PROcalcitonin and NEWS2 evaluation for Timely identification of sepsis and Optimal use of antibiotics in the Emergency Department:

The PRONTO Trial

PROTOCOL VERSION 3.0 DATED 22.11.22

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the relevant trial regulations, GCP guidelines, and CTR's SOPs.

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

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

CTU Director

Name:	**Signature:**	**Date:**
Professor Kerry Hood	Emma Thomas - Jones approved via email on behalf of Kerry Hood	29.11.22

Chief Investigator

Name:	**Signature:**	**Date:**
Professor Neil French	approved via email	29.11.22

General Information This protocol describes the PRONTO clinical trial and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other patients. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance, to CTR.

Contact details – Chief Investigators & Co-Investigators

Co-CHIEF INVESTIGATOR (Lead)	**Co-CHIEF INVESTIGATOR**
Professor Neil French	**Dr Stacy Todd**
Professor Infectious Diseases	NHS Consultant Infectious Diseases
Institute of Infection & Global Health,	Liverpool University Hospitals NHS Foundation Trust
The Ronald Ross Building 8 West Derby Street University of Liverpool	Tropical and Infectious Disease Unit, Royal Liverpool University Hospital, Prescot Street, Liverpool
L69 7BE	L7 8XP
Tel : 0151 7959630	Tel : 0151 706 2000 ext 10858
E-mail : french@liv.ac.uk	E-mail : Stacy.todd@liverpoolft.nhs.uk

CO-INVESTIGATORS	
Professor Kerry Hood	**Dr Emma Thomas-Jones**
Director / Professor of Clinical Trials	Senior Research Fellow
Centre for Trials Research, Cardiff University	Centre for Trials Research, Cardiff University
e-mail : HoodK1@cardiff.ac.uk	e-mail : thomas-jonese@cardiff.ac.uk
Dr Philip Pallmann	**Dr Lucy Brookes-Howell**
Research Fellow /Senior Statistician	Senior Research Fellow / Senior Qualitative Researcher
Centre for Trials Research, Cardiff University	Centre for Trials Research, Cardiff University
e-mail: PallmannP@cardiff.ac.uk	e-mail: Brookes-HowellLC@cardiff.ac.uk
Professor Enitan Carrol	**Honorary Professor Ingeborg Welters**
Chair in Paediatric Infection	Senior Clinical Lecturer
University of Liverpool	University of Liverpool
e-mail: edcarrol@liverpool.ac.uk	e-mail: I.Welters@liverpool.ac.uk
Dr Emmanuel Nsutebu	**Mrs Julie Carman**
Consultant Infectious Diseases Physician & Acting Chief of Infectious Diseases	Patient Representative
Mafraq Hospital, Abu Dhabi, UAE	
e-mail: efnsutebu@gmail.com	e-mail: jandjcarman@yahoo.co.uk
Professor Philip Howard	**Professor Louis Neissen**

Consultant Antimicrobial Pharmacist	Chair in Health Economics
University of Leeds	Liverpool School of Tropical Medicine
e-mail: philip.howard2@nhs.net	e-mail : Louis.Niessen@lstmed.ac.uk
Professor David Taylor-Robinson	
Professor of Public Health and Policy	
University of Liverpool	
e-mail: David.Taylor-Robinson@liverpool.ac.uk	
SITE PRINCIPAL INVESTIGATORS	
Dr Stephen Aston (Co-investigator)	**Professor Martin Llewelyn (Co-Investigator)**
Consultant in Infectious Diseases	Consultant in Infectious Diseases
Royal Liverpool University Hospital	Royal Sussex County Hospital
e-mail: stephen.aston@liverpoolft.nhs.uk	e-mail: m.j.llewelyn@bsms.ac.uk
Dr Fiona McGill(Co-Investigator)	**Dr Paul Schmidt (Co-Investigator)**
Consultant in Infectious Diseases & Microbiology	Consultant in Acute Medicine
St James's University Hospital	Queen Alexandra Hospital
e-mail: f.mcgill@nhs.net	e-mail: paul.schmidt@porthosp.nhs.uk
Dr Gavin Barlow	**Rachel O' Brien**
Honorary Consultant in Infection	Lead Research Nurse
Hull Royal Infirmary	Royal Infirmary of Edinburgh
e-mail : Gavin.Barlow@hey.nhs.uk	email: Rachel.O'Brien@nhslothian.scot.nhs.uk
Dr Andrew Tabner	**Dr Helen Pardoe**
Emergency Medicine Consultant	Chief Clinical Information Officer
Royal Derby Hospital	Princess Alexandra Hospital
e-mail: andrew.tabner@nhs.net	e-mail: helen.pardoe1@nhs.net
Dr Arjun Thaur	
Consultant in Emergency Medicine	
Guys & St. Thomas NHS Trust	
e-mail: Arjun.Thaur@gstt.nhs.uk	

SPONSOR contact details:

Dr Neil French

Head of Clinical Operations

Clinical Directorate

Faculty of health and Life Sciences

University of Liverpool

Tel: 0151 794 8739

Email: sponsor@liv.ac.uk

Trial Co-ordination:

The PRONTO trial is being coordinated by the Centre for Trials Research (CTR), Cardiff University, a Clinical Research Collaboration (UKCRC) registered trials unit.

This protocol has been developed by the PRONTO Trial Management Group (TMG).

For **all queries** please contact the PRONTO team through the main trial email address. Any clinical queries will be directed through the Trial Manager to either the Chief Investigators or Co-Investigators.

Main Study Email:	PRONTO@cardiff.ac.uk		
CTR Trial Lead:	Dr Emma Thomas-Jones	Email: Thomas-JonesE@cardiff.ac.uk	Tel: 02920 687520
Trial Manager:	Dr Joanne Euden	Email: eudenj@Cardiff.ac.uk	Tel: 02922 510771
Data Manager:	Stephanie Gilbert	Email: GilbertS3@cardiff.ac.uk	Tel: 02920 687681
Trial Statistician:	Dr Philip Pallmann	Email: PallmannP@cardiff.ac.uk	Tel: 02920 687461
Trial Administrator:	Mahuampi Perez-Alijas	Email: Perez-AlijasM@cardiff.ac.uk	Tel: 02922 511759
Qualitative Researcher:	Dr Jacqueline Hughes Dr Lucy Brookes-Howell	Email: HughesJ33@cardiff.ac.uk Email: Brookes-HowellLC@cardiff.ac.uk	Tel: 02920 687611 Tel: 02920 687145

Randomisation
Randomisation will be via the study database at: https://pronto.ctr.cardiff.ac.uk/login/

Clinical queries:

Clinical queries
PRONTO@cardiff.ac.uk
All clinical queries will be directed to the most appropriate clinical person.

Serious Adverse Events:

SAE reporting
Where the adverse event meets one of the serious categories, an SAE form should be completed by the responsible clinician and submitted to PRONTO@cardiff.ac.uk within 24 hours of becoming aware of the event (See section 15 for more details).
Contact details:
PRONTO Trial Manager: 02922 510771

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Glossary of abbreviations

AE	Adverse Event
AR	Adverse Reaction
CF	Consent Form
CI	Chief Investigator
CRF	Case Report Form
CTR	Centre for Trials Research
CU	Cardiff University
GCP	Good Clinical Practice
HE	Health Economics
HTA	Health Technology Assessment
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
NHS	National Health Service
NICE	National Institute for Clinical Excellence
PI	Principal Investigator
PIS	Participant Information Sheet
QC	Quality control
QL (QoL)	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

1 Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version
Substantial (Amendment 4)	2.0		1. Change in Site PI and Co-Investigators 2. Changes in CTR team 3. Added COVID related background. 4. Change to risk stratification for high NEWS (>=7) and low PCT (<0.05) to moderate risk. 5. Consent process altered in section 9.3 6. Added planned stratification of all outcomes by COVID-19 diagnosis 7. It should read "low PCT (<0.5)" rather than "low PCT (<0.05) 8. Added Covid to the list of variables to be collected. 9. Added COVID diagnosis to table 1. 10. Added witness consent to Qualitatie interviews. 11. Subgroup and interim analysis updated.
Non-substantial (Amendment 18)	2.1		1. Updated final decisions on primary effectiveness (section 5.3). Decreased mortality with same or

Substantial (Amendment 23)	3.0		equivalent antibiotic initiation changed from 'unclear effect' to 'Effective'. 1. Inserted website information for randomisation, 2. Updated research administrator at CTR. 3. Updated qualitative researchers at CTR. 4. Updated planned number of sites (Section 2) 5. Updated planned trial period (Section 2). 6. Number of sites updated in setting information (Section 6.2). 7. Updated information on the trial intervention to include PathFast BRAHMS PCT reader (section 10)

2 Synopsis

Short title	PROcalcitonin and NEWS2 evaluation for Timely identification of sepsis and Optimal use of antibiotics in the Emergency Department
Acronym	PRONTO
Internal ref. no.	UoL001520
Development phase	Phase III
Funder and ref.	NIHR HTA (ref 17/136/13)
Trial design	Prospective, individually randomised, open label, two arm, group sequential RCT
Trial participants	Adults and adolescents ≥ 16 years presenting to emergency care departments with suspected sepsis.
Planned sample size	7676
Planned number of sites	Maximum of 20 sites
Inclusion criteria	Patients ≥ 16 years presenting to the ED with suspected sepsis
Exclusion criteria	• Currently on intravenous (IV) antibiotics • Current use of any chemotherapy agent associated with myelablation/suppression. • History of solid organ transplantation, allogeneic bone marrow or stem cell transplantation within 3 months prior to consent. • Patients requiring urgent surgical intervention. • 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).
Treatment duration	As determined by treating clinician
Follow-up duration	To 28 days (primary endpoint) and 90 days.
Planned trial period	1st December 2019 - 30th April 2024
Primary objective	To assess whether the addition of Procalcitonin (PCT) measurement to NEWS2 scoring leads to a reduction in IV antibiotic initiation with no increase in 28-day mortality compared to NEWS2 scoring alone in the management of patients seen in the Emergency Department (ED) with suspected sepsis.
Secondary objectives	The assessment of a) feasibility, b) cost-effectiveness and c) acceptability to patients and their family.
Tertiary/Exploratory objectives	N/A
Primary outcomes	Co-primary outcomes: • IV antibiotics initiation at 3 hours (superiority endpoint) • Mortality at 28 days (non-inferiority endpoint). **A positive conclusion will be drawn only if both a decrease in IV antibiotic initiation AND non-inferiority in mortality are demonstrated.**
Secondary outcomes	• Total duration of all antibiotics (IV and oral) within 28 days of recruitment • Type of antibiotic • Readmissions • Antibiotic associated side effects • Health utility (EQ-5D/5L) at 90 days. • Feasibility of implementing PCT testing alongside NEWS2 scoring in Emergency Departments (EDs)

	• Acceptability of implementing PCT testing alongside NEWS2 scoring in EDs, to patients, carers and clinicians
Tertiary/Exploratory outcomes	N/A
Intervention	The addition of point of care testing for PCT to NEWS2 scoring compared to current standard of care using NEWS2 alone.

3 Trial summary & schema

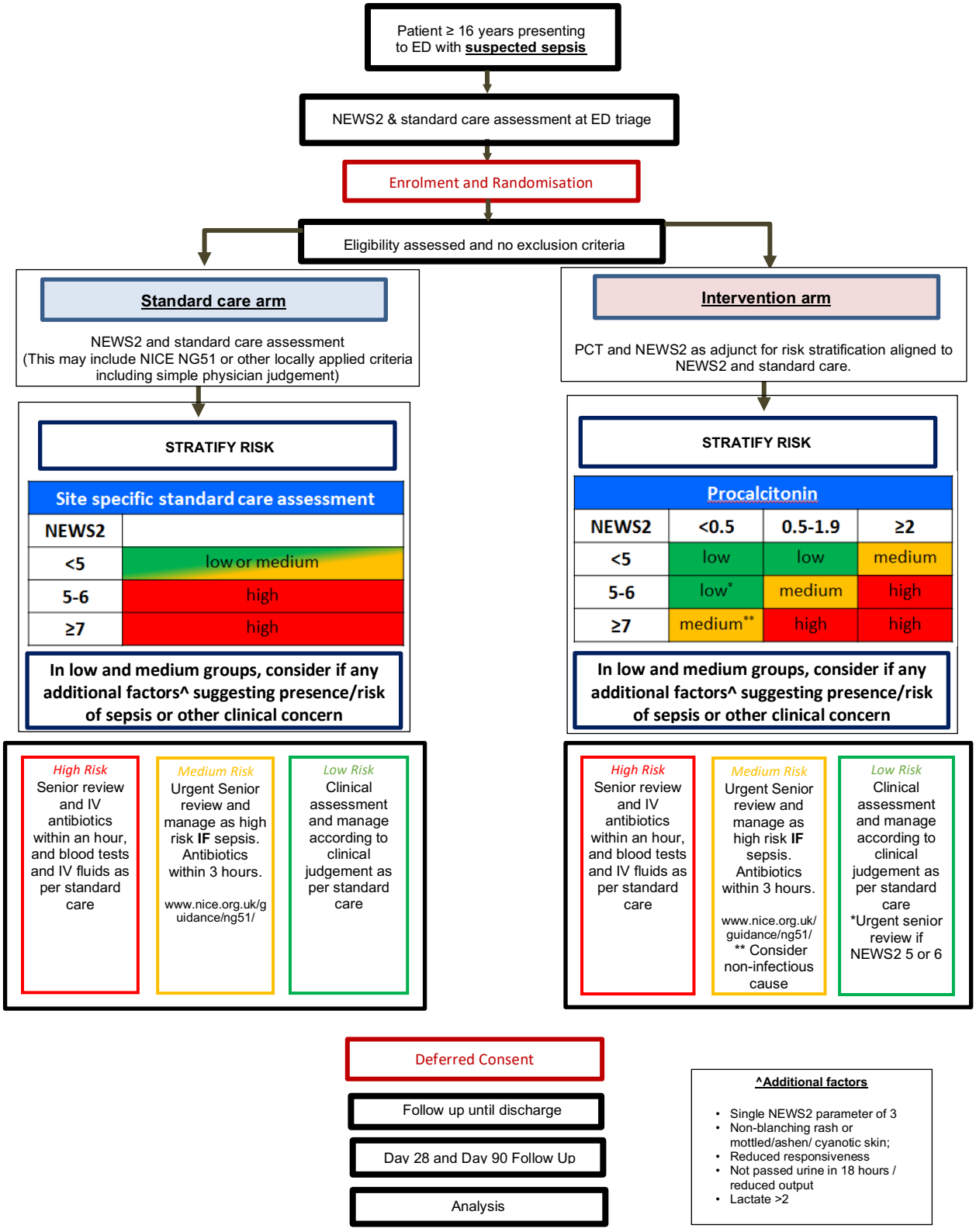


Figure 1. Participant Flow Diagram

3.1 Trial lay summary

Sepsis 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 if required, 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.

Ten to 14 hospitals will take part in the study and 7676 adult patients with suspected sepsis will be randomly assigned to current standard of care or PCT-supported care. In the PCT arm, 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 (see Figure 1 – participant flow diagram). Doctors and patients will know what treatment arm they are in. Doctors remain free to use antibiotics outside the study guidelines using their clinical judgement in any of the

risk groups. The key outcome measures will be whether IV antibiotics are started, and death within 28 days. 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.

4 Background

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1] and is a medical emergency requiring prompt antimicrobial therapy and physiological support. The identification, assessment and management of sepsis is challenging because of its many non-specific symptoms and signs, which can be caused by both infectious and non-infectious diseases. In line with international recommendations, National Institute for Health and Care Excellence (NICE) sepsis guidelines suggest the administration of intravenous antibiotics within an hour to patients displaying features considered to be high risk for ICU admission and death [2]. However, up to 50% of patients initially managed as sepsis in the Emergency department (ED) do not have a final diagnosis of sepsis [3, 4]. The current approach leads to overuse of antibiotics with the associated risk of antimicrobial resistance (AMR). For example, since introduction of the National Commissioning for Quality and Innovation (CQUIN) for sepsis in 2015, intravenous broad spectrum antibiotic use in Emergency Departments has increased by 83% over 3 years [5].

Use of antibiotics brings its own problems including antibiotic-related adverse drug reactions (e.g. *C. difficile* infection) [6], extended hospital stays, and generation of antimicrobial resistance with increased long term adverse consequences to health care. There is some evidence that unnecessary use of broad spectrum antibiotics increases the risk of developing sepsis within 90 days of a previous hospital stay [7]. The O'Neill report on antimicrobial resistance suggests that there are about 1 million deaths a year as a result of AMR and this is likely to rise to an estimated 10 million by 2050 [6]. One of the key recommendations was to promote new, rapid diagnostics to improve accuracy of early diagnosis and cut unnecessary use of antibiotics.

NICE guidelines recommending antibiotics within one hour [2] must be balanced against NICE antimicrobial stewardship guidelines and the Department of Health (DoH) antimicrobial stewardship toolkit that recommend antimicrobials should not be started unless there is clear evidence of infection [8]. Clinical decision support is essential to balance these competing drivers. Patients in our patient and public involvement (PPI) workshop described this situation as *"it seems to me you are damned if you do – damned if you don't because medical professionals won't want to take a chance and the public will be quick to complain – at the moment where there is a gap in knowledge everyone will err on the side of caution."* For similar reasons, a group of clinicians have launched a counter campaign against the surviving sepsis campaign guidelines which recommends antibiotics within 1 hour for all patients with suspected sepsis. They argue that it risks overtesting and overtreating patients with low probability of sepsis, diverting attention away from more evidence-based time-sensitive tasks and patients who require more urgent treatment (https://www.jwatch.org/na46999/2018/08/06/surviving-sepsis-campaign-rush-judgment).

In the busy environment of an ED or Acute Medical Unit (AMU), risk stratification currently relies on NICE sepsis guidelines and the National Early Warning Score (NEWS2) assessment based on six vital signs and requirement for supplemental oxygen [9]. The challenge of delivering high quality sepsis care in an ED setting has been well recognised [10, 11]. Accurate risk stratification could improve antimicrobial stewardship where clinical teams feel confident that they can safely assess and wait for results of initial investigations prior to commencing antibiotics within 3 hours, but not within the 1 hour target. The use of screening tools for sepsis within EDs in the UK remains a point for discussion. The third international consensus definition (Sepsis 3) recommended use of a new, rapid scoring tool, the quick Sequential Organ Failure Assessment (qSOFA) score, to identify patients at high risk of death and prolonged ICU stay [1]. A qSOFA ≥ 2 is used as an indicator of screening tool for sepsis. Current NHS England policy is for NEWS2 score to be adopted by all hospitals in England by April 2019 in order to facilitate detection of deterioration and sepsis [9]. NEWS2 has been demonstrated to have comparable diagnostic accuracy in detection of severe outcomes and is more widely used in the NHS than qSOFA [12, 13]. NHS England recommends that if a NEWS2 ≥ 5 is accompanied by suspicion of sepsis, this should prompt the senior clinical decision-maker,

using clinical judgment, to start appropriate treatment (intravenous antibiotics and fluids), as indicated, within an hour of the risk being recognised. A NEWS2 ≥ 5 rather than qSOFA ≥ 2 (which is more comparable to NEWS2 ≥ 7) as threshold for the screening for sepsis reduces specificity and increases the number of patients considered to be in a high risk group from approximately 20-25% to 50-75% [unpublished RLBUHT data]. Several further evaluations of alternative scoring systems including a retrospective cohort study from our hospital [12] have concluded that whilst differences in the scoring systems exist, no scoring system has both high sensitivity and specificity for predicting adverse outcomes in sepsis in the ED, and NEWS2 is more accurate than qSOFA for predicting adverse outcomes.

The emergence of COVID-19 has exacerbated this previously highlighted problem. COVID-19 is a viral infection which presents within the sepsis syndrome constellation and is unresponsive to antibacterials. NEWS2 scores are broadly predictive of COVID-19 outcome on presentation [14], although there are some concerns on its ability to identify unwell patients with high oxygen requirements [15]. Secondary bacterial infections are uncommon at presentation to AED (3.5%) [16], despite this up to 83% of patients with COVID-19 received antibiotics [16, 17]. NEWS2 in COVID-19 does not appear to have an association with bacterial co-infection at presentation. Initial investigations in the ED can be helpful in distinguishing between COVID-19 and bacterial pneumonia including typical radiographic changes, lymphopenia, and increasingly COVID-19 point of care diagnostics [18]. These results would be available within 3 hours for assessment and could potentially reduce unnecessary antimicrobial usage in COVID-19 management. Presentations with COVID-19 have much reduced since the peak in April 2020, but continued cases are expected for the foreseeable future. COVID-19 will therefore become part of the differential diagnosis in undifferentiated sepsis presenting to EDs and therefore a prime target for PRONTO .

Procalcitonin (PCT) is a reliable biomarker that changes early in the course of bacterial infection. A recent Cochrane meta-analysis [19] demonstrated that the use of PCT to guide antibiotic treatment in patients with acute respiratory infections reduced antibiotic exposure and side-effects, and improved survival. Procalcitonin is currently the biomarker with the

most available evidence to identify bacterial infections and antibiotic prescription decisions. PCT is predictive of outcome in COVID-19 cases and this may be because of its ability to identify superadded bacterial infection [20, 21]. It may also be a useful tool for antibiotic stewardship [22]. It has been used to differentiate viral from bacterial pneumonia prior to COVID-19. The available evidence suggests a low PCT will have good negative predictive value for a bacterial infection in cases of COVID-19 [23].

This trial addresses research recommendations from three separate NICE guidelines; Sepsis recognition, diagnosis and management (NG51) [2], PCT testing for diagnosing and monitoring sepsis (DG18) [24] and Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (NG15) [25]. In addition, it is ideally placed to address the research recommendations from NICE COVID-19 rapid guideline: antibiotics for pneumonia in adults in hospital (NG173) on the utility of PCT in COVID-19 pneumonia [26]. It will help to determine if NEWS2 in combination with PCT can improve the recognition and risk stratification of undifferentiated sepsis including COVID-19, and facilitate prompt and appropriate antibiotics in adults presenting to the ED. It will also determine the clinical and cost effectiveness of PCT point-of-care tests in the ED for the diagnosis of sepsis. NICE antimicrobial stewardship guidelines recommend the use of decision support tools to help clinicians decide whether antibiotics are indicated, including the use of point-of-care tests, but acknowledge that further studies are required to ensure that system changes can be introduced without causing additional harm to patients.

A systematic review and cost-effectiveness analysis funded by the HTA evaluated PCT testing to guide antibiotic therapy for the treatment of sepsis in intensive care settings and for suspected bacterial infection in ED settings in adults and children [27]. The review concluded that addition of a PCT algorithm to the information used to guide antibiotic treatment may be a viable strategy to reduce antibiotic exposure in adults in ICU and ED settings without any adverse consequences and may also be associated with reductions in hospital and ICU stay in adults. None of the identified studies were conducted in the UK, and it was not clear whether

the control arms of these studies were representative of standard practice in the UK. The report recommended further studies of PCT to guide antibiotic treatment in adults with suspected or confirmed sepsis in ED settings, including research examining (short-term) health-state utility values. A recent patient level meta-analysis of randomised trials assessing the use of procalcitonin guided antibiotic treatment on outcomes for patients with infection and sepsis in intensive care settings suggests that procalcitonin use can significantly reduce mortality and antibiotic treatment duration [28]. A large prospective study of adult medical patients presenting to the ED demonstrated that admission PCT was a strong and independent predictor of 30-day mortality. The use of PCT in addition to qSOFA improved prognostic accuracy [29]. This suggests that PCT may help to improve risk stratification in suspected sepsis if combined with NEWS2.

The objective of this trial is not to prevent patients who require antibiotics from receiving antibiotics. It will assess whether by using NEWS2 and PCT, we can identify patients who require antibiotics within 1 hour whilst providing more time for clinicians to decide if antibiotics are required for patients who are less severely ill. It may therefore lead to less antibiotics and more narrow spectrum antibiotics being prescribed as clinicians may have more time to assess patients before they prescribe antibiotics. The rapid result of the PCT test, especially if it indicates a low or medium risk, may also provide reassurance to patients and families, and reduce anxiety.

5 Trial objectives/endpoints and outcome measures

5.1 Primary objectives

The primary research question is whether the addition of PCT measurement to NEWS2 scoring can 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).

5.2 Secondary objectives

To determine if the use of PCT and NEWS2 in the assessment of suspected sepsis is:

i) cost-effective,

ii) feasible

iii) acceptable to patients and their family.

5.3 Primary outcomes measure(s)

The study will use the following as co-primary outcomes:

- Intravenous antimicrobial initiation – binary outcome assessed at 3 hours.
- 28-day mortality – binary outcome.

Final decisions about the primary effectiveness, using these co-primary outcomes will be made based on:

	Reduced antibiotic initiation	Same or more antibiotic initiation
Decreased mortality	Effective	Effective
Equivalent mortality	Effective	Not effective
Increased mortality	Not effective / harmful	Not effective / harmful

5.4 Secondary outcomes measure(s)

Time until initiation of IV antibiotic therapy

Late IV antibiotic initiation – antibiotics commenced after 3 hours

Number of days on IV antibiotics (during admission and total over the first 28 days).

Number of days on any antibiotic (during admission and total over the first 28 days).

Number of days on broad spectrum antibiotics (IV and oral), defined by number of days on an Access group of antibiotics as defined by WHO AWaRe Classification Database (during admission and total over the first 28 days).

ICU admission – at any point during admission

Length of ICU stay

Length of hospital stay

Adverse antibiotic outcomes

Readmission to hospital within 90 days

Mortality within 90 days (and time until death)

Health utility (EQ-5D/5L) at 28 and 90 days

Health resource usage

Feasibility of implementing PCT testing alongside NEWS2 scoring in EDs

Acceptability of implementing PCT testing alongside NEWS2 scoring in EDs, to patients, carers and clinicians

Planned stratification of all outcomes by COVID-19 diagnosis

6 Trial design and setting

6.1 Design

Parallel two-arm open-label individually randomised controlled trial with two co-primary endpoints, an internal pilot phase and group-sequential stopping rules for effectiveness and futility/safety. Participants will be randomised in a ratio of 1:1 to NEWS2 and local standard care or the PCT-guided assessment.

6.2 Setting

NHS Emergency Departments (EDs) in the UK. We have 6 sites (Leeds, Hull, Hampshire, Portsmouth and Brighton & Sussex NHS trusts) with Royal Liverpool University Hospital as the lead NHS site. We aim to recruit a maximum of 20 sites.

Site Inclusion Criteria

- NHS ED sites using NEWS2 (as recommended, not modified)
- Receive patients 16 years and over with suspected sepsis
- Willing to randomise patients to standard care (NEWS2) or NEWS2 + PCT algorithm guided therapy

7 Site and Investigator selection

This trial will be carried out at participating sites within the UK. All sites who are interested in participating in the trial will be required to complete a registration form to confirm that they have adequate resources and experience to conduct the trial.

Before any site can begin recruitment a Principal Investigator at each site must be identified. The following documents must be in place and copies sent to the PRONTO Trial email account (see contact details on page 4):

- The approval letter from the site's R&D Department, following submission of OID (Organisation Information Document) form and the UK local information pack.
- Favourable opinion of host care organisation/PI from Main Ethics committee.
- A signed Trial Site Agreement (PI, sponsor and site signatures).
- Current Curriculum Vitae and GCP training certificate of the Principal Investigator (PI).
- Completed Site Delegation Log, Signature Log and Roles and Responsibilities document.
- Full contact details for all host care organisation personnel involved, indicating preferred contact.
- A copy of the most recent approved version of the Participant Information Sheet(s) and Consent Form(s) on host care organisation headed paper.
- Returned copy of the Self-Evident Correction Log signed by the PI.

Upon receipt of all the above documents, the Trial Manager will send written confirmation to the Principal Investigator/lead Research Nurse detailing that the site is now ready to recruit participants into the trial. This letter/email must be filed in each site's Site File. Along with the written confirmation, the site should receive their trial materials and all the documents required to recruit into the Trial.

Occasionally during the trial, amendments may be made to the trial documentation listed above. CTR will issue the site with the latest version of the documents as soon as they become available. It is the responsibility of the CTR to ensure that they obtain local R&D approval for the new documents.

Site initiation will be by attendance at a PRONTO launch meeting or by teleconference if attendance of key personnel is unfeasible.

8 Participant selection

Participants are eligible for the trial if they meet all of the following inclusion criteria and none of the exclusion criteria apply. All queries about participant eligibility should be directed to the Trial Manager before randomisation/registration.

8.1 Inclusion criteria

Patients ≥ 16 years presenting to the ED with suspected sepsis.

8.2 Exclusion criteria

- Currently on intravenous antibiotics.
- Current use of any chemotherapy agent associated with myeloablation/suppression.
- History of solid organ transplantation, allogeneic bone marrow or stem cell transplantation within 3 months prior to consent.
- Patients known to require urgent surgical intervention (within the course of current admission)

- 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).

9 Recruitment, screening and registration

9.1 Participant identification

Patients with suspected sepsis will be identified at ED triage. After initial NEWS2 and assessment according to current standard of care the eligibility criteria will be assessed and if no exclusion criteria apply, patients will be enrolled into the trial and randomised.

As a deferred consent model is being used patients and their relatives will be informed that a study is ongoing but a lengthy consent discussion will not be had so as not to delay treatment. Should the patient or consultee wish not to take part at this point, then the decision should be respected and the patient should not be enrolled into the trial. Patients who have given verbal consent will be randomised regardless of baseline NEWS2. See study flow chart for the process.

9.2 Screening logs

A screening log of all eligible and randomised patients will be kept at each site so that any biases from differential recruitment will be detected. When at site, logs may contain identifiable information but this **must** be redacted prior to being sent to the CTR. The screening log should be sent to the trial specific email address (PRONTO@cardiff.ac.uk) every month (see section 25 for further detail on data monitoring/quality assurance). Screening logs sent to the CTR that have not been redacted will be identified on receipt by the trial management team and appropriate measures will be taken to ensure site staff are aware of the requirement to redact information (monitoring and training). This will also be relayed during site set up training.

9.3 Informed consent

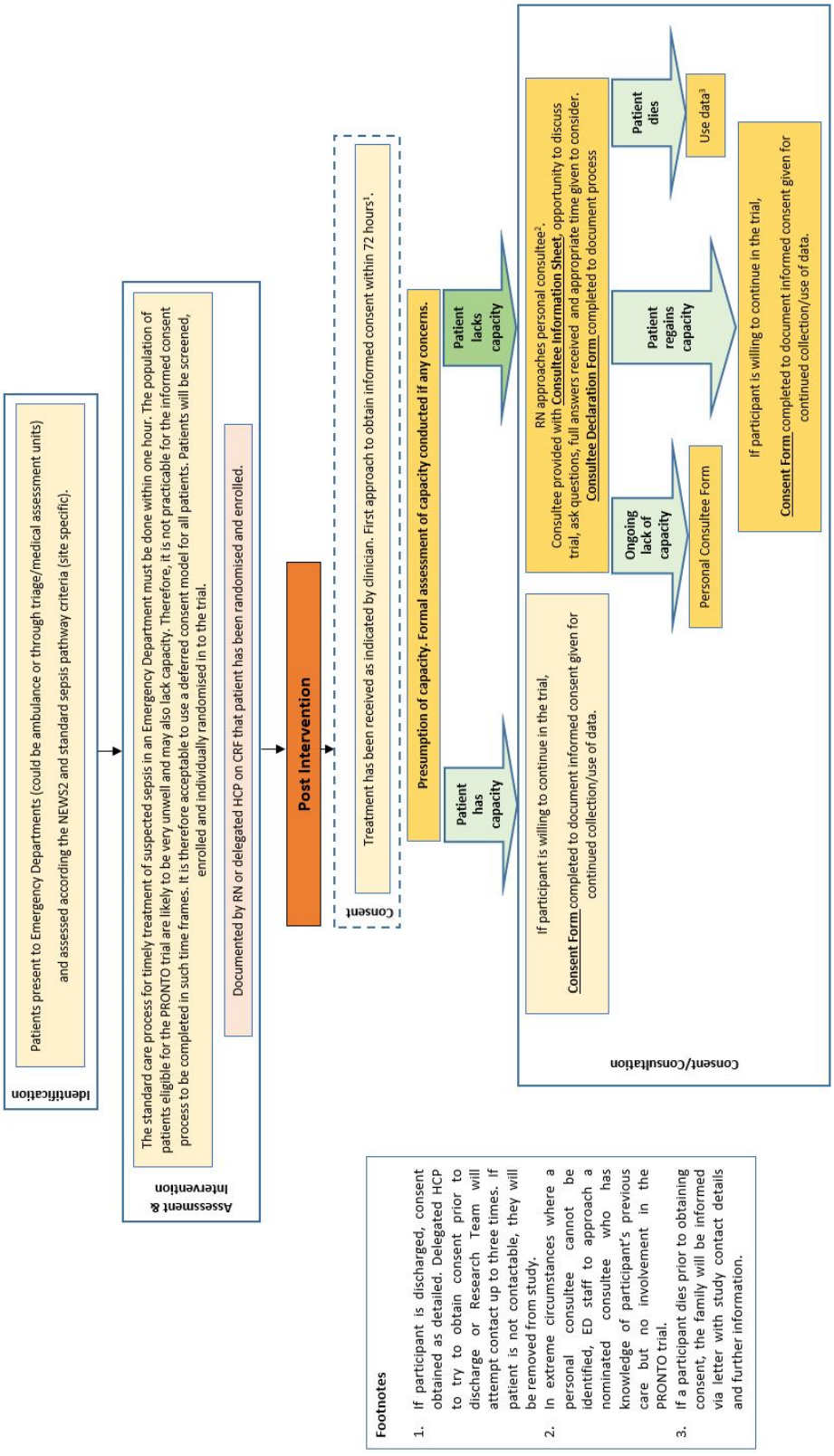
Research carried out in emergency situations is challenging in terms of obtaining consent. Emergency research is when treatment needs to be given urgently, and it is necessary to take urgent action for the purposes of the study. In some emergency situations people may lack capacity to give consent themselves and obtaining consent from a legal representative/consulting others is not reasonably practicable. Patients in this study will be very unwell and although they may self-refer themselves to the ED, they will not have the capacity to provide an informed decision with time to consider the trial in such a setting. In England and Wales, the law allows adults who lack capacity to take part in emergency research without prior consent from a legal representative or consulting others, if certain conditions are met (Medicines for Human Use (Clinical Trials) Amendment (No 2) Regulations SI 2006 2984, Mental Capacity Act s32) [6]. Given the requirement for rapid clinical assessment and treatment in our setting, for this study we will use a deferred consent model. Findings from a recent systematic review indicate that this deferred consent approach is broadly accepted by potential participants, clinicians and researchers for research in emergency settings [30].

Following enrolment in the study, deferred informed consent will be sought from the patient within a reasonable timeframe following clinical assessment/treatment (within 72 hours for first contact). Information will be provided and consent sought for the continuation in the study, and for continued use of data obtained. If the patient lacks capacity, a consultee will be consulted as soon as possible and given information about the study. The consultee will advise as to whether the person should take part in the study, and what the person's wishes and feelings about taking part in the project would be if they had capacity to decide (Mental Capacity Act s32) [1]. The consultee does not give consent themselves. The choice of who acts as consultee is important. A consultee should be someone who is close the patient, is trusted by them, and knows them well enough to advise what their wishes and preferences about participating would be [31]. Informed consent will also be sought from the patient themselves as soon as possible following any regaining of capacity. If the consultee so advises, the participant must not take part and, if already taking part, must be withdrawn. If the person who lacks capacity indicates (in any way) that they wish to be withdrawn from the study, they

must be withdrawn without delay without having to give reasons, if they don't want to and without prejudicing their further treatment. In cases where the participant dies following the intervention, we will continue to use their data. In instances where the original copy of the consent form cannot be obtained, for example due to restrictions on paperwork leaving the bedspace because of confirmed or suspected COVID-19 or use of a continuous positive airway pressure (CPAP) machine, local NHS Trust/Health Board policies will be followed such as taking a photograph of the signed consent form and sending it to the research delivery staff for printing out and filing in the Site File.

The use of anonymous data from deceased persons is lawful, and consent is not legally required from the person before they die or from a nominated representative however a letter informing them of the participants inclusion in the study will be sent along with contact details of the study team if they have further questions. A flowchart for the consent process can be seen in Figure 2.

Figure 2: Participant Consent Flowchart.



We will also pay particular consideration to how the information about the study is provided, as recent evidence suggests that despite undergoing ethical review, study documents lacked essential information, incorrectly used terminology, and conflated professionals' clinical and representation roles, particularly in emergency research and ICU settings [32]. We will involve our patient focus group in the development of these materials. We will also provide training for all HCPs involved in information giving and taking of consent to ensure they fully understand the research governance frameworks.

9.4 Registration and randomisation

9.4.1 Registration

Eligible participants with suspected sepsis will be identified at triage. After initial NEWS2 and structured assessment in line with local standard practice, the eligibility criteria will be assessed and if no exclusion criteria apply, patients will be enrolled and randomised.

9.4.2 Randomisation

Individual patients with suspected sepsis will be randomised in a 1:1 ratio to either standard clinical management (control) or standard clinical management plus PCT guided assessment (intervention). We will use minimisation with NEWS2 score and site as stratification factors and add a random element to reduce the risk of subversion. This will be implemented in a secure 24-hour web-based randomisation programme controlled centrally by the Centre for Trials Research in Cardiff.

10 Trial Intervention

PRONTO uses both the BRAHMS PCT-direct and the PathFast BRAHMS PCT. Both readers are fully validated, CE-marked point-of-care tests to determine levels of Procalcitonin in the blood. Readers for the BRAHMS PCT-Direct and all required reagents for Quality Control tests will be provided by ThermoFisher as part of a supplier agreement. The test requires 20 µl blood which will be obtained from either venous blood during standard care procedures at

triage or via a finger-prick. Recruitment using BRAHMS PCT Direct will continue until end of May 2023

From December 2022 six high recruiting sites will transition from BRAHMS PCT Direct to use the PathFast BRAHMS PCT. Readers, cartridges and associated reagents for Quality Control tests will be provided by AB Scientific as part of a separate supplier agreement. This test requires 100 µl blood which may need to be obtained as a separate venepuncture in situations where standard care phlebotomy has been completed before the PCT test is requested. These six sites will continue to recruit until the end of the study.

This will be used in combination with NEWS2 assessment of adult patients with suspected sepsis in ED, using a guidance-only algorithm for clinicians (see flow chart). It is important to note that clinicians have oversight at all times as to whether to adhere to the algorithm. As currently mandated in NICE clinical guidelines and quality standard QS161, urgent senior review within an hour will take place where any health care provider identifies at least one risk factor indicating high risk of severe illness or death regardless of aetiology. In the intervention arm a NEWS2 score of 5 or 6, combined with a PCT score of <0.5 indicates a low risk of bacterial sepsis, but an urgent senior review is mandated on the basis of the elevated NEWS2 score in keeping with standard QS161. For participants who are identified as medium risk, urgent senior review will occur. Antibiotics will be delivered according to clinical assessment. For participants in the high risk categories (Figure 1, red boxes), antibiotics will be given within the hour along with blood tests and IV fluids given as per standard care.

The PCT result is a decision aid and not to be used as a definitive management decision tool. Trained HCPs will perform the test in the ED, without the need to send the PCT sample to the laboratory. A rapid result, especially if it indicates a low or medium risk, may provide reassurance to patients and families, and reduce anxiety.

Full administrator level training will be provided by Thermofisher or AB Scientific at each site with all users following the appropriate Standard Operating Procedure for QC measurement and routine work flow processes (see example of BRAHMS PCT Direct in Figure 3). For the BRAHMS PCT Direct, Research Nurses or appropriately delegated HCPs will have a unique 4-

digit log in code for the reader. Adults in the control arm will not have the PCT test performed and will simply have NEWS2 assessment for suspected sepsis as per standard care.

Figure 3. Routine work flow for BRAHMS PCT-Direct Reader.

10.1 Adherence

Adherence to the algorithm will be recorded on the CRF and will capture instances where the treating clinician overrules the algorithm if they feel it is appropriate to do so. The ultimate responsibility for clinical care of the patient lies with the treating clinician therefore the cut – off boundaries for initiation times of antibiotics are not mandatory but are recommended guidance to aid clinical decision making. The aim of the trial is to assess whether the use of PCT can improve decision making about which patients receive antibiotics and in what time period. Deviations from the algorithm will not be recorded as protocol violations.

11 Trial procedures

All participants will be prospectively enrolled in the trial from the date of randomisation and will be assessed up to and including day 28 or until they are discharged from clinical care (for those enrolled in the last three months of the trial). Assessments include antibiotic initiation, antibiotic use, adverse events, ICU usage (details of admission to ICU), unscheduled readmissions (ICU re-admissions, re-admissions post discharge), mortality (death for any reason in the 28 days following randomisation), discharge before Day 28, and serious adverse drug reactions (ADRs) to the antibiotic. All clinical management decisions will be recorded at all time points.

At Day 28 and Day 90 there will be a follow-up via telephone or electronically (email/text) about the healthcare utilisation and quality of life of the participant. If unsuccessful a questionnaire booklet will be posted to the participant for them to complete and return with a pre-paid envelope.

11.1 Assessments

Outcome data will be recorded daily by the research nurse for all recruited participants (up to and including Day 28, or until discharge). Patient reported outcome data (health-related quality of life and resource use questionnaires) will be recorded at day 28 and day 90 (with the exception of those recruited within the last 3 months of the study).

Research nurses will review observation and medication charts, and medical notes for all recruited participants to collect the data described in Table 1 below:

Table 1: Outcome data collection

Outcome	Data Source	Type of data	Frequency	By Whom
Antibiotic (Abx) initiation	Observation (Obs) charts/medical notes/drug charts	Time of initiation, Abx type, dose, duration	Admission/Daily	Research Nurse
Abx use (IV and Oral) in-patient	Obs charts/medical notes/drug charts	Abx type, dose, duration	Daily	Research Nurse
Abx use (IV and Oral) post discharge up to 28 days	Obs charts/medical notes/drug charts/patient report/GP record	Abx type, dose, duration	At 28 day	Research Nurse
Adverse events	Obs charts/medical notes	Date, type	Daily	Research Nurse
ICU usage	Medical notes	Date, details of admission to ICU	Daily	Research Nurse
COVID diagnosis	Medical notes	Date, clinical or laboratory confirmed	At 28 day	Research Nurse
Unscheduled readmissions	Medical notes	ICU re-admissions, re-admissions post discharge	Daily	Research Nurse
Mortality	Medical notes	Date, Description	If before Day 28	Research Nurse
Discharge	Medical notes	Date, Description	If before Day 28	Research Nurse
Serious Adverse Drug Reactions (ADRs)	Medical notes	ADR(s)	Daily	Research Nurse
Health utility	Patient reported	-	Day 28 and Day 90	EQ-5D/5L, Patient reported questionnaire, collected by

				telephone or by post
Health-related Quality of Life (EQ-5D/5L)	Patient reported	-	Day 28 and Day 90	Patient reported, collected by telephone, or by post
Resource use	Patient reported	Direct medical costs and resource use	Day 28 and Day 90	Patient reported, collected by telephone, or by post

11.2 Follow-up

Day 28 and Day 90 follow-up will be via telephone or electronic, with both utilised where possible to maximise response. Patient outcomes (readmission, re-treatment, hospital-acquired infection) and use of health care resource (hospital admissions, outpatient parenteral antimicrobial therapy, other prescribed medicines, privately purchased over-the-counter medicines, GP and hospital outpatient attendance) will be captured. In addition, direct non-medical costs borne by patients/carers as a result of attending hospital (travel costs, childcare costs, expenses incurred while in hospital, self-reported lost earnings and other direct non-medical expenses) will be collected.

We will conduct semi-structured interviews with patients after the 90 days follow-up, in order to gain a detailed understanding of patients' experiences of care to aid understanding of trial results. We will encourage patients to include a close family member in the interview also. This will allow us to capture an additional perspective on the patients' care.

12 Withdrawal & lost to follow-up

12.1 Withdrawal

In this trial, the intervention used is in addition to current standard practice and poses minimal risk to the patient with the treating clinician retaining oversight on whether or not to adhere to the interventional algorithm. Due to time constraints of managing suspected sepsis

(see section 9.1), patients will be randomised into either the standard care arm or interventional arm on diagnosis with suspected sepsis, prior to consent being obtained. Participants have the right to withdraw consent for use of clinical data collected in any aspect of the trial at any time. The participants' care will not be affected at any time by declining to participate or withdrawing from the trial. Some participants may wish to withdraw the use of the data upon first approach for deferred consent, following the intervention. If a participant provides deferred consent at this stage but subsequently withdraws from the trial, clear distinction must be made as to what aspect of the trial the participant is withdrawing from. These aspects could be:

i. Partial withdrawal from further data collection (questionnaires, clinical assessments)

ii. Complete withdrawal from further data collection

iii. Withdrawal of permission to use data already collected

The withdrawal of participant consent shall not affect the trial activities already carried out and the use of data collected prior to participant withdrawal.

Participants who consent and subsequently withdraw are invited to complete a withdrawal form (see Withdrawal Form in trial pack). If they decline, the withdrawal form should be completed by the researcher/clinician based on information provided by the participant. This withdrawal form should be sent to the trial manager. Any queries relating to potential withdrawal of a participant should be forwarded to the trial manager.

12.2 Lost to follow up

Data will be obtained from observation and medical notes or drug charts and will be entered into the trial database. We will ask participants who have provided deferred consent to provide contact details for members of the research team to contact them while attempting to make follow-up interviews at days 28 and 90. To minimise loss to follow up, interviews will be via telephone or electronic with both utilised where possible.

Participants will be identified as lost to follow-up if it is not possible to contact them directly for 4 weeks post day 90/hospital discharge.

13 Internal pilot and recruitment rates

We propose an internal pilot, using quantitative and qualitative data, during the first 12 months of recruitment (study months 7-16) to ensure our ability:

- to include appropriate patients,
- to implement the research process in such a way we do not delay treatment time inappropriately,
- to ensure that the results of the test are being considered and used by the treating clinicians.

The internal pilot phase will assess the site and patient absolute recruitment and consent rate, proportion of patients undergoing PCT assessments and the ability to collect the primary outcome data. Qualitative interviews with two staff per site will be conducted in order to understand how the research process and the PCT guided algorithm have integrated into their ED setting. These will be used to understand the quantitative data and provide areas for improvement in processes to enhance the efficiency of the trial.

The progression criteria have been designed to allow for mitigating strategies to be discussed to allow for some adaptation to recruitment processes. We will discuss the results with our Trial Steering Committee, before reporting to the NIHR HTA Programme, for permission to proceed. In accordance with the HTA guidance on internal pilot studies, we will exclude the first two months of recruitment from our calculation of the recruitment rate as we anticipate a 'lag phase' during which the first few sites are still being registered and participating clinicians develop confidence and competence in identifying and recruiting patients. We will constantly be assessing the criteria during the internal phase. To progress from the internal pilot to the full trial, we would be looking to utilise the following criteria in Table 2:

Table 2: Internal Pilot Criteria

Criteria (at month 9 of recruitment)	Level	Action
Number of sites open	>7 5-7 <5	GO Discuss potential mitigating strategies REVIEW/STOP
Number of enrolled participants	>2000 1000-2000 <1000	GO Discuss potential mitigating strategies REVIEW/STOP
Eligible patients randomised *(defined as number randomised/number screened and on screening log*)*	>50% 30-50% <30%	GO Discuss potential mitigating strategies REVIEW/STOP
Consent rate *(defined as number with informed consent from patient or consultee agreement/number randomised)*	>85% 50-85% <50%	GO Discuss potential mitigating strategies REVIEW/STOP
Consideration of the PCT result and algorithm during clinical decision making *(defined as number algorithm adhered too /number PCT result recorded)*	>50% 35-50% <35%	GO Discuss potential mitigating strategies REVIEW/STOP
Ability to collect co-primary outcome data *(defined as number with complete data for both co-primary outcomes/number randomised)*	>90% 70-90% <70%	GO Discuss potential mitigating strategies REVIEW/STOP
Ability to collect 28- and 90-day follow up data *(defined as number with complete follow up data/number randomised)*	>70% 50-70% <50%	GO Discuss potential mitigating strategies REVIEW/STOP
Reduction in the % of patients treated within time windows for usual standard care *(defined as Prospective usual Standard care treatment window data/Retrospective treatment window)*	<10% 10-20% >20%	GO Amend processes REVIEW/STOP
Contamination/changes to usual care in control arm	Qualitative interviews	

- *Screening log will only be active during periods when a research nurse is time tabled to be in the ED/admissions unit*

13.1 Recruitment rates

A feasibility questionnaire was sent out to the six lead study sites. The following numbers of patients fulfilling inclusion criteria per year were reported: Liverpool: 1800, Leeds: 2000, other sites 1000 each, Total: ~11000/year. If only 50- 70% of eligible patients provide deferred consent following randomisation, then the sample size of 7676 is easily achievable over 24 months.

Once all processes of screening and data collection are embedded at each site, we anticipate between 40 - 70 participants per month. In our projections, we have also taken seasonality into account, as the rate of infections is likely to be higher in the winter months.

14 Qualitative data collection and analysis

The qualitative work will have three components: interviews with clinicians, interviews with patients/carers, and observations of trial implementation. Findings will be used to aid understanding of the quantitative data and provide areas for improvement in processes to enhance the efficiency of the trial.

Interviews with ED clinicians

These will take place at two time points. Interview 1 will take place during the pilot phase and will be a semi-structured interview with 10-12 clinicians at <5 study sites (2-3 per site). This will explore the feasibility and acceptability of research processes and integration of the PCT algorithm into their ED setting. Interview 2 will be with clinicians towards the end of the trial when they have more experience of using the PCT algorithm and will identify barriers and facilitators to the use of the PCT test and algorithm in more detail, including reasons for varying from study guidelines.

Interviews with patients

We will conduct semi-structured interviews with patients after the 90 days follow-up point has been reached, in order to gain a detailed understanding of patients' experiences of care

to aid understanding of trial results. We will encourage patients to include a close family member or friend, where possible, in the interview also. This will allow us to capture an additional perspective on the patient's care. Our proposed sample size is 25-30 patients. This was found to be a sufficient sample size in previous qualitative research (BATCH Trial) exploring clinicians' and patients' perspectives on antibiotic resistance and infection management. If a patient lacks capacity at the time of consent for the main trial, consultees will be given an option to consent to being appraoched by qualitative researchers to take part in an interview. Witnessed consent may be obtained over the telephone or web video link if hospital visiting rules or parental infection mean a parent/guardian cannot be physically present.

Observations

Ethnographic observation of trial processes will be carried out in ≤5 participating sites. We propose a period of observation of 1-3 days based on our previous research (BATCH trial). The observations and field notes of trained qualitative researchers will enable us to understand how the individual intervention components and delivery processes work across different local EDs, and the complex environment in which consent is taken. This will allow us to explore adherence, feasibility, implementation, and practicality of intervention. We will observe how HCPs 'use' their clinical judgement to interpret the PCT and NEWS2 assessment to make decisions within a busy ED, and with pressure to initiate intravenous antibiotics for high risk patients within one hour. Including: what is 'treatment as usual', whether there is learned behaviour from professionals as they alter their 'treatment as usual' behaviour in the light of the information they gain on specific patient groups, and what influence the introduction of protocolised behaviour has on clinical behaviour and decision making regardless of the PCT test result. We will also explore reasons for compliance or non-compliance with the algorithm. We will engage key HCPs from the trial to co-produce site-specific data collection plans for observations. This will help us to plan what the observation of trial implementation will include; which aspects of the trial will be of most and least interest to observe and why; whether there are scheduled activities / meetings where an observer would be welcome; what are the different HCP roles within the study and who would be good to observe.

14.1 Qualitative interview sampling methods

We will be pragmatic in sample size and the need to conduct further interviews will be based on preliminary analysis/interviewer field notes indicating whether the data collected sufficiently answers the research questions [33]. We will review whether there is sufficient breadth and depth of data, whether interview participants are representative of the study population, and practical aspects of recruitment (attempts to invite participants, numbers declined, and withdrawn). We will continually review our sampling decisions and we will keep detailed notes on our sampling strategy to maintain transparency [33].

We will purposefully sample participants for interview. To create our sampling framework, we will identify specific interviewee characteristics with input from the TMG (including patient representative and consultants) and information from our rapid literature review. We will use the PRONTO trial patient database to select interviewees with maximum variation in our specified characteristics. We propose that the characteristics for each group are:

Patients:

- Treatment arm (include patients who received standard care and PCT guided care)
- High, low or medium risk of sepsis at time of presentation (to vary severity of case and the degree of anxiety patients may have experienced)
- Antibiotic therapy (to capture experiences of a range of different treatment outcomes)
- Hospital site (to explore local contextual factors influencing patient experiences of care)

Health Professionals:

- Role: e.g. consultant, research nurse, staff nurse, patient flow matron etc. (to gain a wide perspective on how patient cases are assessed and treatment decisions are made and the impact on patient flow through the ED).
- Hospital site (to explore local contextual factors that act as facilitators or barriers to the test in the intervention arm, and whether there are regional differences in standard care).

We will remain flexible in our sampling framework, as once the study begins we may find some characteristics are more or less important than others or identify additional characteristics. Data collection will be iterative, allowing preliminary analysis to guide the subsequent sampling decision and selection of further interviewees.

14.2 Qualitative Analysis

Interview transcripts and field notes of observations will be analysed using a framework approach [34] to take into account the different interviewee characteristics e.g. different sites, different arms of the trial etc. We will develop a thematic framework based on the research objectives and emerging themes. Transcripts will be double-coded until consensus is reached. The thematic framework will be applied to data using the qualitative software package, NVivo 11.

15 Safety reporting

The Principal Investigator is responsible for ensuring that all site staff involved in this trial are familiar with the content of this section.

All SAEs must be reported immediately (and within 24 hours of knowledge of the event) by the PI at the participating site to the CTR Trial team unless the SAE is specified as not requiring immediate reporting (see section 13.2).

For the purposes of this trial, SAEs will need reporting if the event:

- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect

The trial population comprises very sick adults, and hospitalisation is normal in this population. Events such as prolongation of existing hospitalisation, life threatening events and death are also expected in this population and are recorded as part of routine data collection and therefore are not subject to expedited reporting on an SAE form.

15.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which are not necessarily caused by or related to that product
Serious Adverse Event (SAE)	Any adverse event that - • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect

15.2 Trial Specific SAE Reporting requirements

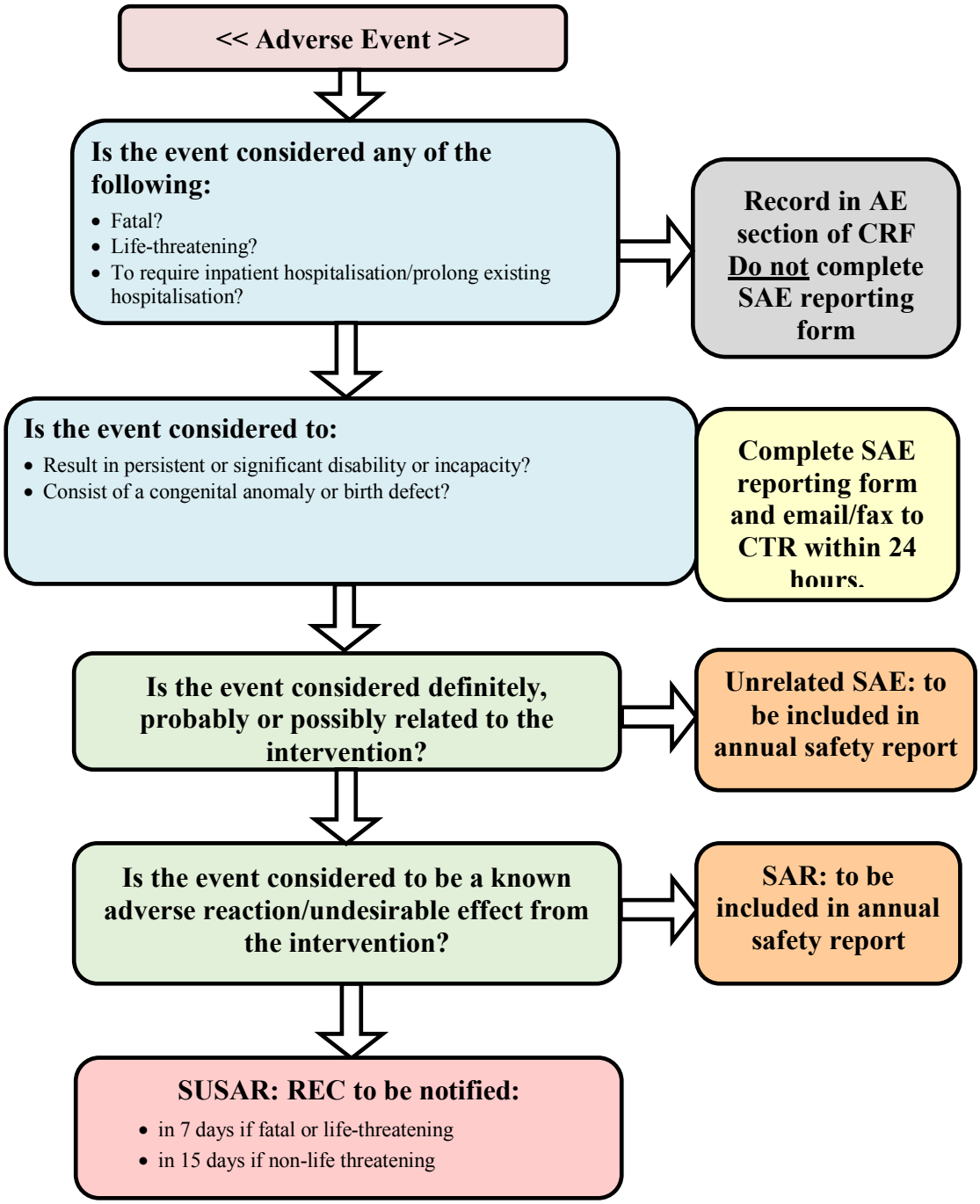
As stated above death is a primary outcome of the trial and is recorded as part of routine data collection, therefore are not subject to expedited reporting on an SAE form.

For the purposes of this trial the following events will **not** require reporting as SAEs:

- Death
- Life threatening event
- Hospitalisation or prolongation of hospitalisation
- Admission to Intensive Care Unit (ICU)
- Non serious AEs potentially attributable to PCT test and step down approach will be collected as part of routine follow up at 28 days.
- Other non-serious AEs will not be collected.

These events should be recorded in the participant's notes and on the relevant CRF and forwarded to the CTR in the normal timeframes for CRF completion. A flowchart (Figure 4) is given below to illustrate reporting procedures.

Figure 4: SAE reporting procedures flow diagram



15.3 Causality

Causal relationship will be assessed for the clinical and data collection procedures. For SAEs this assignment should be made by the PI or delegated research nurse and the assessment confirmed by the Chief Investigator or a delegated Clinical Reviewer.

Relationship	Description	Reasonable possibility that the SAE may have been caused by the intervention?
Unrelated	There is no evidence of any causal relationship with the intervention	No
Unlikely	There is little evidence to suggest there is a causal relationship with the intervention (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	No
Possible	There is some evidence to suggest a causal relationship with the intervention (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	Yes
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes

The causality assessment given by the Principal Investigator (or delegate) cannot be downgraded by the Chief Investigator (or delegate), and in the case of disagreement both opinions will be provided.

15.4 Expectedness

The Chief Investigator (or another delegated appropriately qualified individual) will assess each SAE to perform the assessment of expectedness. Expectedness decisions should not be guided by factors such as the participant population and participant history. Expectedness is not related to what is an anticipated event within a particular disease. SAEs which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected events.

15.5 Reporting procedures

15.5.1 Participating Site Responsibilities

The PI (or delegated appropriately qualified doctor from the trial team) should sign and date the SAE CRF to acknowledge that he/she has performed the seriousness and causality assessments. Investigators should also report SAEs to their own health boards or trust in accordance with local practice.

A completed SAE form for all events requiring immediate reporting should be sent via email to the CTR within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether or not the events had the same date of onset.

The participant will be identified only by trial number, date of birth and initials. The participant's name should not be used on any correspondence.

It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, the CTR may request additional information relating to any SAEs and the site should provide as much information as is available to them in order to resolve these queries.

Serious Adverse Event (SAE) email address:

PRONTO@cardiff.ac.uk

Serious adverse events should be reported from randomisation, throughout the treatment period up to, and including 28 days after the participant is randomised.

An SAE form is not considered as complete unless the following details are provided:

- Full participant trial number
- An Adverse Event
- A completed assessment of the seriousness, and causality as performed by the PI (or another appropriately medically qualified doctor registered on the delegation log).

If any of these details are missing, the site will be contacted and the information must be provided by the site to the CTR within 24 hours.

All other AEs should be reported on the CRF following the CRF procedure described in Section 16.

15.5.2 The CTR responsibilities

Following the initial report, all SAEs should be followed up to resolution wherever possible, and further information may be requested by the CTR. Follow up information must be provided on a new SAE form. The CTR should continue reporting SAEs until 28 days after the participant is randomised. Once an SAE is received at the CTR, it will be evaluated by staff at the CTR and sent to the Chief Investigator (or their delegate) for an assessment of expectedness.

CTR will notify the main REC of all related and unexpected SAEs (i.e. all unexpected SARs) occurring during the study within **15** calendar days of the CI becoming aware of the event. All SAEs and SARs will be reported to the monitoring committees (TMG and TSC/IDMC) as required by the relevant committee/party. All unrelated SAEs will be reported to the TMG and TSC/IDMC, and any arising safety concerns will also be reported to the main REC as part of the annual progress report.

The CTR will not be reporting hospitalisation, prolonged hospitalisation, life threatening events or death to REC as they do not meet the criteria of an SAE in this trial. These will be reported to the IDMC for monitoring.

15.6 Urgent Safety Measures (USMs)

An urgent safety measure is an action that the Sponsor, Chief Investigator or Principal Investigator may carry out in order to protect the subjects of a study against any immediate hazard to their health or safety. Any urgent safety measure relating to this study must be notified to the Research Ethics Committee immediately by telephone, and in any event within 3 days in writing, that such a measure has been taken. USMs reported to the CTR will be handled according to CTR processes.

16 Statistical considerations

16.1 Randomisation

Individual patients with suspected sepsis will be randomised in a 1:1 ratio to either standard clinical management (control) or standard clinical management plus PCT guided assessment (intervention). We will use minimisation with NEWS2 score and site as stratification factors and a random element to reduce the risk of subversion [35]. This will be implemented in a secure 24-hour web-based randomisation programme controlled centrally by the Centre for Trials Research in Cardiff. Details of the randomisation procedure will be specified in a separate randomisation plan.

16.2 Sample size

The sample size calculation is based on two co-primary outcomes [36] :

1. 28-day mortality, for which we want to show non-inferiority of the PCT guided assessment as compared to current standard practice, using an absolute 2.5% non-inferiority margin. Assuming a 28-day mortality of 15% in patients managed as suspected sepsis treated in the ED [3, 12], this means that any increase in 28-day mortality from 15% to not more than 17.5% would be considered non-inferior. For

90% power and one-sided 5% significance level the sample size required is 7002, assuming there is no difference in 28-day mortality between arms. Our patient focus group were also consulted on the 2.5% non-inferiority margin and felt that this was acceptable if there were mechanisms to monitor trial outcomes, and if this was what was needed to provide a sample size which would ensure the trial could be completed as well as answer the research question.

2. Initiation of antibiotics treatment, for which we want to show superiority. Currently around 90% of patients managed as suspected sepsis receive antibiotics (RLBUHT, unpublished data). A reduction by 10 percentage points to 80% would be considered a success. To detect such an effect with 90% power and two-sided 5% significance level the sample size required is 532, which is substantially lower than what is needed for the non-inferiority endpoint. With 7002 patients we would be able to detect effects as small as a reduction from 90% to 87.6% prescriptions, with 90% power.

Accounting for 5% dropout, we need a total sample size of 7372. We include one interim analysis (after 50% of patients have provided data) with options to stop the trial early using group-sequential O'Brien-Fleming boundaries [37, 38]. We will consider stopping for effectiveness if:

- the PCT guided assessment is superior in terms of 28-day mortality (i.e. a significant reduction to less than 15%), or
- the PCT guided assessment is non-inferior in terms of 28-day mortality and superior in terms of initiation of antibiotics.

We will consider stopping for futility if the results of the interim analysis suggest futility for both endpoints.

The group-sequential design will increase the total maximum sample size (if the study is not stopped after the interim analysis) by just over 4% to 7676 (inflated for 5% dropout). However, the sample size will be substantially smaller if the trial does get stopped early.
The sample sizes were calculated using SAS 9.4 PROC POWER and PROC SEQDESIGN.

16.3 Missing, unused & spurious data

Missing primary outcome data is likely to be minimal, so complete case analysis will be used. However, if this exceeds more than 20% of participants we will employ multiple imputation and report the impact on the treatment effect alongside the complete case analysis. Further detail is provided in the PRONTO Statistical Analysis Plan (SAP).

16.4 Procedures for reporting deviation(s) from the original SAP

These will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and SAP.

16.5 Termination of the trial

Progression criteria for the internal pilot phase are described in section 13. There is potential for the study to terminate early if our funder assesses the trial as not being feasible following an assessment of progress against our targets at the end of the internal pilot with input from our TSC and IDMC. There is also the possibility of terminating the trial early for either effectiveness or futility following the planned interim analysis, which will be detailed in the PRONTO IDMC charter and interim SAP.

17 Analysis

17.1 Main analysis

The primary analysis will be intention to treat and will fit separate two-level logistic regression models (patients nested within sites) to both primary outcomes (antibiotic initiation and mortality), controlling for baseline NEWS2 score (minimisation factor). The intervention will be considered effective if there is both a significant reduction in antibiotic initiation AND if the difference in mortality between the two group is negligible (i.e. non-inferior). (See section 5.3 for the primary outcome for effectiveness table which includes antibiotics and mortality outcomes.)

A planned interim analysis of the co-primary outcomes will be conducted when 50% of patients have been recruited and followed up for 28 days. Stopping the study shall be recommended by the IDMC based on group-sequential O'Brien-Fleming boundaries [37, 38]. They shall recommend stopping for effectiveness if:

• the PCT guided assessment is superior in terms of 28-day mortality (i.e. a significant reduction to less than 15%), or

• the PCT guided assessment is non-inferior in terms of 28-day mortality and superior in terms of initiation of antibiotics.

They shall recommend stopping for futility if the results of the interim analysis suggest futility for both endpoints.

In case the 28-day mortality rate in the control arm deviates from the assumed 15%, the absolute 2.5% non-inferiority margin will be replaced with an arcsine difference 'non-inferiority frontier' [39].

The final primary analysis will be adjusted to account for the interim analysis. Imputation of missing data will be done as part of sensitivity analyses.

In a secondary analysis, complier adjusted causal effect models will be fitted to allow for non-adherence to the intervention. Two models will be fitted allowing for two different definitions of adherence:

1. Patients randomised to PCT guided care in whom a PCT test is done and the clinician considers the results as part of their decision making.
2. Patients randomised to PCT guided care in whom a PCT test is done and the clinician follows the algorithm exactly.

All secondary analysis will also be performed based on intention to treat and utilising two level models to allow for patients nested within sites. The following analyses will be undertaken (Table 3):

Table 3: Planned outcomes and analyses

Outcome	Measure	Time frame	Analysis
Antibiotic initiation	Time until initiation	In ED	Cox regression
Antibiotic usage	No of days on IV antibiotics No of days on all antibiotics No of days on broad spectrum antibiotics	In hospital	Linear regression
Antibiotic adverse outcomes	Anticipated drug reactions include: diarrhoea, *C. difficile*, acute kidney injury, hearing loss etc.	In hospital	Logistic regression
ICU usage	People admitted to ICU No of days in ICU	In hospital	Logistic regression Linear regression
Readmission to hospital	People with one or more readmissions	After discharge	Logistic regression
Mortality	Time until death	90* days	Cox regression
Health utility	EQ-5D-5L	90* days	Linear regression of transformed outcome measure

* Except for patients recruited during the last 3 months of the study.
Full details of all analyses will be provided in the PRONTO SAP.

17.2 Sub-group & interim analysis

Analysis will be split by the organ system of the infection (i.e. lower urinary tract, lower respiratory, intra-abdominal, bacteraemia, skin and soft tissue etc).

Stratified analyses will be undertaken at different levels of NEWS2 scoring ≤4, 5-6 and ≥7.

Stratified analysis will also be undertaken by COVID status.

For the interim analysis due to the group-sequential design a separate interim SAP will be created. The interim analysis will be stratified by risk category (Figure 1).

18 Health inequalities and health economics

18.1 Health Inequalities

The outcomes in the trial will be assessed from a health equity perspective [40]. We will collect data *a priori* to allow us to understand the contribution of social inequality to the study findings. Reducing health inequalities is a public health priority in the UK. Infectious diseases cause 7% of deaths and cost 30 billion pounds annually in the United Kingdom and are more common in disadvantaged populations. People living in more disadvantaged circumstances are more likely to have established ill health, be exposed to risk factors for infectious diseases, such as poor housing quality and nutritional status, and also experience worse outcomes with disability and mortality. A secondary aim of this study is therefore to examine the trial dataset from a health equity perspective. The study will be undertaken in sites which will include participants from a wide range of socio-economic backgrounds, and we will collect data on individual and area level measure of SES [41]. We will conduct analyses to examine how the effects of the PCT–guided evaluation under investigation on clinical and healthcare outcomes are moderated by SES in order to assess the intervention impact on health inequalities. These analyses will be tested as part of the pilot.

In addition, we will assess the association of SES with outcomes across the care pathway for people with sepsis. For example, we will explore the extent to which key risk factors for poor outcomes, such as co-morbid conditions, disease severity at presentation, and health behaviours may mediate any association between SES and sepsis mortality. We will also explore any variations in clinical care (for example duration of hospital stay, cost of care, rates of readmission, patterns of antimicrobial use, adverse events related to antimicrobials) on the basis of SES. This study will be the first in recent times to assess social inequalities in the healthcare consequences and outcomes of sepsis in a large population in the UK and should help design better policies and pathways to reduce health inequalities for people with sepsis in the UK.

18.2 Health Economics

Economic analyses of the project have been planned based on expected primary and secondary outcomes of health intervention. As per the primary research question of the project, we expect that in ED patients managed as suspected sepsis, the addition of PCT to the NEWS2 scoring measurement may lead to a reduction in antibiotic initiation with at least no increase in 28-day mortality compared to the NEWS2 scoring alone. The secondary research question considers a broader aspect of economic evaluation that includes the societal perspective including the preferences of patients and family members. So, it examines if the proposed intervention would be cost-effective from the societal perspective (including household consequences).

In economic analyses, we shall apply NHS and societal perspective to address the decision making in the health system and on the society respectively. They will follow the intention-to-treat of the primary clinical effectiveness and safety analyses. Missing economic data will be imputed in a standard manner. The costs borne by NHS and the patients will thus be considered in estimations wherever applicable.

1) Cost of illness per patient from sepsis in intervention arm (IA: PCT + NEWS2) and standard care arm (SCA: NEWS2 alone), from the NHS and patient household perspectives.

2) Cost-saved per unit investment into proposed IA due to avoided antibiotic prescription, reduction of hospitalizations, and other cost-savings

3) Cost-effectiveness analysis of proposed intervention (PCT + NEWS2) in comparison to standard care per life year saved and £ per QALY gained

4) Cost-benefit analysis of proposed intervention (PCT + NEWS2)

18.2.1 Methods

1) Cost of illness

The cost of illness (COI) will be conducted using NHS perspective and patient's perspectives. Together these will constitute the societal perspective. It implies that data will be collected from two sources, i.e. the hospital and patients. Total costs of illness of sepsis care per patient from the ED to hospitalization will be estimated for the treatment of sepsis by multiplying the total incidences of sepsis with the unit cost of caring for a patient throughout an episode up to 28 days after discharge from hospital. In addition, the total cost of screening will be included, again both from health service and household perspective. Considering the need of care, 30 patients of each type (general ward and ICU), of 10 hospitals will be included to calculate the mean costs of illness, which will sum up a total of 30x2x10=600 patients. Direct medical and non-medical as well as indirect costs (income loss) will be captured using a Standardbred questionnaire for patients and departmental- and patient-level costs from hospitals. By multiplying mean cost with incidence rates, the total costs will be estimated.

2) Cost saved per GBP invested in the proposed PCT intervention due to potentially avoided antibiotic prescription, avoided admissions, and other decreased resource use.

Here, the net cost of intervention is to be compared with the cost saved on avoidable antibiotics to estimate the money saved per GBP invested in the intervention arm. The outcome data of the intervention in terms of antibiotic avoided will be collected from a comparison of the two arms. The difference in antibiotic prescribing (number of patients and dosages) for patients between IA and SCA will be recorded from the ED and hospital prescription records. The unit price of antibiotic per dose will be multiplied by the doses avoided. Together with the savings due to reduced hospital admissions this will capture the total costs of antibiotic avoided due to the proposed intervention. The costs of intervention will be captured by identifying and quantifying the inputs used for patients in IA and SCA, valuing the inputs into economic costs with necessary (if applicable) adjustments for time preferences [42]. Such costs of intervention from the existing UK study by Hex et al. [43] might be used if not available in the reporting hospitals. Incremental costs between IA and SCA will constitute the investment on the proposed intervention for comparing with costs saved due

to reduced antibiotic use. It should be noted here that this intervention cost will be used in the cost-effectiveness analysis (CEA) (point 3 below) and cost-benefit analysis (CBA) (point 4 below) for comparing with intervention outcomes.

3) Cost-effectiveness analysis of proposed intervention (PCT + NEWS2) in comparison with standard care.

i) Cost-effectiveness approach

Our CEA will be influenced by the assumption that the outcome on 28 day mortality of IA and SCA is non-inferior (no significant difference). It means that the CEA will in the first instance take the nature of a cost-consequence (minimization) analysis and only the costs of interventions (IA and SCA) need to be compared to find the cost-effective alternative [42, 44]. Here, sepsis care with lower costs (i.e. intervention costs), defined by cost per screened patient and cost per sepsis patient treated will be considered as the more cost-effective alternative.

ii) Cost-utility analysis

Cost-Utility Analysis (CUA) of non-inferiority trials has been conducted elsewhere [45]. For decision making from the analysis, cost-effectiveness planes prove to be a valuable tool in the interpretation of the results in an economic equivalence or non-inferiority trial [45]. We consequently will conduct a CUA due to the expected non-inferiorly health outcomes between IA and SCA. Health outcomes (QALYs) between IA and SCA will be compared with incremental costs of intervention between the arms. To assess QALYs gained in each patient group, the EQ-5D-5L instrument will be used on each patient (or representative if the patient is not in a condition of responding) under investigation of this study at screening, the 28th day, and 90th day after randomization. All primary and secondary empirical outcomes will be compared against existing literature and systematic reviews [27, 46, 47] and other trial-based studies. If possible, a meta-analysis will be carried out. The different in costs of interventions in IA and SCA and change in health outcomes (QALYs gained) will be plotted in cost-effectiveness plane for interpreting the results of this non-inferiority trial [45].

iii) Decision-tree analysis

Using data on health outcome (QALYs) and economic outcome (Cost of intervention) and probability of correct diagnosis (including false positives and false negatives) by both procedure arms (IA and SCA) will be used for conducting probabilistic analyses based on a decision-tree using TreeAge Pros (TreeAge Company, Inc) and STATA in a probabilistic CEA. Here, patients are randomly drawn from the IA and SCA treatment arm datasets in a MonteCarlo procedure, until convergence to stable estimates. The patients may face adverse effects of treatment with antibiotics in both arms and consequently worse health status. Patients correctly treated may face different outcomes in terms of cure and health status change and related resources. All resource use, including those of complications will be related to specific costs of NHS services. Following the TreeAge pathways using transition probability distributions between health states, based on the in-trial findings and literature, costs and health utility (health status) we shall be able to estimate expected societal and health care costs and expected utility of the patients (expressed in QALYs placed in IA and SCA.

4) Cost-benefit analysis

Net cost of benefits (all accumulated benefits in monetary term) will be compared with costs of intervention. In this case, potentially avoided cost, for instance due to less use of antibiotics, less hospitalization days, less productivity loss of patients and caregivers and any such loss, in IA in comparison with SCA would constitute the benefits of the intervention. These benefits will be compared with the intervention costs (incremental as described under point 2). If the benefits are higher, the intervention would be useful for implementation [44].

19 Data Management

The source data for PRONTO trial will be from a variety of sources. Data will be collected using an electronic system with paper CRF back up. There will also be data collected from participants' medical notes and patient reported questionnaires. Source data from the BRAHMS PCT direct reader will be recorded, printed and stored electronically in individual

patient folders within the Trial Master File (TMF). Derived data from this source will be entered into the trial database.

Training for completion of study CRFs will be provided to the appropriate trial staff prior to trial commencement at site initiation.

19.1 Completion of CRFs

All assessments and data collection will be completed using web-based CRFs. This is a secure encrypted system accessed by username and password, and complies with General Data Protection Regulation 2016. In the event that the web-based system is not accessible, paper CRFs will be used to record data. The data will then be inputted into the web-based system once it is accessible. A full Data Management Plan will accompany this protocol and will be stored in the TMF.

19.1.1 Electronic CRFs

It is intended to develop data recording for this trial as a web-based system. This is a secure encrypted system accessed by an institutional password supplied to investigators upon completion of all processes required prior to opening.

19.1.2 Paper CRFs

If the electronic database is not available, paper CRFs will be used and data will be entered on to the database at a later point. In accordance with the principles of GCP, the PI is responsible for ensuring accuracy, completeness, legibility and timeliness of the data reported to the CTR in the CRFs.

CRF pages and data received by the CTR from participating trial sites will be checked for missing, illegible or unusual values (range checks) and consistency over time.

If missing or questionable data are identified, a data query will be raised on a data clarification form. The data clarification form will be sent to the relevant site. The site shall be requested to respond to the data query on the data clarification form. The CRF pages should not be altered. All answered data queries and corrections should be signed off and dated by a delegated member of staff at the relevant site. The completed data clarification form should be returned to the CTR and a copy retained at the site along with the participant's CRFs.

The CTR will send reminders for any overdue data. It is the site's responsibility to submit complete and accurate data in timely manner. Further details of data management procedures will be specified in the Data Management Plan.

19.2 Qualitative study data management

All the information, including any personal information (e.g. patient name), will be kept completely confidential. Recordings will not be labelled with patient name. Any written report of the research will have the patient's name removed. Written quotes of what the patient says in the interview may be used word for word, but quotes will be anonymised. Patient names will not appear on any publications. All study related records will be stored for a minimum of 15 years. The results are likely to be published in medical journals over the next few years. The patient will not be personally identified in any report or publication. Full details of data management will be specified in the Data Management Plan.

20 Protocol/GCP non-compliance

The Principal Investigator should report any non-compliance to the trial protocol or the conditions and principles of Good Clinical Practice to the CTR in writing as soon as they become aware of it. The CTR will assess the nature and severity of any issues of non-compliance in accordance with their SOPs.

21 End of Trial definition

The end of the trial is defined as the date of final data capture to meet the trial endpoints. Sponsor must notify the main REC of the end of a clinical trial within 90 days of its completion or within 15 days if the trial is terminated early.

22 Archiving

The TMF and TSF containing essential documents will be archived at an approved external storage facility for a minimum of 10 years. The CTR will send the TMF and TSFs to Sponsor for archiving. The Principal Investigator is responsible for archival of the ISF at site on approval

from Sponsor. Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor.

23 Regulatory Considerations

23.1 Ethical and governance approval

This protocol will be submitted to a Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval. A favourable ethical opinion will be obtained from the REC before commencement of any study procedures (including recruitment of participants).

This trial protocol will be submitted through the relevant permission system for global governance review via the Health Research Authority (HRA).

Approval will be obtained from the host care organisation who will consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

All substantial protocol amendments must be approved by the REC responsible for the study, in addition to approval by NHS Research and Development (R&D). Minor amendments will not require prior approval by the REC.

If the study is stopped due to adverse events or an urgent safety measure it will not be recommenced without reference to the REC responsible for the study.

The outcome of the study (e.g. completed) will be reported to the REC responsible for the study within 90 calendar days of study closure. In the event of the study being prematurely terminated a report will be submitted to the REC responsible for the study within 15 calendar days.

A summary of the results will be submitted to the REC responsible for the study within one year of completion of study closure.

23.2 Data Protection

Confidentiality of study data will be ensured. Participants will always be identified using only their unique study identification number and any additional identifiers.

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the General Data Protection Regulation 2016/679. The data custodian for this trial is the Chief Investigator at Liverpool University (sponsor).

Participants will always be identified using their unique study identification number and any additional identifiers. This includes collection of NHS number (or equivalent – e.g. CHI number in Scotland), name and postcode to register and trace participants with NHS Digital.

23.3 Indemnity

PRONTO is sponsored by The University of Liverpool and will be co-ordinated by the CTR at Cardiff University. The Sponsor does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. As this is an investigator-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability: NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven. The Sponsor does not accept liability for any breach in any other hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not.

Clinical negligence is defined as:

"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

The Sponsor has vicarious liability for the actions of its staff, when through the course of their employment they are involved in the design and initiation of a clinical trial, including but not limited to the authorship of the Clinical Trial Protocol. The University of Liverpool has appropriate insurance in place to cover this liability.

23.4 Trial sponsorship

University of Liverpool will act as Sponsor for the study. Delegated responsibilities will be assigned to the sites taking part in this study.

The Sponsor shall be responsible for ensuring that the study is performed in accordance with the following:

- Conditions and principles of Good Clinical Practice.
- Declaration of Helsinki (1996)
- UK Policy framework for Health and Social care Research 2017.
- The GDPR (EU2016/679).
- Other regulatory requirements as appropriate.

The Sponsor has/will be delegating certain responsibilities to CTR, the CI, PIs, host sites and other stakeholder organisations as appropriate in accordance with the relevant agreement that is informed by regulation and study type.

23.5 Funding

This project was funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme (project number 17/136/13) and will be published in full in Health Technology Assessment. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS or the Department of Health. The study will be adopted on the NIHR portfolio.

24 Trial management

24.1 Project Team

The Project Team (PT) will meet fortnightly and will include the Co-Chief Investigators, Trial Manager, Data Manager, Statistician, Administrator and other research staff directly employed to the trial. The project team will discuss all day-to-day management issues and will refer any key management decisions to the Trial Management Group (TMG).

24.2 TMG (Trial Management Group)

The Trial Management Group (TMG) will meet monthly by teleconference and quarterly face-to-face. It will include the co-Chief Investigators (co-CIs), all other co-applicants, and the central project team. The TMG will provide specialist advice, develop study procedures/documents and advise on the conduct of the study. The Trial Manager will be responsible for trial conduct and will be accountable to the co-CIs. Regional research staff supervised by the site Principal Investigator (PI) will be responsible for recruitment, assessments and data collection. Data will be securely stored locally and entered on a secure electronic recording system compliant with data management procedures. TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter.

24.3 TSC (Trial Steering Committee)

A Trial Steering Committee (TSC) will be established with an independent chair and at least two other independent members including PPI representatives. The TSC will meet prior to trial commencement to review the protocol, roles, responsibilities, and timelines for meetings and agree the remit and conditions set out in the TSC Charter.

TSC members will be required to sign up to the remit and conditions as set out in the TSC Charter.

24.4 Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be established with an independent chair and at least two other independent members. The main role of the IDMC is to review

the data periodically (bi-annually) and also review the results of the planned interim analysis, and make recommendations to the TSC. IDMC members will be required to sign up to the remit and conditions as set out in the IDMC Charter which will be filed in the TMF.

24.5 Public and Patient Involvement (PPI)

The proposal has benefited from multiple interaction with PPI groups to refine the research question and design.

Julie Carman (JC) is a sepsis survivor and volunteer with the UK Sepsis Trust. She uses her sepsis experience to educate health professionals via Julie's Story (www.patientstories.org.uk/recent-posts/julies-story-now-available/). She has recently contributed to the NHS Right Care Scenario (Sepsis) 2018 (patient perspective). As a lay co-applicant/patient representative, JC has attended trial development meetings to discuss the importance of the trial throughout the early stages of planning. JC has endorsed the importance of this trial and has co-produced and helped finalise the study design. She also contributed to the discussion of the logistics including the day-to-day running of the trial from the patient's perspective. As a co-applicant JC will be a member of the Trial Management Group ensuring that all patient facing materials are presented in a suitable way. Her experience will also be invaluable throughout the life-cycle of the project, including the promotion of the trial to potential participants and appropriate dissemination of findings to the lay public.

As part of the development of this trial, we have convened wider PPI advisory panels. One consisting of up to 10 patients who have had sepsis and relatives and one with the Institute of Infection & Global Health (IGH) panel with members representing a wide variety of interests (https://www.liverpool.ac.uk/infection-and-global-health/public-engagement/pip/). We discussed the trial with the panel at the Royal Liverpool Hospital in August 2018, focusing on need, conception, design and trial management. The group fully supported the need for this trial recognising the potential for PCT measurement to improve outcomes for patients with suspected sepsis. Participants felt strongly that the problem and question being answered by the study were very important and that this study could significantly improve sepsis care,

antimicrobial use, as well as prevent patients with bacterial infections developing sepsis, by being treated earlier. In addition, they felt the proposed randomisation process, deferred consent approach, follow-up period and methods, primary and secondary outcomes as well as non-inferiority design and margin were appropriate. Specific feedback about these aspects has now been used to update the relevant parts of the proposal. These are a few quotes from the focus group to support the need for the trial: *"it seems to me you are damned if you do – damned if you don't because medical professionals won't want to take a chance and the public will be quick to complain – at the moment where there is a gap in knowledge everyone will air on the side of caution." "It is about knowing that someone is listening to you" "It's another diagnostic tool – why would you not use it? It could help patients, reduce cost of hospital care and reduce cost of antibiotic "*

The IGH panel considered and discussed similar aspects of the study rationale and design. They were convinced of the importance of the study and the need to have a study that can deliver results in a meaningful period of time. The approach to deferred consent was seen as appropriate - "*no problems with deferred consent – common sense solution to a real problem*". The study was perceived as safe - "*the study feels safe"* when considered in the light of an active IDMC. Consideration of the frequency of monitoring should be discussed early if funded. Varying practice of health professionals was considered a potentially very important aspect of the study - "*will it highlight doctors in ED who have differing practices e.g. more cautious versus less cautious*". The qualitative aspects were considered very important - "*what will you do if everyone is getting 'rescue' antibiotics*?" We were asked to consider additional questions to extend our understanding of prescribing behaviour – "*Will you collect data on why people are giving rescue antibiotics*? *Consider short questionnaire for those that are giving antibiotics out with trial guidelines to try and determine potential reasons e.g. impaired renal function, gut feeling."* These suggestions have been incorporated into our process evaluation.

There will also be ongoing PPI activity to refine methodology, particularly at the point of the pilot evaluation and to support dissemination of activities and results. We will convene the

PPI advisory panel bi-annually. Their role will be to advise on the design of patient information leaflets, design of qualitative, data analysis, and dissemination strategies. The panel will advise on patient information sheets for research ethics, interview schedules and the production of educational materials for patients on the most appropriate use of antibiotics. Educational materials will be made available in hospitals and on the trial website. We will invite patients to contribute actively to dissemination events, including presenting people's views/stories. Members of the advisory panel will be supported by the research team. In addition, we have collaborated with UK Sepsis Trust in relation to the conception and design of this trial.

Improving public and patient understanding about antimicrobial resistance is a fundamental component of the UK Five Year Antimicrobial Resistance Strategy 2013-2018. Therefore, the issues associated with antimicrobial resistance and the need to educate the public about the misuse of antibiotics is a key feature of the patient and public involvement and engagement component of the PRONTO trial. The PPI advisory panel will seek to collaborate with the British Society for Antimicrobial Chemotherapy (BSAC) and one of its initiatives Antibiotic Action, a charity promoting public awareness about antibiotics and AMR, and utilise their resources. They will be encouraged to register as Antibiotic Champions providing information to peers and other contacts about the importance of antibiotics, how to use them, and the need for new treatments for infections. We will comply with the Public Involvement Standards and will plan to use an audit tool to ensure that we are meeting the new standards. **(https://sites.google.com/nihr.ac.uk/pi-standards/home)**

25 Quality Control and Assurance

25.1 Risk Assessment

A Risk Assessment has been completed to identify the potential hazards associated with the study and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment has been completed in accordance with the MRC/DH/MHRA Joint project guidance document 'Risk-adapted approaches to the management of Clinical Trials of Investigational Medicinal Products' and includes:

- The known and potential risks and benefits to participants
- How high the risk is compared to normal standard practice
- How the risk will be minimised/managed

This trial has been categorised as medium risk, where the risk is somewhat higher than the risk of standard medical care or there is some reputational or data integrity risk. The main risks associated with the trial are non-compliance with the deferred consent process, competence of partner organisations and unreliable data collection. Mitigating strategies for these risks and all other trial associated risks are outlined in the risk assessment form. A copy of the study risk assessment may be requested from the Trial Manager. The trial risk assessment is used to determine the intensity and focus of monitoring activity (see section 25.2).

25.2 Monitoring

The clinical trial risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the PRONTO trial. Low+ monitoring levels will be employed and are fully documented in the trial monitoring plan. Investigators should agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained. Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, PI & local R&D.

25.3 Audits & inspections

The study is participant to inspection by the Health Technology Assessment programme (HTA) as the funding organisation. The study may also be participant to inspection and audit by Liverpool University under their remit as Sponsor.

26 Publication policy

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 IRSCTN. 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 NEWS2letter 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.

27 Milestones

Month 1-6: Study and site set-up (at least 5 sites to be open for month 1 of recruitment)

Month 7-16: Internal pilot phase (assessed by progression criteria). Assess acceptability of the PCT results in clinical management, and finalise management algorithm, based on feedback.

Month 20-22: Interim Analysis (following recruitment of 50% sample size).

Month 17-31: continuation of RCT recruitment and data collection to determine effectiveness and cost effectiveness of the intervention.

Month 31-36: Statistical, health economic and qualitative analysis, prepare for HTA report.

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