ISRCTN47473244 https://doi.org/10.1186/ISRCTN47473244

Biomarker-guided duration of antibiotic treatment for sepsis

Submission date
06/07/2017

Recruitment status
No longer recruiting

Registration date
14/07/2017

Overall study status
Ongoing

Last Edited
14/06/2024

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 is a common life-threatening condition that is triggered by infection. In sepsis, the body's defence mechanisms (immune system) react excessively, resulting in widespread inflammation and swelling. If not treated quickly, sepsis can result in shutdown of vital organs which can result in death. Each year in the UK, about 200,000 people develop sepsis and up to a quarter will die. Previous research indicates that early recognition of sepsis and rapid antibiotic treatments are the most important factors for patient survival. While starting antibiotics for sepsis is crucial, the recommended duration of such treatment is uncertain. The lack of research on when to stop treatment safely can lead to an overuse of antibiotics in this condition. Antibiotic overuse is important because it promotes bacteria that are resistant to antibiotics (antimicrobial resistance), which means that sepsis and, indeed, other infections would become difficult to treat in the future. Shorter courses of antibiotics for a patient with sepsis, if given appropriately, may result in less antibiotic use resulting in fewer side effects, less risk of antibiotic resistance and a reduction in costs. Chemicals circulating in the blood can indicate the level of an infection and how effective the treatment of an infection is. These chemicals are called biomarkers. The two most well researched circulating biomarkers in sepsis are C-reactive protein (CRP) and procalcitonin (PCT). They are both protein chemicals produced by the human body in response to infection and can be readily measured in blood samples using NHS laboratory equipment. The aim of this study is to find out whether the duration of antibiotic treatment given to patients with sepsis can be safely reduced following the close daily monitoring of these biomarkers. A number of studies around the world have shown high levels of both CRP and PCT in the blood of patients with sepsis and that they can fall to low levels during a spell of antibiotics. While these studies suggest that these biomarkers could help determine when to stop antibiotics in sepsis, no studies have been performed to test such strategies for NHS patients.
This study has received Urgent Public Health (UPH) status from the National Institute for Health Research (NIHR).

Who can participate?
Patients aged 18 and over with sepsis

What does the study involve?
Participants are randomly allocated to one of three treatments: a standard antibiotic treatment

course (usually about 7 days), or treatment courses based on the addition of either daily CRP measurement or daily PCT measurement. All biomarker measurements are performed on one extra daily blood sample as part of usual care. The results are used to provide advice to the patient's treating team about when to stop antibiotics. To assure patient safety, the final decision to stop antibiotics rests entirely with the treating team and an independent Monitoring Committee scrutinises study progress. The duration of antibiotic treatment and mortality (death rates) in the three groups are compared over 28 days.

What are the possible benefits and risks of participating?
Individual patients are unlikely to benefit from participating in this study. The aim is to build evidence to guide the duration (how many days it should be taken for) of antibiotic treatment for patients with sepsis. If the number of days that it is necessary to give antibiotic treatment can be safely reduced, individual patients may benefit from the possibility of fewer days suffering from the known side effects of antibiotic treatment and a reduced risk of building up resistance to antibiotics working in the future (antimicrobial resistance). Patients continue to receive standard clinical treatment, and their clinicians continue to decide on how long antibiotic treatment is given. An additional 1 teaspoon of blood (5 ml) is taken daily during antibiotic treatment. The amount of additional blood is small and is taken, in most cases, from an arterial or venous tube at the same time as blood required for routine clinical care. In exceptional cases, blood sampling is from a vein using a needle. There may be a sharp scratch when the needle is inserted and possible bruising from the area from which the blood is taken.

Where is the study run from?
Warwick Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for?
May 2017 to January 2025

Who is funding the study?
Health Technology Assessment Programme (UK)

Who is the main contact?
Prof. Paul Dark, paul.m.dark@manchester.ac.uk

Study website
https://warwick.ac.uk/fac/sci/med/research/ctu/trials/adaptsepsis

Contact information

Type(s)
Scientific

Contact name
Prof Paul Dark

ORCID ID
http://orcid.org/0000-0003-3309-0164

Contact details
c/o Research & Development Department
Summerfield House

Salford Royal NHS Foundation Trust
544 Eccles New Road
Salford
United Kingdom
M5 5AP
+44 (0)161 789 7373
paul.m.dark@manchester.ac.uk

Additional identifiers

EudraCT/CTIS number

IRAS number
209815

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
IRAS (UK) 209815, IRAS (Scotland) 234179, HTA 15/99/02

Study information

Scientific Title
Multicentre randomised controlled trial in critical care patients using biomarker-guided duration of antibiotic treatment for sepsis: the ADAPT-Sepsis trial

Acronym
ADAPT-Sepsis

Study hypothesis
Hospitalised adult patients already receiving empiric intravenous antibiotics for suspected sepsis, who are treated using an antibiotic discontinuation protocol based on either CRP or PCT, will have safe decreases in antibiotic treatment duration compared with those treated with standard care alone.

Ethics approval required
Old ethics approval format

Ethics approval(s)
South Central – Oxford C REC, 20/10/2017, IRAS (UK) 209815, REC Ref: 17/SC/0434, IRAS (Scotland) 234179, REC Ref: 17/SS/0125

Study design
Randomized controlled multi-centre interventional trial

Primary study design
Interventional

Secondary study design

Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Prevention

Participant information sheet
It is expected that inclusion into this trial will need to be considered by providing information in varied formats, the trlaists will be providing the following Information sheets:- Patient Information (at Commencement); Patient Information (with Assent in Northern Ireland); Patient Information (Retrospective Consent); Consultee Information; Information for Guardian/Welfare Attorney/Relative Consent. Documents not available in web format, please use contact details to request a participant information sheet

Condition
Sepsis

Interventions
In-patients receiving Critical Care treatment will be randomised (web-based randomisation) to one of two intervention groups (C-Reactive Protein (CRP) or Procalcitonin (PCT)) guided antibiotic duration) or a standard antibiotic treatment course (control) group (usually about 7 days). Patients continue to receive standard care including antibiotic treatment. Duration to antibiotic discontinuation guidance only.

Patient blood collection (minimum of 2 ml research sample per day) and serum laboratory testing of either CRP, PCT or ‘no laboratory test’ will commence within the first 24 hours following the initiation of intravenous antibiotics for suspected sepsis and continue daily until antibiotics have been discontinued. Daily standardised written advice on either continuing standard care or on antibiotic discontinuation will be issued to the clinical team, repeated in 24 hour intervals. Advice will be based on daily serum testing.

Intervention Type
Other

Primary outcome measure
1. Primary clinical effectiveness outcome: total duration of antibiotic treatment to 28 days following randomisation (superiority) measured in days (24-hour time periods from randomisation)
2. Primary safety outcome: 28-day all-cause mortality (non-inferiority) following randomisation

Secondary outcome measures
Secondary effectiveness and safety outcome measures to 28 days following randomisation:
1. Antibiotic dose, measured as Defined Daily Dose
2. Unscheduled care escalation/re-admission
3. Infection relapse/recurrence requiring further antibiotic treatment
4. Super-infection, defined as new infection at a different anatomical site
5. Suspected antibiotic adverse reactions
6. Time to ‘fit’ for hospital discharge

Overall study start date
01/05/2017

Overall study end date
31/01/2025

Eligibility

Participant inclusion criteria
1. Hospitalised adult patients at least 18 years of age
2. Up to 24 hours of initiation of empiric intravenous antibiotic treatments for a suspicion of sepsis (i.e. “suspected sepsis” – see trial definition below)
3. Likely to remain hospitalised and receiving intravenous antibiotic treatment for at least the next 72 hours
4. Requirement for critical care

Suspected sepsis definition: Within the context of this study, ‘suspected sepsis’ is defined as ‘acute organ dysfunction associated with suspected infection’ (1). The trialists do not mandate a definition for ‘acute organ dysfunction’ and patient information underpinning local clinical decisions will be captured as part of the Case Report Form (CRF) which will include the Sequential Organ Failure Assessment (SOFA) score.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
2760

Participant exclusion criteria
Current exclusion criteria as of 05/02/2021:
1. More than 24 h since receiving first empiric intravenous antibiotic treatments for a suspicion of sepsis
2. Prolonged (greater than 21 days) antimicrobial therapy mandated (e.g. for endocarditis, cerebral/hepatic abscess, tuberculosis, osteomyelitis)
3. Severely immunocompromised (e.g. neutropenia, less than 500 neutrophils/µl)
4. All treatment for suspected sepsis likely to be stopped within 24 hours of its initiation because of futility
5. 5. Any patient given, or anticipated to receive an IL-6 receptor inhibitor drug (e.g. tocilizumab or sarilumab) during their acute hospital admission
6. Consent declined
7. Previously enrolled in this trial

———

Previous exclusion criteria:
1. More than 24 h since receiving first empiric intravenous antibiotic treatments for a suspicion of sepsis
2. Prolonged (greater than 21 days) antimicrobial therapy mandated (e.g. for endocarditis, cerebral/hepatic abscess, tuberculosis, osteomyelitis)
3. Severely immunocompromised (e.g. neutropenia, less than 500 neutrophils/µl)
4. All treatment for suspected sepsis likely to be stopped within 24 hours of its initiation because of futility
5. Consent declined
6. Previously enrolled in this trial

Recruitment start date
29/01/2018

Recruitment end date
05/06/2024

Locations

Countries of recruitment
England

Scotland

United Kingdom

Wales

Study participating centre
Salford Royal Hospital
Stott Lane
Salford
United Kingdom
M6 8HD

Study participating centre
Heartlands Hospital
Heart of England NHS Foundation Trust
Bordesley Green E
Birmingham
United Kingdom
B9 5SS

Study participating centre
James Cook University Hospital
South Tees Hospitals NHS Foundation Trust
Marton Road
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
Aintree Hospital
Lower Lane
Liverpool
United Kingdom
L9 7AL

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

Study participating centre
Royal Bolton Hospital
Minerva Rd
Farnworth
Bolton
United Kingdom
BL4 0JR

Study participating centre
Royal Infirmary of Edinburgh
51 Little France Cres
Old Dalkeith Rd
Edinburgh
United Kingdom
EH16 4SA

Study participating centre
Freeman Hospital
Freeman Rd

High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Royal Victoria Infirmary
Queen Victoria Rd
Newcastle upon Tyne
United Kingdom
NE1 4LP

Study participating centre
Gloucestershire Royal Hospital
Great Western Rd
Gloucester
United Kingdom
GL1 3NN

Study participating centre
Leeds General Infirmary
Great George St
Leeds
United Kingdom
LS1 3EX

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

Study participating centre
Manchester Royal Infirmary
Oxford Rd
Manchester
United Kingdom
M13 9WL

Study participating centre
University Hospital of North Tees
Hardwick Rd
Hardwick
Stockton-on-Tees
United Kingdom
TS19 8PE

Study participating centre
Nottingham City Hospital
Hucknall Rd
Nottingham
United Kingdom
NG5 1PB

Study participating centre
Royal Preston Hospital
Sharoe Green Ln
Fulwood
Preston
United Kingdom
PR2 9HT

Study participating centre
Royal Glamorgan Hospital
Ynysmaerdy
Pontyclun
United Kingdom
CF72 8XR

Study participating centre
Royal Free Hospital
Pond St
London
United Kingdom
NW3 2QG

Study participating centre

Royal Victoria Hospital
Radnor Park Ave
Folkestone
United Kingdom
CT19 5BN

Study participating centre
Russells Hall Hospital
Pensnett Rd
Dudley
United Kingdom
DY1 2HQ

Study participating centre
Royal Oldham Hospital
Rochdale Rd
Oldham
United Kingdom
OL1 2JH

Study participating centre
Sunderland Royal Hospital
Kayll Rd
Sunderland
United Kingdom
SR4 7TP

Study participating centre
University College Hospital
235 Euston Rd,
London
United Kingdom
NW1 2BU

Study participating centre
Wythenshawe Hospital
Southmoor Rd
Wythenshawe
Manchester
United Kingdom
M23 9LT

Study participating centre
York Hospital
Wigginton Rd
Clifton
York
United Kingdom
YO31 8HE

Sponsor information

Organisation
University of Manchester

Sponsor details
Oxford Road
Manchester
England
United Kingdom
M13 9PL
+44 (0)161 275 2725
research.governance@manchester.ac.uk

Sponsor type
University/education

Website
http://www.manchester.ac.uk/

ROR
https://ror.org/027m9bs27

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, HTA

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 study will be authorised by the Trial Management Group. Authorship will be determined according to the internationally agreed criteria for authorship (https://www.icmje.org). Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group and the Study Coordination Centre.

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial co-ordinating team, and the final version will be agreed by the Trial Steering Committee before submission for publication, on behalf of the collaboration. The study will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines and the template for intervention description and replication (TIDieR) checklist and guide.

The success of the trial depends on the collaboration of doctors, nurses, laboratory scientists and researchers from across the UK. Equal credit will be given to those who have wholeheartedly collaborated in the trial.

The trial protocol and statistical analysis plan will be published to ensure transparency in the methodology. The trialists intend to publish the full protocol by January 2018 for open access. The study findings will be presented at national and international meetings with abstracts online, with wide social media coverage so that results and their implications quickly reach all of the relevant UK clinical communities. This will be facilitated by the investigator group which includes key individuals linked to societies, professional bodies, the Department of Health and patient/relative groups across a wide range of responsibilities relevant to the planning of the management of sepsis, laboratory chemistry, antibiotic stewardship and antimicrobial resistance in the NHS. In accordance with NIHR open access policies the clinical findings of the trial as well as a paper describing the cost-effectiveness in the NHS setting will be published in high-quality peer-reviewed open access (via PubMed) journals. Results publications will be submitted around September 2021. A final report will also be published in the NIHR HTA journal. The trialists will actively promote the findings of the study to journal editors, sepsis care and antimicrobial stewardship opinion leaders to ensure the findings are widely disseminated (e.g. through editorials and conference presentations) and are included in future guidelines.

NICE issued guidelines for PCT monitoring of sepsis in 2015 and encouraged clinicians to enter patients into future NHS clinical trials aimed at testing biomarker-guided antibiotic discontinuation protocols for sepsis. The trial has been planned to address NICE’s

recommendations so that subsequent results will inform their future guidance on sepsis. The trial methods proposed would ensure that publications from the trial would be given a good rating by an assessment group using the Cochrane risk of bias score. The trialists will inform NHS managers and commissioners if the study supports a change of practice.

A lay person's summary will be sent to local and national patient support and liaison groups, notably the ICSPRC and ICUSteps. A report of the study findings will be sent to the INVOLVE registry. This is an open-access database which registers research health care projects involving members of the public as partners in the research process. Following peer reviewed publication, appropriate key publication findings will be communicated through press releases led by the NIHR in partnership with the trial host institutions.

Intention to publish date
14/02/2025

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be included in the subsequent results publication.

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 6.0	26/04/2021	07/12/2021	No	No
Protocol file	version 7.0	25/11/2021	30/03/2022	No	No
Protocol article		25/04/2023	23/05/2023	Yes	No
Protocol file	version 9.0	20/03/2023	23/05/2023	No	No
Statistical Analysis Plan	version 1.1	08/03/2022	23/05/2023	No	No
HRA research summary			28/06/2023	No	No
HRA research summary			28/06/2023	No	No