Statistical analysis plan for the HEAT trial: a multicentre randomised placebo-controlled trial of intravenous paracetamol in intensive care unit patients with fever and infection

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ABSTRACT

Background and objective: We describe the statistical analysis plan (SAP) for the Permissive Hyperthermia through Avoidance of Paracetamol in Known or Suspected Infection in the Intensive Care Unit (HEAT) trial, a 700-patient, prospective, randomised, Phase 2b, multicentre, double-blind, parallel-groups, placebo-controlled trial of paracetamol administration for the treatment of fever in critically ill patients with known or suspected infection.

Methods: The data fields described are those outlined in the study protocol published previously. We describe the plan for the presentation and comparison of baseline characteristics, process measures and outcomes. We describe baseline characteristics, and define and categorise trial outcomes according to their assigned importance.

Results and conclusions: We developed an SAP for the HEAT trial, and produced a mock Consolidated Standards of Reporting Trials diagram and tables. Our prespecified SAP accords with high-quality standards of internal validity and should minimise future analysis bias.

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This article outlines the statistical analysis plan for the Permissive Hyperthermia through Avoidance of Paracetamol in Known or Suspected Infection in the Intensive Care Unit (HEAT) trial; a multicentre, double-blind, randomised, placebo-controlled trial of intravenous (IV) paracetamol in intensive care unit patients with fever and known or suspected infection.[1]

This trial is endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG). Publication of a statistical analysis plan (SAP) before analysis of study data has been used for previous randomised controlled trials conducted by the ANZICS CTG, including the Randomised Evaluation of Normal versus Augmented Level of Replacement Therapy (RENAL) study,[2] the Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study,[3] and the Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care (CHEST) study.[4] Use of a prespecified SAP in the HEAT study aims to reduce the risk of analysis bias arising from knowledge of the study findings as they emerge during analysis of the study data.[5]

The SAP for the HEAT trial was developed by the chief investigator (P Y) in consultation with the study statistician (M W) at the Medical Research Institute of New Zealand, before completion of the first interim analysis by the data safety and monitoring board (DSMB), and was approved by the study management committee.

Overview

Design

The HEAT trial is a prospective, Phase IIb, multicentre, parallel-groups, double-blind, randomised, placebo-controlled trial of IV paracetamol for the treatment of fever in critically ill patients with known or suspected infection. The primary outcome variable used in the study is "alive ICU-free days" to Day 28. The trial was prospectively registered (ACTRN12612000513819) and the study protocol has been previously published.[1]

Funding and support

The HEAT trial is primarily funded by a grant from the Health Research Council of New Zealand. In addition, funding has been provided by the Intensive Care Foundation and the Waikato Medical Research Foundation. The funding bodies had no input into the design or conduct of the trial or into the SAP, and all analyses and reports will be conducted independently of them. The George Institute for Global Health and the Medical Research Institute of New Zealand are providing subsidised project management and monitoring.

Table 1. Summary and time schedule of data to be collected in the electronic case report form

Time of study	Data collected
Baseline	Date and time of randomisation, demographic data, comorbid conditions, date and time of ICU admission, ICU admission source, physiological and laboratory data, physiological support received, sepsis status, microbiological data.
Day 0–Day 28	Peak temperature: Day 0–Day 28. Temperature: 6-hourly, Day 0–Day 7. Mean arterial pressure, heart rate, minute ventilation: 6-hourly, Day 0–Day 3; daily, Day 4–Day 7. Hours of individual ICU supports (inotropes/vasopressors, mechanical ventilation, RRT, other extracorporeal supports): Day 0–Day 28. Daily use of steroids, NSAIDs, aspirin, antimicrobial agents, physical cooling, study medication, open-label paracetamol: Day 0–Day 28. Creatinine, bilirubin, prothrombin time, AST or ALT: Day 0–Day 7. CRP, CK: Day 1, Day 3, Day 5, Day 7.
End of study	Vital status at Day 28 and Day 90, cause of death, ICU length of stay, hospital length of stay, ICU-free days, ICU support-free days, hospital-free days, mechanical ventilation support-free days, inotrope/vasopressor support-free days, RRT-free days.
Adverse events	Description, timing and resolution of adverse events from randomisation until Day 90.
Protocol deviations	Randomisation of an ineligible patient, use of an incorrect treatment pack, double randomisation, other deviations.

ICU = intensive care unit. RRT = renal replacement therapy. NSAID = non-steroidal anti-inflammatory drug. AST = aspartate aminotransferase. ALT = alanine aminotransferase. CRP = C-reactive protein. CK = creatine kinase.

Study population and treatment

A total of 700 ICU patients aged 16 years or older will be enrolled in the study, at 22 centres in Australia and New Zealand. All potential participants are being screened for study eligibility. A patient who fulfils eligibility criteria is randomly assigned to receive IV paracetamol or placebo (5% dextrose) every 6 hours until he or she:

- develops a contraindication to paracetamol or permissive hyperthermia
- ceases antimicrobial therapy
- is discharged from the ICU
- reaches study Day 28 (672 hours after randomisation), or
- achieves resolution of fever.

Randomisation is achieved using a secure, password-protected, encrypted, internet-based randomisation system with 24-hour on-call back-up provided by the study management committee and project team. Randomisation is stratified by study centre.

Inclusion criteria

Patients being treated in one of the study ICUs are eligible for inclusion in the study if they meet all the following criteria:

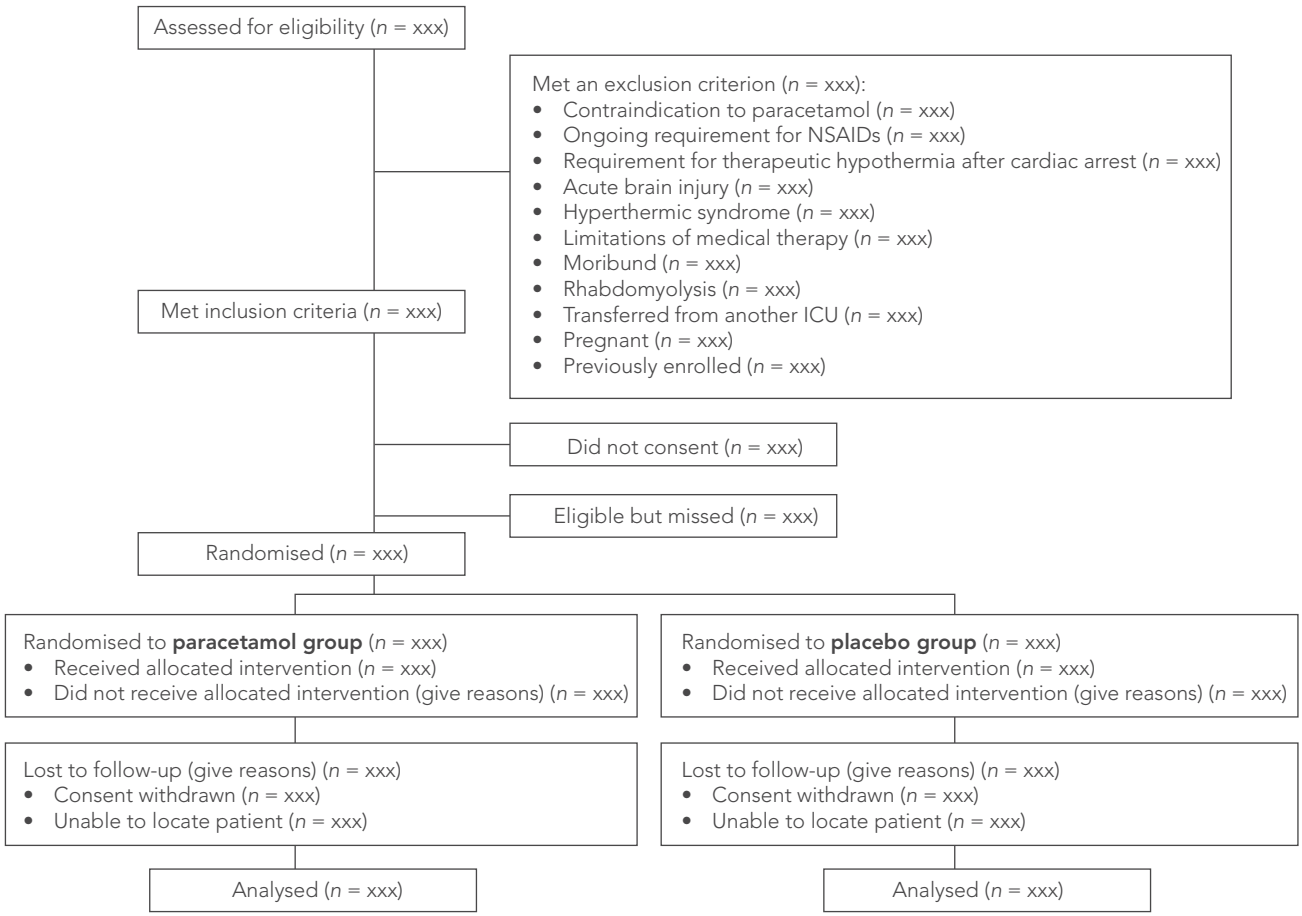
- they are aged 16 years or older
- their body temperature was $\geq 38°C$ in the ICU within the previous 12 hours, and
- they are receiving antimicrobial therapy for a known or suspected infection.

Exclusion criteria

Patients are excluded from the study if they meet one or more of the following criteria:

- their aspartate aminotransferase or alanine aminotransferase level is > 5 times the upper limit of normal, or their bilirubin level is > 2 times the upper limit of normal, or they have any other contraindication to receiving paracetamol 4 g/day
- there is a requirement for a non-steroidal anti-inflammatory drug or for aspirin use in excess of 300 mg/day
- admission to the ICU follows a cardiac arrest being treated with therapeutic hypothermia, or such a need is anticipated
- there is evidence of acute brain injury (any acute traumatic brain injury, subarachnoid haemorrhage, acute ischaemic stroke, acute intracerebral haemorrhage or acute intracranial infection) diagnosed during the current hospital admission
- there is a hyperthermic syndrome such as heat stroke, thyrotoxicosis, malignant hyperthermia, neuroleptic malignant syndrome or other drug-induced hyperthermia
- there is a limitation-of-therapy order in place or aggressive treatment is deemed unsuitable
- the patient is moribund and death is perceived to be imminent (within 24 hours)
- rhabdomyolysis is present and deemed clinically significant
- the patient was transferred from another ICU, fulfilled all inclusion criteria in the other ICU, and spent > 12 hours in the other ICU before transfer
- the patient is pregnant, or
- the patient was previously randomised into the HEAT trial, or was previously eligible for enrolment during the current ICU admission but not enrolled in the study.

Figure 1. Flow of participants through the HEAT trial



HEAT = Permissive Hyperthermia through Avoidance of Paracetamol in Known or Suspected Infection in the Intensive Care Unit trial. NSAIDs = non-steroidal anti-inflammatory drugs.

Aims

Primary aim

Our primary aim is to estimate the difference in alive ICU-free days to Day 28 attributable to the administration of paracetamol in a population of ICU patients with fever and known or suspected infection.

Secondary aims

Our secondary aims are to:

- estimate the difference in the 28-day and 90-day all-cause mortality attributable to paracetamol administration, and to use the estimates for a sample size calculation for a Phase III study
- estimate the effect of paracetamol administration on ICU and hospital support requirements
- estimate the effect of paracetamol administration on body temperature, development of liver dysfunction, creatinine levels, and C-reactive protein (CRP) levels
- determine if there are differences in outcomes in four patient subgroups (those with severe hyperthermia at baseline [temperature ⩾ 39°C]; ICU-acquired versus community-acquired versus other hospital-acquired infection; septic shock; and those taking aspirin)
- estimate the likely recruitment rate at Australian and New Zealand sites for a Phase III trial using the current study design.

Definitions of outcome variables

Primary outcome variable

Our primary outcome variable is alive ICU-free days to Day 28.[6] The number of ICU-free days will be calculated as 28 minus the number of days or part-days in ICU (excluding days of ICU readmission). All patients who die before the Day 90 follow-up will be counted as having zero ICU-free days, on the basis that

Table 2. Baseline patient characteristics

Characteristic	Paracetamol	Placebo
Age (years)	xx (SD)	xx (SD)
Sex (male)	*n* (%)	*n* (%)
Weight (kg)	xx (SD)	xx (SD)
New Zealand–European ethnicity	*n* (%)	*n* (%)
Australian–European ethnicity	*n* (%)	*n* (%)
Maori ethnicity	*n* (%)	*n* (%)
Pacific Islander ethnicity	*n* (%)	*n* (%)
Aboriginal or Torres Strait Islander ethnicity	*n* (%)	*n* (%)
Other ethnicity	*n* (%)	*n* (%)
Comorbid conditions		
Cancer	*n* (%)	*n* (%)
Chronic pulmonary disease	*n* (%)	*n* (%)
Congestive heart failure	*n* (%)	*n* (%)
Diabetes	*n* (%)	*n* (%)
End-stage renal failure	*n* (%)	*n* (%)
HIV	*n* (%)	*n* (%)
Ischaemic heart disease	*n* (%)	*n* (%)
Severe neurological dysfunction	*n* (%)	*n* (%)
Intensive care unit admission data		
From emergency department	*n* (%)	*n* (%)
From hospital ward	*n* (%)	*n* (%)
From another intensive care unit	*n* (%)	*n* (%)
From another hospital*	*n* (%)	*n* (%)
From operating theatre after elective surgery	*n* (%)	*n* (%)
From operating theatre after emergency surgery	*n* (%)	*n* (%)
Time from admission to randomisation (hours)	xx (SD)	xx (SD)
Physiological and laboratory data		
Peak temperature, previous 24 hours (°C)	xx (SD)	xx (SD)
Mean arterial pressure (mmHg)	xx (SD)	xx (SD)
Heart rate (beats per minute)	xx (SD)	xx (SD)
Minute ventilation (breaths per minute)	xx (SD)	xx (SD)
Most recent creatinine (μmol/L)	xx (SD)	xx (SD)
Baseline pre-illness creatinine (μmol/L)	xx (SD)	xx (SD)
Creatine kinase (U/L)	xx (SD)	xx (SD)
Bilirubin (μmol/L)	xx (SD)	xx (SD)
Prothrombin time (seconds)	xx (SD)	xx (SD)
Aspartate aminotransferase (U/L)	xx (SD)	xx (SD)
Alanine aminotransferase (U/L)	xx (SD)	xx (SD)
C-reactive protein (mg/L)	xx (SD)	xx (SD)
APACHE-II score	xx (SD)	xx (SD)
Receiving physiological support (% yes)		
Inotropes or vasopressors	*n* (%)	*n* (%)
Invasive ventilation	*n* (%)	*n* (%)
Non-invasive ventilation	*n* (%)	*n* (%)
Renal replacement therapy	*n* (%)	*n* (%)
Other extracorporeal therapy	*n* (%)	*n* (%)
Steroid therapy	*n* (%)	*n* (%)
Aspirin therapy	*n* (%)	*n* (%)

APACHE = Acute Physiology and Chronic Health Evaluation. * Except from another intensive care unit.

they should be counted as having the worst possible outcome.

Secondary end points

The secondary outcome variables are, in order of importance:

Mortality and survival

- All-cause mortality at Day 90.
- All-cause mortality at Day 28.
- Survival time from randomisation to Day 90, with participants still alive after 90 days treated as censored at that time.

ICU and hospital support requirements

- ICU and hospital length-of-stay from time of randomisation censored at death or Day 90 (whichever is sooner).
- Hospital-free days, mechanical ventilation-free days, inotrope and vasopressor-free days and ICU support-free days will be assessed at Day 90. To be deemed ICU support-free, a patient must be free of any ICU support for an entire calendar day and must remain free from such supports until the time of physical discharge from the ICU. For hospital-free days, mechanical ventilation free-days, and inotrope and vasopressor-free days, the number of individual hours of particular supports will be used to calculate the number of support-free days to Day 28. All patients who die during study follow-up will be assigned zero "free days" for all "free day" outcome measures.

Physiological and biochemical outcome variables

- Mean and maximum axillary temperatures, measured using a Protec BX/144 digital thermometer (Protec Solutions).
- Proportion of patients who stop study treatment due to development of liver dysfunction (as defined in exclusion criteria).
- Mean CRP levels, as measured on Days 1, 4, 5 and 7.
- Proportion of patients with creatine kinase level > 5000 units on Day 1, 3, 5 or 7 will be compared.
- Highest creatinine level measured in the ICU in the first 7 days after randomisation.

Recruitment rate

Average weekly recruitment rate.

Analysis principles

Analyses will be by intention-to-treat. All statistical tests will be two-sided with an α of 0.05, except for the

Table 3. Microbiological and sepsis data

Variable	Paracetamol *n* (%)	Placebo *n* (%)
Sepsis status		
Sepsis	*n* (%)	*n* (%)
Severe sepsis	*n* (%)	*n* (%)
Septic shock	*n* (%)	*n* (%)
Where sepsis was acquired		
Community	*n* (%)	*n* (%)
Hospital (intensive care unit)	*n* (%)	*n* (%)
Hospital (outside intensive care unit)	*n* (%)	*n* (%)
Primary site of infection		
Lung	*n* (%)	*n* (%)
Abdomen	*n* (%)	*n* (%)
Pleura	*n* (%)	*n* (%)
Other thoracic site	*n* (%)	*n* (%)
Ear, nose, throat, teeth	*n* (%)	*n* (%)
Vascular catheter	*n* (%)	*n* (%)
Bone or joint	*n* (%)	*n* (%)
Skin or soft tissue	*n* (%)	*n* (%)
Urinary tract	*n* (%)	*n* (%)
Gynaecological site	*n* (%)	*n* (%)
Endocardium	*n* (%)	*n* (%)
Blood stream	*n* (%)	*n* (%)
Neutropenic sepsis	*n* (%)	*n* (%)
No clear source	*n* (%)	*n* (%)
Causative organisms		
Infecting organism identified	*n* (%)	*n* (%)
Blood culture positive	*n* (%)	*n* (%)
Gram-positive bacteria	*n* (%)	*n* (%)
Gram-negative bacteria	*n* (%)	*n* (%)
Other (fungi, viruses, etc)	*n* (%)	*n* (%)

primary outcome variable where a *P* of 0.0379 will be used to allow for appropriate α spending in the two planned interim analyses to preserve the overall α of 0.05 for the primary end point. All analyses will be conducted masked for treatment allocation. We will maintain allocation concealment until all analyses (including any post-hoc analyses) are completed.

Analyses for the primary outcome variable will be unadjusted. We will use sensitivity analysis incorporating adjustment for important prognostic variables (described below) for Day 90 mortality and survival, as described in subsequent sections. Some important participant characteristics will be the subject of possible subgroup analysis (described below). Whether or not the characteristics are associated with a different treatment outcome will be tested by an interaction term between the characteristic and the treatment. We will not impute missing values and, where there are missing values, we will use a complete case analysis. No adjustment of *P* values for multiple comparisons will be undertaken.

Table 4. Intensive care unit admission diagnoses

Diagnosis	Paracetamol *n* (%)	Placebo *n* (%)
Operative admission diagnoses		
Cardiovascular	*n* (%)	*n* (%)
Gastrointestinal	*n* (%)	*n* (%)
Gynaecological	*n* (%)	*n* (%)
Neurological	*n* (%)	*n* (%)
Orthopaedic	*n* (%)	*n* (%)
Renal	*n* (%)	*n* (%)
Respiratory	*n* (%)	*n* (%)
Trauma	*n* (%)	*n* (%)
Other postoperative	*n* (%)	*n* (%)
Non-operative admission diagnoses		
Cardiovascular	*n* (%)	*n* (%)
Gastrointestinal	*n* (%)	*n* (%)
Haematological	*n* (%)	*n* (%)
Metabolic	*n* (%)	*n* (%)
Neurological	*n* (%)	*n* (%)
Other medical diseases	*n* (%)	*n* (%)
Renal	*n* (%)	*n* (%)
Respiratory	*n* (%)	*n* (%)
Sepsis	*n* (%)	*n* (%)
Trauma	*n* (%)	*n* (%)

Design issues

Data collection follow-up

Table 1 shows a summary and time schedule of data to be collected; patient consent before randomisation may not be possible. If subsequent consent to the use of data is not provided, that patient's data (except for data related to consent) will be removed from the analysis. Censoring will only apply when there is no information available beyond a particular time, in which case the date of censoring applied will be the last day of contact with the patient, or the date of hospital discharge if no other information is available. Patients who withdraw consent to continue study treatment but consent to the use of their data will be analysed on an intention-to-treat basis.

Justification of the sample size

Our study is substantially larger than all previous studies of paracetamol in febrile, critically ill patients combined.[7,8] The sample size calculation for ICU-free survival to Day 28 is

Table 5. Primary outcome and key secondary outcome variables

Variable	Paracetamol	Placebo	Point estimate (95% CI)	Statistical significance
Primary outcome				
ICU-free days, median (IQR)	xx (xx–xx)	xx (xx–xx)	Difference in medians (95% CI)	*P*
Secondary outcomes				
Hospital-free days, median (IQR)	xx (xx–xx)	xx (xx–xx)	Difference in medians (95% CI)	*P*
Mechanical ventilation-free days, median (IQR)	xx (xx–xx)	xx (xx–xx)	Difference in medians (95% CI)	*P*
Inotrope-free or vasopressor-free days, median (IQR)	xx (xx–xx)	xx (xx–xx)	Difference in medians (95% CI)	*P*
RRT-free days, median (IQR)	xx (xx–xx)	xx (xx–xx)	Difference in medians (95% CI)	*P*
ICU support-free days, median (IQR)	xx (xx–xx)	xx (xx–xx)	Difference in medians (95% CI)	*P*
Day 28 mortality	*n* (%)	*n* (%)	Relative risk (unadjusted) (95% CI) Relative risk (adjusted) (95% CI)	*P* (unadjusted) *P* (adjusted)
Day 90 mortality	*n* (%)	*n* (%)	Relative risk (unadjusted) (95% CI) Relative risk (adjusted) (95% CI)	*P* (unadjusted) *P* (adjusted)

ICU = intensive care unit. IQR = interquartile range. RRT = renal replacement therapy.

based on an unpaired *t* test. Based on our pilot work, we estimate that the baseline alive ICU-free days to Day 28 is 16 days (SD, 9.2 days).[9] The consensus of the investigators is that a difference of 2.5 days is likely to represent a clinically important difference. We previously identified that the distribution of alive ICU-free days to Day 28 is not Gaussian.[9] To account for this, we inflated our sample size, which is based on a *t* test, by 15% to allow for subsequent use of a Mann–Whitney test for analysis.[10] A sample size of 700 patients thus has 80% power to allow us to detect a difference of 2.2 days, with an α of 0.05, allowing for a 5% dropout rate. In a secondary power calculation, we determined that our sample size will provide 80% power to detect a reduction in 28-day mortality from a baseline mortality of 16% to a mortality of 9% at an α of 0.05.

Interim analyses and the DSMB

The DSMB will review data at interim analyses planned after data collection has been completed for one-third and two-thirds of the enrolled patients. For the planned interim analyses after one-third and two-thirds of the data collection, we will use a *P* of 0.00021 and 0.01189, respectively, to define early stopping criteria. We will use a group sequential α-spending function, calculated using the O'Brien–Fleming method, with two-sided symmetric bounds.

The DSMB will also review summaries of adverse events. There is potential for Type 1 error in examining multiple adverse events, there is considerable existing knowledge about the safety of paracetamol,[11] and paracetamol is commonly used in routine practice.[11] Therefore, the guidelines from the management committee indicate that advice to stop the clinical trial early on the basis of reported adverse events should be given only in exceptional circumstances.

The DSMB consists of three members: Jeff Lipman, Chair (Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital), Michael Bailey (Australian and New Zealand Intensive Care Research Centre), and Brian Anderson (Paediatric Intensive Care Unit, Auckland District Health Board). The members of the DSMB have changed since the study protocol was published,[1] but the current committee was established shortly after the commencement of trial recruitment and met before any interim analyses and before any serious adverse events or protocol deviations had been reported.

Statistical analysis

Trial profile

The flow of patients through the study will be presented in a Consolidated Standards of Reporting Trials (CONSORT) diagram[12] (Figure 1).

Characteristics of patients and baseline comparisons

Baseline characteristics will be presented by treatment group (Table 2). Discrete variables will be presented as numbers and percentages (calculated using the number of patients for whom data are available). When values are missing, the denominator will be stated. Continuous variables will be summarised as a mean (with SD), and a minimum, maximum and median (with interquartile range) will be provided for each variable in a supplementary appendix. Microbiological and sepsis status data will

be reported in a separate table from other baseline data, as outlined in Table 3. ICU admission diagnoses will be presented in a supplementary appendix as shown in Table 4.

Concomitant treatments

In this study, open-label paracetamol use is only allowed in patients who have completed the course of study medication. Any use of open-label paracetamol in the ICU will be recorded daily until Day 28 for patients who remain in ICU. Similarly, the use of treatments that alter temperature management will be recorded: physical cooling measures, non-steroidal anti-inflammatory drugs, low-dose aspirin and steroid use. Time until cessation of antibiotics, for paracetamol and placebo groups, will be reported as a process measure in a time-to-event analysis with data truncated at death or ICU discharge.

Consent and permanent discontinuation of study medication

Patient consent type will be recorded and categorised into the following groups, with number and percentage:

- prior informed consent from the patient
- prior informed consent from a legal surrogate
- delayed informed consent from the patient
- delayed informed consent from a legal surrogate
- consent from another legal body before the patient's consent
- no consent obtained; data withdrawn.

The reason for discontinuation of study medication will be documented in all patients and will be categorised into the following groups, with number and percentage:

- discharge from the ICU
- resolution of fever
- cessation of antimicrobials
- reached Day 28
- withdrawal of consent while study drug is indicated
- acute myocardial infarction
- rhabdomyolysis
- liver dysfunction
- accidental administration of non-study paracetamol
- other treatment-related adverse event
- focus changed to palliative care because death imminent
- death
- clinician's decision to withdraw for other reasons
- other reason.

Description of analyses

Primary outcome

A Mann–Whitney test will be used as the primary analysis of the effect of treatment allocation on alive ICU-free days to Day 28. Data will be presented as point estimates of the difference in medians between the treatment groups, with 95% CI, calculated using the Hodges–Lehmann method.[13]

Secondary outcomes

The risks of death at Day 28 and Day 90 will be calculated by logistic regression, estimated as odds ratios with 95% CI. For Day 90 mortality, multivariate logistic regression analysis will be used to adjust for important potential predictors of outcome: age, ICU admission source and Acute Physiology and Chronic Health Evaluation II score. Survival time from randomisation to Day 90 will be analysed using the log-rank test and supplemented by a Cox proportional hazards model to calculate hazard ratios for survival. The proportional hazard assumption across treatment arms will be checked graphically using a log-cumulative hazard plot or the addition of time-dependent covariate to the model. Probability of survival by treatment group will also be presented as Kaplan–Meier curves.

ICU and hospital length-of-stay will be calculated from randomisation until discharge, death, or Day 90 (whichever comes first). In addition to comparing the ICU and hospital length-of-stay between treatment groups for all patients, we will also report ICU and hospital length-of-stay for survivors and non-survivors separately. Data distribution assumptions will be tested for normality. If data are normally distributed, comparisons between groups will be undertaken using an unpaired *t* test. If normality assumptions are not met, we plan to compare groups using the Mann–Whitney test and Hodges–Lehmann confidence intervals.

Hospital-free days, mechanical ventilation-free days, inotrope-free and vasopressor-free days, renal replacement therapy-free days, and ICU support-free days will be compared between treatment groups using the Wilcoxon rank-sum test. The effect of treatment will be represented using point estimates of the difference in medians between the treatment groups, with 95% CI, calculated using the Hodges–Lehmann method.

Peak and mean temperature measurements will be analysed in mixed linear models incorporating the peak temperature in the 24 hours before randomisation as a fixed effect covariate, to account for the repeated measurements. Different possible covariance matrices will be fitted and assessed by the Akaike information criterion to find a

suitable structure less complex than a full unstructured matrix. CRP levels will be analysed similarly.

The highest recorded creatinine level during the first 7 days in the ICU will be compared between treatment groups, using a regression approach incorporating baseline creatinine as a covariate. The proportion of patients whose creatine kinase level, measured on Day 1, Day 3, Day 5 and Day 7, exceeds 5000 units will be compared between treatment groups by logistic regression.

Subgroups

The primary outcome for planned subgroup analyses will be 28 day ICU-free survival. Subgroup analyses are exploratory analyses which aim to generate new hypotheses. Four prespecified subgroup analyses will be undertaken, for patients:

- with severe hyperthermia at baseline (temperature $\geqslant 39°C$)
- with ICU-acquired, community-acquired or other hospital-acquired infection
- with septic shock
- taking aspirin.

Presentation of outcome data

We will present principal outcome data as shown in Table 5; daily temperature data in a figure that compares the mean and peak temperatures between treatment groups over time; and survival time up to Day 90, by treatment group, as Kaplan–Meier survival curves.

Conclusion

We propose that this prespecified SAP accords with high quality standards of internal validity and should minimise future analysis bias.

Competing interests

None declared.

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