start of that index course of antibiotics. It is likely that this start date is a pre-randomisation event in the majority of patients.

Sepsis is generally treated with broad-spectrum antibiotics and so antimicrobial resistance is likely to be uncommon. However, if the initial course of antibiotics for sepsis proves to be inadequate due to a blood culture-proven resistant organism and antibiotics are changed, then 'trial day 1' will be reset with the index course of antibiotics starting with the adequate treatment. This can occur post-randomisation if necessary. This can only occur if the blood culture sample was collected at the start of sepsis treatment (e.g. as part of septic screen). Once the index course is identified, the clock will not be reset for empiric changes to antibiotics, including escalations.

Defining this index course of antibiotics should be undertaken by the research team, seeking agreement with the clinical team, to ensure that the trial aligns with clinical care.

3.3.2 Co-primary outcomes

- 28-day all-cause mortality (non-inferiority safety outcome)
- Total antibiotic treatment measured at 28 days (superiority clinical effectiveness outcome)

Antibiotic day outcomes will be measured in calendar days of antibiotic treatment (see 7.6.1 Schedule of events and 8.3 Schedule & Modifications). Breaks in antibiotic administration of less than 24 hours will be considered a continuous course. Only antibiotics for the active treatment of an infection will count towards this outcome. Antibiotics for prophylaxis, non-antimicrobial interventions (e.g. prokinetic effects) and those that are not systemically active (e.g. topical or local agents) will not be counted. Assessment of antibiotic indications will be undertaken by the local PI and research nurses with agreement from clinical teams.

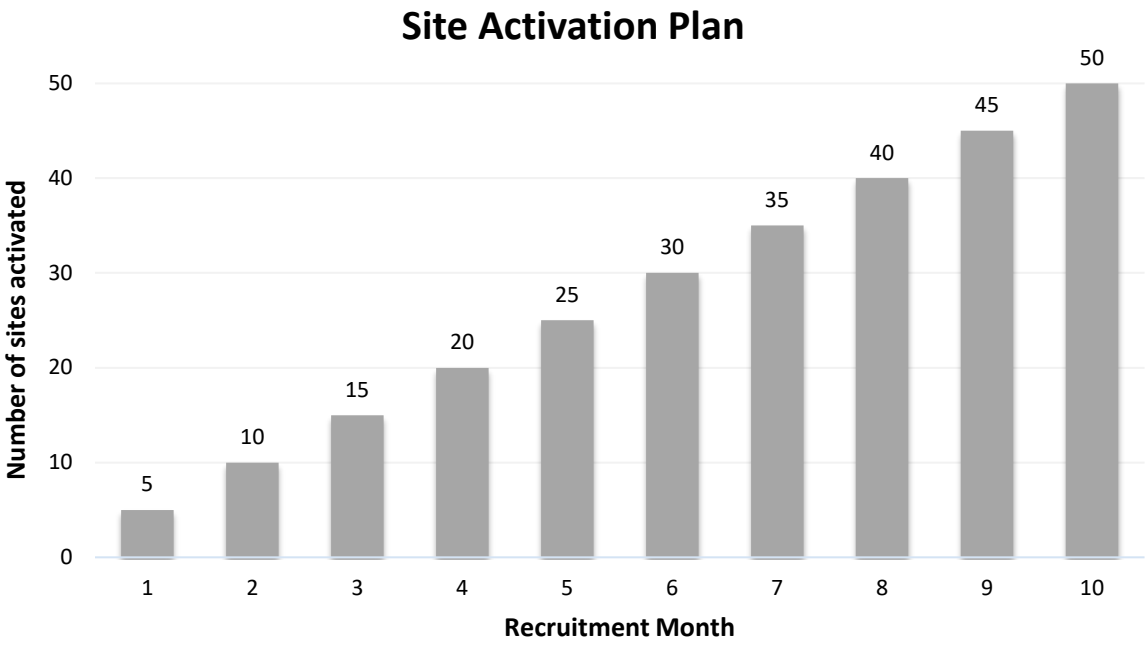
3.3.3 Secondary outcomes

- 90-day all-cause mortality and time until death
- Suspected clinically relevant antibiotic-associated adverse events during index hospital admission occurring from randomisation up to discharge
- Days alive and out of hospital up to 90 days
- Length (in days) of critical care unit stay up to 90 days for initial index episode of sepsis
- Length (in days) of hospital stay up to 90 days
- Duration of initial antibiotic course for sepsis
- Rate of further/recurrence of infections requiring additional antibiotic courses following the index sepsis episode up to 28 days. This will be assessed by the local team considering indication and restarting of antibiotics.
- Occurrence of readmission to critical care or hospital during the 90 day follow up period
- Incremental cost per death avoided
- Incremental cost per Quality Adjusted Life Year (QALY) gained at 90 days
- Cost-effectiveness acceptability curves (CEACs) to assess the probability of the intervention being considered cost-effective at different willingness-to-pay (WTP) thresholds for a gained QALY at 90 days
- Average healthcare costs per participant over 90 days for each area of resource use.
- Utility scores derived from responses to the EQ-5D-5L questionnaire at 90 days
- Average QALYs per participant at 90 days
- Incremental cost per QALY gained over the patient's lifetime
- Cost-effectiveness acceptability curves (CEACs) to assess the probability of the intervention being considered cost-effective at different willingness-to-pay (WTP) thresholds for a gained QALY over the participant's lifetime

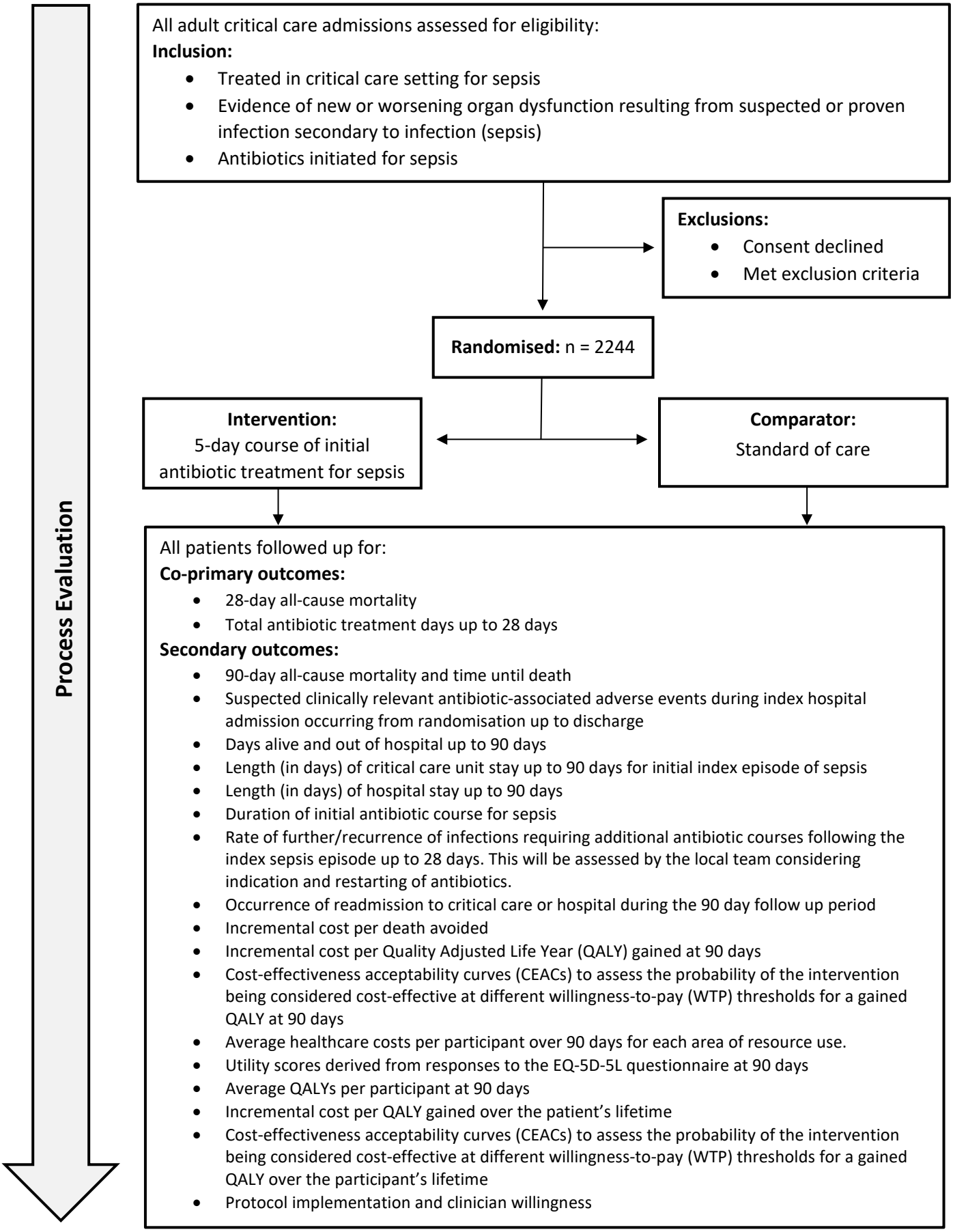
4 TRIAL DESIGN

This is a pragmatic, open-label, multi-centre, parallel arm, randomised controlled trial (RCT), with two co-primary outcomes, an internal pilot phase and an embedded process evaluation, to assess the clinical and cost-effectiveness of short, fixed-course antibiotics compared to standard of care in adult patients admitted to critical care with confirmed or suspected sepsis. Critical care units include both high dependency units (HDU) and intensive care units (ICU). A HDU setting provides 'level 2' care including monitoring of two organ systems and advanced support of one organ system (other than advanced respiratory support). An ICU setting provides 'level 3' care including advanced respiratory support alone, or advanced support of two or more organ systems (27).

The trial will involve up to 50 UK NHS sites which will be opened as soon as possible in a phased manner over a 10-month period. An example of the site activation plan is shown in the chart below, however, site set up is not restricted to this plan and sites ready to open earlier than planned will be activated earlier by the trial management team, where possible. Following the end of the 10-month site activation period there will be a further 16 months of recruitment.



4.1 Trial flow diagram



4.2 Internal pilot

An internal pilot will be conducted for the first 12 months of recruitment to assess site opening and recruitment rates. Screening, recruitment, and the difference between arms for the duration of antibiotics during the intervention period will be monitored. Data will be collected from screening logs, case report forms (CRFs) and during site monitoring.

The following progression criteria will be used to assess progression to the full trial at 12 months:

Progression criteria	**Red**	**Amber**	**Green**
Trial recruitment 30% complete (i.e. 673 recruited)	<50%	≥50%, <100%	100%
Recruitment rate/site/month	<1/site/month	1-2/site/month	2/site/month
Number of sites open	<25	≥25, <50	50
Between group difference (control-intervention) in duration of initial antibiotic course (intervention period; antibiotic days)	<1	≥1, <2	≥2

To ensure that all 12-month data are available for review of progression criteria, the review will take place approximately 1 month after the 12-month point has been reached. Recruitment to the trial will continue while the progression review is ongoing.

The Trial Steering Committee (TSC) will review progress against these progression criteria. Green criteria will result in seamless transition into the main trial. Amber criteria will allow progression to main trial with expansion of sites and alterations to recruitment plan. In the event of red criteria, the TSC in association with the Health Technology Assessment secretariat will consider the viability of the trial.

5 STUDY SETTING

5.1 Recruitment

This is a multi-centre trial; patients will be recruited from approximately fifty adult general critical care units throughout the UK. Recruiting sites will be identified and selected following feasibility assessments. The lead site is The Newcastle upon Tyne Hospitals NHS Foundation Trust.

5.2 Trial assessments

Trial assessment will be completed during the participant's in-patient stay. Depending on the date of the participants discharge from hospital, assessments may be completed in out-patient clinics, remotely via telephone or post (for questionnaires) by local research teams. Follow up data may also be collected without participant contact via the General Practitioner (GP) or Intensive Care National Audit & Research Centre (ICNARC) (or equivalent in the devolved nations) data requests.

6 ELIGIBILITY CRITERIA

Eligibility will be assessed by site research teams and this assessment documented in the patient's medical records. Only personnel formally delegated to assess eligibility by the Principal Investigator (PI) at each site may perform this task.

6.1 Inclusion criteria

Sepsis is defined as new or worsening organ dysfunction resulting from a suspected or proven infection (23). Patients admitted to critical care for support or monitoring of an organ dysfunction (e.g. invasive blood pressure monitoring or oxygen therapy), while treated for a suspected infection, are the population of interest.

Patients must fulfil all of the following inclusion criteria prior to randomisation:

1. Adult patients, aged ≥ 18, treated within a critical care setting (ICU or HDU) for suspected or confirmed sepsis due to either community- or hospital-acquired infections
2. Evidence of new or worsening acute organ dysfunction resulting from suspected or confirmed infection (e.g. the treatment or monitoring of an organ dysfunction)
3. Antibiotics initiated for suspected or confirmed sepsis and able to be randomised within 4 days of the initiation of this course of antibiotics (see 3.3.1 Defining index course of antibiotics for sepsis).

6.2 Exclusion criteria

Patients must not meet any of the following exclusion criteria to be randomised:

1. Comorbidity with immunosuppression (e.g. Chemotherapy, maintenance steroids equivalent to >10mg/day of prednisolone, post-transplantation)

2. Blood neutrophil count less than 0.5 x 10^9/L secondary to a pre-existing comorbidity
3. Infection source where usual practice involves more than 14 days of antibiotics (e.g. undrainable abscess, endocarditis, *Staphylococcus aureus* bacteraemia, osteomyelitis)
4. Receiving end-of-life care
5. Life-sustaining treatment expected to be withdrawn within the next 24 hours
6. The clinician responsible for the patient's care is unable to adhere to the intervention

Enrolling a patient onto the trial who does not meet the inclusion/exclusion criteria is considered a protocol waiver; protocol waivers are not permitted.

7 TRIAL PROCEDURES

7.1 Recruitment

7.1.1 Screening and patient identification

Site research teams, who are embedded in and part of the usual care team, will screen all adult patients (≥ 18 years old) admitted to critical care on a daily basis. Potentially eligible patients will be identified by the initiation of new courses of antibiotics. Of these patients, those treated with antibiotics for either suspected or confirmed sepsis, caused by either community- or hospital-acquired infections, may be eligible for the trial. The start date of a new course of antibiotics indicated for sepsis/suspected sepsis will be identified, patients will only be screened for eligibility/recruited to the trial during antibiotic treatment days 1 to 4.

The potentially eligible patients identified will be highlighted to the clinical team as suitable to approach for the trial. Patients or consultees will be approached about the trial following agreement from the clinical team.

A screening log will be maintained at each research site to record reasons for potential patients not being eligible and reasons for patients or consultees declining consent.

7.1.2 Consent

Potential participants within a critical care setting may or may not have capacity, and their capacity may change during their hospital stay. Capacity may be lacking due to severity of illness or sedative

medications used as part of the critical care treatment (e.g. patients sedated while on mechanical ventilation). Capacity will be assessed by delegated members of the site trial team prior to consent and documented in the patients' medical records.

Consent discussion must be documented in the patients' medical records by the person taking consent. Documentation should include the following details:

- Date that the patient/Consultee/Legal Representative was given a trial information sheet
- Name, date and version of the trial information sheet given
- Any questions asked by the patient/Consultee/Legal Representative and whether these were satisfactorily answered
- Name, date and version of the Informed Consent Form (ICF) used

7.1.2.1 Consent for patients with capacity

Patients who have capacity will be approached to provide informed consent. The patient will be informed of the trial by a member of the site research team, who are embedded in and part of the usual care team, and given a Participant Information Sheet (PIS). Patients will be given sufficient time to consider participation in the trial and the opportunity to ask questions and have these satisfactorily answered. If the patient decides to proceed with the trial, they will be asked to provide consent by completing and signing an ICF; this will be prior to any further trial specific activity. Consent will be taken by the site PI or another appropriately trained and delegated member of the site research team.

A copy of the ICF will be retained by the patient, a copy will be placed in the patient's medical records and the original will be retained in the Investigator Site File (ISF).

Ongoing consent will be monitored while the patient remains in hospital. Patients who are transferred or discharged prior to the 28-day follow up data collection points will be assumed to have ongoing consent to participation.

7.1.2.2 Consent for patients lacking capacity in England, Wales and Northern Ireland

7.1.2.2.1 Assent

Assent procedures follow the legal requirements of the Mental Capacity Act 2005 (England and Wales) and the Mental Capacity Act 2016 (Northern Ireland). The responsible clinician or delegated member

of the research team will approach an individual who has an interest in the patient's welfare, usually the next of kin, to act as a Personal Consultee. This individual will provide an opinion on the views of the patient towards participation in the trial. The Personal Consultee will be provided with a Consultee Information Sheet and given sufficient time to consider the patient's participation in the trial. The research team may contact the Personal Consultee by telephone to ascertain whether the Consultee considers that the patient would wish to participate. If the Personal Consultee considers that the patient would wish to participate, a written record of this must be made using a Consultee Declaration Form.

Every effort will be made by the research team to contact a patient's next of kin to act as a Personal Consultee. In the event that there is no suitable person to act as a Personal Consultee, then a medical professional who is independent of the research team can act as a Nominated Consultee. This will usually be the patient's critical care consultant. Consultees will be informed that the patient's consent will be sought if capacity is regained.

7.1.2.2.2 Regaining capacity

Patients will be followed up during the trial to determine whether capacity is regained. In the event that capacity is regained during participation in the trial, the patient will be informed of their participation in the trial. They will be provided with a PIS and be given sufficient time to consider ongoing trial participation. If the patient agrees to ongoing participation, they will be asked to sign a Retrospective Informed Consent Form. If the patient does not agree to ongoing participation, they will be withdrawn from the trial (see section 7.7).

7.1.2.2.3 Loss of capacity

Patients who provide consent cannot be assumed to provide ongoing consent in the event of loss of capacity. Since loss of capacity is a likely outcome for a significant proportion of critically ill patients, this will be anticipated when the patient provides consent. Patients will be asked to identify an individual who is able to provide ongoing consent monitoring in the event of loss of capacity. When capacity is lost, the research team will discuss ongoing participation in the trial with the patient's representative. If any objections are raised, the research team will discuss potentially withdrawing the patient from the trial with the representative (see section 7.7). Outcome data collected from routinely collected electronic data sources will continue to be collected.

7.1.2.3 Consent for patients with incapacity in Scotland

7.1.2.4 Consent

Consent procedures will follow the legal requirements of the Adults with Incapacity Act 2000 (Scotland). A patient's Welfare Guardian, Welfare Attorney or nearest relative can act as a Legal Representative for an adult with incapacity. As per the legal framework, anyone seeking consent in Scotland must ensure that there is no Welfare Guardian or Welfare Attorney in place to act as the Legal Representative before seeking consent from the nearest relative for this role. As this trial is a non-CTIMP (Clinical Trials of an Investigational Medicinal Product) there will be no professional (i.e. Consultant/Medical Practitioner) Legal Representatives.

The Legal Representative will be informed of the trial and provided with a Legal Representative Information Sheet. The Legal Representative will be given sufficient time to consider the patient's participation in the trial. If the Legal Representative, after considering the past and present feelings and wishes of the patient, considers that the patient would wish to participate in the trial, then a Legal Representatives Consent form will be signed. In the event that the Legal Representative is unable to attend in person to provide consent, telephone consent will be permitted. This telephone conversation will be witnessed by a second member of staff and documented in the patient's medical records. The Legal Representative will provide written consent at the next available opportunity. Legal Representatives will be informed that patient consent will be obtained if the patient regains capacity.

7.1.2.4.1 Regaining capacity

Patients will be followed up during the trial to determine whether capacity is regained. In the event that capacity is regained during participation in the trial, the patient will be informed of their participation in the trial. They will be provided with a PIS and be given sufficient time to consider ongoing trial participation. If the patient agrees to ongoing participation, they will be asked to sign a Retrospective Consent Form. If the patient does not agree to ongoing participation, they will be withdrawn from the trial (see section 7.7).

7.1.2.4.2 Loss of capacity

Since loss of capacity is a possible event for patients, provision for this event will be covered in the original patient consent. Monitoring of ongoing consent will be sought through a Legal Representative. The Legal Representative can withdraw that patient from the trial if they raise objections (see section 7.7), although consideration must be given to the patient's prior wishes.

7.2 Randomisation

For those patients where informed consent is in place and the eligibility criteria are fulfilled, randomisation will be carried out up to day 4 of antibiotic treatment. Patients will be randomised 1:1 to short-course antibiotic therapy (intervention) or standard of care (comparator). The randomisation sequence will be generated using random permuted blocks. Randomisation will be stratified by:

- Centre
- Community-acquired versus hospital-acquired infection (Hospital-acquired infections will be defined as occurring after 48hrs after admission to hospital)

Randomisation will be performed by a delegated and trained member of the site trial team using Sealed Envelope's Red Pill System. This is a secure web-based randomisation system with concealed allocation. Appropriately delegated members of the site trial team will be provided with a unique login and password for the randomisation system, arranged via Newcastle Clinical Trials Unit (NCTU).

Randomisation system web address: https://www.sealedenvelope.com/access/

The system is available 24 hours a day, 7 days a week

In the unlikely event that the online randomisation system is not accessible, the site trial team should contact the NCTU data management team within normal working hours (9am-5pm Monday to Friday, excluding bank holidays and Newcastle University closures) by emailing:

NCTU Data Management team email: nctu.database.support@newcastle.ac.uk

The information required to be entered prior to randomisation are:

- Infection type: community or hospital acquired
- Date and time that the antibiotic treatment for sepsis was started

Each patient considered for the trial will be assigned a unique trial ID. This is a 6-digit code assigned by the site trial staff made up of a 2-digit site number and a sequential 4-digit number, for example, site 11 would assign 110001, 110002, 110003 etc. For patients screened who go on to be randomised to the trial, the unique trial ID assigned to them will remain unchanged. No unique trial ID will be re-issued, for example when there is a patient screened and deemed not eligible to take part in the trial.

Once randomisation is complete, confirmation of successful randomisation will be displayed on the screen. For patients randomised to the intervention arm, the confirmation of randomisation will also include the date and time that the initial antibiotic treatment should be stopped.

7.3 Blinding

This will be an open-label trial. Clinical and research teams will not be blinded to trial arm. Any trial analysis will occur once the Statistical Analysis Plan is finalised as those assessing outcomes will not be blinded.

7.4 Out of hours contact

No out of hours contact is required for this trial. Trial participants are admitted to a critical care unit and will be managed at the care team's discretion.

7.5 Payment

No payments will be made to participants. Participants are not required to travel for trial follow-up.

7.6 Trial assessments

7.6.1 Schedule of events

Trial days will be counted in days starting from day 1 which is the day of the initiation of antibiotics for suspected/confirmed sepsis. The research team should discuss with the clinical team to agree on the start date/time of the antibiotic treatment for suspected/confirmed sepsis (see 3.3.1 Defining index course of antibiotics for sepsis). This will be recorded in the participants medical records and in the trial database as part of randomisation. All trial intervention and outcome days will be counted from this start point.

Antibiotics for sepsis	*Day 1*	*Day 2*	*Day 3*	*Day 4*	*Day 5*	*Day 6 – Day 14 (according to course length)*				
Trial day	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 7-28**	**Discharge**	**Day 90**
Record date and time of first dose of antibiotics for sepsis	X									
Screening & Identification	Screening of patients on antibiotics for sepsis									
Consent	Patient consent (or Consultee declaration/Legal Representative consent)									
Randomisation	Following consent on days 1-4									
Add antibiotic stop date and time* to prescribing system for participants randomised to short-course antibiotic therapy (intervention)	X (as soon as possible following randomisation)									
Baseline data collection	X									
Laboratory data collection	$X^{+/-}$		$X^{+/-}$		$X^{+/-}$		$X^{+/-}$		$X^{+/-}$	
SOFA score	$X^{+/-}$				$X^{+/-}$		$X^{+/-}$			
Functional Comorbidity Index	X									

Antibiotics for sepsis	*Day 1*	*Day 2*	*Day 3*	*Day 4*	*Day 5*	*Day 6 – Day 14 (according to course length)*				
Trial day	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 7-28**	**Discharge**	**Day 90**
APACHE II Score	Within 24 hours of admission to critical care									
Antibiotic stop date for participants randomised to short-course antibiotic therapy (intervention)					X*[$]					
Antibiotic stop date for participants randomised to standard care (comparator)	Antibiotic duration as per standard of care									
Assessment of duration of initial course					Between days 5-14					
All-cause mortality assessment								X		X
Antibiotic treatment days to 28 days								X		
Adverse event reporting (suspected clinically relevant antibiotic-associated adverse events and serious adverse events)	Reported from randomisation up to discharge									
Length of critical care unit stay									X	
Length of hospital stay									X	
Further/reoccurrence of infection requiring antibiotic courses								X		
Readmission to hospital										X
Readmission to critical care										X
EQ-5D-5L									X	X[¥]

Antibiotics for sepsis	*Day 1*	*Day 2*	*Day 3*	*Day 4*	*Day 5*	*Day 6 – Day 14 (according to course length)*				
Trial day	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 7-28**	**Discharge**	**Day 90**
Healthcare utilisation questionnaire										X¥
Time and Travel questionnaire										X¥

+/- Assessment may take place within +/- 1 day

* As per instruction of antibiotic stop date and time given at randomisation.

$ Depending on the start time of antibiotics, this may occur on day 6 in practice.

¥ Completed by participants or by proxy at day 90 (+ 14 days).

7.6.2 Baseline data collection

Baseline data collection will include collection of the following data:

- NHS/Community Health Index (CHI)/Health & Care (H&C) (or local equivalent) number, date of birth, sex at birth, ethnicity, employment status and postcode
- For sites taking part in ICNARC; CMP (Case Mixed Programme) number
- For sites taking part in SICSAG; Ward Watcher patient ID number
- Admission diagnosis (at admission to critical care)
- Start date and time of antibiotics for sepsis
- Date and time of admission to hospital
- Date and time of admission to critical care
- Infection source including investigations confirming source
- Sequential organ failure assessment (SOFA) (see section 7.6.6) at baseline
- Functional comorbidity index (see section 7.6.4)
- Acute Physiology And Chronic Health Evaluation (APACHE) II score (see section 7.6.5) within 24 hours of admission to critical care
- Organ support at baseline (including detail of use of any vasopressors, respiratory support or renal replacement therapy) up to treatment day 5 of the initial course of antibiotic treatment for sepsis
- Antibiotic treatment
- Corticosteroid treatment up to treatment day 5 of the initial course of antibiotic treatment for sepsis
- Routine laboratory values (e.g. white cell count, CRP)

7.6.3 Laboratory data collection

Data from routine blood samples taken as part of standard care will be collected at trial days 3, 5 and 7 and at discharge. These will include the white cell count with differentials (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and C-Reactive Protein (CRP).

7.6.4 Functional comorbidity index

The Functional Comorbidity Index (FCI) is an 18-item list of diagnoses used to determine the level of function of patients. FCI has been shown to correlate with Health Related Quality of Life (HRQoL) following critical illness survival (28). Each diagnosis is scored, if the diagnosis is not present for the

patient the score is 0 and if it is present the score is 1. The Functional Comorbidity Index gives a total score between 0 and 18 (29).The Functional Comorbidity Index is assessed at trial day 1.

Table 1. Functional Comorbidity Index

Functional Comorbidity Index		**Score** Absent = 0, Present = 1
1	Arthritis (rheumatoid and osteoarthritis)	
2	Osteoporosis	
3	Asthma	
4	Chronic Obstructive Pulmonary Disease (COPD), Acute Respiratory Distress Syndrome (ARDS) or emphysema	
5	Angina	
6	Congestive heart failure (or heart disease)	
7	Heart Attack (Myocardial Infarct)	
8	Neurological disease (such as Multiple Sclerosis or Parkinson's)	
9	Stroke or Transient Ischaemic Attack (TIA)	
10	Peripheral vascular disease	
11	Diabetes type I and II	
12	Upper gastrointestinal disease (ulcer, hernia, reflux)	
13	Depression	
14	Anxiety or panic disorders	
15	Visual impairment (such as cataracts, glaucoma, macular degeneration)	
16	Hearing impairment (very hard of hearing, even with hearing aids)	
17	Degenerative disc disease (back disease, spinal stenosis, or severe chronic back pain)	
18	Obesity and/or body mass index > 30 (weight in kg, height in m^2)	
	Total score:	

7.6.5 Acute Physiology And Chronic Health Evaluation (APACHE) II score

The Acute Physiology And Chronic Health Evaluation (APACHE) II Score is a measure of disease severity based on scores given to 12 physiological measurements along with age and previous health status (30). The APACHE II score ranges from 0 to 71, with higher scores indicating increased risk of mortality. The APACHE II score will be assessed within 24 hours of admission to critical care.

7.6.5.1 APACHE II data collected for sites participating in the ICNARC Case Mix Programme (CMP) or SICSAG

Those sites taking part in the ICNARC Case Mix Programme (CMP) will record each participants CMP number in the trial database. Sites taking part in SICSAG will record each participants Ward Watcher patient ID number in the trial database. This will be used to collect APACHE II data centrally.

7.6.5.2 APACHE II data collected for sites NOT participating in the ICNARC Case Mix Programme (CMP)

For those sites not taking part in the ICNARC CMP or SICSAG the following data, accounting for the first 24 hours in the critical care unit, will be recorded in the database:

- Detail of whether the participant was admitted from operating theatre/recovery
- Past medical history (to include whether or not the following are present biopsy proven cirrhosis, portal hypertension, hepatic encephalopathy, very severe cardiovascular disease, severe respiratory disease, home ventilation, chronic renal replacement, HIV. AIDS, steroid treatment [daily for 6 months], radiotherapy, chemotherapy, metastatic disease, acute myelogenous/lymphocytic leukaemia or multiple myeloma, chronic myelogenous/lymphocytic leukaemia, lymphoma, congenital immunohumoral or cellular immune deficiency state)
- Arterial Blood Gas (ABG) with lowest PaO_2
- ABG with lowest pH (or highest H^+)
- Temperature (central and non-central), blood pressure, heart rate, non-ventilated/ventilated respiratory rate
- Serum sodium, potassium, creatinine, white blood cell count
- Assessment of Glasgow Coma Score (GCS)
- Primary reason for admission to critical care (to include detail of body system [e.g. respiratory, cardiovascular, gastrointestinal etc])

7.6.6 Sequential Organ Failure Assessment (SOFA) score

The Sequential Organ Failure Assessment (SOFA) score is a scoring system used to assess the performance of organ systems in the body, as detailed in Table 2 (23). The SOFA score will be assessed at trial days 1, 5 and 7. If measurements used to calculate the SOFA score have been taken routinely prior to a participants' consent to the trial, the most recent measurements from the medical records should be used to assess the SOFA score at trial day 1. The components of the SOFA score (as detailed in Table 2) will be recorded on the trial database.

Table 2. SOFA Score

Organ System, Measurement	SOFA Score				
	0	**1**	**2**	**3**	**4**
Respiration PaO_2/FiO_2, mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7)*	<100 (13.3)*
Coagulation Platelets x $10^3/mm^3$	≥150	<150	<100	<50	<20
Liver Bilirubin, mg/dL (µmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular Hypotension	Mean Arterial Pressure (MAP) ≥ 70mmHg	MAP <70mmHg	Dopamine <5 or dobutamine (any dose)**	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1**	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1**
Central Nervous System Glasgow Coma Score	15	13-14	10-12	6-9	<6
Renal Creatinine, mg/dL (µmol/L) or urine output	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) or <500mL/day	>5.0 (440) or <200mL/day

* with respiratory support

**Adrenergic agents administered for at least 1 hour (doses given are in µg/kg/min)

7.6.7 Mortality assessments

All-cause mortality will be assessed at trial days 28 and 90. The information recorded in the participants medical records and the trial database will be:

- Is the participant alive? Yes/No
    - If no: please record the date of death

7.6.8 Hospital and critical care admission information

The following data will be recorded for each participant from trial day 1 up to trial day 90. Where possible these data will be collected via data requests with ICNARC or other local equivalents who collect these data routinely. Data recorded on the trial database are:

- Date of admission and discharge from hospital for index sepsis
- Date of admission and discharge from critical care unit for index sepsis
- Date of start and stop of organ support for index sepsis
- Date of any/each readmission and discharge from hospital
- Date of any/all readmissions and discharges from critical care

7.6.9 Antibiotic treatment information

The following data will be recorded for each participant from trial day 1 up to trial day 28. Information will be taken from participants medical records or from the local site research team gathering the information from primary care GP practices. Data collected and recorded on the trial database are:

Antibiotic course	Data collected
Initial course of antibiotics for index sepsis	• Antibiotic name • Start date and time first dose administered • Actual stop date and time last dose administered* • Dose (including any dose changes) • Number of doses administered per day • Route of administration
Any further antibiotic treatment (up to trial day 28)	• Antibiotic name • Start date and time first dose administered • Actual stop date and time last dose administered • Dose (including any dose changes) • Number of doses administered per day • Route of administration

* this should be the actual stop date and time of the antibiotic treatment given for the index sepsis irrespective of any antibiotic stop date and times indicated at the point of randomisation

7.6.10 Infection data

Data related to infection source for sepsis episode will be collected. Suspected or confirmed site of infection will be collected. Hospital-acquired infection will be defined as occurring after 48hrs after admission to hospital. Microbiology culture results supporting diagnosis will be collected for the initial sepsis episode and subsequent infections requiring antibiotics. In addition, occurrence of

antimicrobial resistant infections and *Clostridium difficile* infections will be recorded as part of the 'suspected clinically relevant antibiotic-associated adverse events' outcome.

7.6.11 Co-enrolment

Co-enrolment of SHORTER participants to observational studies is permitted. Co-enrolment of SHORTER participants to other interventional trials will be permitted following consideration of potential trial interactions and burden to participants. In these cases, co-enrolment will be agreed between both trial teams following review of both protocols by the CIs and agreement by the SHORTER TMG.

A list of approved interventional trials for co-enrolment is available on the trial website (www.shortertrial.com) in the 'Information for Sites' section.

Data related to any other studies in which a participant is enrolled will be collected and recorded on the SHORTER trial database. These data will include;

- Study name
- Participant/Study/Trial ID assigned in the co-enrolled study
- Date of enrolment into co-enrolled study
- Time of randomisation in co-enrolled study (only if the date of co-enrolment is the same date as randomisation to SHORTER)
- Allocated treatment group (including any crossovers) in co-enrolled study, if known (i.e. co-enrolled study is open label)

7.6.12 Trial questionnaires

7.6.12.1 5-level EuroQol 5D index (EQ-5D-5L)

EQ-5D-5L is a validated questionnaire that is applicable to a wide range of health conditions; it provides a simple descriptive profile and a single index value for health status. It consists of two parts which are completed by participants. Part 1 is descriptive and consists of a visual analogue scale which records the participant's self-rated health on a 20 cm vertical with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'. Part 2 is profile based on 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression considered at 5

increasingly worsening levels. Published, validated tariff values can then be easily attached to the returned profiles to use as health state valuations in determining Quality Adjusted Life Years (QALY).

Site trial staff will advise participants how to complete the EQ-5D-5L and about the contents of the questionnaire. Participants with capacity will self-complete the EQ-5D-5L. In cases where participants lack capacity, a proxy version of the EQ-5D-5L can be completed by the participant's next of kin/Consultee (for sites in England, Wales and Northern Ireland) or the participant's next of kin/Welfare Attorney/Welfare Guardian/Nearest Relative (for sites in Scotland). In all cases, the EQ-5D-5L should be completed at discharge and at trial day 90.

7.6.12.2 Healthcare Utilisation Questionnaire

The Healthcare Utilisation Questionnaire assesses participants' use of healthcare services during their trial participation. It will be self-completed by participants with capacity. In cases where participants lack capacity, the Healthcare Utilisation Questionnaire can be completed by proxy (i.e. next of kin/Consultee for sites in England, Wales and Northern Ireland or next of kin/Welfare Attorney/Welfare Guardian/Nearest Relative for sites in Scotland). In all cases, the Healthcare Utilisation Questionnaire should be completed at trial day 90.

7.6.12.3 Time and Travel Questionnaire

The Time and Travel Questionnaire assesses the transport and time used to utilise healthcare appointments. It will be self-completed by participants with capacity. In cases where participants lack capacity, the Time and Travel Questionnaire can be completed by proxy (i.e. next of kin/Consultee for sites in England, Wales and Northern Ireland or next of kin/Welfare Attorney/Welfare Guardian/Nearest Relative for sites in Scotland). In all cases, the Time and Travel Questionnaire should be completed at trial day 90.

7.7 Withdrawal criteria

Participants have the right to withdraw from all or some aspects of the trial at any time without having to give a reason or having their ongoing care effected. Although a reason does not need to be given, it is encouraged that Investigators at sites try to ascertain the reason for withdrawal and document this reason in the participant's medical records and on the trial database.

Participants may withdraw from the following aspects of the trial:

- Withdrawal from trial intervention, trial follow-up, or both, but allow follow up data collection and use of routinely available electronic data
- Withdrawal from trial intervention, trial follow-up, or both, withdrawal from follow up data collection but allow use of routinely available electronic data that does not involve further patient contact
- Withdrawal from trial intervention, trial follow-up, or both and further data collection

Participants may withdraw themselves or be withdrawn by their Consultee or Legal Representative if the participant lacks capacity. Participants may also be withdrawn by an investigator where continuing to undergo trial assessments or follow up would place unreasonable demands on the participant. If an investigator chooses not to follow the antibiotic stop date and time given at randomisation, the participant should NOT be withdrawn from the trial. If an Investigator withdraws a participant, the participant/Consultee/Legal Representative must be informed of the decision and asked their wishes in regard to further data collection.

A Withdrawal form will be completed for all participant withdrawals. This will be either a Participant/Consultee/Legal Representative Led Withdrawal form or an Investigator Led Withdrawal form. This will be stored in the participants medical records and on the trial database.

Participant withdrawal may also take place if the trial is terminated early by the sponsor. Participants who withdraw from the trial will not be replaced.

7.8 Post-trial care

Participants will receive standard NHS care for treatment of their sepsis alongside their trial participation. After the final trial follow up is complete participants will continue to receive the standard NHS care.

7.9 End of trial

The trial will end when the final participant has completed the 90-day follow up period, all information has been collected, questionnaires completed (as determined by trial management staff with reasonable effort from the site trial team to gather these data) and the database is locked.

The trial will be stopped early if:

- Mandated by the Research Ethics Committee (REC)
- Following recommendation from the TSC
- Funding for the trial is withdrawn

The REC that provided a favourable ethical opinion will be notified within 90 days, or within the relevant regulatory time frame, of the trial ending.

8 TRIAL INTERVENTION

8.1 Intervention: short, 5-day, fixed course antibiotic therapy

The intervention is a 5-day, fixed, initial course of antibiotic treatment. The index course of antibiotics are antibiotics for the active treatment for sepsis as outlined in section 3.3.1.

The initiation of antibiotics will be a pre-randomisation event. The date and time of the initiation of antibiotics for suspected/confirmed sepsis, as agreed by the clinical team, must be entered into the database at randomisation. After randomisation, for participants randomised to short course antibiotics (intervention), a stop date and time will be confirmed which will account for a 5-day course of antibiotics from the date and time that the index antibiotic course for sepsis was initiated (as entered at randomisation).

Sites should identify a process to add the stop date and time of antibiotics given for sepsis to the local prescribing system. For participants randomised to the intervention arm only, the stop date and time of antibiotics must be entered onto the local prescribing system as soon as possible after randomisation. This approach will ensure that antibiotics are not continued unnecessarily and will ensure that if antibiotics need to continue, that there has been a review of the participant with an active and documented decision to extend antibiotic treatment.

As outlined in section 3.3.1, if the initial course of antibiotics for sepsis are inadequate due to a blood culture-proven resistant organism, then the course start time can be reset at the initiation of adequate antibiotics. This could be a post-randomisation event. This event will be recorded in the electronic Case Report Form (eCRF), with the new start and date time. The research team will ensure that the course of adequate antibiotics in the intervention arm will be 5-days duration.

The intervention only relates to the *duration* of the *initial* course of antibiotics. The choice or combination of antibiotics will be according to clinical teams according to local antibiotic guidelines. Any biomarker-guided antibiotic duration algorithm that is in use at a trial site should not be used to extend the antibiotic duration beyond 5 days in the intervention arm. Additional antibiotics may be given after the initial course, if indicated. All other aspects of usual care such as multi-disciplinary antibiotic stewardship will continue in the intervention arm.

Antibiotics for prophylaxis are not considered 'active' treatment. In addition, antibiotics used for non-antimicrobial indications (e.g. prokinetic effects) and those that are not systemically active (e.g. topical or local agents) will not count towards the intervention.

8.2 Comparator

The duration of antibiotics will be according to the standard of care. This will be guided by the treating clinician, local antibiotic guidelines and usual antibiotic stewardship practice.

8.3 Schedule and modifications

Antibiotic duration will be measured in days (referred to as trial days in the schedule of events). Since antibiotics are initiated at different times of the day, antibiotic days in the intervention and comparator arms will be measured centrally in 24-hour periods from the date and time of initiation of antibiotics for sepsis. The intervention is 5x 24-hour periods of antibiotics; a stop date and time based on this criteria will be confirmed at randomisation for those randomised to the intervention arm.

Any breaks in antibiotic administration of less than 24-hours will be counted as a continuous duration. Alterations in dose and frequency during the course (e.g. adjustments for renal function) do not constitute a new course. Change in antibiotic class (e.g. broadening or narrowing of antibiotic cover) once the index course has started, does not constitute a new course.

Example 1:

24-hour period	Mon 6am – Tues 6am	Tues 6am – Wed 6am	Wed 6am – Thurs 6am	Thurs 6am – Fri 6am	Fri 6am – Sat 6am
Antibiotic day	Day 1	Day 2	Day 3	Day 4	Day 5

	Mon	Tues	Wed	Thurs	Fri
Example drug chart	6am ✓	6am ✓	6am ✓	6am ✓	6am ✓
	2pm ✓	2pm ✓	2pm ✓	2pm ✓	2pm ✓
	10pm ✓	10pm ✓	10pm ✓	10pm ✓	10pm ✓

Example 2:

24-hour period	Mon 2pm–Tues 2pm	Tues 2pm–Wed 2pm	Wed 2pm – Thurs 2pm	Thurs 2pm – Fri 2pm	Fri 2pm – Sat 2pm
Antibiotic day	Day 1	Day 2	Day 3	Day 4	Day 5

	Mon	Tues	Wed	Thurs	Fri	Sat
Example drug chart	6am	6am ✓	6am ✓	6am ✓	6am ✓	6am ✓
	2pm ✓	2pm ✓	2pm ✓	2pm ✓	2pm ✓	2pm
	10pm ✓	10pm ✓	10pm ✓	10pm ✓	10pm ✓	10pm

8.4 Assessment of compliance

Duration of initial course of antibiotics will be monitored during the trial. Participants will be followed up between days 5-14 to determine the actual duration of the initial antibiotic course. Duration of initial course will be monitored by the DMC and will form part of the progression criteria for the internal pilot phase.

9 PROCESS EVALUATION

A process evaluation (PE) will be undertaken within the SHORTER trial given that antibiotic use in critically ill patients is a complex decision-making process influenced by a range of cultural, contextual, and behavioural factors. Based on previous evidence, it is likely that antibiotic practices vary across ICU sites. Therefore, it is essential that we develop a detailed understanding of how the study intervention is operationalised in individual sites with a view to developing an understanding of the relationship between implementation and trial outcomes. The results of the process evaluation, in the context of the trial outcomes, will help us to distinguish between intervention failure and implementation failure, which will be essential information for interpreting trial results.

9.1 Aim of process evaluation

The aim of the process evaluation is to explore the processes involved in intervention delivery and implementation and identify the factors and mechanisms of their interaction likely to impact trial outcomes. Specific objectives are:

- To establish the extent to which the intervention is delivered as intended (implementation fidelity);
- To ascertain how clinical staff understand and respond to the intervention;
- To identify barriers and facilitators that affect the implementation of the trial protocol;
- To explore the importance of context (the environment and its characteristics, including inter-critical care unit differences).

9.2 Theoretical approach

The process evaluation used in the trial is based on a theory-driven approach including:

- developing a logic model to represent graphically how an intervention works from its delivery through to mechanisms of change and outcomes;
- drawing on the Conceptual Framework for Implementation Fidelity (31);
- using a theoretical implementation framework, Normalisation Process Theory (NPT), to understand the contextual, organisational and cultural factors that facilitate or hinder embedding the intervention into `real-world` clinical practice.

9.3 Process evaluation methods

The process evaluation will utilise a mixed methods approach, combining both qualitative and quantitative data. Data will be collected during the following stages of the trial:

Pre-trial: A baseline data collection questionnaire will be employed at all sites to collect information during the site recruitment process regarding usual antibiotic stewardship practices. Data will also be collected relating to unit structure and resources. These data will then be combined to create a sampling matrix which will ensure a maximum variation of sites with differing usual antibiotic practices, resources, and contextual factors are included in the pilot phase. These data will also be used at a later stage to explore and understand under what conditions the intervention works best, and how intervention fidelity is optimised.

During the internal pilot: In a purposive sample of 10 sites (taken from the sampling matrix), we will administer the Normalisation Measure Development survey instrument (NoMAD-23 item) (32) to clinical staff. We will conduct interviews with clinical staff to determine the acceptability of the trial protocol, their current antibiotic practice, the barriers and enablers impacting antibiotic use practices within different unit contexts and any other processes that might affect the operationalisation of the study. The NoMad-23 responses will be used to help guide the interviews.

During the main study: A purposive selection of sites (approximately 10) will be involved in semi-structured interviews (either face-to-face or remotely via tele/video conferencing) to assess the implementation process, including the acceptability of the intervention, barriers and facilitators to implementation, and clinical decisions affecting fidelity to the trial protocol. We will administer the NoMad 23-item questionnaire to the remaining 40 sites and use the responses to help guide the interviews.

At the purposively selected sample of sites, we will conduct observations of clinical practice to obtain rich data that will help us understand the decision-making process related to antibiotic use, and antibiotic changes not related to protocol adherence but driven by embedded practice. We will also aim to capture observations pertaining to intervention delivery and receipt at the selected sites to explore factors, including structures and processes in ICU that act as barriers or facilitators beyond those mentioned in the interviews. The observations will focus only on the clinical teams' actions and reasoning. A dedicated researcher will be present at the bedside to observe the clinical staff involved in the decision-making, for example when initial care plans are developed and discussed during the ward round. Due to the setting and nature of the activities being observed, the researcher will have access to persons in receipt of healthcare services (and their relatives) but will not be providing healthcare or other types of regulated activities and will have no bearing on the quality of care delivered. A structured observational data collection tool will be developed to ensure data uniformity and that only pertinent data relevant to antibiotic decision-making are captured. The field notes taken by the researcher will not include any confidential or sensitive patient information.

Final site visits: Semi-structured interviews (either face-to-face or via tele/video conferencing) with staff involved in the delivery of the intervention will be conducted. We will employ maximum variation sampling to obtain 10 sites and purposive sampling to obtain a range of participants according to grade, profession and role. We will explore reflections on the use of the trial protocol, including perceived barriers, enablers and work processes affecting antibiotic prescribing practice.

10 SAFETY REPORTING

10.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant, including occurrences which are not necessarily caused by or related to the intervention under study.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death • Is life-threatening* • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect • Is considered by the investigator to be an important medical event that jeopardises the participant or requires intervention to prevent one of the above consequences * life-threatening refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Unexpected Related Serious Event (URSE)	Any SAE where there is evidence to suggest there is a causal relationship between the event and the intervention, where the event is unexpected

10.2 Recording and reporting AEs and SAEs

10.2.1 Adverse Event (AE) reporting

It is the responsibility of designated site personnel to collect and record adverse events in accordance with this protocol. AEs will be reported for participants from randomisation up to discharge. AEs should be recorded in participant medical records.

A high frequency of AEs are expected to be observed in a trial population of critically ill patients. To avoid reporting large numbers of expected AEs, the safety reporting for this trial focuses on reporting the following AEs:

- Events meeting seriousness criteria (see section 10.2.2)
- Events that are not already captured as a trial outcome on the trial database (these are excluded from safety reporting to avoid data duplication)
- Any events considered related to the intervention. These may be reported at the investigator's discretion, even if the event would otherwise be excluded from safety reporting (see point above)

Events excluded from safety reporting (due to already being recorded on the database, for example as a trial outcome) are:

- organ support at admission to critical care
- death
- further infections requiring antibiotics
- the following clinically relevant antibiotic-associated adverse events (i.e., suspected antibiotic-associated AEs where the related antibiotic treatment has been changed or stopped due to a suspected event):
  - Anaphylaxis
  - Gastrointestinal
  - Haematological
  - Hepatobiliary
  - Renal
  - Neurological
  - Dermatological
  - Cardiac
  - Muscular
  - *Clostridium difficile* diarrhoeal infection
  - Multi-drug resistant organism
  - Other (i.e. clinician's discretion)

10.2.2 Serious Adverse Event (SAE) reporting

The PI, or a medically qualified individual delegated to the task, should make an assessment of seriousness for each reportable AE. Serious Adverse Events (SAEs) will be reported for participants from randomisation up to discharge by completing and sending a SAE reporting form.

Please send completed SHORTER SAE report forms via secure email to:

nctu.shorter.sae@nhs.net within 24 hours of awareness of the event.

No personal identifiable data should be documented on the SAE report form

The nctu.shorter.sae@nhs.net email address is a distribution list that ensures all relevant individuals (CI, NCTU personnel and Sponsor) are informed of a SAE in a timely manner. All confirmed SAEs will be allocated a unique SAE number and a confirmation of receipt returned to the sender. SAEs will be recorded by trial management personnel on the trial's safety database.

Preliminary reporting to NCTU via email or telephone is acceptable in order to meet the 24-hour reporting timeline, where circumstances do not allow for immediate completion of the SAE form. However, the SAE form should be completed and submitted as soon as possible after the initial notification is made in order to comply with reporting timelines.

Since the trial primary outcome includes mortality, this does not require separate reporting as an SAE. In addition, secondary outcome measures including relapse of infection, and readmission capture most commonly occurring safety events. Therefore, any safety event that is captured as a trial outcome measure (see section 10.2.1 for a full list) does not require separate reporting as a SAE. However, any SAE that is thought to be related to the intervention may be reported at the investigator's discretion, including events which would otherwise be excluded from safety reporting. For each SAE, the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Severity
- Action taken
- Outcome
- Seriousness criteria
- Causality in the opinion of the investigator

In the case of incomplete information at the time of initial reporting, or change of condition or follow up information, a follow up report form must be completed and sent to NCTU via secure email (nctu.shorter.sae@nhs.net) as soon as possible. Events will be followed up until the event has resolved or a final outcome has been reached.

10.2.3 Severity assessment

The PI, or a medically qualified individual delegated to the task, should make an assessment of severity for each reportable AE according to the following criteria:

Intensity	Description
Mild	An event tolerated by the patient, causing minimal discomfort and not interfering with everyday activities
Moderate	An event sufficiently discomforting to interfere with normal everyday activities
Severe	An event that prevents normal everyday activities

10.2.4 Causality assessment

Causality related to the trial intervention, i.e. the short 5-day fixed course of initial antibiotics for sepsis, will be assessed by the site PI, or a medically qualified individual delegated to the task, for each reportable AE using the following criteria:

- *Unrelated:* There is no evidence of any causal relationship
- *Unlikely to be related:* There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the intervention), or there is another reasonable explanation for the event (e.g. the patient's condition).
- *Possible relationship:* There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after the administration of the trial intervention). However, the influence of other factors many have contributed to the event (e.g. the patient's condition).
- *Probable relationship:* There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
- *Definitely related:* There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

The Chief Investigator (CI) will undertake a documented review of the PIs assessment of causality for each reported AE.

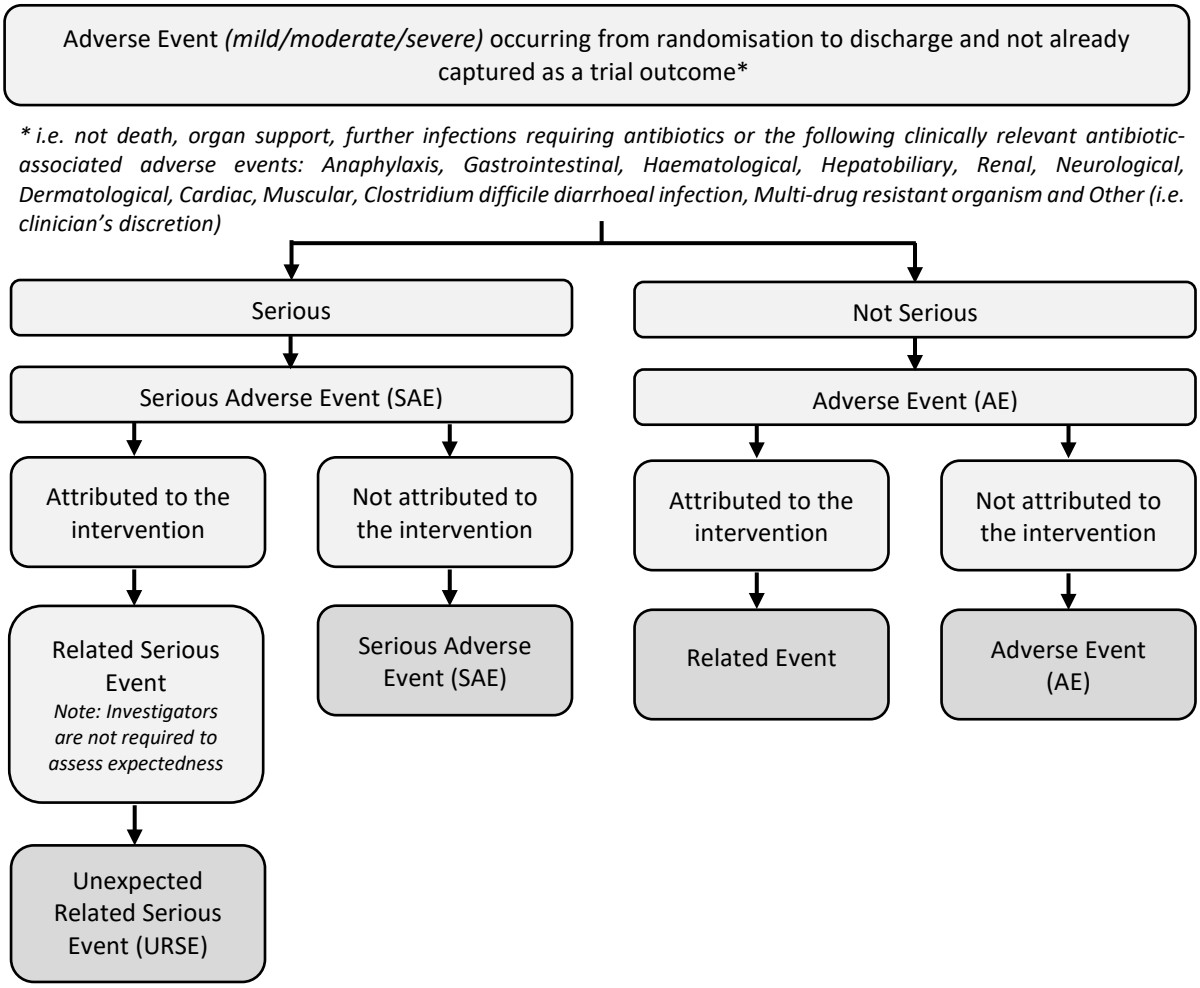
10.2.5 Reference safety information

There are no known expected reactions for the trial intervention (fixed 5-day short course antibiotics).

10.2.6 Expectedness assessment

As there is no reference safety information of known expected reactions for the intervention for this trial (5-day fixed course of antibiotics), it is not possible to complete expectedness reviews of SAEs. As a result, each SAE assessed to have a causal relationship to the trial intervention (i.e. possible, probable or definite relationship) will be classified as an Unexpected Related Serious Event (URSE) and reported by the NCTU to the REC as per the Standard Operating Procedure (SOP) in place at the time of the occurrence.

10.2.7 Safety reporting summary



10.3 Responsibilities

10.3.1 Principal Investigator

- Checking for AEs and SAEs during the trial.
- Ensuring that AEs are recorded and reported in line with the requirements of the protocol.
- Using medical judgement in assigning seriousness, severity and causality to reportable safety events.
- Ensuring that all reportable SAEs are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available

10.3.2 Chief Investigator

- Clinical oversight of the safety of trial participants, including an ongoing review of the risk/benefit
- Using medical judgement to confirm agreement, or not, with the PI's assessment of causality for all reportable SAEs.
- Review of specific SAEs in accordance with the trial risk assessment and protocol.

10.3.3 Sponsor

The Sponsor (Newcastle Hospitals NHS Foundation Trust) has delegated full trial delivery responsibilities to NCTU but will retain overarching responsibility for:

- Central data collection and verification of AEs and SAEs, according to trial protocol.
- Reporting of safety information to the CI or delegate for the ongoing assessment of the risk/benefit (according to the trial Monitoring Plan).

10.3.4 Trial Steering Committee (TSC)

- Review of aggregate safety data collected to date to identify any trends and liaise with the DMC regarding safety issues.

10.3.5 Data Monitoring Committee (DMC)

- The DMC will review safety data by randomised treatment group to determine patterns and trends of events or to identify safety issues which would not be apparent on a case-by-case basis

10.4 Reporting Urgent Safety Measures (USMs)

An Urgent Safety Measure (USM) is an action that the Sponsor or an Investigator may take in order to protect the subjects of a trial against any immediate hazard to their health or safety. Upon implementation of an USM by an Investigator, the NCTU must be notified immediately and details of the USM given. The Sponsor must inform the NHS REC within 3 days of the USM taking place in accordance with the Sponsor's standard operating procedures.

11 STATISTICAL CONSIDERATIONS

11.1 Analysis population

The following populations will be defined for the purpose of analysis and reporting:

Analysis Population	Description
Intention-to-treat	Includes all randomised participants, analysed according to their randomised treatment allocation.

11.2 Statistical analyses

Full details of all statistical analyses will be pre-specified in a statistical analysis plan which will be written and approved prior to release of any unblinded data to the trial statisticians. Any changes to the statistical analysis plan made after unblinding will be documented and reviewed by a statistician who has not had access to unblinded outcome data.

11.2.1 Analysis of the co-primary outcome measure

The co-primary clinical questions of interest are:

1. What is the absolute difference in the rate of 28-day all-cause mortality in adult patients admitted to a critical care unit with suspected or confirmed sepsis treated with an initial fixed 5-day antibiotic course compared to an antibiotic course determined as per standard of care, regardless of deviations from the allocated intervention for any reason or initiation of additional antibiotic courses? This estimand is described by the following attributes:

Estimand attribute	Description
Population	Adult patients admitted to a critical care setting with antibiotics initiated for suspected or confirmed sepsis
Treatment conditions	Fixed 5-day initial antibiotic course (intervention) Duration of initial antibiotic course as per standard of care (control)
Outcome measure	All-cause mortality 28-days from starting treatment – binary outcome

Strategies used to handle intercurrent events	• Deviation from fixed 5-day course for any reason – treatment policy • Initiation of additional antibiotic courses – treatment policy
Population-level summary measure	Absolute difference (intervention – control) in the rate of 28-day all-cause mortality

2. What is the absolute difference in the total number of antibiotic treatment days within 28 days of starting treatment? This estimand is described by the following attributes:

Estimand attribute	**Description**
Population	Adult patients admitted to a critical care setting with antibiotics initiated for suspected or confirmed sepsis
Treatment conditions	Fixed 5-day initial antibiotic course (intervention) Duration of initial antibiotic course as per standard of care (control)
Outcome measure	Total number of antibiotic treatment days within 28-days of starting treatment
Strategies used to handle intercurrent events	Death – while alive; zero antibiotic days assumed following death
Population-level summary measure	Mean difference (intervention – control) in 28-day antibiotic treatment days

For the analysis of 28-day all-cause mortality, a complete case analysis will be performed in the intention-to-treat (ITT) population. Participants who withdraw from the continued collection of routinely available data prior to day 28 will not be included in the analysis. To allow for centre-effects, the absolute risk difference (intervention – control) and 95% confidence interval will be obtained from a binomial generalised estimating equation model with identity link function, adjusted for other stratification factors, following recommended methods (33). Non-inferiority will be demonstrated if the upper limit of the 95% confidence interval is below the non-inferiority margin of 6%. Alternative methods may be employed should the model fail to converge. This will be described in the statistical analysis plan.

A supplementary analysis will estimate the relative difference between randomised treatment groups using a mixed-effects logistic regression model with centre included as a random effect and other stratification factors as fixed effects.

If non-inferiority is demonstrated for 28-day mortality, we will analyse for a between-arm reduction in total antibiotic treatment days to 28 days using a mixed-effects linear regression model, with centre included as a random effect and other stratification factors as fixed effects. This analysis will be conducted in the ITT population.

This approach may be biased if there are differences in 28-day mortality rates between treatment groups. To address this, we will also consider a supplementary analysis using causal effect models to estimate the Survivor Average Causal Effect (SACE); the treatment effect in the sub-population of participants who would have survived to day 28 regardless of treatment allocation. Further details will be provided in the Statistical Analysis Plan.

Views on an acceptable non-inferiority margin for the primary safety outcome may vary by stakeholder. To address this, we will utilise a Bayesian multilevel binomial generalised linear model to calculate posterior probabilities that short duration treatment is non-inferior to standard of care for a range of non-inferiority thresholds up to 6%. We will use an uninformative prior if there is no suitable quality evidence available. Further details will be specified in the statistical analysis plan. This analysis will provide supplementary information that can allow further insight and transparency for inference. The results will be presented graphically as non-inferiority acceptability curves.

11.2.2 Analysis of secondary outcome measures

Duration of the initial antibiotic course and adherence to the fixed 5-day initial antibiotic course will be reported. Secondary outcomes will be analysed similarly to the co-primary outcome measure, using mixed effects regression models suitable to the type of outcome, and adjusted for stratification factors and centre. 90-day all-cause mortality will be analysed in the same way as for the 28-day mortality outcome. Length of critical care unit and hospital stay (time to discharge) will be compared by arm using time-to-event models. Days alive and out of hospital will be compared in a similar way to the total antibiotic treatment days to 28 days. Further infection and readmission to critical care will be analysed using both logistic regression and time-to-event models. Full details will be provided in the Statistical Analysis Plan.

11.2.3 Missing data

As most outcome data can be collected from routine sources, we do not anticipate high levels of missing data. If there is substantial differential dropout between treatment groups, we will undertake sensitivity analyses to explore the robustness of results to the “missing not at random” assumption.

11.2.4 Subgroup analyses

Exploratory analyses will be carried out on the following sub-groups:

- Culture-negative sepsis. Defined as no positive culture results from samples taken in relation to index course of antibiotics for sepsis.
- Positive blood culture. Defined as a positive blood culture from a sample taken in relation to index course of antibiotics for sepsis.
- Site of infection including CAP, urinary tract infection and intra-abdominal infection
- Septic shock status
- Baseline severity of illness

11.2.5 Interim analyses and criteria for the premature termination of the trial

A Data Monitoring Committee will review accumulating safety and outcome data over the course of the trial, however no formal interim analyses are planned and there are no pre-defined stopping rules for safety, efficacy or futility.

11.3 Sample size calculations

The sample size is based on assessing non-inferiority for 28-day all-cause mortality. Assuming a 28-day mortality of 24% (34), a sample size of 1065 patients per arm will have 90% power, with a one-sided alpha of 2.5%, to demonstrate non-inferiority with a margin of 6%. Allowing for a 5% drop out rate, the total sample size will be 2244 patients. The sample size will also have 90% power to detect a 1.1-day difference in total antibiotic treatment days to 28 days, assuming a standard deviation of 7.7 (based on ADAPT-sepsis data) and a two-sided alpha of 5%.

Determining non-inferiority margins for antibiotic trials is a challenge due to the lack of historical placebo-controlled trials. The Food and Drug Administration (FDA) recommends a 10% non-inferior margin for mortality outcomes in CAP trials (35). In addition, recommended non-inferiority margins for healthcare-associated pneumonia trials range from 7-10% (36,37). Previous trials of antibiotic durations for VAP (22) and biomarker-guided antibiotic durations for critically ill patients with sepsis have used non-inferiority margins of 8-10% for mortality outcomes (38,39). We have selected a non-inferiority of 6% margin that will be one of the lowest used in antibiotic duration trials.

12 HEALTH ECONOMIC ANALYSIS

We will perform a within-trial health economic analysis from the perspective of the NHS, personal and social services, and wider social costs. All analyses will be in accordance with NICE guidance (40,41). Information on costs will be collected for every trial participant. Intervention costs (e.g. medications), adverse events and treatments required during the intervention phase will be captured via the eCRF. Health care utilisation data will be collected using a Health Care Utilisation Questionnaire (HCUQ), administered at 90 days following the initiation of antibiotics treatment. Data collection will take the perspective of the UK NHS and personal social services (PSS) and it will focus on estimating all relevant costs of the interventions (e.g. materials, staff) and use of health and social services (e.g. general practice and hospital visits, use of community health services etc.). Unit costs for these health care resources will be derived from routine data sources and study specific estimates. Data on the cost of the intervention and subsequent use of services will be combined with unit costs to produce a cost for each trial participant.

We will take a wider perspective by including costs borne by families (e.g. time off work, out of pocket payments for attending health services appointments). These data will be collected via a Time and Travel (T&T) questionnaire administered at 90 days. The T&T questionnaire (when combined with the HCUQ) will estimate the costs incurred in accessing health care services. All unit costs will be derived using routine data sources and study-specific estimates.

The within-trial analysis will compare changes in health-related quality of life (HRQoL), based on responses to the EQ-5D-5L questionnaire at discharge and at 90 days post-randomisation. The data from the EQ-5D-5L will be combined with study participant's mortality to estimate quality-adjusted life years (QALYs). Results will be presented as incremental cost per death avoided and incremental cost per QALY gained at 90 days. These data will be presented as point estimates, cost and QALY plots, and cost-effectiveness and cost-effectiveness acceptability curves.

The timeline of the trial may not capture all the costs and health outcomes associated with the intervention. Hence, a decision model will also be developed to estimate costs and outcomes over the lifetime of the patient. The model will be developed in accordance with the NICE reference case (42). Modelling will be carried out to assess costs beyond the 90-day follow-up period. These data will be derived from the literature and other existing data sources, following best practice guidance (43). For

the longer-term model, discounting will be applied at appropriate rates as per NICE guidance and deterministic and probabilistic sensitivity analyses will be conducted.

12.1 Analysis of process evaluation

Qualitative data will be analysed based on the Conceptual Framework for Implementation Fidelity. This will allow us to use themes identified a priori alongside those that emerge de novo in the development of the final analytical framework. To ensure confirmability and trustworthiness, a sample of textual data will be double coded, and the independent analyses shared to identify key difference and similarities before an agreed final analysis. We will generate a collective body of evidence on the barriers and facilitators related to the implementation, including intervention fidelity, to inform progress of the main trial.

The integration of process and trial outcome data and subsequent analyses will be explanatory and separate from the primary effectiveness analysis. The qualitative evidence will be systematically combined with process and outcome data to identify the dose of the intervention that has been implemented (in regard to both frequency of antibiotic prescriptions and de-escalation, and duration of antibiotic use), the coverage of the intervention (including number and characteristics of included and excluded patients and reasons for not recruiting), and intervention fidelity (including the extent of protocol implementation), and how these relate to observed outcomes.

13 DATA HANDLING

Trial data for an individual participant will be collected by the PI or their delegated nominees and recorded in the relevant eCRFs for the trial. Patient identification on the eCRF will be through a unique participant Subject ID, allocated at screening. A Patient Identification Log linking the patient's name to the participant Subject ID will be held within the ISF stored in a locked room at site and is the responsibility of the PI. As such, patients cannot be identified from eCRFs.

The Clinical Data Management System (CDMS) used for the electronic case report forms (eCRFs) in this trial is fully compliant with all regulatory frameworks for research of this nature. The CDMS is Red Pill supplied by Sealed Envelope™, in summary Red Pill is:

- Registered as a data controller with the Information Commissioner's Office (ICO) and has been inspected by the Medicines and Healthcare Products Regulatory Agency (MHRA), the UK clinical trials regulator.
- Certified as meeting Cyber Essential requirements (a UK Government led and industry – backed scheme) by a Council of Registered Ethical Security Testers (CREST) accredited security company.
- It has an inbuilt daily back-up facility, stored redundantly at two sites, which is encrypted.
- It uses a secure web-based interface for data entry, no data is stored on computers at site.
- Users are assigned role-based permissions specific to their site and study role.

The CI or nominated designee will continually monitor the completeness and quality of data recording in eCRFs and will correspond regularly with site staff with the aim of capturing any missing data where possible and ensuring continuous data quality.

Participants will complete paper assessment tool(s) (i.e., questionnaires) as required. The tools will also only be identified using the participant Subject ID. Data will be entered at sites onto corresponding eCRF in Red Pill, Sealed Envelope, with the paper originals remaining at site.

13.1 Data collection tools and source document identification

Source data will constitute original records of information including patients' clinical records, clinical investigations, prescription records and original documentation related to the trial. All source data will be retained for auditing and verification of the trial data.

In addition to data collected from sites, data will be collected from routinely collected electronic data sources. Outcome data for organ support in critical care, duration of critical care and hospital stay, and critical care unit readmission will be collected from ICNARC or local equivalents i.e. Scottish Intensive Care Society Audit Group (SICSAG) in Scotland.

13.2 Data handling and record keeping

Data will be collected via an electronic case report form (eCRF), which will be designed by NCTU in conjunction with the Chief Investigator and Statistician. The eCRF is a web-based secure remote data capture platform.

All data for patients will be collected by the site PI or their delegate and recorded on the eCRF. Patients will be assigned a unique identifier at the time of randomisation. Data will be collected from trial enrolment until discharge from hospital. In the event that a patient is transferred to another hospital, the trial team will liaise with the receiving hospital to ensure complete data collection.

To ensure accurate, complete and reliable data, NCTU will:

- Provide instructional material to sites;
- Provide the PI and research teams support though a site initiation meeting;
- Be available to site personnel via email (preferably), although site teams can also telephone NCTU reception who will arrange for a member of the trial team to call back;
- Review and evaluate eCRF data, source data and detect errors in data collection.

Data will be stored in accordance with the Data Protection Act 2018.

13.3 Access to data

All essential documentation and trial records will be stored by NCTU according to regulatory requirements. Access to stored data will be restricted to authorised personnel. Any paper data forms will be stored in a secure location with access restricted to research teams. Electronic data will be stored in a secure location with access restricted to research staff. All databases with patient identifiable data will be password protected. Any data transferred out of the secure environment (e.g. for statistical analysis) will conform to NCTU standard operating procedures.

Direct access to source data held at sites will be required for monitoring throughout the trial. Monitoring will be carried out by members of the trial team.

Data will be shared with ICNARC, or other local equivalents, for the purpose of data linkage to collect critical care outcome measures. Data linkage will be performed using NHS/CHI/H&S/local equivalent number, date of birth and sex at birth or audit data specific identifiers (e.g. CMP number for ICNARC requests). The process evaluation will be carried out by collaborators at Edinburgh Napier University. Data sharing agreements will be agreed through collaboration agreements.

14 ARCHIVING

Trial documentation and data will be archived for 5 years after completion of the trial.

15 MONITORING, AUDIT AND INSPECTION

The trial may be subject to audit by representatives of the Sponsor or inspection by the funder (Health Technology Assessment (HTA) fund). Each investigator site will permit trial-related monitoring, audits and regulatory inspection including access to all essential and source data relating to the trial.

16 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Research Ethics Committee (REC) review and reports

NCTU staff will obtain a favourable ethical opinion from an NHS Research Ethics Committee (REC) prior to the start of the trial. All parties will conduct the trial in accordance with this ethical opinion.

NCTU staff will notify the REC of all required substantial amendments to the trial and those non-substantial amendments that result in a change to trial documentation (e.g. protocol or patient information sheet). Substantial amendments that require a REC favourable opinion will not be implemented until this REC favourable opinion is obtained. NCTU staff will notify the REC of any serious breaches of GCP or the protocol, or urgent safety measures that occur during the trial.

An annual progress report will be submitted each year to the REC by NCTU staff until the end of the trial. This report will be submitted within 30 days of the anniversary date on which the original favourable ethical opinion was granted.

NCTU staff will notify the REC of the early termination or end of trial in accordance with the required timelines.

16.2 Peer review

As part of the competitive grant awarding process by the Health Technology Assessment (HTA) Programme, this project has undergone extensive peer review. This includes independent peer review and assessment by the HTA General Board.

16.3 Public and patient involvement

This trial has been developed with patient and public involvement (PPI) from its inception and has ongoing PPI engagement through the trial. The importance of the research question has been recognised by two PPI groups, VOICE and ICU-steps. The research team includes two experienced PPI co-applicants. The PPI co-applicants have personal and family experience of antibiotic use and the need for antibiotic stewardship. Our PPI co-applicants have contributed to the development and amendments of the protocol and patient-facing documentation. The trial has PPI representation on the TMG and TSC.

16.4 Regulatory compliance

The trial will be conducted in accordance with the Research Governance Framework. Before any site can enrol patients into the trial, that site must have received NHS permission from the site management organisation/Higher Education Institution or NHS Research & Development department.

16.5 Protocol compliance

It is the responsibility of the CI to ensure that the clinical trial is run in accordance with GCP and the protocol. Trial tasks may be delegated to a suitably qualified or experienced member of the research team, but the CI and PI will retain overall responsibility for adherence to protocol and GCP. The trial will be monitored by NCTU staff, to measure protocol compliance and manage deviations. Site staff are responsible for compliance with the protocol in their everyday trial activities and must report anything that they feel constitutes an AE, SAE, protocol deviation, serious breach, anything that requires an USM, or anything else that should be reported and documented between monitoring visits.

Protocol deviations, violations, non-compliances or breaches are departures from the approved protocol. Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used.

Deviations from the protocol and GCP occur in clinical trials and the majority of these events are technical deviations that are not serious breaches. These events must be documented on the protocol deviation log, including the relevant Corrective and Preventive Actions (CAPA) required.

There may be instances where a participant randomised to the intervention arm receives more or fewer than 5 days of antibiotic treatment.

- If this is a **clinical decision**, taken in the best interests of the participant, please **record this in the "Short Course Intervention Compliance" eCRF in the trial database**.
- If this **occurs due to an error**, please **record this in the "Short Course Intervention Compliance" eCRF in the trial database AND as a deviation,** and notify NCTU.

Protocol violations are a consistent variation in practice from the study protocol that could potentially impact on study participant's rights/safety or affect the scientific value or outcome of a study. The PI will sign off each deviation and decide whether this is a deviation or violation. Violation documentation must be completed within 3 days of the violation being discovered using the violation reporting form.

Deviations or violations that are found to frequently recur at a site are not acceptable and could be classified as a serious breach.

16.6 Notification of serious breaches to GCP and/or the protocol

A serious breach is a breach which is likely to effect to a significant degree –

a) the safety or physical or mental integrity of the subjects of the trial

b) the scientific value of the trial

The Sponsor must be notified immediately of any incident that may be classified as a serious breach. NCTU will notify the NHS REC within the required timelines in accordance with the NCTU Standard Operating Procedure (SOP).

16.7 Data protection and patient confidentiality

The trial will be run in accordance with the Data Protection Act 2018, to maintain the confidentially of trial participants and trial data integrity.

Overall responsibility for data collection lies with the CI. Data will be handled, computerised and stored in accordance with the Data Protection Act 2018. Where trial related documentation is maintained as paper copies as part of standard practice at a trial site, these will be annotated, signed and dated, and filed in the medical records. The format of trial documentation and medical records (i.e. paper based, paper light and/or electronic) at trial sites will be in accordance with each sites usual practice and policies and procedures. The overall quality and retention of trial data is the responsibility of the Chief Investigator. All trial data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy.

All investigators and trial site staff must comply with the requirements of the applicable legislation with regards to the collection, storage, processing and disclosure of personal information and will uphold the core principles of the legislation. Explicit consent must be obtained via the informed consent form to allow data sharing to occur.

Personal data will be regarded as strictly confidential. All trial files will be securely stored, and access restricted to staff involved in the trial. Research staff at sites will enter data onto a secure web-based electronic database (Red Pill, Sealed Envelope) maintained by the NCTU. Data will be entered using unique participant trial numbers. Access to this database will be password protected and limited to staff at research sites or those employed by Newcastle University who are involved in the trial.

16.8 Indemnity

The Sponsor will provide indemnity in the event that trial participants suffer negligent harm due to the management of the trial provided under the NHS indemnity arrangements for clinical negligence claims in the NHS.

The substantial employers of the protocol authors will provide additional indemnity for the university employees in the event that trial participants suffer negligent harm due to the design of the trial.

The trial sites will provide indemnity in the event that trial participants suffer negligent harm due to the conduct of the trial at their site. For NHS Organisations this indemnity will be provided under the NHS indemnity arrangements for clinical negligence claims in the NHS. NHS Organisations must ensure that site staff without substantive NHS contracts hold honorary contracts to ensure they can access patients and are covered under the NHS indemnity arrangements. Trial staff without NHS contracts e.g., General Practitioners or Dentists will provide their own professional indemnity.

16.9 Amendments

It is the responsibility of the Research Sponsor to determine if an amendment is substantial or not and study procedures must not be changed without the mutual agreement of the CI, Sponsor and the Trial Management Group (TMG).

Substantial amendments will be submitted to the Health Research Authority (HRA) and REC and will not be implemented until all necessary approvals are in place. It is the responsibility of the NCTU, on behalf of the Sponsor, to submit substantial amendments.

Non-substantial amendments may be made at any time with a record of the amendment held in the Trial Master File (TMF). Any non-substantial amendment that requires an update to the trial documentation will be submitted to the HRA and REC for acknowledgement of the revised version of the document.

Substantial amendments and those minor amendments which may impact sites will be submitted to the relevant NHS Research & Development (R&D) Departments for notification to determine if the amendment affects the NHS permission for that site. Amendment documentation will be provided to sites by the NCTU.

16.10 Access to the final trial dataset

Until publication of the trial results, access to the full dataset will be restricted to the Trial Management Group and authors of the publication.

Anonymised/pseudo anonymised data from this trial may be available to the scientific community subject to appropriate ethical and TMG approval. Requests for data should be directed to the lead author, Chief Investigator and NCTU in line with any applicable data sharing policies.

17 DISSEMINATION POLICY

During the set up and conduct of the trial we will promote the trial to clinicians, researchers and the wider public. We will develop a dedicated trial website that will provide stakeholders with information and give regular updates. We will set up dedicated social media accounts to provide updates and link in with PPI groups (VOICE, ICU-steps). Details of the trial will be published on online registries including International Standard Randomised Controlled Trials Number (ISRCTN). PPI co-applicants will take a leading role, including facilitation, in workshops with PPI groups, with representation from charities such as UK Sepsis Trust, Antibiotic Research UK and ICU-Steps, to ensure that we reach stakeholders and to assist in dissemination of findings. We will publish the trial protocol in peer-reviewed journals.

The main trial findings will be publicised throughout the clinical community, PPI groups and society more widely. Information will be disseminated to the clinical community via professional societies, through social media and by presentation at national and international conferences. Patients and the public will be informed through dissemination of results to PPI groups with the assistance of our PPI co-applicants and also through press-releases to the media. Our findings will be published in open-access high-quality peer reviewed publications and also in the NIHR HTA journal.

We anticipate that the findings of this trial will be rapidly incorporated in UK and international guidelines (e.g. the Surviving Sepsis Campaign (SSC) guidelines, NICE guidelines, and UK guidelines for the provision of intensive care services). We anticipate a rapid transfer of trial findings into UK clinical practice given the pragmatic and generalisable nature of the trial.

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19. APPENDICES

19.1. Appendix 1 – amendment history

Amendment Number	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
01	3.0	30 October 2023	Phil Hall, Zoë Walmsley, Miranda Morton, Tom Hellyer, TMG review	• Correction of typographical errors, editing of formatting and re-wording for clarifications made throughout the protocol • Clarifications made throughout the safety reporting section • As per TSC request, ability for investigators to complete safety reporting for events they believe related to the intervention even if the event is already captured as an outcome measure or recorded on the database • Addition of section relating to co-enrolment for the trial • Addition of collection of additional data; ethnicity, postcode, employment status, Ward Watcher ID
07	4.0	12 March 2024	Zoë Walmsley, Miranda Morton, Tom Hellyer, TMG review	• Update of trial contacts • Clarifications and formatting changes made throughout the protocol • Addition of telephone calls to ascertain the wishes of Personal Consultees with regards to patient participation. • Addition of specification to add antibiotic stop date and time to site local prescribing systems for participants randomised to the intervention arm. • Addition of text relating to completion of trial questionnaires by participants' next of kin. • Removal of all references to NHS England. • Addition of a deviation reporting exclusion to cover any clinical decision that results in a participant receiving fewer or more than 5 days of antibiotic treatment when randomised to the intervention arm.