
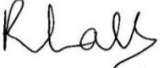

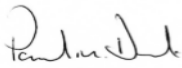


KEY DOCUMENT REVIEW/APPROVAL

Trial:	BiomArker-guided Duration of Antibiotic treatment in hospitalised PaTients with suspected Sepsis: the ADAPT-Sepsis Trial.		
Chief Investigator:	Professor Paul Dark		
Document:	Version: 2.0	Date: 16-03-2023	
<input type="checkbox"/> Protocol / amendment* <input type="checkbox"/> PIS/ amendment* <input type="checkbox"/> Consent form / amendment* <input type="checkbox"/> CRF / amendment* <input type="checkbox"/> Publication(s) <i>(add details)</i> <input type="checkbox"/> Risk Assessment <input type="checkbox"/> Monitoring Plan <input type="checkbox"/> Statistical Analysis Plan			
Reviewers:			
By signing this form, you confirm the content of the document specified has been reviewed and found to be correct.			
Name	Role in trial	Signature	Date
Dr Anower Hossain	<i>Statistician</i>		08/03/2022
Professor Ranjit Lall	<i>Senior Statistician</i>		8/03/2022
Dr Ly-Mee Yu	<i>DMC chair</i>		23 March 2022
Chief Investigator Approval:			
I confirm that the document specified has been reviewed and I approve the use of this version.			
Signature:		Date: 8 th March 2022	
			

The signed form should be filed with the approved document in the TMF.

Date	Amendments
15 March 2023	Scenario 1: Main analysis: use randomisation date and time as the first antibiotic start date and time for every participant in the study.
	Scenario 2: 1. If the start date and time of the first antibiotic is missing, the randomisation date and time will be used. 2. If the start date and time of the first antibiotic exists which might be different from the randomisation date and time, we will use it in the calculation of the total antibiotic duration.
16 March 2023	The clinical outcomes (primary and secondary) will be compared between the ROCHE CRP sites and non-ROCHE CRP sites.

Introduction

Background and rationale

Sepsis is a common life-threatening condition where early antibiotic treatment is an important factor in determining survival¹. For patients with suspected sepsis, it is recommended that antibiotics are commenced within 1 hour, an NHS standard incentivised by a payment framework². However, once commenced, the duration of antibiotic treatment is less certain, as identified within the brief for this call. Fixed duration antibiotic courses are widely used in the NHS because clinical signs and microbiology culture tests are not useful to monitor treatment efficacy to guide the decision to stop antibiotics³. Readily available circulating serum proteins such as C-reactive protein (CRP) and procalcitonin (PCT) are often raised in sepsis and usually fall in response to effective antibiotic treatment⁴. This provides a potential opportunity to personalise antibiotic duration which could lead to reductions in population antibiotic burden, adverse effects for patients, improved healthcare resource utilisation and downstream effects relating to antimicrobial resistance - an urgent priority. Biomarker-guided antibiotic discontinuation protocols in sepsis have been associated with shorter treatment durations in other healthcare systems internationally^{5,6}, but according to NICE, studies are low quality and with uncertain relevance to NHS practice.

The ADAPT-Sepsis trial is a randomised controlled trial to determine the clinical and cost-effectiveness of both CRP and PCT-guided antibiotic duration, using discontinuation protocols, when compared with standard practice in hospitalised adults with sepsis. A more detailed explanation of the background, rationale, and intervention and trial design can be found in the protocol paper. A brief overview of the trial is presented in this paper.

This paper presents the statistical analysis plan for the ADAPT-Sepsis trial which has been developed in line with published guidelines and the planned cost-effectiveness analysis.

Objectives

The primary objective of this trial is to determine whether treatment protocols based on monitoring CRP or PCT in hospitalised adult patients with suspected sepsis reduces the duration of antibiotic therapy

(superiority) while maintaining treatment safety (non-inferiority) as measured by 28-day mortality. A supplementary objective is to estimate the relative cost-effectiveness of each protocol.

Study methods

Trial design

The ADAPT-Sepsis is a multi-centre three-arm randomised controlled trial with internal pilot. Participants are randomly allocated using a ratio 1:1:1 to CRP: PCT: Usual care. A computerised minimisation randomisation system was used, created by the Warwick Clinical Trials unit, to randomise participants. The randomisation allocation was made following consent processes and baseline assessments. Stratification factors were (i) sepsis severity (sepsis or septic shock), (ii) recruitment centre and (iii) surgery within the last 72 hours or not.

Primary and secondary outcomes

The primary outcomes are effectiveness outcome of total duration of antibiotics used to 28 days post randomisation and safety outcome of 28 days all-cause mortality. Secondary outcomes include escalation of care/re-admission; infection re-lapse/recurrence; dose of antibiotics; length and level of critical care stay, length of hospital stay, and 90-days all-cause mortality.

Sample size

A total sample size of 2760 would be able to detect both a mean of 1-day reduction in antibiotic use duration (using a mean antibiotic duration of 7 days, a pooled standard deviation of 6 days, 90% power, a significance level of 5%, with a 5% withdrawals rate) and a non-inferiority safety margin of 5.4 % (using a 1-sided significance level of 2.5%, 90% power and 5% withdrawal rate) assuming 28-day mortality is 15%.

Timing of final analysis

The end of the trial is defined when the last recruited participant completed 28-days follow-up post randomisation. Once all the data have been entered onto the database, the data will be fully validated and cleaned after which the database will be locked, and the final analyses will be undertaken.

Timing of outcome assessments

Primary and secondary outcome data will be collected daily from randomisation until hospital discharge. Data will also be collected post hospital discharge up to 28-days post randomisation. All-cause mortality

will be collected at 90 days using linked data. Any SAE's will also be reported up to 28 days post-randomisation.

Reporting of results

All primary and secondary clinical effectiveness outcomes will be reported in an earlier publication, with process of care and health economics outcomes reported in subsequent publications, when all the data are available.

In addition, the sub-study, RISC-sepsis will also be reported in a further publication (and has its own approved statistical analysis plan).

Statistical principles

Confidence intervals and p-values

All statistical tests will be two-sided at the 5% significance level except for the non-inferiority safety test that will use a 1-sided significance level of 2.5%⁷. The estimate, 95% confidence interval (95% CI) and P value will be reported for each test undertaken.

Analysis populations

All analyses will be based on 'Intention-to-treat' (ITT) following ICH E9 guidelines. The participants will be analysed according to the treatment they were randomised to, irrespective of the treatment they actually received. All participants will be included in the analysis, regardless of whether they adhered to the protocol.

The Per Protocol (PP) population is usually defined as all participants who completing the study without major protocol deviations. We will identify the participants in this study who completed the study without major protocol deviations and then perform a PP analysis as secondary analysis.

Adherence and protocol deviations

The idea of site protocol adherence has been developed over a series of TMG discussions. Protocol processes have been developed through 4 key steps to help identify 'protocol adherence' and will be closely monitored during the trial. These include assessment of blood samples, production of advice, delivery of advice and the decisions taken for antibiotic treatment.

Trial population

Screening data

A detailed summary of the screening data will be presented as frequencies and percentages to describe the representativeness of the trial sample. This will include total number of hospitalised adult patients screened for eligibility, and number (percentage) of patients randomised to intervention arms.

Eligibility

The ADAPT-Sepsis trial protocol provides full details of the eligibility criteria (inclusion/exclusion criteria). The eligibility will be summarised using frequencies and percentages to describe how many patients were:

- Eligible and randomised
- Eligible and not randomised (summarising the main reasons for not randomised)
- Ineligible and not randomised (summarising the main reasons for exclusion)
-

Recruitment

A Patient Flow diagram will be used to illustrate the flow of participants throughout the trial. This will include:

- Number of patients screened for eligibility
- Number of eligible patients randomised to each intervention arm
- Number of withdrawals, died and lost to follow-up after randomisation
- Number of randomised patients included in the final analyses at the primary endpoint(s)

Withdrawal and follow-up

Participants may be discontinued from the trial at any time. They can either withdraw from the intervention alone but remain on follow-up or they can withdraw completely from the trial. Unless a participant explicitly withdraws their consent, they will be followed-up wherever possible and data collected as per the protocol until the end of the trial. The number of withdrawals from the trial will be summarised by treatment arms, that is, how many participants withdrew from intervention alone but remained on follow-up and how many withdrew completely from the trial. In addition, the withdrawal timings will also be summarised by treatment arms. It will include withdrawals after randomisation but before hospital discharge, and withdrawals after hospital discharge but before 28 days follow-up. The withdrawal decision i.e. decision made by the participant, consultant, clinical team, antibiotic stopped due to futility, required >21 days of antibiotics post randomisation and

other, will be summarised by treatment arms. Follow-up rates will be computed at the 28-day and 90-day follow-up time-points. At 90 days, only all-cause mortality data will be collected using NHS digital and the Intensive Care National Audit and Research Centre.

Baseline patient characteristics

The baseline demographic characteristics and pre-randomisation clinical measures of all randomised participants will be summarised by treatment arms. Moreover, important process data (e.g. date and time of hospital admission and ICU/HDU admission) will also be collected and summarised by treatment arms. Continuous data will be summarised using the statistics the number of participants (n), mean, standard deviation (sd), median and interquartile range (IQR) whereas categorical data will be summarised using the statistic the number (%) of participants. The table below lists the demographic, clinical measures and process variable data that will be collected and summarised.

- Age
- Gender
- Suspected septic shock
- Surgery within last 72 hours
- Core body temperature
- White cell count
- Critical care admission category
- Critical care origin
- Initial care bundle
- qSOFA score
- SOFA score
- APACHE II score
- Infection data:
 - Community/hospital acquired infection
 - Site of infection
 - Causative microorganism identified for infection
 - If yes to the above, detail pathogen
- Process of care/adherence variables:

Time from:

- Hospital admission to ICU/HDU admission
- Hospital admission to first diagnosis of suspected sepsis or suspected septic shock
- Randomisation to first research blood sample taken
- First blood sample taken to first blood sample delivered to laboratory

Analysis

Outcome definitions

The primary outcomes of the trial are (i) total duration of antibiotic treatment to 28 days following randomisation (superiority) measured in days as primary clinical effectiveness outcome, and (ii) 28-day all-cause mortality (non-inferiority) following randomisation as primary safety outcome. For the clinical effectiveness outcome, the use of antibiotics data will be recorded to the point where the participant stopped antibiotics. The use of antibiotics will also be recorded if participants either restarts antibiotics in hospital or discharged from hospital and the re-admitted and receives systemic antibiotics or discharged with antibiotics provided that these events are within 28 days following randomisation. The duration of antibiotics use will be calculated for each participant as the sum of the duration of each course of antibiotics administered from randomisation to day 28. For the safety outcome, all-cause mortality status on day 28 following randomisation will be recorded.

The Secondary effectiveness and safety outcome measures to 28 days following randomisation are

- Antibiotic duration and dose for the initial sepsis episode (duration in days from randomisation and dose measured as Defined Daily Dose)
- Antibiotic dose (measured as Defined Daily Dose)
- Unscheduled care escalation/re-admission
- Infection relapse/recurrence requiring further antibiotic treatment
- Super-infection defined as new infection at a different anatomical site
- Suspected antibiotic adverse reactions
- Time to 'fit' for hospital discharge

The 90-days all-cause mortality will also be analysed as secondary outcome using linked data, for example, from NHS Digital and the Intensive Care National Audit and Research Centre.

Analysis methods

Participants' baseline characteristics and outcomes will be summarised mean and standard deviation if data are continuous or frequency and percentage if data are categorical. The median and interquartile range will be presented if data are non-normal.

The primary effectiveness analyses will assess whether any of the biomarker interventions are better than standard care. The primary analysis approach for the duration of antibiotics will be intention-to-treat (ITT). ITT analysis will consist of all randomised patients and will assess the effect of treatment assignment. For the ITT analysis, linear mixed effects regression models will be fitted to estimate the treatment effect having adjusted for age, gender and the stratification variables (sepsis severity, recruiting centre (random effect) and surgery within the last 72 hours). After fitting the model, we will investigate the validity of the assumption of normality. Alternative methods of analyses will be considered if the distribution of the primary effectiveness outcome is non-normal. In this trial, participants may die before antibiotic therapy is discontinued. In such cases the outcome is undefined and is referred to as 'truncated by death'. A crude comparison between the survivors on each treatment arm may give rise to biased outcome comparisons. Therefore, we will consider undertaking some sensitivity analyses to estimate treatment effect having account for the deaths. This will explore different approaches to analysis of ICU trials, that allow incorporation of multiple relevant outcomes, including death, into a single overall measure (e.g., the win ratio⁸, global ranking score⁹, and weighted composite outcome¹⁰).

The primary safety outcome (28-day all-cause mortality) is based on assessing non-inferiority and we specify the null hypothesis that the biomarker interventions are much worse compared with standard-of-care. The primary safety outcome will be analysed using mixed effect logistic regression models, using the same adjustments variables as the primary effectiveness analysis. We will derive risk difference from the fitted logistic regression model to compare the non-inferiority margin for the safety outcome. The unadjusted and adjusted estimates and the 95% confidence intervals will be compared with the non-inferiority margin to accept/reject the null hypothesis. Therefore, our primary effectiveness outcome (antibiotic duration) will not provide all the information as regards the treatment effect. Safety (28-day all-cause mortality) is paramount - only if an intervention arm is not worse than the control (standard care only) will it be acceptable.

Secondary outcomes will be assessed using an ITT approach. Continuous secondary outcomes will be analysed in the same way to the primary outcome and the categorical outcomes will be assessed using mixed effects logistic regression models. Time-to-event outcomes will be analysed using Cox

proportional hazards models. For all analyses, the adjusted effect estimates will be presented along with their associated 95% confidence interval (CI). In addition, the primary outcomes will also be analysed using Bayesian method as secondary analysis considering both non-informative and informative priors.

Exploratory sub-group analyses for primary effectiveness outcome will be reported using 99% confidence intervals. Linear mixed effect regression will be used with interaction terms (treatment group by sub-group) to estimate sub-group effects. The following sub-groups selected from a recent report about the management of infection causing sepsis in the NHS will be explored:

- Community-acquired pneumonia (CAP)
- Hospital-acquired pneumonia (HAP)
- Urinary tract infection (UTI)
- Intra-abdominal infection
- Infection with positive blood culture

In addition, community acquired, hospital acquired infections and SARS-COV-2 will be analysed as subgroup. Moreover, we will do the following subgroups analysis

- Sepsis vs Septic Shock
- Ward vs ICU where the intervention was stopped
- Surgery vs non-surgery on previous 72 hours

An exploratory analysis will be done to investigate weekend effect on the primary effectiveness outcome, the total duration of antibiotic treatment to 28 days from randomisation. Monitoring of the protocol processes and compliance measures is important in this trial (as detailed in section 4). These measures will be monitored and reported to the DMC throughout the trial. A final summary of the protocol processes and compliance will be presented at the end of the trial.

Handling missing data

Every effort will be made to minimise missing data both in baseline and outcome in the trial. Missing data will be assessed carefully. For the primary outcome (duration of antibiotics), start and stop dates for each course of antibiotics are required in order to compute the total duration for each participant. There will be no missing for start dates as the start dates and times will be the

randomisation dates and times. In the event that stop dates are unobtainable and thus missing, we will first look to see if the participant either withdrew completely or died. If so, we will use the withdrawal/death date as the stop date to estimate the duration for a particular course of antibiotics. If they did not withdraw or die, then we would impute the duration for that particular course of antibiotics using the mean duration of all antibiotics for the participant.

The SOFA score is to be collected baseline at day 3 and day 7, however, date may not be available on these particular days hence this score would be missing. In this situation, we'll use the value from the day before. If this is not available, then we'll use the value of the day after. If neither are available, then the value for that particular day will be missing.

Additional analyses

The primary analysis looks at the total duration of antibiotic days from randomisation to day 28. However, it is also of interest to assess the duration of antibiotics during the intervention phase only i.e., when the biomarker guidance is in use, and also from randomisation to ICU discharge. Therefore, additional analyses will estimate the treatment effect for the duration of antibiotic days during the intervention phase only and also to the point of ICU discharge. Similarly, we will also estimate the same treatment effects for the daily defined dose (DDD) secondary outcome.

The impact of COVID-19 pandemic on the trial will be assessed on completion of the trial. The baseline demographics and primary outcomes for participants recruited before COVID-19 will be compared to those recruited during COVID-19. The objective is to assess if there is any change in the population considered for the trial. In addition, for participants recruited during the COVID-19 pandemic period, baseline demographics and primary outcomes will be compared for COVID positive versus COVID negative participants. We also perform a sensitivity analysis by dropping COVID positive participants to see if COVID pandemic has an impact on the trial. We will do a sensitivity analysis to account for the non-compliant sites with PCT testing during intervention and follow-up phase. The plan is to run the primary outcome analysis excluding the non-compliant sites and see if any difference between the arms.

Safety

The frequency and percentages of serious adverse event and adverse event in the trial will be compared between the treatment arms using either chi-square test or Fisher's exact test for which the p-values will be reported. The event type, severity assessment, expectedness and relatedness to intervention will also be summarised by treatment arm.

Statistical software

The statistical analyses will be conducted in Stata SE version 17.0.

Health economic analysis plan

Decision-analysis modelling will be used to estimate for cohorts receiving each treatment protocol and standard care, the expected costs incurred and patient outcomes; patient outcomes will be evaluated in terms of quality-adjusted life years (QALYs). From these results, incremental cost per QALY ratios will be estimated for the two treatment protocols and standard care. These cost per QALY ratios will be used to form an efficiency frontier which will indicate the most cost-effective strategy at chosen cost per QALY thresholds. Results will be presented at two time periods: firstly, at the end of the study, as directed by the funder's brief, and secondly using a mathematical model employing a time horizon of a patient's lifetime, in order that the long-term consequences of avoided mortality or morbidity are appropriately captured.

The structure and methodology used within the mathematical model will be determined when the data are available in order to select the most appropriate approach. The model will be populated with trial data and will include key outcomes such as: rates of mortality; costs associated with length of stay for the index hospitalisation, including escalation of care; costs associated with readmission; and costs associated with antibiotic use. Extrapolations will be made based on the outcomes for each arm at the end of the study resulting in estimates of absolute costs and QALYs for each cohort conditional on the proportion of patients who are alive, and of these, the proportion that would have reduced health-related quality of life in the future. The modelling undertaken will be fully compliant with the current recommendations provided by the National Institute for Health and Care Excellence related to the methods of technology appraisal and will include any changes to this guidance before completion of the work. Extensive sensitivity analyses will be conducted in order to assess the robustness of the results to changes in key assumptions and parameter values.

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TEMPLATE TABLES

Version: 0.2

Contents

SECTION 1 - SCREENING THROUGH TO RANDOMISATION	19
SECTION 2 - PARTICIPANT BASELINE AND DEMOGRAPHIC DATA	23
SECTION 3 - PARTICIPANT FOLLOW-UP	29
SECTION 4 - INTERVENTION DATA	33
SECTION 5 - STUDY OUTCOME DATA	39
SECTION 6 - ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS.....	48

List of Tables

Table 1: Screening of potential participants summarised by recruitment centre	21
Table 2: Randomised participants summarised by recruitment centre and treatment.....	21
Table 3: Randomised participants summarised by treatment and randomisation strata ..	22
Table 4: Baseline demographic characteristics of all randomised participants by treatment group	24
Table 5: Initial care bundle at baseline summarised by treatment arm.....	25
Table 6: Baseline outcome measures.....	27
Table 7: Summary of process data at baseline summarised by treatment arm.....	27
Table 8: Follow-up rates throughout the trial.....	30
Table 9: Overall summary of withdrawals by treatment arm*	30
Table 10: Primary cause of death summarised by treatment arm	30
Table 11: Number of participant’s withdrawing completely throughout the trial	30
Table 12: Number of deaths throughout the trial.....	31
Table 13: Time from randomisation to death, withdrawal and follow-up summarised by treatment arm	31
Table 14: Daily data collection – summary of patient status	34
Table 15: Summary of blood sampling process by treatment arm.....	35
Table 16: Summary of advice produced and delivery to the clinical team by treatment arm	36
Table 17: Summary of the number of days usual care, stop advice and strong stop advice given at the participant level for those who went into the follow-up phase having received advice by treatment arm	36
Table 18: Summary of discharge data by treatment arm	37
Table 19: Summary of readmission data by treatment arm	38
Table 20: Summary of day 3 and day 7 SOFA score by treatment arm	40
Table 21: Summary of total duration of antibiotic treatment from randomisation to 28 days by treatment group (Primary outcome)	40
Table 22: Summary of 28-day all-cause mortality by treatment group (Primary outcome).	41
Table 23: Summary of secondary effectiveness and safety outcomes by treatment group	41
Table 24: Sub-group analyses on the duration of antibiotic days from randomisation to day 28.....	42
Table 25: Summary of total duration of antibiotic treatment during the intervention phase only by treatment group	43
Table 26: Summary of total Daily Defined Dose (DDD) from randomisation to 28 days by treatment group	44
Table 27: Summary of total Daily Defined Dose (DDD) during the intervention phase only by treatment group	44
Table 28: Baseline demographic characteristics comparing pre-COVID participants versus participants recruited during COVID	44
Table 29: Baseline outcome measures comparing pre-COVID participants versus participants recruited during COVID	46
Table 28: Summary of suspected clinically relevant antibiotic related events during inpatient stay (includes events during readmissions)	49

Table 29: Summary of suspected clinically relevant antibiotic related events post hospital discharge to 28 day follow-up.....	50
Table 30: Serious adverse events (SAE) summarised by treatment group	51
Table 31: Assessment of SAE's summarised by treatment group	51

List of Figures

Figure 1: CONSORT diagram	20
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SECTION 1 - SCREENING THROUGH TO RANDOMISATION

Figure 1: CONSORT diagram

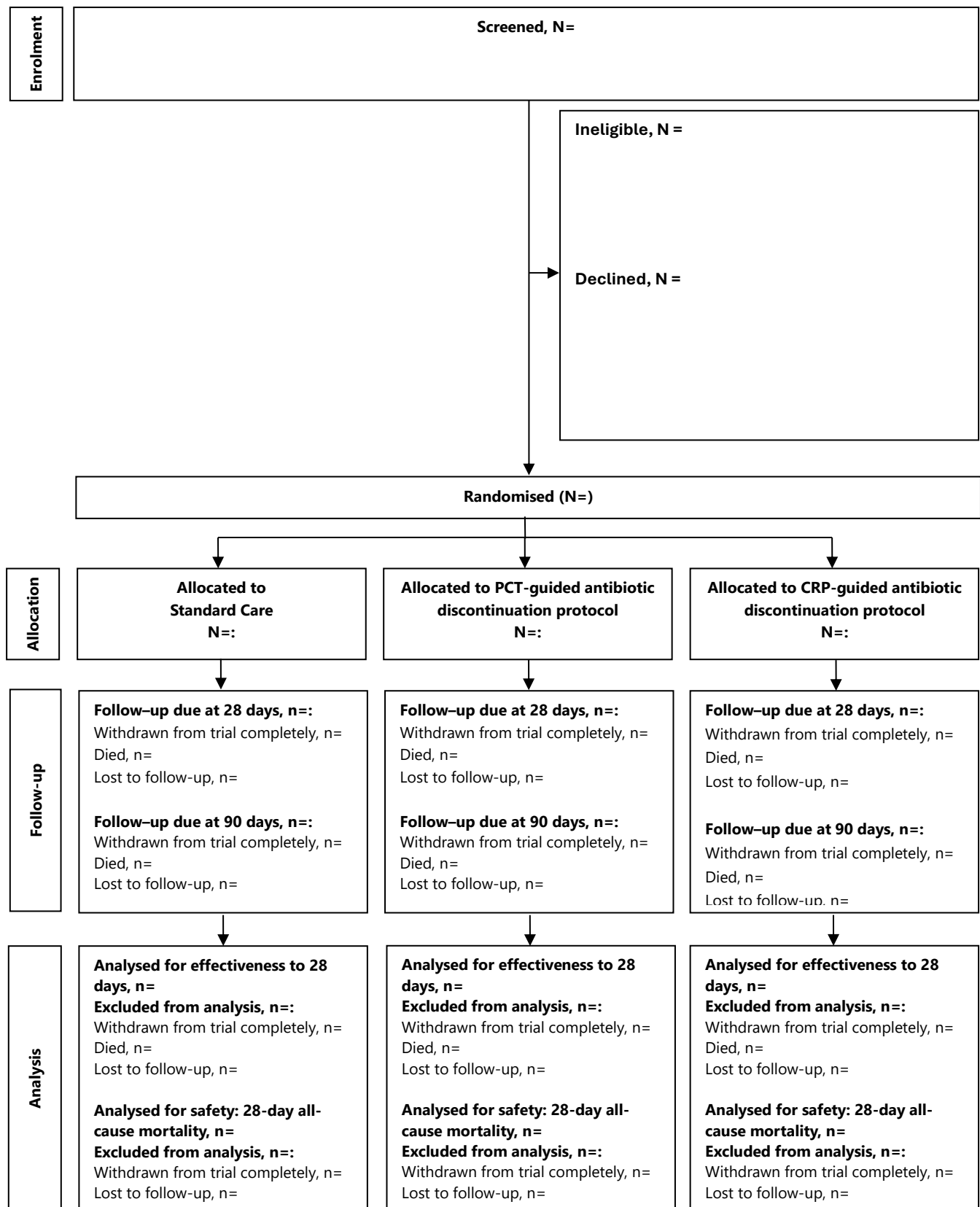


Table 1: Screening of potential participants summarised by recruitment centre

Recruitment Centre	Number screened	Total Number eligible	Total Number Ineligible	Total Number declined	Total Number consented & randomised
	n	n	n	n	n
	n	n	n	n	n
	n	n	n	n	n
	n	n	n	n	n
	n	n	n	n	n
Total:	N	N	N	N	N

Table 2: Randomised participants summarised by recruitment centre and treatment

Recruitment centre	Standard care	PCT	CRP	Total
	n (%)	n (%)	n (%)	n (%)
	n (%)	n (%)	n (%)	n (%)
	n (%)	n (%)	n (%)	n (%)
	n (%)	n (%)	n (%)	n (%)
	n (%)	n (%)	n (%)	n (%)
TOTAL:	N	N	N	N

Table 3: Randomised participants summarised by treatment and randomisation strata

Recruiting centre	Surgery within last 72 hours						No surgery within last 72 hours					
	Sepsis			Septic shock			Sepsis			Septic shock		
	Standard care	PCT	CRP	Standard care	PCT	CRP	Standard care	PCT	CRP	Standard care	PCT	CRP
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
TOTAL:	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

SECTION 2 - PARTICIPANT BASELINE AND DEMOGRAPHIC DATA

Table 4: Baseline demographic characteristics of all randomised participants by treatment group

	Standard care	PCT	CRP	TOTAL
Age (years)				
N	xx.xx	xx.xx	xx.xx	xx.xx
Mean (SD)	xx.xx	xx.xx	xx.xx	xx.xx
Median (IQR)	xx.xx	xx.xx	xx.xx	xx.xx
Missing	xx.xx	xx.xx	xx.xx	xx.xx
Gender				
Male	n (%)	n (%)	n (%)	n (%)
Female	n (%)	n (%)	n (%)	n (%)
Missing	n (%)	n (%)	n (%)	n (%)
Critical care admission category				
Medical	n (%)	n (%)	n (%)	n (%)
Elective surgical	n (%)	n (%)	n (%)	n (%)
Emergency surgical	n (%)	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)	n (%)
Missing	n (%)	n (%)	n (%)	n (%)
Origin				
Emergency department	n (%)	n (%)	n (%)	n (%)
Emergency admissions unit	n (%)	n (%)	n (%)	n (%)
Medical ward	n (%)	n (%)	n (%)	n (%)
Surgical ward	n (%)	n (%)	n (%)	n (%)
Another critical care unit	n (%)	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)	n (%)
Missing	n (%)	n (%)	n (%)	n (%)
Core body temperature (°C)				
N	n (%)	n (%)	n (%)	n (%)
Mean (SD)	n (%)	n (%)	n (%)	n (%)
Median (IQR)	n (%)	n (%)	n (%)	n (%)
Missing	n (%)	n (%)	n (%)	n (%)
White cell count (x10⁹/L)				
N	xx.xx	xx.xx	xx.xx	xx.xx
Mean (SD)	xx.xx	xx.xx	xx.xx	xx.xx
Median (IQR)	xx.xx	xx.xx	xx.xx	xx.xx
Missing	xx.xx	xx.xx	xx.xx	xx.xx
Infection acquirement				
Community acquired	n (%)	n (%)	n (%)	n (%)
Hospital acquired	n (%)	n (%)	n (%)	n (%)
Missing	n (%)	n (%)	n (%)	n (%)

Site of infection causing sepsis*				
Respiratory tract	n (%)	n (%)	n (%)	n (%)
If yes above, was it pneumonia	n (%)	n (%)	n (%)	n (%)
If yes above (pneumonia), was it ventilator related	n (%)	n (%)	n (%)	n (%)
Central nervous system	n (%)	n (%)	n (%)	n (%)
Skin and soft tissue	n (%)	n (%)	n (%)	n (%)
Is yes above, was it a surgical site infection	n (%)	n (%)	n (%)	n (%)
Central line related infection	n (%)	n (%)	n (%)	n (%)
Intra-abdominal	n (%)	n (%)	n (%)	n (%)
Urinary tract	n (%)	n (%)	n (%)	n (%)
If yes above, was it associated with a urinary catheter	n (%)	n (%)	n (%)	n (%)
Ear, nose and throat	n (%)	n (%)	n (%)	n (%)
Blood stream	n (%)	n (%)	n (%)	n (%)
If yes above, was it primary	n (%)	n (%)	n (%)	n (%)
Unknown focus	n (%)	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)	n (%)
Is there a causative microorganism identified for the infection causing sepsis				
No	n (%)	n (%)	n (%)	n (%)
Yes	n (%)	n (%)	n (%)	n (%)
Missing	n (%)	n (%)	n (%)	n (%)
Pathogens				
	n (%)	n (%)	n (%)	n (%)
	n (%)	n (%)	n (%)	n (%)

* Each site of infection is summarised separately for all participants. Therefore, it is possible that participants report more than one presumed site of infection causing sepsis.

Table 5: Initial care bundle at baseline summarised by treatment arm

	Standard care	PCT	CRP	TOTAL
Within 3 hours of presentation				
Was lactate level measured				

	No	n (%)	n (%)	n (%)	n (%)
	Yes	n (%)	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)	n (%)
Were blood cultures obtained prior to first antibiotics					
	No	n (%)	n (%)	n (%)	n (%)
	Yes	n (%)	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)	n (%)
Was intravenous crystalloid fluid administered for hypotension or raised lactate level					
	No	n (%)	n (%)	n (%)	n (%)
	Yes	n (%)	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)	n (%)
Were broad spectrum antibiotics administered					
	No	n (%)	n (%)	n (%)	n (%)
	Yes	n (%)	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)	n (%)
Was anti-fungal treatment used as part of the 3-hour treatment bundle					
	No	n (%)	n (%)	n (%)	n (%)
	Yes	n (%)	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)	n (%)
Was anti-viral treatment used as part of the 3-hour treatment bundle					
	No	n (%)	n (%)	n (%)	n (%)
	Yes	n (%)	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)	n (%)
Within 12 hours of presentation					
Source control (e.g. surgical/radiological abscess drainage, vascular line removal)					
	No	n (%)	n (%)	n (%)	n (%)
	Yes	n (%)	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)	n (%)
Within 24 hours of presentation					
Was the patient started on systemic steroids (IV or oral)					
	No	n (%)	n (%)	n (%)	n (%)
	Yes	n (%)	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)	n (%)

Was the patient put on renal replacement therapy				
	No	n (%)	n (%)	n (%)
	Yes	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)

Table 6: Baseline outcome measures

		Standard care	PCT	CRP	TOTAL
qSOFA	N	xx.xx	xx.xx	xx.xx	xx.xx
	Mean (SD)	xx.xx	xx.xx	xx.xx	xx.xx
	Median (IQR)	xx.xx	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx	xx.xx
SOFA	N	xx.xx	xx.xx	xx.xx	xx.xx
	Mean (SD)	xx.xx	xx.xx	xx.xx	xx.xx
	Median (IQR)	xx.xx	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx	xx.xx
APACHE II	N	xx.xx	xx.xx	xx.xx	xx.xx
	Mean (SD)	xx.xx	xx.xx	xx.xx	xx.xx
	Median (IQR)	xx.xx	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx	xx.xx

Table 7: Summary of process data at baseline summarised by treatment arm

		Standard care	PCT	CRP	TOTAL
Time from consent to randomisation (mins)	N	xx.xx	xx.xx	xx.xx	xx.xx
	Mean (SD)	xx.xx	xx.xx	xx.xx	xx.xx
	Median (IQR)	xx.xx	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx	xx.xx
Time from hospital admission to randomisation (mins)	N	xx.xx	xx.xx	xx.xx	xx.xx
	Mean (SD)	xx.xx	xx.xx	xx.xx	xx.xx
	Median (IQR)	xx.xx	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx	xx.xx
Time from ICU/HDU admission to randomisation					

	N	xx.xx	xx.xx	xx.xx	xx.xx
	Mean (SD)	xx.xx	xx.xx	xx.xx	xx.xx
	Median (IQR)	xx.xx	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx	xx.xx
Time from randomisation to first research blood sample taken for the trial					
	N	xx.xx	xx.xx	xx.xx	xx.xx
	Mean (SD)	xx.xx	xx.xx	xx.xx	xx.xx
	Median (IQR)	xx.xx	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx	xx.xx
Time from first research blood sample taken for the trial to first research blood sample delivered					
	N	xx.xx	xx.xx	xx.xx	xx.xx
	Mean (SD)	xx.xx	xx.xx	xx.xx	xx.xx
	Median (IQR)	xx.xx	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx	xx.xx

SECTION 3 - PARTICIPANT FOLLOW-UP

Table 8: Follow-up rates throughout the trial

Treatment Group	Time-point	Total to reach time point	Completed	Withdrawn completely	Deceased	Incomplete data
Standard Care	Baseline	N	n (%)	n (%)	n (%)	n (%)
	28 days	N	n (%)	n (%)	n (%)	n (%)
	90 days	N	n (%)	n (%)	n (%)	n (%)
PCT	Baseline	N	n (%)	n (%)	n (%)	n (%)
	28 days	N	n (%)	n (%)	n (%)	n (%)
	90 days	N	n (%)	n (%)	n (%)	n (%)
CRP	Baseline	N	n (%)	n (%)	n (%)	n (%)
	28 days	N	n (%)	n (%)	n (%)	n (%)
	90 days	N	n (%)	n (%)	n (%)	n (%)

Table 9: Overall summary of withdrawals by treatment arm*

Withdrawal decision	Withdrawn from intervention only but remains on follow-up			Withdrawn from intervention completely and will not be followed-up		
	Standard care	PCT	CRP	Standard care	PCT	CRP
Participant's decision						
Consultee's decision						
Clinical team decision						
Antibiotics stopped due to futility						
Determined to require long term antibiotics (>21 days) after randomisation						
Other						

* Summary of total number of withdrawal requests i.e. participants may have more than one request

Table 10: Primary cause of death summarised by treatment arm

	Standard care	PCT	CRP	TOTAL	P-value
Sepsis or sepsis related (including organ/multi-organ failure)	n (%)	n (%)	n (%)	N	
Not related to sepsis	n (%)	n (%)	n (%)	N	

Table 11: Number of participant's withdrawing completely throughout the trial

	Standard care	PCT	CRP	TOTAL	P-value
Post-randomisation to ICU discharge	n (%)	n (%)	n (%)	N	
ICU discharge to Hospital discharge	n (%)	n (%)	n (%)	N	
Hospital discharge to 28 day follow-up	n (%)	n (%)	n (%)	N	
28 day follow-up to 90 day follow-up	n (%)	n (%)	n (%)	N	
Overall	n (%)	n (%)	n (%)	N	

Table 12: Number of deaths throughout the trial

	Standard care	PCT	CRP	TOTAL	P-value
Post-randomisation to ICU discharge	n (%)	n (%)	n (%)	N	
ICU discharge to Hospital discharge	n (%)	n (%)	n (%)	N	
Hospital discharge to 28 day follow-up	n (%)	n (%)	n (%)	N	
28 day follow-up to 90 day follow-up	n (%)	n (%)	n (%)	N	
Overall	n (%)	n (%)	n (%)	N	

Table 13: Time from randomisation to death, withdrawal and follow-up summarised by treatment arm

	Standard care	PCT	CRP	PCT vs. Standard care Unadjusted mean difference (95% CI); p-value	CRP vs. Standard care Unadjusted mean difference (95% CI); p-value
Time from randomisation to withdrawing completely from trial					
N	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx		
Missing	xx.xx	xx.xx	xx.xx		
Time from randomisation to death					
N	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx		
Missing	xx.xx	xx.xx	xx.xx		
Time from randomisation to 28- day follow-up					
N	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx		
Missing	xx.xx	xx.xx	xx.xx		
Time from randomisation to 90-day follow-up					
N	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx		

Missing	xx.xx	xx.xx	xx.xx		
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SECTION 4 - INTERVENTION DATA

Table 14: Daily data collection – summary of patient status

	Standard care	PCT	CRP	PCT vs. Standard care Adjusted mean difference (95% CI)	CRP vs. Standard care Adjusted mean difference (95% CI)
Number of days as hospital inpatient					
N	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx		
Missing	xx.xx	xx.xx	xx.xx		
Number of days not a critical care inpatient					
N	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx		
Missing	xx.xx	xx.xx	xx.xx		
Number of days in level 3 unit (ICU)					
N	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx		
Missing	xx.xx	xx.xx	xx.xx		
Number of days level 2 unit (HDU)					
N	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx		
Missing	xx.xx	xx.xx	xx.xx		
Number of days deemed fit for hospital discharge by treating clinical team					
N	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx		
Missing	xx.xx	xx.xx	xx.xx		

Table 15: Summary of blood sampling process by treatment arm

	Standard care	PCT	CRP	Total	PCT vs. Standard care Adjusted estimate (95% CI)	CRP vs. Standard care Adjusted estimate (95% CI)
Duration from the time blood sample taken to the time blood analysis starts (minutes)						
N	xx.xx	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx	xx.xx		
Missing	xx.xx	xx.xx	xx.xx	xx.xx		
Time taken to analyse blood sample (minutes)						
N	xx.xx	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx	xx.xx		
Missing	xx.xx	xx.xx	xx.xx	xx.xx		
Duration of the entire procedure (Sample taken to analysis stop time), (minutes)						
N	xx.xx	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx	xx.xx		
Missing	xx.xx	xx.xx	xx.xx	xx.xx		
Participant had all research blood samples delivered to the laboratory on days a blood sample was taken						
Participants, N	n (%)	n (%)	n (%)	n (%)		
All samples delivered - n (%)	n (%)	n (%)	n (%)	n (%)		
Some missing - n (%)	n (%)	n (%)	n (%)	n (%)		
Of those with some missing above, how many days were missing						
1	n (%)	n (%)	n (%)	n (%)		
2	n (%)	n (%)	n (%)	n (%)		
3	n (%)	n (%)	n (%)	n (%)		
4	n (%)	n (%)	n (%)	n (%)		
5	n (%)	n (%)	n (%)	n (%)		
6	n (%)	n (%)	n (%)	n (%)		
7	n (%)	n (%)	n (%)	n (%)		
8	n (%)	n (%)	n (%)	n (%)		
9	n (%)	n (%)	n (%)	n (%)		

10	n (%)	n (%)	n (%)	n (%)	
13	n (%)	n (%)	n (%)		

Table 16: Summary of advice produced and delivery to the clinical team by treatment arm

	Standard care	PCT	CRP	Total	PCT vs. Standard care Adjusted estimate (95% CI)	CRP vs. Standard care Adjusted estimate (95% CI)
Advice produced and delivered (number of days)						
No. of days	n (%)	n (%)	n (%)	n (%)		
Yes - n (%)	n (%)	n (%)	n (%)	n (%)		
No- n (%)	n (%)	n (%)	n (%)	n (%)		
Missing - n (%)*	n (%)	n (%)	n (%)	n (%)		

* Either the samples weren't processed by the lab or a result had been produced by the lab but it was just not received by the trial/research team

Table 17: Summary of the number of days usual care, stop advice and strong stop advice given at the participant level for those who went into the follow-up phase having received advice by treatment arm

	Standard care	PCT	CRP	PCT vs. Standard care Adjusted estimate (95% CI)	CRP vs. Standard care Adjusted estimate (95% CI)
Usual care advice given, days					
N	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx		
Range	xx.xx	xx.xx	xx.xx		
Stop advice given, days					
N	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx		
Range	xx.xx	xx.xx	xx.xx		
Strong stop advice given, days					
N	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx		

Median (IQR)	xx.xx	xx.xx	xx.xx		
Range	xx.xx	xx.xx	xx.xx		
Stop or Strong stop advice (combined), days					
N	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx		
Range	xx.xx	xx.xx	xx.xx		

Table 18: Summary of discharge data by treatment arm

	Standard care	PCT	CRP	Total	PCT vs. Standard care Adjusted estimate (95% CI)	CRP vs. Standard care Adjusted estimate (95% CI)
Participant discharged alive from treating hospital						
No	n (%)	n (%)	n (%)	n (%)		
Yes	n (%)	n (%)	n (%)	n (%)		
Missing	n (%)	n (%)	n (%)	n (%)		
Discharge location						
Home	n (%)	n (%)	n (%)	n (%)		
Another hospital	n (%)	n (%)	n (%)	n (%)		
Nursing/residential home						
Other	n (%)	n (%)	n (%)	n (%)		
Missing	n (%)	n (%)	n (%)	n (%)		
Participant discharged on a course of systemic (IV/oral/rectal) antibiotics						
No	n (%)	n (%)	n (%)	n (%)		
Yes	n (%)	n (%)	n (%)	n (%)		
Missing	n (%)	n (%)	n (%)	n (%)		
Time from randomisation to discharge						
N	xx.xx	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx	xx.xx		

Median (IQR)	xx.xx	xx.xx	xx.xx	xx.xx	
Missing	xx.xx	xx.xx	xx.xx	xx.xx	

Table 19: Summary of readmission data by treatment arm

	Standard care	PCT	CRP	Total	PCT vs. Standard care Adjusted estimate (95% CI)	CRP vs. Standard care Adjusted estimate (95% CI)
Participant unscheduled readmission						
No	n (%)	n (%)	n (%)	n (%)		
Yes	n (%)	n (%)	n (%)	n (%)		
Missing	n (%)	n (%)	n (%)	n (%)		
Participant readmission to						
Same hospital	n (%)	n (%)	n (%)	n (%)		
Different hospital	n (%)	n (%)	n (%)	n (%)		
Missing	n (%)	n (%)	n (%)	n (%)		
Participant readmitted from						
Home	n (%)	n (%)	n (%)	n (%)		
Another hospital	n (%)	n (%)	n (%)	n (%)		
Nursing/residential home	n (%)	n (%)	n (%)	n (%)		
Other	n (%)	n (%)	n (%)	n (%)		
Missing	n (%)	n (%)	n (%)	n (%)		
Participant required antibiotics as part of reason for readmission or prior to readmission						
No	n (%)	n (%)	n (%)	n (%)		
Yes	n (%)	n (%)	n (%)	n (%)		
Missing	n (%)	n (%)	n (%)	n (%)		
Time from discharge to readmission						
N	xx.xx	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx	xx.xx		
Missing	xx.xx	xx.xx	xx.xx	xx.xx		

SECTION 5 - STUDY OUTCOME DATA

Table 20: Summary of day 3 and day 7 SOFA score by treatment arm

	Standard care	PCT	CRP	PCT vs. Standard care Adjusted mean difference (95% CI)	CRP vs. Standard care Adjusted mean difference (95% CI)
Day 3 SOFA score					
N	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx		
Missing	xx.xx	xx.xx	xx.xx		
Day 7 SOFA score					
N	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx		
Missing	xx.xx	xx.xx	xx.xx		

Primary effectiveness outcome

Table 21: Summary of total duration of antibiotic treatment from randomisation to 28 days by treatment group (Primary outcome)

	Standard care	PCT	CRP	PCT vs. Standard care Adjusted mean difference (95% CI)	CRP vs. Standard care Adjusted mean difference (95% CI)
Duration of antibiotic treatment to 28 days (days)					
N	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx		
Missing	xx.xx	xx.xx	xx.xx		

Primary safety outcome

Table 22: Summary of 28-day all-cause mortality by treatment group (Primary outcome)

	Standard care	PCT	CRP	PCT vs. Standard care Adjusted OR (95% CI)	CRP vs. Standard care Adjusted OR (95% CI)
Mortality status 28 days post randomisation					
Dead	n (%)	n (%)	n (%)		
Alive	n (%)	n (%)	n (%)		
Missing	n (%)	n (%)	n (%)		

Secondary effectiveness and safety outcomes to 28 days

Table 23: Summary of secondary effectiveness and safety outcomes by treatment group

	Standard care	PCT	CRP	PCT vs. Standard care Adjusted estimate (95% CI)	CRP vs. Standard care Adjusted estimate (95% CI)
Mortality status 90 days post randomisation					
Dead	n (%)	n (%)	n (%)		
Alive	n (%)	n (%)	n (%)		
Missing	n (%)	n (%)	n (%)		
Antibiotic dose (Daily Defined Dose)					
N	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx		
Missing	xx.xx	xx.xx	xx.xx		
Patient required unscheduled care escalation					
No	n (%)	n (%)	n (%)		
Yes	n (%)	n (%)	n (%)		
Missing	n (%)	n (%)	n (%)		
Number of unscheduled care escalations					
1	n (%)	n (%)	n (%)		

	2	n (%)	n (%)	n (%)		
	...	n (%)	n (%)	n (%)		
	Total	n	n	n		
	Missing	n (%)	n (%)	n (%)		
Patient had infection relapse/recurrence requiring further antibiotic treatment						
	No	n (%)	n (%)	n (%)		
	Yes	n (%)	n (%)	n (%)		
	Missing	n (%)	n (%)	n (%)		
Number of infection relapses/recurrences						
	1	n (%)	n (%)	n (%)		
	2	n (%)	n (%)	n (%)		
	...	n (%)	n (%)	n (%)		
	Total	n	n	n		
	Missing	n (%)	n (%)	n (%)		
Number of super-infections defined as new infection at a different anatomical site						
	1	n (%)	n (%)	n (%)		
	2	n (%)	n (%)	n (%)		
	...	n (%)	n (%)	n (%)		
	Total	n	n	n		
	Missing	n (%)	n (%)	n (%)		
Time from randomisation to first 'fit' for hospital discharge						
	N	xx.xx	xx.xx	xx.xx		
	Mean (SD)	xx.xx	xx.xx	xx.xx		
	Median (IQR)	xx.xx	xx.xx	xx.xx		
	Missing	xx.xx	xx.xx	xx.xx		

Subgroup analyses

Table 24: Sub-group analyses on the duration of antibiotic days from randomisation to day 28

Subgroups	Standard care	PCT	CRP	Effect estimate (95% CI)	PCT vs. Standard care	CRP vs. Standard care
	N; mean(sd)	N; mean(sd)	N; mean(sd)		Adjusted interaction effect (95% CI)	Adjusted interaction effect (95% CI)
Community-acquired pneumonia (CAP)						
	1					
	2					
Hospital-acquired pneumonia (HAP)						
	1					
	2					
Urinary tract infection (UTI)						
	1					
	2					
Intra-abdominal infection						
	1					
	2					
Infection with positive blood culture						
	1					
	2					
Severity (SOFA/APACHE II)						
	1					
	2					

ADDITIONAL ANALYSES

Table 25: Summary of total duration of antibiotic treatment during the intervention phase only by treatment group

	Standard care	PCT	CRP	PCT vs. Standard care Adjusted mean difference (95% CI)	CRP vs. Standard care Adjusted mean difference (95% CI)
Duration of antibiotic treatment (days)					
N	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx		
Missing	xx.xx	xx.xx	xx.xx		

Table 26: Summary of total Daily Defined Dose (DDD) from randomisation to 28 days by treatment group

	Standard care	PCT	CRP	PCT vs. Standard care Adjusted mean difference (95% CI)	CRP vs. Standard care Adjusted mean difference (95% CI)
Daily Defined Dose (DDD) to 28 days (days)					
N	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx		
Missing	xx.xx	xx.xx	xx.xx		

Table 27: Summary of total Daily Defined Dose (DDD) during the intervention phase only by treatment group

	Standard care	PCT	CRP	PCT vs. Standard care Adjusted mean difference (95% CI)	CRP vs. Standard care Adjusted mean difference (95% CI)
Daily Defined Dose (DDD)					
N	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx		
Missing	xx.xx	xx.xx	xx.xx		

Table 28: Baseline demographic characteristics comparing pre-COVID participants versus participants recruited during COVID

Characteristic	Pre-COVID	During Covid	Total	P-Value
Age (years)				
N	xx.xx	xx.xx	xx.xx	x.xx
Mean (SD)	xx.xx	xx.xx	xx.xx	
Median (IQR)	xx.xx	xx.xx	xx.xx	
Missing	xx.xx	xx.xx	xx.xx	
Gender				
Male	n (%)	n (%)	n (%)	x.xx
Female	n (%)	n (%)	n (%)	
Missing	n (%)	n (%)	n (%)	
Critical care admission category				
Medical	n (%)	n (%)	n (%)	x.xx
Elective surgical	n (%)	n (%)	n (%)	
Emergency surgical	n (%)	n (%)	n (%)	
Other	n (%)	n (%)	n (%)	
Missing	n (%)	n (%)	n (%)	
Origin				
Emergency department	n (%)	n (%)	n (%)	x.xx
Emergency admissions unit	n (%)	n (%)	n (%)	
Medical ward	n (%)	n (%)	n (%)	
Surgical ward	n (%)	n (%)	n (%)	
Another critical care unit	n (%)	n (%)	n (%)	
Other	n (%)	n (%)	n (%)	
Missing	n (%)	n (%)	n (%)	
Core body temperature (°C)				
N	n (%)	n (%)	n (%)	x.xx
Mean (SD)	n (%)	n (%)	n (%)	
Median (IQR)	n (%)	n (%)	n (%)	
Missing	n (%)	n (%)	n (%)	
White cell count (x10⁹/L)				
N	xx.xx	xx.xx	xx.xx	x.xx
Mean (SD)	xx.xx	xx.xx	xx.xx	
Median (IQR)	xx.xx	xx.xx	xx.xx	
Missing	xx.xx	xx.xx	xx.xx	
Infection acquirement				
Community acquired	n (%)	n (%)	n (%)	x.xx
Hospital acquired	n (%)	n (%)	n (%)	
Missing	n (%)	n (%)	n (%)	
Site of infection causing sepsis*				
Respiratory tract	n (%)	n (%)	n (%)	x.xx

If yes above, was it pneumonia	n (%)	n (%)	n (%)	x.xx
If yes above (pneumonia), was it ventilator related	n (%)	n (%)	n (%)	x.xx
Central nervous system	n (%)	n (%)	n (%)	x.xx
Skin and soft tissue	n (%)	n (%)	n (%)	x.xx
Is yes above, was it a surgical site infection	n (%)	n (%)	n (%)	x.xx
Central line related infection	n (%)	n (%)	n (%)	x.xx
Intra-abdominal	n (%)	n (%)	n (%)	x.xx
Urinary tract	n (%)	n (%)	n (%)	x.xx
If yes above, was it associated with a urinary catheter	n (%)	n (%)	n (%)	x.xx
Ear, nose and throat	n (%)	n (%)	n (%)	x.xx
Blood stream	n (%)	n (%)	n (%)	x.xx
If yes above, was it primary	n (%)	n (%)	n (%)	x.xx
Unknown focus	n (%)	n (%)	n (%)	x.xx
Other	n (%)	n (%)	n (%)	x.xx
Is there a causative microorganism identified for the infection causing sepsis				
No	n (%)	n (%)	n (%)	x.xx
Yes	n (%)	n (%)	n (%)	
Missing	n (%)	n (%)	n (%)	
Pathogens				
	n (%)	n (%)	n (%)	x.xx
	n (%)	n (%)	n (%)	

* Each site of infection is summarised separately for all participants. Therefore, it is possible that participants report more than one presumed site of infection causing sepsis.

Table 29: Baseline outcome measures comparing pre-COVID participants versus participants recruited during COVID

Outcome	Pre-COVID	During Covid	Total	P-Value	
qSOFA	N			x.xx	
	Mean (SD)	xx.xx	xx.xx		xx.xx
	Median (IQR)	xx.xx	xx.xx		xx.xx
	Missing	xx.xx	xx.xx		xx.xx

SOFA				x.xx	
	N	xx.xx	xx.xx		xx.xx
	Mean (SD)	xx.xx	xx.xx		xx.xx
	Median (IQR)	xx.xx	xx.xx		xx.xx
	Missing	xx.xx	xx.xx	xx.xx	
APACHE II				x.xx	
	N	xx.xx	xx.xx		xx.xx
	Mean (SD)	xx.xx	xx.xx		xx.xx
	Median (IQR)	xx.xx	xx.xx		xx.xx
	Missing	xx.xx	xx.xx	xx.xx	

SECTION 6 - ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Table 30: Summary of suspected clinically relevant antibiotic related events during inpatient stay (includes events during readmissions)

	Standard care	PCT	CRP	Total	PCT vs. Standard care Adjusted estimate (95% CI)	CRP vs. Standard care Adjusted estimate (95% CI)
Number of days patients experienced a suspected clinically relevant antibiotic related event						
N	xx.xx	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx	xx.xx		
Missing	xx.xx	xx.xx	xx.xx	xx.xx		
Number of patients experiencing each of the following events						
Anaphylaxis	n (%)	n (%)	n (%)	n (%)		
Gastrointestinal	n (%)	n (%)	n (%)	n (%)		
Haematological	n (%)	n (%)	n (%)	n (%)		
Hepatobiliary	n (%)	n (%)	n (%)	n (%)		
Renal	n (%)	n (%)	n (%)	n (%)		
Neurological	n (%)	n (%)	n (%)	n (%)		
Dermatological	n (%)	n (%)	n (%)	n (%)		
Cardiac	n (%)	n (%)	n (%)	n (%)		
Muscular	n (%)	n (%)	n (%)	n (%)		
Other	n (%)	n (%)	n (%)	n (%)		
Missing	n (%)	n (%)	n (%)	n (%)		
Patient experienced proven new Clostridium difficile diarrhoeal infection						
N	xx.xx	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx	xx.xx		
Missing	xx.xx	xx.xx	xx.xx	xx.xx		
Patient experienced a proven new infection with a multi-drug resistant organism						
N	xx.xx	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx	xx.xx		

Median (IQR)	xx.xx	xx.xx	xx.xx	xx.xx	
Missing	xx.xx	xx.xx	xx.xx	xx.xx	

Table 31: Summary of suspected clinically relevant antibiotic related events post hospital discharge to 28 day follow-up

	Standard care	PCT	CRP	Total	PCT vs. Standard care Adjusted estimate (95% CI)	CRP vs. Standard care Adjusted estimate (95% CI)
Number of days patients experienced a suspected clinically relevant antibiotic related event						
N	xx.xx	xx.xx	xx.xx	xx.xx		
Mean (SD)	xx.xx	xx.xx	xx.xx	xx.xx		
Median (IQR)	xx.xx	xx.xx	xx.xx	xx.xx		
Missing	xx.xx	xx.xx	xx.xx	xx.xx		
Number of patients experiencing each of the following events						
Anaphylaxis	n (%)	n (%)	n (%)	n (%)		
Gastrointestinal	n (%)	n (%)	n (%)	n (%)		
Haematological	n (%)	n (%)	n (%)	n (%)		
Hepatobiliary	n (%)	n (%)	n (%)	n (%)		
Renal	n (%)	n (%)	n (%)	n (%)		
Neurological	n (%)	n (%)	n (%)	n (%)		
Dermatological	n (%)	n (%)	n (%)	n (%)		
Cardiac	n (%)	n (%)	n (%)	n (%)		
Muscular	n (%)	n (%)	n (%)	n (%)		
Other	n (%)	n (%)	n (%)	n (%)		
Missing	n (%)	n (%)	n (%)	n (%)		
Patient experienced proven new Clostridium difficile diarrhoeal infection						
No	n (%)	n (%)	n (%)	n (%)		
Yes	n (%)	n (%)	n (%)	n (%)		
Missing	n (%)	n (%)	n (%)	n (%)		
Patient experienced a proven new infection						

with a multi-drug resistant organism	No	n (%)	n (%)	n (%)	n (%)		
	Yes	n (%)	n (%)	n (%)	n (%)		
	Missing	n (%)	n (%)	n (%)	n (%)		

Table 32: Serious adverse events (SAE) summarised by treatment group

		Standard care	PCT	CRP	Total
SAE's					
	Number of SAE's reported	n (%)	n (%)	n (%)	n (%)
Reason Serious Adverse Event deemed serious					
	Death	n (%)	n (%)	n (%)	n (%)
	Life-threatening	n (%)	n (%)	n (%)	n (%)
	Hospitalisation or prolongation of existing hospitalisation	n (%)	n (%)	n (%)	n (%)
	Persistent or significant disability or incapacity	n (%)	n (%)	n (%)	n (%)
	Congenital anomaly/birth defect	n (%)	n (%)	n (%)	n (%)
	Other	n (%)	n (%)	n (%)	n (%)
SAE severity assessment					
	Mild	n (%)	n (%)	n (%)	n (%)
	Moderate	n (%)	n (%)	n (%)	n (%)
	Severe	n (%)	n (%)	n (%)	n (%)
	Fatal/life threatening	n (%)	n (%)	n (%)	n (%)

Table 33: Assessment of SAE's summarised by treatment group

Assessment of SAE's		Standard care	PCT	CRP	TOTAL
SAE related to trial intervention:					
	Definitely	n (%)	n (%)		n (%)
	Probably	n (%)	n (%)		n (%)
	Possibly	n (%)	n (%)		n (%)
	Unlikely	n (%)	n (%)		n (%)
	Unrelated	n (%)	n (%)		n (%)
Expectedness of SAE:					
	Expected	n (%)	n (%)		n (%)
	Unexpected	n (%)	n (%)		n (%)
Outcome of event:					
	Resolved – no sequelae	n (%)	n (%)		n (%)
	Resolved – with sequelae	n (%)	n (%)		n (%)

	Unresolved	n (%)	n (%)		n (%)
	Death	n (%)	n (%)		n (%)