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A point of care test to aid in diagnosis of suspected sepsis and optimal use of antibiotics in adults presenting to A & E

Submission date
13/12/2019

Recruitment status
No longer recruiting

Registration date
19/12/2019

Overall study status
Completed

Last Edited
02/04/2025

Condition category
Infections and Infestations

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

Plain English Summary

Background and study aims
Sepsis (also known as septicaemia or blood poisoning) is a common, potentially life-threatening complication of infection. The optimal treatment for sepsis includes early recognition, prompt antibiotics and fluids into a vein (intravenous/IV). Currently, clinicians assess severity in patients in the Emergency Department (ED) with a scoring system based on simple to measure observations: the National Early Warning Score (NEWS2). NEWS2 helps clinicians identify the sickest patients. It is not specific and tends to over-diagnose sepsis leading to over-prescribing of antibiotics and promoting antimicrobial resistance. It is the best we have and currently used in over 70% of English hospitals. Adults with suspected sepsis fall into one of three categories: a) those looking ill needing urgent IV antibiotics and fluids within 1 hour, b) those that are unwell, but will not come to harm if IV antibiotics are not administered within 1 hour, allowing time for further assessment prior to starting antibiotics within 3 hours, c) those not critically unwell who may or may not need IV antibiotics. Procalcitonin (PCT), a blood test not widely used in the NHS, helps to identify bacterial infection. The National Institute for Health and Care Excellence (NICE) recommended further research on PCT testing in EDs for guiding antibiotic use in people with suspected sepsis.

In this study, we will conduct a randomised controlled trial to compare PCT-supported assessment with standard care of suspected sepsis in adults presenting to the ED, and measure whether this approach reduces prescriptions of antibiotics without increasing mortality by decreasing uncertainty in the group who may not need IV antibiotics urgently within 1 hour, or not need antibiotics at all.

Who can participate?
Patients ≥16 years presenting to the ED with suspected sepsis.

What does the study involve?
Adult patients with suspected sepsis will be randomly assigned to current standard of care or PCT-supported care. In the PCT group, a bedside test (taking 20 minutes) is performed plus the NEWS2 assessment. Depending on the result of the PCT plus the NEWS2, patients will receive IV

antibiotics and fluids within the current recommended time frame depending on severity. Doctors and patients will know what treatment arm they are in. An analysis will be done to understand how well clinicians follow the recommendations, ease of use of the additional test in a busy ED, and its cost effectiveness. A sample of patients interviewed at 90 days follow up will assess experiences of care.

What are the possible benefits and risks of participating?
Participants who do not have sepsis will avoid being given IV antibiotics unnecessarily and therefore might avoid side effects. Taking part in the trial will mean that participants may have to give up some of their time to complete some follow up questionnaires. There are no other disadvantages or risks in taking part in the trial.

Where is the study run from?
University of Liverpool (UK)

When is the study starting and how long is it expected to run for?
December 2019 to April 2024

Who is funding the study?
National Institute for Health Research (NIHR), UK

Who is the main contact?
Dr Joanne Euden, eudenj@cardiff.ac.uk

Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
268723

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
17/136/13, IRAS 268723, UoL001520

Study information

Scientific Title
PROcalcitonin and NEWS2 evaluation for Timely identification of sepsis and Optimal use of antibiotics in the Emergency department.

Acronym
PRONTO

Study hypothesis
The addition of procalcitonin measurement to NEWS2 scoring will lead to a reduction in intravenous antibiotic initiation in ED patients managed as suspected sepsis, with at least no increase in 28-day mortality compared to NEWS2 scoring alone (in conjunction with local standard care pathways).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 21/07/2020, Wales Research Ethics Committee 2 Cardiff (Health and Care Research Wales Castlebridge 4 15-19 Cowbridge Road East Cardiff, CF11 9AB, UK; +44 (0)2920 785738; Wales.REC2@wales.nhs.uk), REC ref: 20/WA/0058

Study design
Multi-centre parallel two-arm open-label individually randomised controlled trial with two co-primary endpoints

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Diagnostic

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

Condition
Suspected sepsis

Interventions
A procalcitonin (PCT) point-of-care test (testing equipment provided by ThermoFisher) used in combination with NEWS2 assessment of adult patients with suspected sepsis in emergency departments, using a stratification algorithm.

Individual patients will be screened for eligibility and randomised in a 1:1 ratio to either standard clinical management (control) or standard clinical management plus the Procalcitonin biomarker guided assessment (intervention). This will be implemented in a secure 24-h web-based randomisation programme controlled centrally by the Centre for Trials Research in Cardiff. In the intervention arm, levels of procalcitonin will be detected from a small blood sample which is read in a BRAHMS PCT Direct machine, taking 20 min. The result will aid in clinician's diagnosis of sepsis.

Adults in the control arm will not have the procalcitonin test performed and will simply have NEWS2 assessment for suspected sepsis as per standard care.

Intervention Type
Device

Phase
Phase III

Drug/device/biological/vaccine name(s)
BRAHMS PCT Direct (ThermoFisher)

Primary outcome measure
Co-primary outcomes:
1. IV antibiotics initiation at 3 hours (superiority endpoint)
2. Mortality at 28 days (non-inferiority endpoint)

Secondary outcome measures
Current secondary outcome measures as of 03/05/2022:
1. Time until initiation of IV antibiotic therapy: time of antibiotic initiation, antibiotic type, dose and duration are taken at admission and daily as required
2. Late IV antibiotic initiation: antibiotics commenced after 3 hours, time of IV antibiotic initiation, dose and duration are taken as required)
3. Number of days on IV antibiotics: type, dose and duration of antibiotic taken during admission and total over the first 28 days as required
4. Number of days on any antibiotic: type, dose, and duration of antibiotic taken during admission and total over the first 28 days s required
5. Number of days on broad-spectrum antibiotics (IV and oral), defined by the number of days on an Access group of antibiotics as defined by the WHO AWaRe Classification Database (type, dose and duration of broad-spectrum antibiotic during admission and total over the first 28 days as required)
6. ICU admission: date and details of admission to ICU at any point during admission
7. Length of ICU stay: number of days in ICU taken from medical notes
8. Length of hospital stay: number of days of admission taken from medical notes

9. Adverse antibiotic outcomes: date and type of adverse events taken from medical notes as required
10. Readmission to hospital within 90 days: ICU re-admissions post-discharge date
11. Mortality within 90 days: date and description of death and time until death in days from admission
12. Health utility measured using EQ-5D/5L at 28 and 90 days
13. Health resource usage: patient reported medical costs and resource use collected at 28 and 90 days
14. Feasibility of implementing PCT testing alongside NEWS2 scoring in EDs assessed using qualitative interviews with HCPs throughout the duration of the trial
15. Acceptability of implementing PCT testing alongside NEWS2 scoring in EDs, to patients, carers and clinicians, assessed using qualitative interviews with HCPs throughout the duration of the trial
16. Total average cost per patient per arm and cost per gained (health-adjusted) life year, taken from patient-reported questionnaires and patient medical notes as required

Previous secondary outcome measures:
1. Total duration of all antibiotics (IV and oral). (Number of days on any antibiotics up to day 28)
2. Type of antibiotic (defined by the number of days on Access group broad-spectrum IV and/or oral antibiotics during the 28-day follow-up period, as defined by WHO AWaRe Classification Database). Type, dose and duration recorded in medical notes daily
3. Readmissions (number of times participant readmitted to ICU during the 28-day follow up period. Monitored daily)
4. Antibiotic-associated side effects. (Recorded in medical notes and observation charts. Daily observation)
5. Health utility (EQ-5D/5L) at 90 days. (patient-reported questionnaire collected on day 28 and day 90)
6. Feasibility of implementing Procalcitonin testing alongside NEWS2 scoring in Emergency Departments (EDs) (qualitative interviews with HCPs during the internal pilot phase)
7. Acceptability of implementing Procalcitonin testing alongside NEWS2 scoring in EDs, to patients, carers and clinicians, (qualitative interviews with clinicians towards the end of the trial)

Overall study start date
01/12/2019

Overall study end date
30/04/2024

Eligibility

Participant inclusion criteria
Patients ≥16 years presenting to the ED with suspected sepsis

Participant type(s)
Patient

Age group
Adult

Lower age limit
16 Years

Sex
Both

Target number of participants
7,676

Total final enrolment
7676

Participant exclusion criteria
1. Currently on intravenous antibiotics
2. Current use of any chemotherapy agent associated with myeloablation/suppression
3. History of solid organ transplantation, allogeneic bone marrow or stem cell transplantation within 3 months prior to consent
4. Patients known to require urgent surgical intervention (within the course of current admission)
5. Presence of an advance directive to withhold life-sustaining treatment (patients not wishing to receive Cardiopulmonary Resuscitation (CPR) may qualify provided they receive all other resuscitative measures e.g. respiratory support, fluid resuscitation)

Recruitment start date
01/11/2020

Recruitment end date
01/11/2023

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Royal Liverpool University Hospital
Prescot St
Liverpool
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L7 8XP

Study participating centre
St James's University Hospital
Beckett St
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United Kingdom
LS9 7TF

Study participating centre
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Study participating centre
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University of Liverpool

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Sponsor type
University/education

Website
https://www.liverpool.ac.uk/

ROR
https://ror.org/04xs57h96

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
All publications and presentations relating to the trial will be authorised by the Trial Management Group and will be in accordance with the trial's publication policy.
The trial protocol will be published, and the trial will be registered with ISRCTN. At the end of the study, a final report will be published in The Health Technology Assessment Journal. The results of this study will be disseminated locally, nationally and internationally amongst scientific, clinical and lay groups. At the local level, we will interact with and promote the

research findings through wider NHS Trusts (Health Boards in Wales), the NIHR Clinical Research Network: North West Coast, North West Coast CLAHRC, North West Coast AHSN (Innovation Agency). The Innovation Agency is the national lead within AHSNs for sepsis through the Patient Safety Collaborative.
Nationally, we will engage with NICE, the Royal College of Physicians, The Royal College of Emergency Medicine, The British Society for Antimicrobial Chemotherapy, The British Infection Association, NHS Improvement and the UK Sepsis Trust. Internationally, we will disseminate our findings at high impact conferences such as European Congress of Clinical Microbiology and Infectious Diseases, Federation of Infection Societies, The Interscience Conference on Antimicrobial Agents and Chemotherapy, The International Society for Pharmacoeconomics and Outcomes Research, and The European Health Economics Association. We anticipate publication outputs reporting the effectiveness and cost-effectiveness findings in high impact Journals such as The Lancet, The Journal of the American Medical Association, The British Medical Journal and Lancet Infectious Diseases. We will set up a study website and produce an annual NEWS letter for clinicians, academics and policy makers.

We will engage with patient groups and the wider public through our involvement as members of the UK Sepsis Trust, Antibiotic Action (a public awareness group of the British Society for Antimicrobial Chemotherapy), and the Meningitis Research Foundation, and publicise the study through these channels, and seek to present study updates at their annual conferences. We will use press releases and social media outlets (Facebook and Twitter) to publicise the study and disseminate findings. We will also feedback study findings to participants, their families and clinicians. We will use public engagement officers based at the University of Liverpool and participating hospital trusts to develop and disseminate public messages.

Intention to publish date
01/04/2025

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Cardiff Centre for Trials Research by contacting the study manager (Dr Joanne Euden) at PRONTO@cardiff.ac.uk. Anonymised data will be provided upon production of the requestor's study protocol and agreement by Centre of Trials Research and study sponsor (University of Liverpool).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		13/06/2022	15/06/2022	Yes	No
HRA research summary			28/06/2023	No	No
Statistical Analysis Plan	version 2.0	03/12/2024	19/03/2025	No	No