Short title:	ISAP / SAP Template

Statistical Analysis Plan for PRONTO: PROcalcitonin and NEWS2 evaluation for Timely identification of sepsis and Optimal use of antibiotics in the emergency department

ISRCTN No:	54006056	Version Number:	2.0 (03/12/24)

Final Plan

Based on protocol version: 3.2 (25/03/24)

SAP Revision History

Protocol version	Updated SAP version	Section number changed	Description and reason for change	Date changed
3.2	2.0	SAP deviation log	Added in post hoc exploratory analyses	03/12/24

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ROLES AND RESPONSIBILITIES

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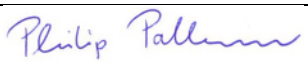
Date:	15/01/25	Signature:	
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Role: Co-Chief Investigators			
Date:	15/01/25	Signature:	
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Role: N/A			

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1. INTRODUCTION

This statistical analysis plan (SAP) provides guidelines for the final presentation and analysis for the PROcalcitonin and NEWS2 evaluation for Timely identification of sepsis and Optimal use of antibiotics in the emergency department (PRONTO) trial. This plan, along with all other documents relating to the analysis of this trial, will be stored in the Statistical Analysis Master File electronically within the Trial Master File.

Any deviations from the SAP will be recorded and justified in the SAP deviation log (at the end of this document) and the final report. The analysis will be conducted by an appropriately qualified statistician, who will ensure data integrity by adhering to the guidelines set out in the CTR's (Centre for Trials Research) SOPs (Standard Operating Procedures). This SAP will be reviewed by the senior trial statistician (STS) and approved by the Trial Management Group (TMG) before being signed off by the author (Jennifer Condie), STS (Dr Philip Pallmann), and the Chief Investigators (Professor Neil French and Dr Stacy Todd). A copy of the SAP will be sent to the Trial Steering Committee (TSC) and Independent Data Monitoring Committee (IDMC) statisticians for review and amended as appropriate. This SAP includes the quantitative aspects of the analysis; health economics and qualitative analysis plans will be provided separately.

2. BACKGROUND

2.1 RATIONALE AND RESEARCH QUESTION

Full trial details are provided in the PRONTO trial protocol and the protocol paper (Euden et al., 2022).

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 the National Early Warning Score (NEWS2). It is not specific and tends to over-diagnose sepsis leading to over-prescribing of antibiotics and promoting antimicrobial resistance. 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 who are unwell, but will not come to harm if IV antibiotics are not administered within 1 hour, allowing time for further assessment prior to starting antibiotics within 3 hours, c) those not critically unwell who may or may not need IV antibiotics. Procalcitonin (PCT), a blood test not widely used in the NHS, helps to identify bacterial infection. The National Institute for Health and Care Excellence (NICE) recommended further research on PCT testing in EDs for guiding antibiotic use in people with suspected sepsis.

2.2 OBJECTIVES

Primary objective: To determine whether the addition of PCT measurement to NEWS2 scoring can lead to a reduction in IV 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).

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 families

3. STUDY MATERIALS

3.1 TRIAL 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. Participants are randomised in a ratio of 1:1 to PCT-guided assessment added to NEWS2 and local standard care, or NEWS2 and local standard care alone. The participant flow diagram (Figure 1) provides further details.

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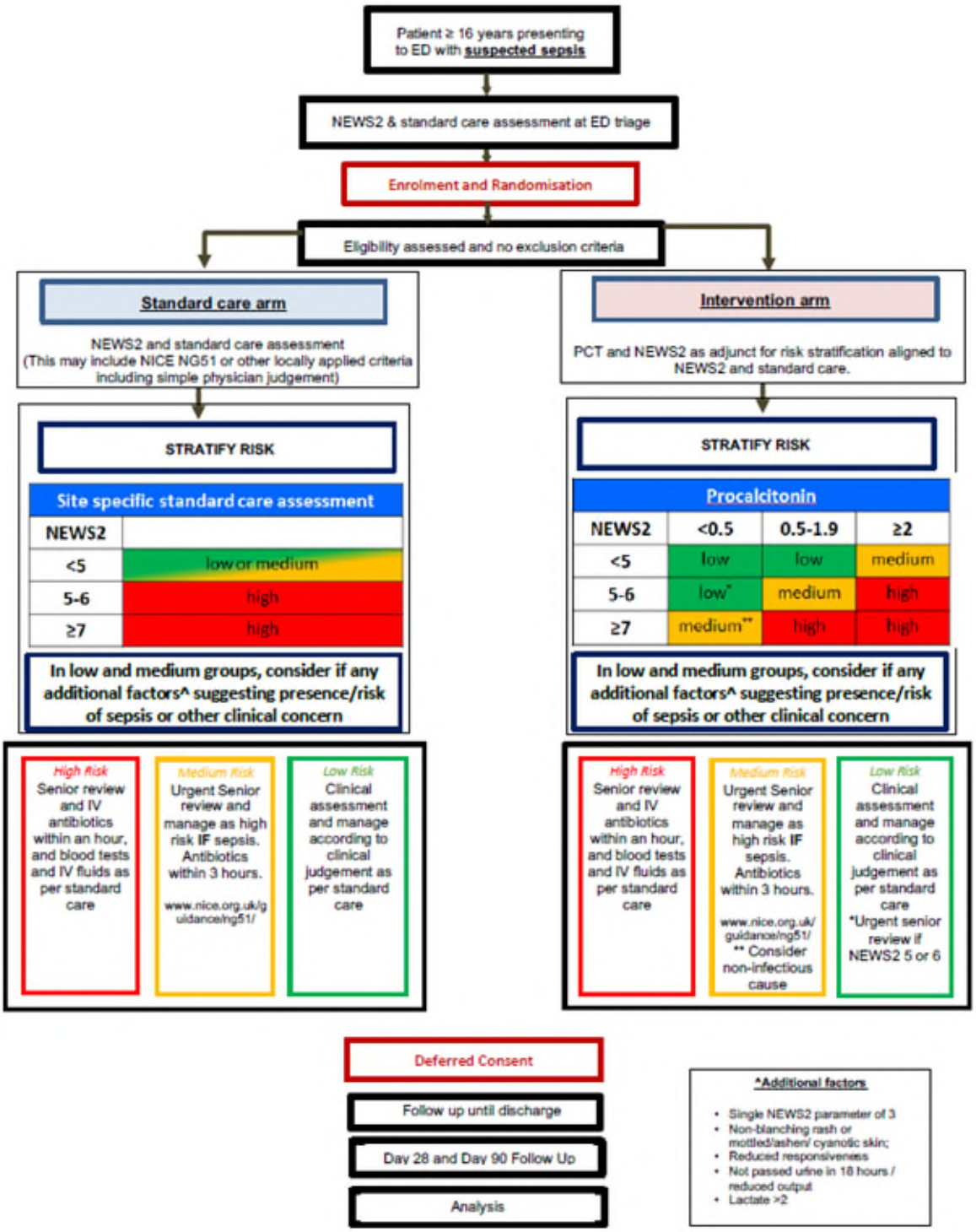

Figure 1: PRONTO trial participant flow diagram.

3.2 RANDOMISATION

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

The first patient was allocated at random. For each subsequent patient the software calculated the covariate sums as explained in Altman & Bland (2005) and determined which arm the patient should be allocated to in order to minimise the covariate imbalance. The patient was then randomised with an 80% chance of being allocated to the arm that minimised the imbalance (and a 20% chance of being allocated to the other arm). If neither arm minimised the imbalance because the covariate sums were equal for both arms (i.e., a state of perfect balance) the patient was allocated at random.

3.3 SAMPLE SIZE

The sample size calculation was based on two co-primary outcomes:

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 28-day mortality of 15% in patients managed as suspected sepsis treated in the ED, 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 antibiotic treatment, for which we want to show superiority. Currently, around 90% of patients managed as suspected sepsis receive antibiotics (Royal Liverpool and Broadgreen University Hospitals NHS Trust, unpublished data). Reducing this by 10 percentage points to 80% would be seen as a success. To detect such an effect with 90% power and a 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, a fixed-sample design would need a total sample size of 7372.

We planned to conduct one interim analysis (after 50% of patients provided data) with options to stop the trial early using group-sequential boundaries based on O'Brien-Fleming type alpha spending (O'Brien & Fleming, 1979, DeMets & Lan, 1994). We used a hierarchical approach (Figure 2) to recommend stopping for effectiveness if:

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

The group-sequential design increased the total maximum sample size (in case the study was not stopped after the interim analysis) by just over 4% to 7676 (inflated for 5% dropout). The sample sizes were calculated using PROC POWER and PROC SEQDESIGN in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

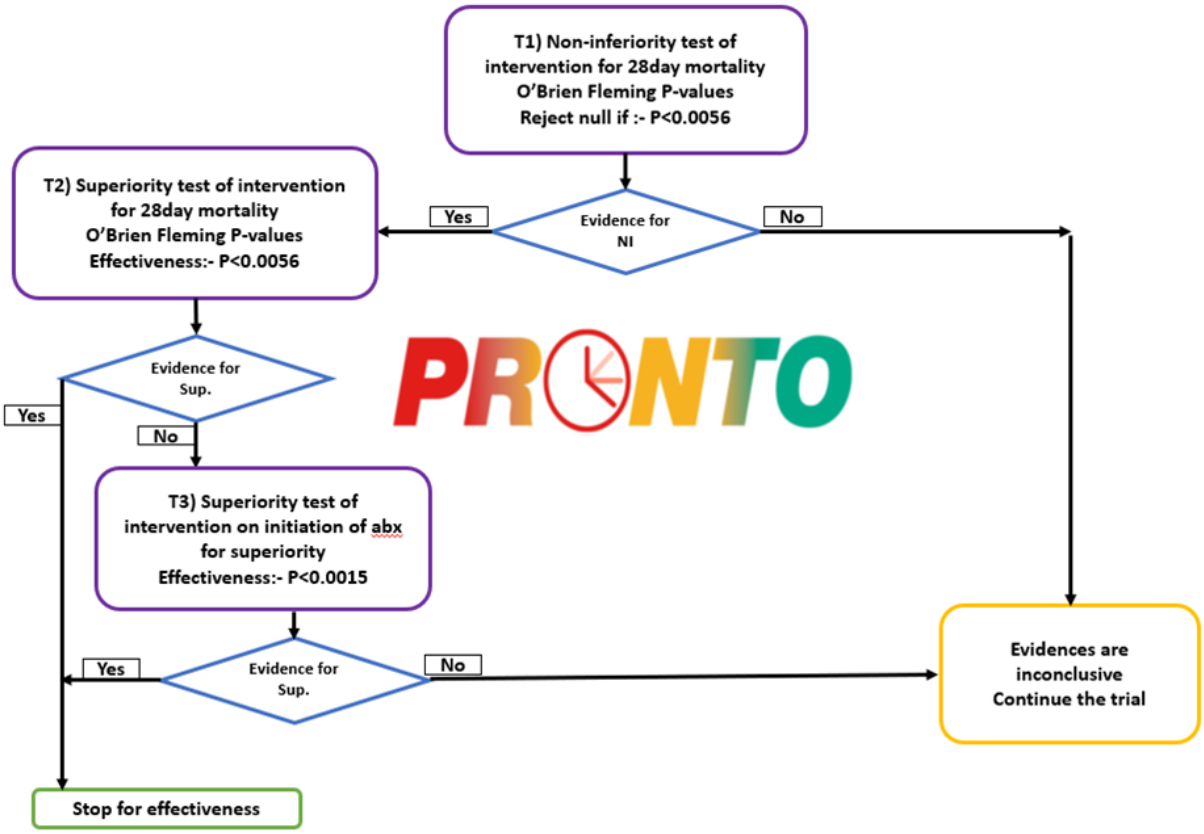

Figure 2: Overview of decision-making at the interim analysis of the co-primary outcomes.

3.4 FRAMEWORK

The effect of 28-day mortality will be investigated for non-inferiority of the PCT-guided assessment as compared to current standard practice, using an absolute 2.5% non-inferiority margin. For measuring the effect of initiation of antibiotics treatment, we want to show superiority.

3.5 INTERIM ANALYSES

A planned interim analysis was conducted after 43% (3040/7002) of participants had been recruited and followed up for 28 days. A second, unplanned interim analysis was requested by the Independent Data Monitoring Committee (IDMC) and conducted after 57% (3973/7002) of participants had been recruited and followed up for 28 days.

A full description of the interim analysis strategy and stopping rules is provided in the interim SAP.

3.5.1 PLANNED SAMPLE SIZE ADJUSTMENT

Not applicable.

3.5.2 STOPPING RULES

The planned interim analysis cut-offs were fixed on 50% information, but the actual analysis used 43% (3040 patients). As described in the interim SAP, we have re-estimated the stopping boundaries accordingly (Table 1). The exact stopping criteria for each test (T1-T3, see Figure 2) and associated operating characteristics of the design are listed below:

Table 1: Modified boundaries for the interim analysis

		Interim analysis*	Final analysis
Test 1: non-inferiority test for 28-day mortality **Test 2: superiority test for 28-day mortality**	Information rate	0.430	1.000
	Effectiveness boundary (test statistic)	2.770	1.654
	One-sided local significance level	0.0028	0.0491
	Exit probability under the null (i.e., cumulative **one-sided** alpha spent)	0.0028	0.0500
	Exit probability under the alternative (i.e., cumulative power)	0.198	0.900
Test 3: superiority test for IV antibiotic initiation	Information rate	0.430	1.000
	Effectiveness boundary (test statistic)	3.225	1.964
	Two-sided local significance level	0.0013	0.0496
	Exit probability under the null (i.e., cumulative **two-sided** alpha spent)	0.0013	0.0500
	Exit probability under the alternative (i.e., cumulative power)	0.1362	>0.999
* We followed a conservative approach of adjusting the level of information to 43%, which is based on test 1 sample size estimation (used in the study).			

3.6 TIMING OF FINAL ANALYSIS

Data collection will be completed by November 2023. Data cleaning will take place between November 2023 and March 2024. Data analysis will take place between April and July 2024 and be published in the autumn of 2024.

3.7 TIMING OF OUTCOME ASSESSMENT

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 (to maximise recruitment, we stopped collecting these questionnaires on the 29/04/22 so they have not been collected for all participants). Research nurses will review observation and medication charts, and medical notes for all recruited participants to collect the data described in Table 2 below:

Table 2: 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	Up to 28 days	Research Nurse
Adverse events	Obs charts/medical notes	Date, type	Daily	Research Nurse
Intensive care unit (ICU) usage	Medical notes	Date, details of admission/discharge to ICU	Daily	Research Nurse
COVID diagnosis	Medical notes	Date, clinical or laboratory confirmed	Up to 28 days	Research Nurse
Unscheduled readmissions	Medical notes	ICU readmissions, readmissions post discharge	Daily	Research Nurse
Mortality	Medical notes	Date, description	Up to 90 days	Research Nurse
Discharge	Medical notes	Date, description	Up to 90 days	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

4. STATISTICAL PRINCIPLES

4.1 LEVELS OF CONFIDENCE AND P-VALUES

The trial follows the group-sequential approach with one interim analysis; thus, p-values will be adjusted using the O'Brien-Fleming type alpha spending approach. For the hypothesis testing, any p-value less than the adjusted level of significance at the final analysis (Table 1 in Section 3.5.2) will be considered sufficient evidence to reject the hypothesis.

We will consider the 95% confidence limit (corresponding to a 5% significance level) as a benchmark for all analyses. We will estimate a two-sided 90% confidence interval (corresponding to a 95% one-sided confidence level) to assess the non-inferiority of the 28-day mortality outcome, and a two-sided 95% confidence interval to assess the superiority of the IV antibiotic initiation outcome. We will report both unadjusted and OBF adjusted confidence intervals for both co-primary outcomes.

We will also report bias-adjusted confidence intervals for group sequential designs, calculated using Jennison and Turnbull's repeated CI approach (Jennison & Turnbull, 1989).

Results will be presented in line with the CONSORT statement and its extensions for non-inferiority (Piaggio et al., 2012) and adaptive designs (Dimairo et al., 2020).

4.1.1 ADJUSTMENT FOR MULTIPLICITY

We have used the O'Brien-Fleming type alpha spending method to adjust the interim analysis and final analysis level of significance. Adjustment for multiplicity of endpoints is not required because they are co-primary, therefore the resulting test procedure is an intersection-union test (Offen et al., 2007).

4.2 ADHERENCE AND PROTOCOL DEVIATIONS

4.2.1 DEFINITION AND ASSESSMENT OF 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 trial aims 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.

4.2.2 PRESENTATION OF ADHERENCE

Descriptive statistics on adherence will be presented in a table, overall and by trial arm. The proportion of non-adherence and reason for non-adherence will be reported overall and as group-wise relative frequencies and percentages.

4.2.3 DEFINITION OF PROTOCOL DEVIATION

A protocol deviation occurs when the participant, study coordinator or investigator fails to adhere to significant protocol requirements, including eligibility violations, deviation from intervention or other non-adherence to the protocol. Due to the nature of the trial, the treating clinicians are allowed to overrule the algorithm when they feel it is appropriate. Protocol deviations will be classified as a deviation, protocol violation or serious breach and the impact on participants' rights, safety, wellbeing, and data integrity will be classified as major, minor or no impact. We will also record whether the deviation requires follow-up, and the PI will determine if a violation results in withdrawal of a participant.

4.2.4 PRESENTATION OF PROTOCOL DEVIATIONS

The number and percentage of patients with major and minor protocol deviations will be summarised by treatment group with details of the type of deviation provided. Deviations that affect data integrity will be summarised in the final report.

4.3 ANALYSIS POPULATION

The primary analysis population will include all participants with a completed 'record of consent' form (completed by participants with capacity, a personal consultee if a participant lacks capacity, or a nominated consultee if a personal consultee cannot be identified, or if the participant died prior to obtaining consent) regardless of protocol deviations and adherence, and according to their randomised allocations (intention to treat), with complete data for both co-primary outcomes. A

participant is considered to have complete 28-day mortality data if they have either been confirmed to have died within 28 days or they are known to have been alive at day 28. A sensitivity analysis will be performed including all participants for whom consent has been obtained with complete data for at least one of the co-primary outcomes.

A secondary/sensitivity analysis will estimate the complier average causal effect (CACE) to account for departures from the randomised intervention. For the purposes of this sensitivity analysis, we will define different analysis populations depending on the level of adherence with the PCT-guided algorithm (Figure 3):

- Patients randomised to PCT-guided care in whom a PCT test is done, and a PCT result is available
- Patients randomised to PCT-guided care in whom a PCT test is done, a PCT result is available, and the clinician has seen the PCT result
- Patients randomised to PCT-guided care in whom a PCT test is done, a PCT result is available, the clinician has seen the PCT result and followed the algorithm exactly.

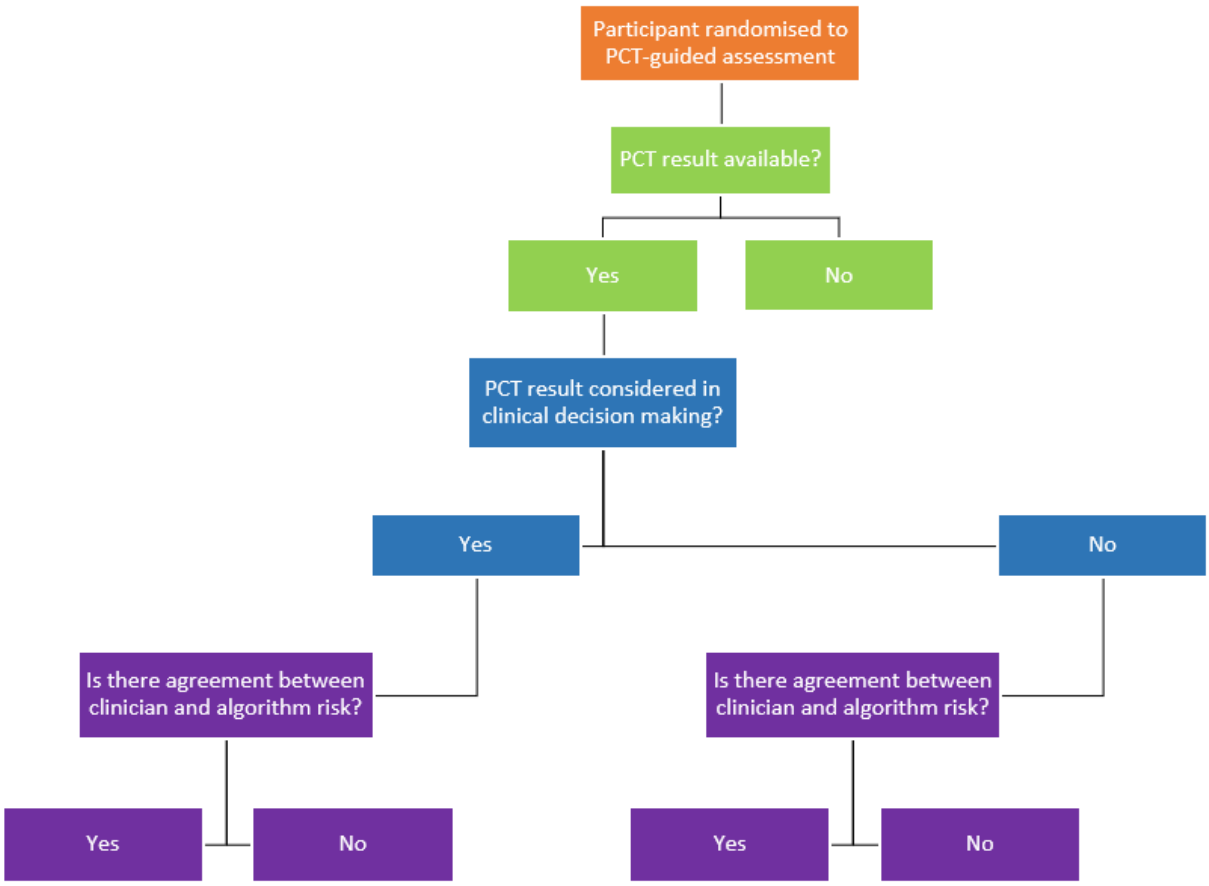

Figure 3: Flow diagram defining the different analysis populations in participants randomised to PCT-guided care

We will include a 4 by 4 table comparing the outcomes of the clinical risk assessment and the risk stratification/algorithm (Appendix Table A1).

5. STUDY POPULATION

5.1 SCREENING DATA

Patients with suspected sepsis will be identified at ED triage. After initial NEWS2 and assessment according to the 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. 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. Tables will present the following summaries (overall and by study site): the number of days recruiting, number of patients screened, number of patients recruited, number of patients recruited per day, number of screened patients not recruited, and the reason for non-recruitment.

5.2 ELIGIBILITY

Participants are eligible for the trial if they meet all the following inclusion criteria and none of the exclusion criteria apply.

Inclusion criteria

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

Exclusion criteria

- Currently on IV 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 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).

5.3 RECRUITMENT

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. The process is described in the participant flow diagram (PRONTO Protocol Version 3.1 dated 23/10/23; Section 3; Figure 1).

5.4 TIERED CONSENT PROCESS

Due to time constraints in managing suspected sepsis, patients will be randomised into either the standard care arm or interventional arm on diagnosis with suspected sepsis prior to consent being obtained. The participant will be approached within 72 hours of randomisation to complete the formal informed consent process. The process is described in the participant consent flowchart (PRONTO Protocol Version 3.1 dated 23/10/23; Section 9.3; Figure 2). During this process participants can consent to different aspects of the trial using a tiered consent approach.

Participants can agree to the following aspects of the study:

1. Information collected as part of the trial and data from medical records from the date of randomisation up to the date of consent can be used in the trial.
2. Data from medical records can be collected from the date of randomisation to 90 days after this date.
3. Participant to be contacted by research staff at day 28 and day 90 to ask about health, wellbeing and any further medical treatment they may have received.

5.5 WITHDRAWAL/FOLLOW UP

If a patient does not wish to take part in any aspects of the trial, they will be withdrawn from the study and all clinical data up until that point will be removed from the study database. Participants have the right to withdraw consent for the use of clinical data collected in any aspect of the trial at any time. A participant's care will not be affected at any time by declining to participate or withdrawing from the trial.

5.5.1 LEVEL OF WITHDRAWAL

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:

1. Partial withdrawal from further data collection (questionnaires, clinical assessments)
2. Complete withdrawal from further data collection
3. Withdrawal of permission to use data already collected.

5.5.2 TIMING OF WITHDRAWAL

The numbers (with reasons) of losses to follow-up (dropouts and withdrawals) over the course of the trial (baseline, randomisation, treatment phase, day 28 and day 90 follow-up) will be presented in a CONSORT flow diagram.

5.5.3 REASONS FOR WITHDRAWAL

Participants who consent and subsequently withdraw are invited to complete a withdrawal form. If they decline, the withdrawal form should be completed by the researcher/clinician based on information provided by the participant. Participants will be identified as lost to follow-up if it is not possible to contact them directly for 4 weeks post day 90.

5.5.4 PRESENTATION OF WITHDRAWAL/LOSS TO FOLLOW-UP

We will report frequencies and percentages of participant withdrawal, overall and by trial arm, broken down by level, timing, and (where available) reason for withdrawal.

5.6 BASELINE PARTICPANT CHARACTERISTICS

5.6.1 LIST OF BASELINE DATA

- Age
- Gender
- Ethnicity
- Timing of initial assessments and ED admission
- Duration of symptoms
- Initial diagnosis
- Initial treatment
- History of oral antibiotic use in 14 days prior to admission
- Comorbidities (Charlson Comorbidity Index)
- COVID-19 status
- C-reactive protein (CRP) at baseline

5.6.2 DESCRIPTIVE STATISTICS

Participant characteristics will be summarised as frequencies and percentages, means and standard deviations, or medians and interquartile ranges, depending on the type of variable, for all randomised participants, overall and by trial arm, as well as for analysis populations as defined in Section 4.3, and by risk category based on NEWS2 score at baseline (≤4, 5-6 and ≥7).

6. ANALYSIS

6.1 OUTCOME DEFINITIONS

6.1.1 PRIMARY OUTCOME(S)

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

- IV antimicrobial initiation at 3 hours (binary outcome)
- 28-day mortality (binary outcome)

Decisions about effectiveness using these co-primary outcomes will be made based on Table 3.

Table 3: determining whether the intervention is effective using the co-primary outcomes.

	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

6.1.2 TIMING, UNITS AND DERIVATION OF PRIMARY

We will assess 28-day mortality from the date of randomisation, and IV antimicrobial initiation within 3 hours of ED admission. Both outcomes are recorded in binary format.

6.1.3 LIST OF SECONDARY OUTCOMES

1. Time until initiation of IV antibiotic therapy
2. Late IV antibiotic initiation – antibiotics commenced after 3 hours
3. Number of days on IV antibiotics (during admission and total over the first 28 days)
4. Number of days on any antibiotics (during admission and total over the first 28 days)
5. Number of days on broad spectrum antibiotics (IV and oral), defined by number of days on an 'Watch/Reserve' group antibiotic as defined by WHO AWaRe Classification Database (during admission and total over the first 28 days)
6. Critical care admission (ICU or HDU) – at any point during hospital admission
7. Length of ICU/HDU stay (overnight stays)
8. Length of hospital stay (overnight stays)
9. Adverse antibiotic outcomes (including *C. difficile* cases and hospital acquired infections (HAIs))
10. Readmission to hospital within 90 days (defined as readmission due to original diagnosis as per CRF)
11. Mortality within 90 days (and time until death)
12. Health utility (EQ-5D-5L) at 28 and 90 days
13. Health resource usage (described in the health economics analysis plan)
14. Feasibility of implementing PCT testing alongside NEWS2 scoring in EDs (described in the qualitative analysis plan)
15. Acceptability of implementing PCT testing alongside NEWS2 scoring in EDs, to patients, carers, and clinicians (described in the qualitative analysis plan)

6.1.4 ORDER OF TESTING

Not applicable.

6.1.5 TIMING, UNITS AND DERIVATION OF SECONDARIES

Individual timing and measurements of secondary outcomes are described in the table below:

Table 4: Timing and measurement of secondary outcomes

Outcome	Measure	Time frame
Antibiotic initiation	Time until initiation Late IV antibiotic initiation (after 3 hours) (yes/no)	In ED/hospital
Antibiotic usage	No of days on IV antibiotics* No of days on all antibiotics* No of days on broad spectrum antibiotics (Watch/Reserve)*	In hospital and total over first 28 days
Critical care usage (ICU and HDU)	Admitted to ICU or HDU (yes/no) No of overnight stays in ICU and HDU	In hospital
Hospital stay	No of overnight stays in hospital	In hospital
Antibiotic adverse outcomes	Anticipated drug reactions include diarrhoea, *C. difficile*, acute kidney injury, hearing loss, etc.	In hospital
Readmission to hospital	People with one or more readmissions	After discharge within 90 days
Mortality	Mortality within 90 days No of days until death*	90 days
Health utility	EQ-5D-5L	28 and 90 days

*Days will be counted if an event occurs at any time between 00:00 and 23:59.

6.2 ANALYSIS METHODS

6.2.1 LIST OF METHODS AND PRESENTATION

6.2.1.1 BASELINE DEMOGRAPHICS ANALYSIS

Baseline data (e.g., age, gender, comorbidities, etc.) will be summarised by trial arm using appropriate descriptive statistics (section 5.5.2) and for those who completed follow-up compared to those lost to follow-up.

6.2.1.2 PRIMARY OUTCOME ANALYSIS

We will use complete case analysis for the co-primary outcomes, meaning that we will only include participants with valid responses to both co-primary outcomes in the primary analysis. We will fit separate two-level logistic regression models (patients nested within sites) to model both co-primary outcomes, controlling for baseline NEWS2 score (minimisation variable). Results will be reported as risk differences with corresponding confidence intervals (calculated via the delta method (Norton et al., 2013)); a two-sided 90% interval for 28-day mortality (OBF adjusted to 90.18%), and a two-sided

95% interval for IV antibiotic initiation at 3 hours (OBF adjusted to 95.04%). Non-inferiority in 28-day mortality will be concluded if the upper bound of the confidence interval is below +2.5% on the risk difference scale.

The individual analyses for the co-primary outcomes and corresponding inferences are described in the table below:

Table 5: Inferences for analyses of co-primary outcomes

Test	Outcome	Hypothesis test and statistical method used*	Inference
1	28-day mortality	Non-inferiority test with a margin of 2.5% H_0: $p_2 - p_1 \geq 0.025$	O'Brien-Fleming alpha spending (one-sided alpha = 0.05) Reject null if P < 0.0491 Critical value = 1.654
2	28-day mortality	Superiority test H_0: $p_1 - p_2 \leq 0$	O'Brien-Fleming alpha spending (one-sided alpha = 0.05) Reject null if P < 0.0491 Critical value = 1.654
3	IV antibiotic initiation at 3 hours	Superiority test H_0: $p_1 - p_2 \neq 0$	O'Brien-Fleming alpha spending (two-sided alpha = 0.05) Reject null if P < 0.0496 Critical value = 1.964
*p_1 and p_2 represent the outcome proportions in the control and intervention arm, respectively.			

It has been recognised that the option to stop the trial early in sequential designs introduces bias to the standard maximum likelihood estimator (MLE) (Cox, 1952). Therefore, we will also calculate unconditional bias-adjusted point estimates. We will derive the bias-adjusted maximum likelihood estimates proposed by Whitehead, by subtracting an estimate of the bias from the MLE (Whitehead, 1986). We will also calculate the uniformly minimum variance unbiased estimator (UMVUE) using the Rao-Blackwell technique. We will calculate the unconditional bias-adjusted point estimates, as we want to determine the point estimates regardless of the stage at which the trial stops. We are interested in the bias as averaged over all possible stopping times, weighted by the respective stage-wise stopping probabilities (Robertson et al., 2023, Grayling & Wason, 2022).

Table 6: Summary of analyses of primary outcomes

Outcome	Analysis	Covariates
	Primary analysis:	Trial arm and baseline NEWS2

IV antimicrobial initiation at 3 hours (superiority)	Two-level logistic regression	Trial arm, baseline NEWS2, age, number of comorbidities and gender
	Secondary analysis: Two-level logistic regression with bias-adjusted point estimates	Trial arm and baseline NEWS2
		Trial arm, baseline NEWS2, age, number of comorbidities and gender
	Subgroup analyses: Two-level logistic regression (interaction test by model comparison)	Trial arm, baseline NEWS2, and the organ system of the infection (lower urinary tract, lower respiratory, intra-abdominal, bacteraemia, skin, soft tissues, etc.)
		Trial arm, baseline NEWS2, and risk category based on NEWS2 score at baseline (≤4, 5-6 and ≥7)
		Trial arm, baseline NEWS2, and managed as suspected COVID-19 during admission (yes/no)
		Trial arm, baseline NEWS2, and has a positive COVID-19 test result +/- 5 days from admission (yes/no)
		Trial arm, baseline NEWS2, and PCT machine used at the time of recruitment (BRAHMS PCT-direct/PathFast BRAHMS PCT)
		Trial arm, baseline NEWS2, and recruitment date (before 01/12/21, between 01/12/21 and 30/11/22, after 30/11/22)
		Trial arm, baseline NEWS2, and level of site ED crowding (upper, middle and lower tercile of national monthly figures)
	Complier average causal effect (CACE)	Trial arm, baseline NEWS2, and intervention adherence
28-day mortality (non-inferiority)	*Primary analysis:* Two-level logistic regression	Trial arm and baseline NEWS2
		Trial arm, baseline NEWS2, age, number of comorbidities and gender
	Secondary analysis: Two-level logistic regression with bias-adjusted point estimates	Trial arm and baseline NEWS2
		Trial arm, baseline NEWS2, age, number of comorbidities and gender
	Subgroup analyses:	Trial arm, baseline NEWS2, and the organ system of the infection (lower urinary tract, lower respiratory, intra-

	Two-level logistic regression (interaction test by model comparison)	abdominal, bacteraemia, skin, soft tissues, etc.)
		Trial arm, baseline NEWS2, and risk category based on NEWS2 score at baseline (≤4, 5-6 and ≥7)
		Trial arm, baseline NEWS2, and managed as suspected COVID-19 during admission (yes/no)
		Trial arm, baseline NEWS2, and has a positive COVID-19 test result +/- 5 days from admission (yes/no)
		Trial arm, baseline NEWS2, and PCT machine used at the time of recruitment (BRAHMS PCT-direct/PathFast BRAHMS PCT)
		Trial arm, baseline NEWS2, and recruitment date (before 01/12/21, between 01/12/21 and 30/11/22, after 30/11/22)
		Trial arm, baseline NEWS2, and level of site ED crowding (upper, middle and lower tercile of national monthly figures)
	Complier average causal effect (CACE)	Trial arm, baseline NEWS2, and intervention adherence

6.2.1.3 SECONDARY OUTCOME ANALYSIS

All secondary analyses will be performed on an intention to treat basis using the primary analysis population as defined in section 4.3, utilising two-level models to allow for patients nested within sites.

Table 7 – Summary of secondary analyses

	Outcome	Analysis	Covariates
1	Time until initiation of IV antibiotic therapy	We will present the result as a groupwise boxplot with median and range of number of hours. Cox regression analysis will be used, with the results reported as hazard ratios (HR) and 95% confidence intervals. We will also produce a Kaplan Meier plot and cumulative incidence plot.	a) Trial arm and baseline NEWS2 b) Trial arm, baseline NEWS2, age, number of comorbidities and gender

2	Late IV antibiotic initiation – antibiotics commenced after 3 hours	We will report the groupwise frequency and percentage of late initiations. Logistic regression will be used, with the results reported as odds ratios (OR) and 95% confidence intervals.	a) Trial arm and baseline NEWS2 b) Trial arm, baseline NEWS2, age, number of comorbidities and gender
3	Number of days on IV antibiotics (during admission) Number of days on IV antibiotics (total over the first 28 days)	We will present the result as a groupwise boxplot with median and range of number of days. Poisson regression analysis will be used, with results reported as incidence rate ratios (IRR) and 95% confidence intervals.	a) Trial arm and baseline NEWS2 b) Trial arm, baseline NEWS2, age, number of comorbidities and gender
4	Number of days on any antibiotic (during admission) Number of days on any antibiotic (total over the first 28 days)	We will present the results as a groupwise boxplot with median and range of number of days. Poisson regression analysis will be used, with results reported as IRRs and 95% confidence intervals.	a) Trial arm and baseline NEWS2 b) Trial arm, baseline NEWS2, age, number of comorbidities and gender
5	Number of days on broad-spectrum antibiotics (IV and oral) (during admission) Number of days on broad-spectrum antibiotics (IV and oral) (total over the first 28 days)	We will represent the result as a groupwise boxplot with median and range of number of days. Poisson regression analysis will be used, with results reported as IRRs and 95% confidence intervals.	a) Trial arm and baseline NEWS2 b) Trial arm, baseline NEWS2, age, number of comorbidities and gender
6	Critical care admission (ICU or HDU) – at any point during admission	We will report the groupwise frequency and percentage of ICU and HDU admissions. Logistic regression will be used, with results reported as ORs and 95% confidence intervals.	a) Trial arm and baseline NEWS2 b) Trial arm, baseline NEWS2, age, number of comorbidities and gender
7	Length of critical care stay (overnight stays)	We will represent the result as a groupwise boxplot with median and range of number of days. Poisson regression analysis will be used, with results reported as IRRs and 95% confidence intervals.	a) Trial arm and baseline NEWS2 b) Trial arm, baseline NEWS2, age, number of comorbidities and gender

8	Length of hospital stay (overnight stays)	We will represent the result as a groupwise boxplot with median and range of number of days. Poisson regression analysis will be used, with results reported as IRRs and 95% confidence intervals.	a) Trial arm and baseline NEWS2 b) Trial arm, baseline NEWS2, age, number of comorbidities and gender
9	Adverse antibiotic outcomes	We will report the groupwise frequency and percentage of adverse outcomes events, overall and broken down by type of adverse event. Logistic regression will be used, with results reported as ORs and 95% confidence intervals.	a) Trial arm and baseline NEWS2 b) Trial arm, baseline NEWS2, age, number of comorbidities and gender
10	Readmission to the hospital within 90 days	We will report the groupwise frequency and percentage of readmissions. Logistic regression will be used, with results reported as ORs and 95% confidence intervals.	a) Trial arm and baseline NEWS2 b) Trial arm, baseline NEWS2, age, number of comorbidities and gender
11	Mortality within 90 days	We will report the groupwise frequency and percentage of deaths. Logistic regression will be used, with results reported as ORs and 95% confidence intervals.	a) Trial arm and baseline NEWS2 b) Trial arm, baseline NEWS2, age, number of comorbidities and gender
	Mortality within 90 days – days until death	Additionally, we will represent the result as groupwise a boxplot with median and range of number of days until death. Cox regression analysis will be used, with results reported as HR and 95% confidence intervals. We will also produce a Kaplan Meier plot and a cumulative incidence plot.	a) Trial arm and baseline NEWS2 b) Trial arm, baseline NEWS2, age, number of comorbidities and gender
12*	Health utility (EQ-5D-5L) at 28 days – summary index score (0-1)	We will report the mean (SD) of the score. A linear regression analysis will be used to test the difference between the groups.	a) Trial arm and baseline NEWS2 b) Trial arm, baseline NEWS2, age, number of comorbidities and gender
	Health utility (EQ-5D-5L) at 28 days – visual analogue scale (VAS) (0-100)		
	Health utility (EQ-5D-5L) at 90 days - summary index score (0-1)		

	Health utility (EQ-5D-5L) at 90 days – VAS (0-100)		

* For health utility (EQ-5D-5L) analyses, the current NICE guidelines suggest using the mapping function developed by van Hout et al. (2012). We will follow NICE guidelines at the time of analysis.

6.2.2 COVARIATE ADJUSTMENT

Other covariates of potential interest, including age, comorbidities and gender, will be adjusted for in secondary analyses together with minimisation factors. Subgroup analyses are described in section 6.2.6.

6.2.3 ASSUMPTION CHECKING

Modelling and distributional assumptions will be checked prior to analysis and reporting. Specifically, time-to-event models will be tested for the proportional hazard assumption, Poisson regression models will be assessed for overdispersion and baseline NEWS2 score will be assessed for non-linearity.

6.2.4 ALTERNATIVE METHODS IF DISTRIBTIONAL ASSUMPTIONS NOT MET

If the data does not meet the distributional assumptions of the analyses described above, variables will be transformed if possible. If transformations do not improve the distributions, the model choice may vary from what is described above. For example, if the effect of baseline NEWS2 is distinctly non-linear we may account for it using higher-order terms or splines. If the number of days on antibiotics/in critical care do not meet the Poisson regression assumption that the variance is equal to the mean, we may use negative binomial or quasi-Poisson models to account for the overdispersion. A time interaction term may be added to Cox regression if the proportional hazards assumption is not met. Additionally, if the proportional hazards assumption is not met, we may consider restricted mean survival analysis, or possibly the Fine-Gray model if the assumption is badly violated. If censoring is an issue, rather than using boxplots, we will use the median and centiles from the survival distribution. Any changes will be fully documented.

6.2.5 SENSITIVITY ANALYSES

The primary analysis described in section 6.2.1 uses the joint complete case population for both co-primary outcomes. As a sensitivity analysis we will repeat the analysis using the complete case populations of each of the co-primary outcomes individually (i.e., including participants with valid responses to at least one of the co-primary outcomes) using the same methods as described in section 6.2.1.

A sensitivity analysis will estimate the CACE to account for departures from the randomised intervention. For the purposes of this sensitivity analysis, we will define different analysis populations depending on the level of adherence to the PCT-guided algorithm (Figure 3):

- Patients randomised to PCT-guided care in whom a PCT test is done, and a PCT result is available
- Patients randomised to PCT-guided care in whom a PCT test is done, a PCT result is available, and the clinician has seen the PCT result
- Patients randomised to PCT-guided care in whom a PCT test is done, a PCT result is available, the clinician has seen the PCT result and followed the algorithm exactly.

The non-inferiority margin is defined using a fixed risk difference of 2.5%. If the observed 28-day mortality in the control arm deviates from the 15% (by more than 3% points above or below) assumed in the sample size calculation, we will additionally repeat the primary analysis with the non-inferiority margin modified according to the power-stabilising arcsine transformation proposed by Quartagno et al. (2020 & 2023).

Also, the protocol allows patients to be recruited more than once into the study. If the proportion of repeatedly randomised patients exceeds 5%, we will perform a sensitivity analysis excluding repeat episodes.

6.2.6 SUBGROUP ANALYSES

We will conduct seven separate subgroup analyses, stratified by:

- The organ system of the infection (initial working diagnosis):
  - Upper respiratory tract infection
  - Skin/soft tissue infection
  - Urinary tract infection/urosepsis
  - Central nervous system infection
  - Gastrointestinal tract/abdominal infection
  - Bone/joint/muscle infection
  - Lower respiratory tract infection/community-acquired pneumonia
  - Sepsis (unknown source)
  - Other infections
  - Not infection
- Risk category based on NEWS2 score at baseline:
  - ≤4
  - 5-6
  - ≥7
- Managed as suspected COVID-19 during admission:
  - Yes
  - No
- Positive COVID-19 test result +/- 5 days from admission:
  - Yes
  - No
- PCT machine used at time of recruitment:
  - BRAHMS PCT-direct

    - PathFast BRAHMS PCT
- Recruitment date:
    - Before 1st December 2021
    - Between 1st December 2021 and 30th November 2022
    - After 30th November 2022
- Level of site ED crowding (percentage of patients who spent >12 hours from decision to admit to admission) at time of randomisation:
    - Upper tercile of national monthly figures
    - Middle tercile of national monthly figures
    - Bottom tercile of national monthly figures

We will investigate whether the treatment effect varies between subgroups by including the subgroup variable as a covariate in the main analysis model, both with and without a treatment-arm interaction term. The models with and without the interaction term will be compared using a likelihood-ratio test (LRT). We will report the LRT χ^2 statistic and illustrate the direction of the subgroup effect using forest or interaction plots.

We will also assess whether adherence to the intervention varies according to levels of ED crowding at the time of randomisation. We will conduct a two-level logistic regression (patients nested within sites) with algorithm adherence (yes/no) as the outcome variable and the level of ED crowding as the explanatory variable, controlling for baseline NEWS2 score (minimisation variable). NHS England publishes monthly A&E attendances and emergency admissions data. We will calculate the percentage of emergency admission patients who spent >12 hours from decision to admit to admission per month per site and compare these to the national monthly figures. We will rerun the co-primary analyses for subgroups of the least, middle, and most crowded EDs. As an exploratory analysis we may include ED crowding as an additional covariate and include time varying interaction terms. If the data allows, we may also explore the effect of daily ED crowding levels on the co-primary outcomes for a subgroup of sites.

6.3 MISSING DATA

During data entry, validations have been written into the system to minimise the amount of missing data, however, missing data may still occur. The frequency and percentage of missing values will be reported overall and by arm. If missing primary outcome data is greater than 5% (as accounted for in the sample size calculation), we will conduct sensitivity analyses using multiple imputations (separately for both randomisation groups) (Sullivan et al., 2018). Missing data will be investigated for cause and extent and multiple imputation. The assumption of missingness at random (MAR) will be tested by analysing each baseline covariate in a separate logistic regression model to determine which (if any) are associated with the missingness of the primary outcome, and the associated p-values will be reported alongside the summary statistics. Missing observations will be replaced by multiple imputations by chained equations (MICE). A sensitivity analysis will be conducted on the primary analysis, including any baseline factors that were found to be associated with the

missingness of the primary outcome. Any changes to the assumptions made in the primary analysis will be considered in a sensitivity analysis.

6.4 ADDITIONAL ANALYSES

We will compare the initial working diagnosis versus the final diagnosis by arm.

We may perform a linear regression analysis on an intention to treat basis using the primary analysis population as defined in section 4.3, utilising two-level models to allow for patients nested within sites, to explore the differences in Daily Defined Doses of antibiotics by arm.

The health economics and qualitative analysis plans are detailed separately from the SAP.

6.5 HARMS

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 outcome data collection and 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 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 will be recorded in the participant's notes and on the relevant CRFs.

The following will be reported as SAEs within 24 hours:

- Events resulting in persistent or significant disability or incapacity
- Congenital anomalies or birth defects

The frequency (percentage) of AEs and SAEs will be tabulated overall and by trial arm and compared using a chi-square test.

6.6 STATISTICAL SOFTWARE

The data will be extracted and imported into Stata (version 17.0 or higher). All analyses will be carried out in Stata (StataCorp LLC, College Station, TX, USA).

7. REFERENCES

7.1 NON-STANDARD STATISTICAL METHODS

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7.2 DATA MANAGEMENT PLAN

Data management plan: P:\152310305\PRONTO\eTMF\8.0 Data Management\8.1 Data Management \DOCUMENTS\DMP

7.3 TRIAL MASTER FILE AND STATISTICAL MASTER FILE

Trial master file: P:\152310305\PRONTO\eTMF

Statistical master file: P:\152310305\PRONTO\eTMF\8.0 Data Management\8.5 Statistics

7.4 OTHER SOPS OR GUIDANCE DOCUMENTS

Randomisation plan: P:\152310305\PRONTO\eTMF\8.0 Data Management\8.5 Statistics\ Randomisation

Interim SAP: P:\152310305\PRONTO\eTMF\8.0 Data Management\8.5 Statistics\Statistical Analysis Plan\Interim SAP

SAP DEVIATION LOG

Document number:		**Document version:**	
Reason for deviation:			

Deviations from the planned analyses:

- For the ED subgroup analysis, we have used the site's % of participants waiting greater than >12hours from decision to admit at the time of randomisation, rather than the tercile, to reflect the increasing ED crowding
- We have not calculated the MLE or UMVUE estimates described in section 6.2.1.2 as the IDMC decided to continue the trial after the interim analysis even though the trial could have stopped according to the stopping criteria described in section 3.5.2

The following post-hoc exploratory analyses have been conducted on the following dates to understand the mechanism behind the results:

24/06/24:

- Descriptive tabulation of antibiotics and broad-spectrum antibiotics by arm
- Descriptive tabulation of ventilation and vasopressor by arm
- Descriptive tabulation of the participant timeline/pathway by arm
- Descriptive tabulation of the co-primary outcomes (28-day mortality and IV abx within 3-hours) by arm and NEWS2 score
- Descriptive tabulation of the algorithm risk vs clinical risk assessment by arm and NEWS2

11/07/24:

- Breakdown of amoxicillin and co-amoxiclav by IV/oral in the descriptive table of antibiotics by arm
- Descriptive tabulation of non-antibiotics (e.g., antivirals, anti-parasitic etc.) prescribed by arm
- Descriptive tabulation of the 10 most frequent combinations of first 2 abx prescribed simultaneously
- Descriptive summary (median [IQR]) of the number of days on broad-spectrum abx per participant per arm
- Descriptive tabulation of the proportion of participants who received two narrow spectrum abx simultaneously as their first abx
- Descriptive tabulation of 28-day mortality by algorithm risk category by arm
- Descriptive summary of the mean days on any abx by algorithm risk category by arm
- Explore whether mortality (adjusted for NEWS2) differed by site using post estimation of random effects

15/08/24:

- Descriptive tabulation of the first prescription given by arm
- Post-hoc subgroup analysis (using same methods described in section 6.2.6) of time to IV (secondary outcome #1) by NEWS2
- Poisson regression analysis of days on IV/any abx in first 14 days
- Logistic regression analysis of whether IV abx was initiated within 12 hours

- Logistic regression analysis of whether IV abx was initiated within 7-days
- Descriptive summaries of the following, to explore whether the treatment pathway may have changed between the arms
    - Time from triage (+/- randomization) to prescription of antibiotics
    - Time from triage (+/- randomization) to administration of antibiotics
    - Time between prescription and administration of antibiotics
    - % blood cultures taken in first 24 hours (No other measure in CRF)
    - Broad spectrum Abx (Watch/Reserve) vs narrow spectrum (Access)
    - Initial Diagnosis Infection vs Not Infection
    - Cause of Death
    - Time to HDU/ITU admission
    - Broad spectrum Abx (Watch/Reserve) vs narrow spectrum (Access)
    - Abx choice – Compare distribution of No Antibiotics> PO>IV Narrow>IV broad
    - % Microbiology tests in first 24 hours (Blood cultures only)
    - % Microbiology tests in first 24 hours (Any)
    - % Any antimicrobial resistance detected, if yes which by %
    - Duration of antibiotics (initial course started within 24 hours of attendance)
    - Length of hospital stay
    - % No antibiotics vs any antibiotics
    - % Late course of antibiotics (2-28 days)
    - Time to late antibiotics
    - % Readmitted to hospital
- Descriptive summary of the days on no abx, oral, iv broad, iv narrow, combination for each NEWS score and arm

05/09/24

- Tabulate first prescription within 24 hours from triage by arm
- Tabulate arm by final diagnosis with mortality in the cells – infection vs non infection
- Tabulate deaths in withdrawals by arm

19/09/24

- Tabulate 28-day mortality in different algorithm adherence groups – including the discordant groups (low clinical risk & high algorithm risk and vice versa) (unexpected vs expected PCT result)
- A logistic regression analysis of trial arm's effect on being alive and not readmitted at 90 days
- Subgroup analysis (as described in section 6.2.6) of grading of clinician conducting assessment
- Subgroup analysis (as described in section 6.2.6) of index of deprivation decile
- Tabulate time between 1st and 2nd assessment overall, by arm and by NEWS2
- Time series plot of ED crowding by site
- Subgroup analysis (as described in section 6.2.6) of initial diagnosis of LRTI/CAP vs all other initial diagnoses

- Subgroup analysis (as described in section 6.2.6) of initial diagnosis of respiratory infection vs all other initial diagnoses

02/12/24

- Descriptive comparison of initial diagnosis and final diagnosis by arm using Sankey diagrams

09/12/24

- Descriptive tabulation of 28-day morality by arm by type of abx received within 12 hours

8. APPENDICES

8.1 Dummy tables

8.1.1 Primary outcomes

Table A1 – Adherence to PCT-guided algorithm

	Clinical risk assessment				
Algorithm	Risk	Low	Low/medium	Medium	High
	Low	N =			
	Low/medium				
	Medium				
	High				

Table A2 – Analysis populations defined by adherence to intervention.

	Level	**n/N (%)**
PCT test result available	Yes	
	No	
	Missing	
PCT test result considered in clinical decision making	Yes	

	No	
	Missing	
Algorithm adhered to	Yes	
	No	
	Missing	

Table A2 – Primary outcome analysis results

Outcome	Analysis	Treatment effect estimate [95% CI]	p-value
IV antimicrobial initiation at 3 hours (superiority)[a]	Primary	RD =	
	Adjusted for covariates	RD =	
	Bias-adjusted	RD =	
	CACE	RD =	
28-day mortality (non-inferiority) [a]	Primary	RD =	
	Adjusted for covariates	RD =	
	Bias-adjusted	RD =	
	CACE	RD =	

CI = confidence interval, RD = risk difference.
Analysis method: (a) multilevel logistic regression.
Confidence intervals are two-sided for IV initiation and one-sided for 28-day mortality.
Covariates in all models: baseline NEWS2.

8.1.2 Secondary outcomes

Table A3 – Secondary outcome analysis results

	Outcome	Analysis	Treatment effect estimate [95% CI]	p-value
1	Time until initiation of IV antibiotic therapy[a]	Primary	HR =	
		Adjusted for covariates	HR =	
2	Late IV antibiotic initiation – antibiotics commenced after 3 hours[b]	Primary	OR =	
		Adjusted for covariates	OR =	

3	Number of days on IV antibiotics (during admission) [(a)]	Primary	IRR =	
		Adjusted for covariates	IRR =	
	Number of days on IV antibiotics (total over first 28 days) [(a)]	Primary	IRR =	
		Adjusted for covariates	IRR =	
4	Number of days on any antibiotic (during admission) [(a)]	Primary	IRR =	
		Adjusted for covariates	IRR =	
	Number of days on any antibiotic (total over first 28 days) [(a)]	Primary	IRR =	
		Adjusted for covariates	IRR =	
5	Number of days on broad-spectrum antibiotics (IV and oral) (during admission) [(a)]	Primary	IRR =	
		Adjusted for covariates	IRR =	
	Number of days on broad-spectrum antibiotics (IV and oral) (total over the first 28 days) [(a)]	Primary	IRR =	
		Adjusted for covariates	IRR =	
6	ICU or HDU admission – at any point during admission[(b)]	Primary	OR =	
		Adjusted for covariates	OR =	
7	Length of ICU/HDU stay[(a)]	Primary	IRR =	
		Adjusted for covariates	IRR =	
8	Length of hospital stay[(a)]	Primary	IRR =	
		Adjusted for covariates	IRR =	
9	Adverse antibiotic outcomes[(b)]	Primary	OR =	
		Adjusted for covariates	OR =	
10	Readmission to the hospital within 90 days[(b)]	Primary	OR =	
		Adjusted for covariates	OR =	
11	Mortality within 90 days[(b)]	Primary	OR =	
		Adjusted for covariates	OR =	
	Mortality within 90 days - time until death[(a)]	Primary	HR =	
		Adjusted for covariates	HR =	
12	Health utility (EQ-5D-5L) at 28 days[(c)]	Primary	MD =	
		Adjusted for covariates	MD =	
		Primary	MD =	

	Health utility (EQ-5D-5L) at 28 days[(c)]	Adjusted for covariates	MD =	
	Health utility (EQ-5D-5L) at 90 days[(c)]	Primary	MD =	
		Adjusted for covariates	MD =	
	Health utility (EQ-5D-5L) at 90 days[(c)]	Primary	MD =	
		Adjusted for covariates	MD =	
CI = confidence interval, HR = hazard ratio, OR = odds ratio, MD = mean difference. *Analysis method: (a) cox regression, (b) logistic regression, (c) linear regression* *Covariates in all models: baseline NEWS2.*				

8.1.3 Subgroup analyses

Table A4 – Subgroup analyses of primary outcomes

Outcome	Subgroups	LRT χ^2 (df)	p-value
IV antimicrobial initiation at 3 hours (superiority)[(a)]	The organ system of the infection		
	Risk category based on NEWS2 score at baseline		
	Managed as suspected COVID-19 during admission		
	Positive COVID-19 test result +/- 5 days from admission		
	PCT machine used		
	Recruitment date		
	Level of ED crowding		
28-day mortality (non-inferiority) [(a)]	The organ system of the infection		
	Risk category based on NEWS2 score at baseline		
	Managed as suspected COVID-19 during admission		
	Positive COVID-19 test result +/- 5 days from admission		
	PCT machine used		
	Recruitment date		
	Level of ED crowding		
Analysis method: (a) multilevel logistic regression. Interaction tests by model comparison. *Covariates in all models: baseline NEWS2.*			

Short title:	ISAP / SAP Template