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A trial comparing short course antibiotics and standard course antibiotics for the treatment of sepsis

Submission date
07/11/2023

Recruitment status
Recruiting

Registration date
12/12/2023

Overall study status
Ongoing

Last Edited
03/03/2025

Condition category
Infections and Infestations

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Sepsis is a life-threating condition due to a severe infection. It is a common reason for patients to require “life-support”. Sepsis is a leading cause of death worldwide.

Antibiotics are a major part of the treatment of sepsis, but antibiotics also carry significant risks. The overuse of antibiotics promotes the emergence of “superbugs”, can also be toxic to organs such as the liver and can occasionally be responsible for life-threatening bowel infections.

Striking the right balance of using antibiotics appropriately, while avoiding their potential harm, is a challenge. Antibiotics are initiated rapidly for sepsis because of the severity of illness but once started, the exact duration needed to treat an infection adequately is unknown. Determining a duration of antibiotics that effectively treats sepsis, but is not unnecessarily prolonged, could have a big impact on antibiotic use overall.

We aim to determine whether short-duration antibiotic treatment is as good as routine practice, which is usually a longer duration of antibiotics, for critically ill patients with sepsis.

We will carry out a clinical trial including adult patients with sepsis who are admitted to a critical care unit. We will randomly allocate patients to receive a short fixed-course of antibiotics (5 days) or usual care (this is typically a 9-day course). This trial will only specify the duration of antibiotics, and the clinical team will know what duration the patient is getting. The choice or combination of antibiotics will be decided by the clinical team. All patients will have antibiotics managed according to standard antibiotic stewardship practice. The only difference between the two trial groups is that the short-duration group will have 5 days of antibiotics.

We will determine whether short-course antibiotic treatment is as effective as routine practice by assessing clinical outcomes for patients when they are in hospital and at 90-day follow-up.

Who can participate?
The SHORTER trial will recruit adults patients (aged 18 or over) who are being treated in a critical care setting for suspected or confirmed sepsis.

What does the study involve?
Antibiotics are essential in treating sepsis. But we also know that there are side effects of being treated with antibiotics, especially in people being treated in an intensive care setting. These include developing more infections, some of these might not respond to antibiotic treatment, and side effects in the body especially the kidneys. Commonly antibiotics are given for 7 or more days to treat sepsis. In the SHORTER trial we want to know whether we can safely and effectively treat sepsis with a shorter 5-day course of antibiotics and what the effect this would have on patients.
Participants hospital stay will not change at all. Participants will be selected at random, by a computer, to take part in the intervention arm or control arm of the trial. If taking part in the intervention arm participants will have a short 5 day course of antibiotics to treat their sepsis, if taking part on the control arm participants will have the length of their antibiotics chosen by their hospital team, typically the would be 7 or more days of antibiotic.
Participants will take part in the trial for up to 90 days (approximately 3 months). Up to the 90 days data will be collected from participants' medical records, participants will not be contacted for this. At 90 days participants will be contacted and asked to complete some trial questionnaires.

What are the potential benefits and risks of participating?
Participants may experience some potential benefits but it is also possible that they do not have any direct benefit. Though, participation could influence the treatment patients with sepsis receive in the future.
The main risk is if antibiotics are stopped before the infection is treated fully. Hospital teams will monitor participants' health closely, as they would normally, to ensure that they are not put at risk. If participants need to continue receiving antibiotics for longer, then they will be given these without hesitation. Participant safety always comes first. If this does happen data will still be used for the trial.

Where is the study run from?
The Newcastle upon Tyne Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
February 2023 to August 2026

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK).

Who is the main contact?
SHORTER.Trial@newcastle.ac.uk

Study website
http://www.shortertrial.com

Contact information

Type(s)
Scientific

Contact name
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Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
317788

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 57052, NIHR134101, IRAS 317788

Study information

Scientific Title

A randomised controlled trial of SHORT duration antibiotic thERapy for critically ill patients with sepsis

Acronym
SHORTER

Study objectives
1. To determine whether short duration antibiotic therapy is as good asd standard care in treating sepsis in terms of mortality and whether it reduces overall antibiotic exposure
2. To assess the effect of short duration antibiotic therapy on:
2.1. Suspected clinically relevant antibiotic-associated adverse events
2.2. Length of critical care unit stay
2.3. Length of hospital-stay
2.4. Rate of further/recurrence of infections
2.5. Readmission to critical care or hospital
3. Health Economic analysis:
3.1. Is short course antibiotic therapy cost effective compared to usual care at 90 days post intervention
3.2. Is short course antibiotic therapy cost effective compared to usual care over the patient's lifetime
4. Process Evaluation:
4.1. To understand the implementation of the trial protocol and willingness of clinicians to follow a fixed short-duration intervention

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 12/09/2023, Wales REC 4 (Health and Care Research Wales Support and Delivery Centre, Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, United Kingdom; +44 2922 940989; Wales.REC4@wales.nhs.uk), ref: 23/WA/0197

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet.

Health condition(s) or problem(s) studied
Sepsis

Interventions
Current interventions as of 22/04/2024:

Patients will be randomised to one of two arms; the intervention arm and the comparator arm. Participants randomised to the intervention arm, will have the duration of antibiotics adjusted to a 5-day course. This duration commences from the initiation of antibiotics. This short course of antibiotics relates only to the initial course of antibiotics and to its duration. The choice of antibiotics will be according to the clinical team.

Duration of antibiotics in the comparator arm will be according to best practice and guidelines as per standard care. All other aspects of care between the two trial groups will be according to best practice, including antibiotic adjustments according to test results and antibiotic stewardship multi-disciplinary team involvement.

Participant follow up will extend to 90-days. Outcome data will be collected from clinical records and routinely collected electronic data including Intensive Care audit bodies such as Intensive Care National Audit & Research Centre (ICNARC). The majority of outcome data will be collected before participants are discharged from hospital. Participants will be asked to complete questionnaires for
health economic analysis (quality of life, time and travel) at 90 days. Participants will be contacted by telephone if discharged by this point.

In summary, patients will be screened for eligibility and have antibiotic duration for sepsis adjusted if randomised to the intervention arm. All other aspects of routine care will be unchanged. Participants will be followed up for 90 days following randomisation. The majority of outcome data will be collected from clinical records or routine electronic data sources. Participants will be asked to complete questionnaires at 90-day follow up for health economic analysis.

Process Evaluation:
We will utilise mixed methods, using purposive sampled qualitative data together with quantitative data from the trial. Data will be collected during the following stages of the trial:
1. Pre-trial: We will assess the current practice of antibiotic use with a baseline questionnaire sent to all 50 sites.
2. During the internal pilot: In a purposive sample of 10 sites (max of 40 participants) we will administer the Normalisation Measure Development survey instrument (NoMAD-23 item) and conduct interviews with clinical staff to determine the acceptability of the trial protocol.
3. During the main study: We will conduct semi-structured interviews (either face-to-face or remotely via tele/video conferencing) with clinical staff from approximately 10 sites (max of 40 participants) to assess the implementation and acceptability of the intervention and clinical decisions affecting fidelity to the trial protocol. We will also conduct non-participant observations to understand the decision-making process related to antibiotic use.
4. Final site visits: We will conduct semi-structured interviews (either face-to-face or via tele /video conferencing) with staff (max of 40 participants) in purposively selected 10 sites involved in the intervention delivery to reflect on the use of the trial protocol, including perceived barriers, enablers, and work processes affecting antibiotic prescribing practice.

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Previous interventions:

Patients will be randomised to one of two arms; the intervention arm and the comparator arm. Participants randomised to the intervention arm, will have the duration of antibiotics adjusted to a 5-day course. This duration commences from the initiation of antibiotics. This short course of antibiotics relates only to the initial course of antibiotics and to its duration. The choice of antibiotics will be according to the clinical team.

Duration of antibiotics in the comparator arm will be according to best practice and guidelines as per standard care. All other aspects of care between the two trial groups will be according to best practice, including antibiotic adjustments according to test results and antibiotic stewardship multi-disciplinary team involvement.

Participant follow up will extend to 90-days. Outcome data will be collected from clinical records and routinely collected electronic data including the Hospital Episode Statistics (HES), Office for National Statistics (ONS) and Intensive Care audit bodies such as Intensive Care National Audit & Research Centre (ICNARC). The majority of outcome data will be collected before participants are discharged from hospital. Participants will be asked to complete questionnaires for health economic analysis (quality of life, time and travel) at 90 days. Participants will be contacted by telephone if discharged by this point.

In summary, patients will be screened for eligibility and have antibiotic duration for sepsis adjusted if randomised to the intervention arm. All other aspects of routine care will be unchanged. Participants will be followed up for 90 days following randomisation. The majority of outcome data will be collected from clinical records or routine electronic data sources. Participants will be asked to complete questionnaires at 90-day follow up for health economic analysis.

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Intervention Type
Drug

Pharmaceutical study type(s)
Not Applicable

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Antibiotics

Primary outcome measure
Measured using patient records:
1. 28-day all-cause mortality (non-inferiority safety outcome)
2. Total antibiotic treatment days measured at 28 days (superiority clinical effectiveness outcome)

Secondary outcome measures
1. All-cause mortality measured at 90 days
2. Suspected clinically relevant antibiotic-associated adverse events during index hospital admission occurring from randomisation up to discharge
3. Length (number of days) of critical care unit stay for the initial index episode of sepsis measured up to 90 days
4. Length (number of days) of hospital stay measured up to 90 days
5. Number of further/recurrence of infections requiring additional antibiotic courses following the index sepsis episode, measured up to 28 days
6. Occurrence of readmission to critical care or hospital during the 90 day follow up period
7. Incremental cost per death avoided at 90 days measured using mortality data and the Health Resource Usage & Time and Travel Questionnaire
8. Incremental cost per Quality Adjusted Life Year (QALY) gained at 90 days measured using the EQ-5D-5L questionnaire
9. 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 measured using the EQ-5D-5L and Health Resource Usage & Time and Travel Questionnaires
10. Average healthcare costs per participant over 90 days for each area of resource use measured using the Health Resource Usage & Time and Travel Questionnaire.
11. Utility scores derived from responses to the EQ-5D-5L questionnaire at 90 days
12. Average QALYs per participant at 90 days measured using the EQ-5D-5L questionnaire
13. Incremental cost per QALY gained over the patient's lifetime measured using the EQ-5D-5L questionnaire
14. 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 measured using the EQ-5D-5L and Health Resource Usage & Time and Travel Questionnaires

Overall study start date
01/02/2023

Completion date
31/08/2026

Eligibility

Key inclusion criteria

1. Adult patients, age >=18 years, 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

Process evaluation:
Clinical staff involved in everyday prescribing and/or managing of antibiotics within critical care.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 2,244; UK Sample Size: 2,244

Key exclusion criteria
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.

The following participant exclusion criteria was added on 03/03/2025:
7. Concomitant enrolment in another interventional trial, except where a co-enrolment agreement with SHORTER exists (a list of interventional trials approved for co-enrolment can be found on the trial website: https://www.shortertrial.com/).

Date of first enrolment
30/11/2023

Date of final enrolment
30/09/2025

Locations

Countries of recruitment
United Kingdom

Study participating centre
The Newcastle upon Tyne Hospitals NHS Foundation Trust
Freeman Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Blackpool Teaching Hospitals NHS Foundation Trust
Victoria Hospital
Whinney Heys Road
Blackpool
United Kingdom
FY3 8NR

Study participating centre
Darlington Memorial Hospital
Darlington Memorial Hospital
Hollyhurst Road
Darlington
United Kingdom
DL3 6HX

Study participating centre
East Kent Hospitals University NHS Foundation Trust
Kent & Canterbury Hospital
Ethelbert Road
Canterbury
United Kingdom
CT1 3NG

Study participating centre
Kettering General Hospital NHS Foundation Trust
Rothwell Road
Kettering
United Kingdom
NN16 8UZ

Study participating centre
Milton Keynes University Hospital NHS Foundation Trust
Standing Way
Eaglestone
Milton Keynes
United Kingdom
MK6 5LD

Study participating centre
Northumbria Healthcare NHS Foundation Trust
North Tyneside General Hospital
Rake Lane
North Shields
United Kingdom
NE29 8NH

Study participating centre
Royal Papworth Hospital NHS Foundation Trust
Papworth Road
Cambridge Biomedical Campus
Cambridge
United Kingdom
CB2 0AY

Study participating centre
Sandwell and West Birmingham Hospitals NHS Trust
City Hospital
Dudley Road
Birmingham
United Kingdom
B18 7QH

Study participating centre
Somerset NHS Foundation Trust
Trust Management
Lydeard House
Musgrove Park Hospital
Taunton
United Kingdom
TA1 5DA

Study participating centre
South Tyneside and Sunderland NHS Foundation Trust
Sunderland Royal Hospital
Kayll Road
Sunderland
United Kingdom
SR4 7TP

Study participating centre
Surrey and Sussex Healthcare NHS Trust
Trust Headquarters
East Surrey Hospital
Canada Avenue
Redhill
United Kingdom
RH1 5RH

Study participating centre
Whittington Health NHS Trust
The Whittington Hospital
Magdala Avenue
London
United Kingdom
N19 5NF

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

Sponsor details
Freeman Hospital
Freeman Road
High Heaton
Newcastle-upon-Tyne
England
United Kingdom
NE7 7DN
+44 1912825959
tnu-tr.sponsormanagement@nhs.net

Sponsor type
Hospital/treatment centre

Website
http://www.newcastle-hospitals.org.uk/

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC)

Results and Publications

Publication and dissemination plan
A dedicated trial website (www.SHORTERTrial.com) will provide stakeholders with information and give regular updates. 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 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.

Intention to publish date
31/08/2027

Individual participant data (IPD) sharing plan
Data from this trial will be available to the scientific community subject to request and appropriate ethical approval. Requests for data should be directed to the Chief Investigator and Newcastle Clinical Trials Unit.

IPD sharing plan summary
Available on request