Statistical analysis plan for the Australasian Resuscitation In Sepsis Evaluation: FLUid or vasopressors In emergency Department Sepsis (ARISE FLUIDS) trial

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Abstract

Background: The Australasian Resuscitation In Sepsis Evaluation: FLUid or vasopressors In emergency Department Sepsis (ARISE FLUIDS) trial is a 1,000-participant international multi-centre randomised controlled trial comparing restricted intravenous (IV) fluid volume and earlier introduction of vasopressors (vasopressor strategy) to larger initial IV fluid volume and later introduction of vasopressors if required (fluids strategy), in adults with early septic shock.

Objective: To describe the pre-specified ARISE FLUIDS statistical analysis plan (SAP).

Methods: This SAP was written prior to completion of recruitment. All authors were blinded to treatment allocations. We describe the planned analysis of the primary, secondary, tertiary, and safety outcomes, as well as a secondary Bayesian analysis and sub-group analysis.

Results: The primary outcome is days alive and out of hospital at 90 days (DAOH-D90) post-randomisation and the difference in medians between the two treatment groups will be estimated using a linear quantile mixed-effects regression model. Secondary outcomes include duration of survival censored at day 90, ventilator-, vasopressor-, and acute renal replacement-free days censored at day 28, and death or disability at 6- and 12-months.

Conclusion: ARISE FLUIDS will compare the effects of a vasopressor vs. fluids strategy on days alive and out of hospital at 90 days in adults with early septic shock. The prespecified SAP is reported here to mitigate analysis bias.

Introduction

The optimal approach to haemodynamic resuscitation in patients with septic shock is uncertain. International consensus guidelines give a weak recommendation for the administration of at least 30 mL/kg of intravenous (IV) fluid for newly diagnosed septic shock with the addition of vasoactive agents for persistent shock refractory to further fluid resuscitation[1]. However, the quality of evidence for this recommendation is low, and there is emerging evidence of harm associated with excessive IV fluids[2]. This has led to variation in practice in the management of patients presenting to Emergency Departments (ED) with septic shock[3].

The Australasian Resuscitation In Sepsis Evaluation: FLUid or vasopressors In emergency Department Sepsis (ARISE FLUIDS) trial will provide high-quality evidence to inform international guidelines on the initial haemodynamic resuscitation of patients presenting to the Emergency Department with septic shock.

We describe the pre-specified ARISE FLUIDS statistical analysis plan (SAP), written by the chief investigators and blinded trial statisticians. This SAP has been finalised prior to completion of patient enrolment.

Study design

ARISE FLUIDS is a multi-centre, open-label, parallel group, two-arm, 1:1 randomised controlled trial that compares a strategy of restricted IV fluid volume and earlier introduction of vasopressors (vasopressor strategy) to a strategy which involves a larger initial IV fluid volume and later introduction of vasopressors if required (fluids strategy), in adult patients with early septic shock. Recruitment commenced in October 2021 and is

projected to finish in late 2025. A total of 1,000 patients will be recruited from 49 participating hospitals in Australia, New Zealand, and Ireland.

The patient population, inclusion and exclusion criteria, randomisation and blinding, study interventions, and data collection and management are described in the published protocol[4].

Primary outcome

The primary outcome is the number of days alive and out of hospital to 90 days post-randomisation (DAOH-D90). For each patient, days alive and out of hospital, that is, days not in an acute care hospital in the index hospitalisation or any subsequent acute hospital overnight readmissions, between randomisation and Day 90 will be subtracted from 90 to calculate their number of DAOH-D90 post randomisation. Participants who die on or prior to day 90 will be assigned zero DAOH-D90[5,6].

Secondary outcomes

1. All-cause mortality at 28 and 90 days post-randomisation
2. Time from randomisation until death (to day 90)
3. Days alive and at home at 90 days post-randomisation[&]
4. Ventilator-free days to day 28 post-randomisation (invasive ventilation only)^
5. Vasopressor-free days to day 28 post-randomisation^
6. Acute renal replacement therapy-free days to day 28 post-randomisation^
7. Death or disability at 6- and 12-months post-randomisation*

Tertiary outcomes

1. Incidence and duration of invasive mechanical ventilation

2. Incidence and duration of vasopressor support
3. Incidence and duration of acute renal replacement therapy
4. ED duration of stay in hours
5. ICU duration of stay in days
6. Hospital duration of stay in days
7. In hospital mortality (censored at 90 days)
8. Mortality to 6- and 12- months post-randomisation*
9. Quality of life at 6- and 12- months using EQ5D-5L*
10. Cost-effectiveness at 12-months measured as cost/QALY*

[&] Days alive and at home is return to pre-admission place of residence as a consumer informed outcome of importance that is similar but more difficult to measure than DAOH-D90. For each patient, days at home (not in the index hospitalisation, acute hospital readmission, inpatient rehabilitation, in a nursing home) between randomisation and Day 90 will be subtracted from 90 to calculate their number of days alive and at home to day 90 post randomisation. Patients who die on or prior to day 90 will be assigned zero days alive and at home.

^ Patients who die on or prior to day 28 will be assigned zero organ-support free days. Patients who never receive any listed organ-support therapies will be assigned 28 organ-support free days.

* Disability determined by the World Health Organisation Disability Assessment Schedule version 2.0 (WHODAS 2.0) questionnaire. Death or moderate-to-severe disability (i.e., WHODAS score $\geqslant$25%); To be reported separately when 12-month follow up complete.

Safety outcomes

1. Complication related to the administration of vasopressors via a peripheral line from randomisation up to 24 hours post-randomisation (tissue necrosis, other)
2. Complication related to CVC/PICC line inserted from randomisation up to 24 hours post-randomisation (pneumothorax, arterial puncture, infection, thrombosis, other)
3. Development of acute pulmonary oedema related to the study intervention in the opinion of the treating clinician.
4. Development of ischaemic complications related to the study intervention in the opinion of the treating clinician, including bowel, digits, cardiac, and other ischaemic complications.

Sample size

Based on data from the ARISE trial[7], the mean DAOH-D90 was 60 with a standard deviation of 31. Assuming a clinically important increase of 7 days in the vasopressor arm, a sample size of 950 participants will have 90% power to detect this difference with a type I error rate of 0.05 (including a 15% inflation factor to account for the non-parametric distribution). Allowing for a 5% drop out rate, we will recruit 1,000 participants to the trial. DAOH-D90 is supported by consumer consultation as a patient-centred outcome[5,8]. The ARISE Fluids management committee includes two consumer members who have contributed to the design and conduct of the trial from inception.

Statistical analysis

Analysis principles

The primary analysis will be conducted using a frequentist approach. A secondary analysis of the primary outcome will be conducted using a Bayesian approach to provide a

complementary interpretation of the main trial result. The primary manuscript and this SAP will only include analysis of outcomes up to 90 days post randomisation with analyses of 180 day and 12-month outcomes presented separately. Analyses will be conducted on an intention-to-treat basis with patients analysed according to their allocated treatment group excluding participants who withdrew consent. All tests will be two-sided and the level of statistical significance will be 5%. No adjustments for multiplicity will be conducted. Normality will be assessed qualitatively using histograms and quantile-quantile plots and the appropriate parametric or non-parametric method applied. Analysis will be conducted using RStudio, version 2023.06.1 or later, and SAS, version 9.4 or later.

Interim analysis

Following the recruitment of the first 500 participants, an unblinded interim review was undertaken by the unblinded trial statistician and the data safety and monitoring committee (DSMC). Stopping rules for efficacy were based on the Haybittle-Peto boundary approach with a P-value of 0.005, with no pre-defined stopping rules for safety, and no plans to stop ARISE FLUIDS for futility. No adjustments for the effect of the interim analysis on the type 1 error rate will be made as the method used has a negligible impact on the final type 1 error rate. The DSMC charter is published as an appendix to the trial protocol[9].

Trial flow

The status of participants in the trial will be shown using a Consolidated Standards of Reporting Trials diagram, as shown in Figure 1. The number of patients who met all inclusion criteria will be reported. The number who were excluded, the reason for exclusion, the number of patients randomised, and the number lost to follow up will be reported. Details of the consent status for all participants will also be described in detail, as shown in Figure 2.

Patient characteristics and baseline variables

Baseline characteristics will be presented by treatment group. Baseline, pre-randomisation variables will include patient demographics, co-morbidities, laboratory values and vital signs (most recent prior to randomisation), severity of illness scores, time from meeting eligibility criteria to randomisation, volumes of IV fluid administered and time to start vasopressor infusion if commenced prior to randomisation, primary site of infection, time to first antimicrobial and appropriateness of first antimicrobial therapy. Categorical variables will be summarised by frequencies and percentages (calculated as a percentage of the number of patients for whom data is available). The numbers of missing data will be reported. Continuous variables will be summarised using mean with standard deviation (SD) for normally distributed data or median with quartiles (Q1-Q3) for non-normally distributed data. Significance tests of baseline differences will not be performed.

Delivery of the study intervention

The delivery of the study intervention will be described by:

- The median volume of fluid administered in the first 6 hours, hours 6-24, and hours 0-24 post-randomisation. These time periods have been chosen as the intervention is protocolised to be delivered for a minimum of 6 hours and a maximum of 24 hours.
- Median time to start any vasopressor infusion post-randomisation. Participants who are receiving vasopressors at the time of randomisation will be assigned a time of 0 hours.
- As data collection and the intervention ceased at time of ICU discharge for participants who were discharged from the ICU or died before 24 hours, delivery of the study intervention in the context of these competing events will be reported separately. The number of participants who remained in the ICU, those that died, and those that were

discharged to the ward within the first 24 hours post-randomisation will be reported, along with total fluid administered and time to initiation of any vasopressor.

- Number and proportion of participants administered any vasopressor in the first 24 hours post-randomisation.
- The number and proportion of participants who had a central venous catheter (CVC) or peripherally inserted central catheter (PICC) inserted in the first 24 hours post-randomisation.
- The number and proportion of participants who received a vasopressor infusion via a peripheral line or CVC/PICC in the first 24 hours post-randomisation.

Compliance with the study protocol

Compliance will be assessed by:

- The number and proportion of participants who did not receive the intervention for a minimum of 6 hours post-randomisation due to being discharged to the ward or a non-participating hospital within 6 hours post-randomisation, excluding those that died before 6 hours. This will be analysed using a hierarchical (multilevel) binomial model. Specifically, a generalised linear mixed model (GLMM) with a log link function will be fitted, estimating relative risks while incorporating a random intercept for site to account for between-site variation. The effect of the treatment will be reported as relative risks with 95% CI.
- The difference in time to start any post-randomisation vasopressor infusion between treatment groups. This will be estimated using a Cox proportional hazards mixed effects model. The covariates in this model will be the randomised treatment group as a fixed effect and the study site as a random effect, censored at 24 hours. The

cause-specific hazard ratio and its 95% CI will be reported, and a cumulative incidence curve will be plotted with mortality and early discharge as competing risks.

The difference in volume of IV fluid (in mL) administered over the first hour post-randomisation between treatment groups. This will be estimated using either a linear quantile mixed-effects regression model at the 0.5 quantile or a linear mixed-effects regression model, with study site as a random effect. The results will be reported as the difference in medians or means respectively, and its 95% CI.

Intercountry differences in protocol compliance and changes in adherence over the duration of the trial will be reported. Box and whisker plots will illustrate the median (IQR) fluid administered over 0-6 hours and 6-24 hours and the time to start vasopressor therapy post-randomisation by treatment arm and bar charts will illustrate the proportion of patients commenced on vasopressors by treatment arm. These will be reported by: 1) country for countries with a minimum of 10 patients recruited, and 2) every 200 patients recruited overall.

Protocol deviations

Protocol deviations that are reported by sites or detected during trial monitoring will be summarised at a participant and event level, and will include the following pre-specified deviations:

- Patient randomised but not eligible
    - One or more inclusion criteria not met
    - One or more exclusion criteria met

- Fluids arm: one or more boluses of 500 mL not administered for hypotension and/or hypoperfusion
- Vasopressor arm: Vasopressors not commenced for hypotension and/or hypoperfusion
- Vasopressor arm: Fluid boluses administered without specified indication as per study protocol e.g. persistent hypotension/hypoperfusion
- Vasopressor arm: One or more fluid boluses > 250 mL administered

All deviations will be listed along with the reason for the deviation.

Concomitant therapies

The incidence and time to initiation of the following concomitant therapies received during the hospital admission and not included as outcome measures will be summarised as counts (percentages) and medians (IQR):

- Administered IV steroids for admission diagnosis of septic shock
- Underwent surgery or a procedure for the presumed or known source of infection
- Received extra-corporeal membrane oxygenation

Laboratory tests and vital signs

Vital signs and laboratory tests measured during the intervention period will be reported as means (SD) or medians (IQR) at 6 (± 1), 12 (± 2), 18 (± 2), and 24 (± 4) hours post randomisation. For the selected parameters heart rate, mean arterial pressure (MAP), ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2:FiO_2 ratio), and lactate level, means and 95% CI will also be plotted over time by treatment group. The effect of treatment group on the selected parameters will be analysed using a repeated-measures,

linear mixed model. The fixed effects will be the value of the variable at baseline, treatment group, time point, and the interaction term between the latter two, and the random effects will be patient and study site.

Microbiology and antimicrobials

The appropriateness (as determined by the site principal investigator) of antimicrobial therapies administered in the first 72 hours following ED presentation, and types, will be reported as counts (percentages), as well as the median (IQR) time to administration by type. The number and proportion of participants with at least one positive culture taken within 72 hours of ED presentation will be reported, along with the number of positive cultures by sample type/body site and organism category.

Safety outcomes analysis

Adverse events, including serious adverse events, that are possibly, probably, or definitely related, as determined by the study investigator based on pre-defined criteria[10,11], to participation in the study will be categorised and summarised as counts and proportions. The number and proportion of patients experiencing at least one event, and the total number of events by category will be reported. Adverse events at a patient level will be compared between treatment groups using Fisher's exact tests. At an event level, where sufficient repeat data is available, analysis will be performed using a generalised linear mixed-effects model with a logit link, incorporating random effects for subject to account for within-subject correlation over time and a fixed effects for treatment.

The incidence of complications related to the administration of vasopressors via a peripheral line, CVC complications related to the study intervention, acute pulmonary oedema, and

ischaemic complications will be reported for both treatment arms as counts (percentages) including by sub-category where relevant.

Comparisons at a patient level between the two allocated treatment groups will be made using a mixed effects logistic regression model with treatment group as a fixed-effect and the study site as a random effect and reported as odds ratios (95% CI).

Analysis of the primary outcome

Primary analysis

The median difference in DAOH-D90 between the two treatment groups will be estimated using a linear quantile mixed-effects regression model at the 0.5 quantile. To account for the stratification variable at randomisation (study site), the main analysis model will use treatment group allocation as the fixed effect and study site as a random effect. Where model convergence is not achievable, smaller sites may be combined, primarily within countries. The results will be reported as the median difference in DAOH-D90, its 95% CI, and *p* value.

The crude median difference in DAOH-D90 will also be reported as an unadjusted median difference and its 95% CI.

A sensitivity analysis will be conducted by repeating the primary analysis with participants who die on or prior to day 90 assigned a DAOH-90 of -1. This approach accounts for death being worse than being in hospital for 90 days and then recovering.

Adjusted analysis

Additional adjusted analysis will be performed by adding the following covariates to the linear quantile mixed-effects regression model of the main analysis:

- APACHE II
- Site of infection
- Country
- Baseline lactate level

The adjusted treatment effect will be reported as the adjusted median difference and 95% CI.

If there are unexpected imbalances in baseline variables perceived to be of clinical relevance and not in the pre-specified list above, then a secondary sensitivity analysis will be performed by running the adjusted model with the inclusion of the imbalanced variables.

Secondary Bayesian analysis

A secondary analysis will be conducted using a Bayesian approach to estimate the treatment effect on DAOH-D90. The model will focus on the posterior distribution of the median difference in DAOH-D90 between the intervention and control groups, with results summarised as the posterior median and 95% credible interval (CrI). A Bayesian quantile regression model will be used at the 0.5 quantile (median), employing weakly informative priors to reflect uncertainty about the treatment effect without unduly influencing the results. Specifically, a normal prior will be placed on the regression coefficient for treatment, centred at zero (no effect) with a standard deviation of 1. This prior places 95% of the prior probability mass within approximately ±2 on the DAOH-D90 scale and is considered sufficiently vague to allow the data to predominantly inform the posterior estimates. In addition to the CrI, the posterior probability that the treatment improves DAOH-D90 (i.e., median difference > 0) will be reported.

Subgroup analysis

The following subgroups will be analysed for the primary outcome:

- Age <65 years vs ≥65 years
- Sex
- Lactate <3 mmol/L vs ≥3 mmol /L at baseline
- APACHE II score < 15 vs ≥15
- Source of infection (respiratory, urinary, other)
- Fluid volume prior to randomisation dichotomised at the median volume.

The analysis for each of these subgroups will be performed by adding the respective variable and its interaction with treatment group as fixed effects to the main analysis model. The results will be presented as a forest plot with median and IQR, the median difference from the regression model and its 95% CI. To assess the credibility of observed treatment-subgroup interactions, we will apply the ICEMAN criteria[12] to each subgroup analysis. This will help determine whether any apparent heterogeneity of treatment effect is likely to be real or a result of chance.

Treatment of missing data

Multiple imputation will be used to handle missing data for the primary outcome (DAOH-90) under the assumption that data are missing at random. This assumption will be supported by exploration of missingness patterns and by including relevant baseline and auxiliary variables in the imputation model. Iterations of an imputation model will create 10 imputed datasets. The model will include relevant variables from the main and adjusted analyses to ensure appropriate estimation. Suitable imputation methods will be applied depending on

the type and distribution of each variable. The primary and adjusted analyses will be performed on each imputed dataset, and results will be pooled to obtain overall estimates, including the mean and 95% confidence interval of the estimated treatment effect. A sensitivity analysis will also be performed by repeating the primary analysis using complete cases only.

Secondary outcomes analysis

All-cause mortality at 28 and 90 days. To account for clustering of patients within sites, a hierarchical (multilevel) binomial model will be used to analyse binary outcomes. Specifically, a generalised linear mixed model (GLMM) with a log link function will be fitted, estimating relative risks while incorporating a random intercept for site to account for between-site variation. The effect of the treatment will be reported as relative risks with 95% CI with no additional adjustment or subgroup analysis performed.

The *time from randomisation until death*, censored at the latest by day 90 or at the time when the patient was last known to be alive prior to day 90, will be analysed using a Cox proportional hazards mixed effects model. The covariates in this model will be the randomised treatment group as a fixed effect and the study site as a random effect. The effect of the treatment will be summarised as the hazard ratio and it's 95% CI, and a Kaplan-Meir plot will illustrate the survival rates. The proportional hazards assumption will be assessed visually by plotting the log-negative-log of the Kaplan-Meier estimator by treatment group.

Days alive and at home at 90 days, ventilator-free days to day 28, *vasopressor-free days to day 28,* and *renal replacement therapy-free days to day 28* will be estimated using a linear quantile mixed-effects regression model at the 0.5 quantile. The covariates in this model will

be treatment group allocation as a fixed effect and study site as a random effect. The results will be reported as the effect of the treatment on median differences and their 95% CI.

Tertiary outcomes analysis

The incidence of mechanical ventilation, vasopressor support, and acute renal replacement therapy during the hospital admission, as well as in-hospital mortality at 90 days, will be reported as counts and proportions. The effect of treatment group on the proportions will be assessed a hierarchical (multilevel) binomial model will be used to analyse binary outcomes. Specifically, a generalised linear mixed model (GLMM) with a log link function will be fitted, estimating relative risks while incorporating a random intercept for site to account for between-site variation. The effect of the treatment will be reported as a relative risk with 95% CI.

Time to event analysis methods will be used to assess the effect of treatment group allocation on the duration (that is, the probability of cessation) of mechanical ventilation, vasopressor support, and acute renal replacement therapy; and ICU, and hospital length of stay (that is, the probability of discharge), in those that experience these events. As mortality is a competing risk for these outcomes, cumulative incidence curves will be generated, and the cause-specific hazard ratios with their 95% CI will be reported using a Cox proportional hazards model. The covariates in this model will be the randomised treatment group as a fixed effect and the study site as a random effect.

Quality of life and long-term outcomes analysis

Quality of life outcomes (disability as determined by the European Quality of Life 5 Dimensions 5 Level questionnaire and functional status using the World Health Organisation

Disability Assessment Schedule version 2.0 questionnaire) and mortality at 180 days and 12 months, along with a cost-effectiveness analysis will be reported separately to the primary manuscript as part of a broader health economics and long-term outcomes program of research.

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Figure 1. CONSORT flowchart (reproduced with permission from the ARISE-Fluids protocol, Howe et al 2025[9])

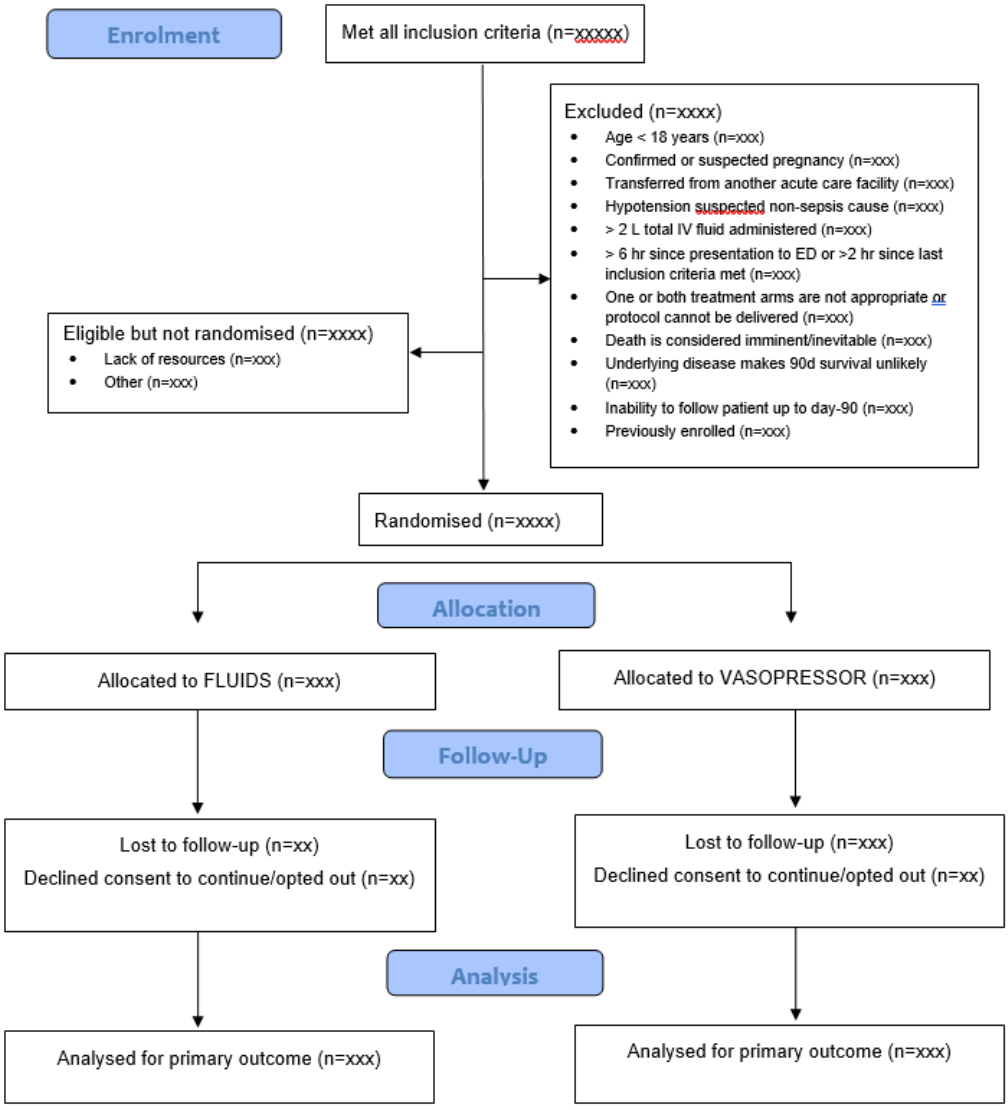

Figure 2. Consent flowchart

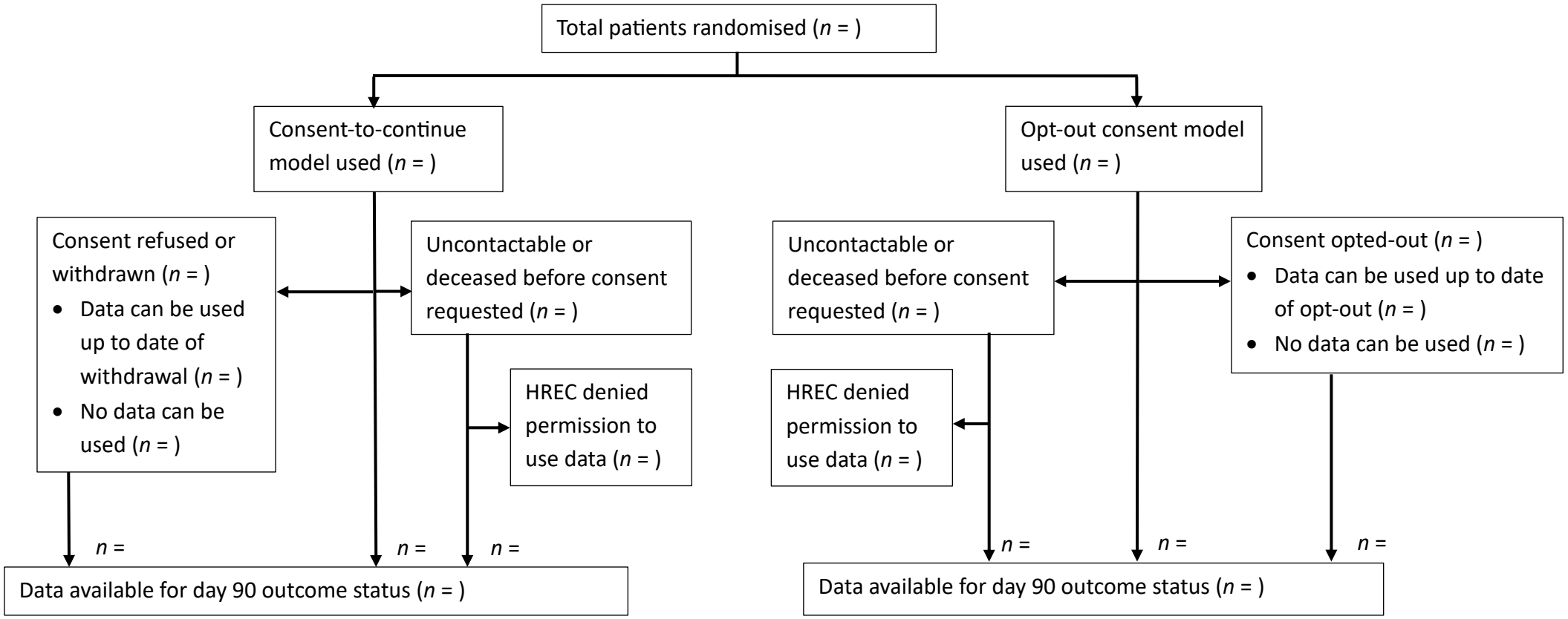

Table 1. Planned tables and figures

Main manuscript
Table 1: Baseline characteristics
Table 2: Fluid and vasopressor administration during the trial intervention period
Table 3: Primary and secondary outcomes
Figure 1: Fluid and vasopressor administration trial algorithm
Figure 2: Kaplan–Meier plot of time to death Hazard ratio, *P* value, and 95% CI from the mixed effects Cox regression model will be displayed.
Figure 3: Forest plot for subgroup analysis of DAOH-D90 Counts and percentages will be displayed, along with the median differences and their 95% CIs, and respective *P* values for the interaction term for each subgroup from the mixed effects linear quantile regression model.
Supplement
Table S1: Additional baseline characteristics
Table S2: Compliance with the study protocol
Table S3: Protocol deviations summary
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Table S5: Concomitant therapies during hospital admission
Table S6: Laboratory tests and vital signs
Table S7: Microbiology and antimicrobials
Table S8. Fluid and vasopressor administration from 0 hr to 24 hr post-randomisation by time period

Table S9: Complications related to the study intervention

Table S10: Adverse events

Figure S1: CONSORT flowchart

Figure S2: Consent flowchart

Figure S3: Recruitment rate over time

Figure S4: Cumulative incidence curve of time to start any post-randomisation vasopressor infusion

Hazard ratio, *P* value, and 95% CI from the cumulative incidence curve with mortality as a competing risk.

Figure S5: Box and whisker plots – fluid administered over time by country and study arm

Median fluid administered and IQR over 0-6 hours and 6-24 hours post-randomisation by treatment arm and by: 1) country for countries **with a minimum of 10 patients recruited and 2) by every 200 patients recruited overall to illustrate any changes in protocol adherence over time.**

Figure S6: Box and whisker plots – time to start vasopressor therapy

By 1) country for countries with a minimum of 10 patients recruited and 2) by every 200 patients recruited overall to illustrate any changes in protocol adherence over time.

Figure S7: Bar charts – proportion of patients commenced on vasopressors

By 1) country for countries with a minimum of 10 patients recruited and 2) by every 200 patients recruited overall to illustrate any changes in protocol adherence over time.

Figure S8: Longitudinal mean plot of heart rate over the first 24 hr

Mean and 95% CI for 0, 6, 12, 18, and 24 hr will be indicated, by treatment group. Mean difference, 95% CI, and P value from the repeated-measures, linear mixed model will be displayed.

Figure S9: Longitudinal mean plot of mean arterial pressure over the first 24 hr

Mean and 95% CI for 0, 6, 12, 18, and 24 hr will be indicated, by treatment group. Mean difference, 95% CI, and P value from the repeated-measures, linear mixed model will be displayed.

Figure S10: Longitudinal mean plot of PaO2:FiO2 ratio over the first 24 hr

Mean and 95% CI for 0, 6, 12, 18, and 24 hr will be indicated, by treatment group. Mean difference, 95% CI, and P value from the repeated-measures, linear mixed model will be displayed.

Figure S11: Longitudinal mean plot of lactate level over the first 24 hr

Mean and 95% CI for 0, 6, 12, 18, and 24 hr will be indicated, by treatment group. Mean difference, 95% CI, and P value from the repeated-measures, linear mixed model will be displayed.

Figure S12: Cumulative incidence curve of time to cessation of mechanical ventilation

Hazard ratios, *P* value, and 95% CI from the cumulative incidence curve with mortality as a competing risk.

Figure S13: Cumulative incidence curve of time to cessation of vasopressor support

Hazard ratios, *P* value, and 95% CI from the cumulative incidence curve with mortality as a competing risk.

Figure S13: Cumulative incidence curve of time to cessation of acute renal replacement therapy

Hazard ratios, *P* value, and 95% CI from the cumulative incidence curve with mortality as a competing risk.

Figure S14: Cumulative incidence curve of time to time to ICU discharge

Hazard ratios, *P* value, and 95% CI from the cumulative incidence curve with mortality as a competing risk.

Figure S15: Cumulative incidence curve of time to hospital discharge

Hazard ratios, *P* value, and 95% CI from the cumulative incidence curve with mortality as a competing risk.

Statistical analysis plan for the Australasian Resuscitation In Sepsis Evaluation: FLUid or vasopressors In emergency Department Sepsis (ARISE FLUIDS) trial

ONLINE SUPPLEMENT

Contents

Appendix 1 – ARISE-Fluids Working Party

Member	Affiliation
Prof Sandra L. Peake	Discipline of Acute Care Medicine, The University of Adelaide, Adelaide, South Australia, Australia; Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Victoria, Australia; Department of Intensive Care Medicine, The Queen Elizabeth Hospital, Woodville South, South Australia, Australia.
Clin/A Prof Stephen P. J. Macdonald	Centre for Clinical Research in Emergency Medicine, Harry Perkins Institute of Medical Research, Perth, Western Australia, Australia
A/Prof Anthony Delaney	Intensive Care, Royal North Shore Hospital, Sydney, New South Wales, Australia; Professorial Fellow, Critical Care Program, The George Institute for Global Health, University of New South Wales, New South Wales, Australia
Dr Alisa M. Higgins	Senior Research Fellow, ANZIC-RC, Monash University, Melbourne, Victoria, Australia
Ms Belinda D. Howe	Project Manager, ANZIC-RC, Monash University, Melbourne, Victoria, Australia
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Prof Gerben Keijzers	Department of Emergency Medicine, Gold Coast Hospital and Health Service, Gold Coast, Queensland, Australia; Faculty of Health Sciences and Medicine, Bond University, Queensland, Australia; School of Medicine and Dentistry, Griffith University, Queensland, Australia
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Appendix 2 – ARISE-Fluids Management Committee

Member	Affiliation
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Prof Diana Egerton-Warburton	Emergency Medicine, Monash Medical Centre, Melbourne, Victoria, Australia; School of Clinical Science and Monash Health, Monash University Melbourne, Victoria, Australia
Prof Daniel Fatovich	Emergency Medicine, Royal Perth Hospital, Western Australia, Australia

	Centre for Clinical Research in Emergency Medicine, Harry Perkins Institute of Medical Research.
Prof John Fraser	Critical Care Research Group, University of Queensland and The Prince Charles Hospital, Queensland, Australia
Dr Alisa M. Higgins	Senior Research Fellow, ANZIC-RC, Monash University, Melbourne, VIC, Australia
Ms Belinda D. Howe	Project Manager, ANZIC-RC, Monash University, Melbourne, Victoria, Australia
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Dr Elissa Milford	Staff Specialist, Intensive Care Unit, Royal Brisbane and Women's Hospital, Queensland, Australia; Senior Lecturer, Faculty of Medicine, University of Queensland, Queensland, Australia; Adjunct Senior Research Fellow, Department of Acute and Critical Care, Monash University, Victoria, Australia
Ms Leana Stendell	Consumer representative, Western Australia, Australia
Prof Andrew Udy	Intensive Care, The Alfred Hospital, Melbourne, Victoria, Australia
Ms Korina Valentine	Consumer representative, New South Wales, Australia

Ms Patricia Williams	Discipline of Acute Care Medicine, The University of Adelaide, Adelaide, South Australia, Australia; Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Victoria, Australia; Department of Intensive Care Medicine, The Queen Elizabeth Hospital, Woodville South, South Australia, Australia.
Dr Paul Young	Intensive Care, Wellington Hospital, Wellington, New Zealand

Appendix 3 – Changes made since publication of the protocol

A small number of changes have been made to the statistical analysis plan since publication of the protocol, noting that these changes have been made prior to the end of patient recruitment and while the investigators are still blinded to the study results. A summary of these changes are provided below:

Change	**Rationale**
28-day mortality added as a secondary outcome.	This was added for greater transparency of outcomes, particularly given the reported organ support free days will be censored at day 28.
Protocol stated that there would be no imputation of missing data, however this has been changed to the use of multiple imputation to handle missing data for the primary outcome.	On review of the plan to handle missing data, it was felt that multiple imputation using a model-based method, was a superior approach than complete-case analysis[1]. A sensitivity analysis will be performed by repeating the primary analysis using complete cases only.

References:

1. Ware JH, Harrington D, Hunter DJ, D'Agostino RB. Missing Data. New England Journal of Medicine 2012;367(14):1353-1354. DOI: doi:10.1056/NEJMsm1210043.

Appendix 3 – Planned tables

Appendix 1. Dummy tables

Table 1. Baseline characteristics

Characteristic	Vasopressor arm (N=)	Fluids arm (N=)
Age – yr	x.x ± x.x	x.x ± x.x
Male sex – no./total no. (%)	x/x (x.x)	x/x (x.x)
Weight – kg~	x.x ± x.x	x.x ± x.x
Usual residence – no./total no. (%)		
Home	x/x (x.x)	x/x (x.x)
Long-term care facility	x/x (x.x)	x/x (x.x)
Charlson comorbidity index	x.x ± x.x	x.x ± x.x
Baseline physiology*		
Systolic blood pressure – mmHg	x.x ± x.x	x.x ± x.x
Lactate level – mmol/L	x.x ± x.x	x.x ± x.x
Severity of illness		
APACHE II score^	x.x (x.x – x.x)	x.x (x.x – x.x)
SOFA score^	x.x (x.x – x.x)	x.x (x.x – x.x)
Total volume of IV fluid administered prior to randomisation#		
mL	x.x (x.x – x.x)	x.x (x.x – x.x)
mL/kg	x.x (x.x – x.x)	x.x (x.x – x.x)
Received invasive mechanical ventilation prior to randomisation – no./total no. (%)	x/x (x.x)	x/x (x.x)
Received vasopressor infusion prior to randomisation – no./total no. (%)	x/x (x.x)	x/x (x.x)
Time between ED presentation and starting a vasopressor infusion prior to randomisation – hr	x.x (x.x – x.x)	x.x (x.x – x.x)
Time from ED presentation to randomisation – hr	x.x (x.x – x.x)	x.x (x.x – x.x)
Time from inclusion criteria met to randomisation – hr	x.x (x.x – x.x)	x.x (x.x – x.x)
Primary site of infection – no./total no. (%)		
Pulmonary	x/x (x.x)	x/x (x.x)
Primary blood stream&	x/x (x.x)	x/x (x.x)
Urinary tract	x/x (x.x)	x/x (x.x)
Skin and soft tissue	x/x (x.x)	x/x (x.x)
Intra-abdominal	x/x (x.x)	x/x (x.x)
Central nervous system	x/x (x.x)	x/x (x.x)
Unknown	x/x (x.x)	x/x (x.x)
Other	x/x (x.x)	x/x (x.x)
Time from ED presentation to first antimicrobial – hr	x.x (x.x – x.x)	x.x (x.x – x.x)

Plus-minus are mean ± SD. Ranges are median (Q1-Q3).

* Values taken closest to but prior to randomisation.

^ Worst parameters during the 24 hours prior to randomisation.

[#] Includes pre-hospital and ED bolus fluids and blood products, does not include fluids for medication delivery.
[&] e.g. malaria
[~] Actual or estimated weight

Table 2. Fluid and vasopressor administration during the trial intervention period

Therapy	**Vasopressor arm (N=)**	**Fluids arm (N=)**	**Difference (95% CI)**
Median volume of fluid administered post randomisation – mL			
0-6 hr	x (x – x)	x (x – x)	x
6-24 hr	x (x – x)	x (x – x)	x
0-24 hr	x (x – x)	x (x – x)	x
Participants **administered any vasopressor in the first 24 hours post-randomisation** – no./total no. (%)	x/x (x.x)	x/x (x.x)	x
Median time to start any vasopressor infusion post-randomisation – hr	x (x – x)	x (x – x)	x
Participants who had a CVC or PICC inserted in the first 24 hours post-randomisation – no./total no. (%)	x/x (x.x)	x/x (x.x)	x
Participants who received a vasopressor infusion via a peripheral line in the first 24 hours post-randomisation – no./total no. (%)	x/x (x.x)	x/x (x.x)	x
Participants who received a vasopressor infusion via a CVC or PICC in the first 24 hours post-randomisation – no./total no. (%)	x/x (x.x)	x/x (x.x)	x

Plus-minus are mean ± SD. Ranges are median (Q1-Q3).

CVC: central venous catheter, PICC: peripherally inserted central catheter.

Table 3. Primary, secondary and tertiary outcomes

Outcome	**Vasopressor arm (N=)**	**Fluids arm (N=)**	**Difference, hazard ratio, or relative risk (95% CI/CrI)**	***P* value**
Primary outcome				
DAOH-D90 – days	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)*	
Adjusted median difference	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)*	0.xx
Secondary outcomes				
28-day all-cause mortality – no./total no. (%)	x/x (x.x)	x/x (x.x)	x.x (x.x – x.x)[#]	
90-day all-cause mortality – no./total no. (%)	x/x (x.x)	x/x (x.x)	x.x (x.x – x.x)[#]	
Time from randomisation until death - hr	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)[~]	
Days alive and at home at 90 days – days	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)*	
Ventilator-free days to day 28 – days	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)*	
Vasopressor-free days to day 28 – days	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)*	
Renal replacement therapy-free days to day 28 – days	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)*	
Tertiary outcomes				

Incidence of invasive mechanical ventilation – no./total no. (%)	x/x (x.x)	x/x (x.x)	x.xx (x.xx – x.xx)#
Incidence of vasopressor support – no./total no. (%)	x/x (x.x)	x/x (x.x)	x.xx (x.xx – x.xx)#
Incidence of acute renal replacement therapy – no./total no. (%)	x/x (x.x)	x/x (x.x)	x.xx (x.xx – x.xx)#
Duration of invasive mechanical ventilation – hr	x.x (x.x – x.x)	x.x (x.x – x.x)	x.xx (x.xx – x.xx)+
Duration of vasopressor support – hr	x.x (x.x – x.x)	x.x (x.x – x.x)	x.xx (x.xx – x.xx)+
Duration of renal replacement therapy – hr	x.x (x.x – x.x)	x.x (x.x – x.x)	x.xx (x.xx – x.xx)+
ED length of stay – hr	x.x (x.x – x.x)	x.x (x.x – x.x)	x.xx (x.xx – x.xx)+
ICU length of stay – hr	x.x (x.x – x.x)	x.x (x.x – x.x)	x.xx (x.xx – x.xx)+
Hospital length of stay – hr	x.x (x.x – x.x)	x.x (x.x – x.x)	x.xx (x.xx – x.xx)+
In-hospital mortality, censored at 90 days – no./total no. (%)	x/x (x.x)	x/x (x.x)	x.xx (x.xx – x.xx)#

Plus-minus are mean ± SD. Ranges are median (Q1-Q3). The analysis of DAOH-90 reported in this table was performed using a linear quantile mixed-effects regression model at the 0.5 quantile with treatment group allocation as a fixed effect and study site as a random effect.

* Difference

^ Posterior probability of odds ratio

Relative risk

~ Hazard ratio

+ Cause-specific hazard ratio

Table S1. Additional baseline characteristics

Characteristic	**Vasopressor arm (N=)**	**Fluids arm (N=)**
Functional status – no./total no. (%)		
Independent with all activities of daily living	x/x (x.x)	x/x (x.x)
Requires help with at least one activity of daily living	x/x (x.x)	x/x (x.x)
Country – no./total no. (%)		
Australia	x/x (x.x)	x/x (x.x)
New Zealand	x/x (x.x)	x/x (x.x)
Republic of Ireland	x/x (x.x)	x/x (x.x)
Ethnicity – no./total no. (%)		
Identifies as Indigenous – Aus no./total no. (%)	x/x (x.x)	x/x (x.x)
European	x/x (x.x)	x/x (x.x)
Maori	x/x (x.x)	x/x (x.x)
Pacific peoples	x/x (x.x)	x/x (x.x)
Asian	x/x (x.x)	x/x (x.x)
Middle East/Latin American/African	x/x (x.x)	x/x (x.x)
Other	x/x (x.x)	x/x (x.x)
Comorbidities – no./total no. (%)		
Myocardial infarction	x/x (x.x)	x/x (x.x)
Congestive cardiac failure	x/x (x.x)	x/x (x.x)

Peripheral vascular disease	x/x (x.x)	x/x (x.x)
Cerebrovascular disease	x/x (x.x)	x/x (x.x)
Dementia	x/x (x.x)	x/x (x.x)
Chronic obstructive pulmonary disease	x/x (x.x)	x/x (x.x)
Peptic ulcer disease	x/x (x.x)	x/x (x.x)
Kidney disease	x/x (x.x)	x/x (x.x)
Connective tissue disease	x/x (x.x)	x/x (x.x)
Hemiplegia or paraplegia	x/x (x.x)	x/x (x.x)
Liver disease		
Mild	x/x (x.x)	x/x (x.x)
Moderate-severe	x/x (x.x)	x/x (x.x)
Diabetes		
Moderate~	x/x (x.x)	x/x (x.x)
End organ damage	x/x (x.x)	x/x (x.x)
Solid tumour	x/x (x.x)	x/x (x.x)
Leukaemia/Lymphoma	x/x (x.x)	x/x (x.x)
Metastatic solid tumour	x/x (x.x)	x/x (x.x)
AIDS	x/x (x.x)	x/x (x.x)
Baseline physiology&		
Heart rate – beats/min	x.x ± x.x	x.x ± x.x
Mean arterial pressure – mmHg	x.x ± x.x	x.x ± x.x
Non-sedated Glasgow Coma Score no./total no. (%)		
<9	x/x (x.x)	x/x (x.x)
9 to 12	x/x (x.x)	x/x (x.x)
13 to 15	x/x (x.x)	x/x (x.x)
Core temperature – °C	x.x ± x.x	x.x ± x.x
Diastolic blood pressure – mm Hg	x.x ± x.x	x.x ± x.x
Respiratory rate – breaths/min	x.x ± x.x	x.x ± x.x
FiO_2	0.x ± 0.x	0.x ± 0.x
Creatinine level – mg/dL	x.x ± x.x	x.x ± x.x
SpO_2 – %	x.x ± x.x	x.x ± x.x
Bilirubin level – mg/dL	x.x ± x.x	x.x ± x.x
Haemoglobin level – g/dL	x.x ± x.x	x.x ± x.x
White cell count – cells $x10^9$/L	x.x ± x.x	x.x ± x.x
Platelet count – $x10^9$/L	x.x ± x.x	x.x ± x.x
pH	x.xx ± x.xx	x.xx ± x.xx
SOFA score components+		
SOFA Respiratory	x.x (x.x – x.x)	x.x (x.x – x.x)
SOFA Cardiovascular	x.x (x.x – x.x)	x.x (x.x – x.x)
SOFA Liver	x.x (x.x – x.x)	x.x (x.x – x.x)
SOFA Coagulation	x.x (x.x – x.x)	x.x (x.x – x.x)
SOFA Renal	x.x (x.x – x.x)	x.x (x.x – x.x)
Total volume of IV fluid administered to time final eligibility criterion met#		
mL	x.x (x.x – x.x)	x.x (x.x – x.x)
mL/kg	x.x (x.x – x.x)	x.x (x.x – x.x)

Total volume of IV fluid administered between time final eligibility criterion met until randomisation[#]		
mL	x (x – x)	x (x – x)
mL/kg	x (x – x)	x (x – x)
Acute COVID-19 infection – no./total no. (%)	x/x (x.x)	x/x (x.x)
According to subgroup – no./total no. (%)		
Age ≥ 65 years	x/x (x.x)	x/x (x.x)
Lactate ≥ 3 mmol/L at baseline	x/x (x.x)	x/x (x.x)
APACHE II score ≥ 15	x/x (x.x)	x/x (x.x)
IV fluid prior to randomisation ≥ median volume	x/x (x.x)	x/x (x.x)

Plus-minus are mean ± SD. Ranges are median (Q1-Q3).

[~] Moderate diabetes defined as on medication

[#] Includes pre-hospital and ED bolus fluids and blood products, does not include fluids for medication delivery.

[&] Closest to but prior to randomisation

[+] Worst parameters during the 24 hours prior to randomisation

Table S2. Compliance with the study protocol

	Vasopressor arm (N=)	**Fluids arm (N=)**	**Difference, hazard ratio, or relative risk (95% CI/CrI)**
Participants who did not receive the intervention for a minimum of 6 hours post-randomisation^ – no./total no. (%)	x/x (x.x)	x/x (x.x)	x.x (x.x – x.x)[#]
Time to start any post-randomisation vasopressor infusion between 0 to 24 hr – hr	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)[+]
Fluid administered over the first hour post-randomisation – mL	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)*
Participants alive and present in ICU at 24 hours post-randomisation – no./total no. (%)	x/x (x.x)	x/x (x.x)	x
Participants who received a vasopressor infusion in the first 24 hours post-randomisation – no./total no. (%)	x/x (x.x)	x/x (x.x)	x
Median fluid administered 0-24 hr – mL	x (x – x)	x (x – x)	x
Median time to start any vasopressor - hr	x (x – x)	x (x – x)	x
Participants who died within the first 24 hours post-randomisation – no./total no. (%)	x/x (x.x)	x/x (x.x)	x
Participants who received a vasopressor infusion in the first 24 hours post-randomisation – no./total no. (%)	x/x (x.x)	x/x (x.x)	x
Median fluid administered 0-24 hr – mL	x (x – x)	x (x – x)	x
Median time to start any vasopressor - hr	x (x – x)	x (x – x)	x
Participants discharged to the ward in the first 24 hours post-randomisation – no./total no. (%)	x/x (x.x)	x/x (x.x)	x

Participants who received a vasopressor infusion in the first 24 hours post-randomisation – no./total no. (%)	x/x (x.x)	x/x (x.x)	x
Median fluid administered 0-24 hr – mL	x (x – x)	x (x – x)	x
Median time to start any vasopressor - hr	x (x – x)	x (x – x)	x

Plus-minus are mean ± SD. Ranges are median (Q1-Q3). The analysis of protocol compliance in this table was performed using mixed-effects logistic, Cox proportional hazards, and linear quantile regression, with randomised treatment group as a fixed effect and the study site as a random effect.

^ Participants who did not receive the intervention for a minimum of 6 hours post-randomisation due to being discharged to the ward or a non-participating hospital within 6 hours, excluding those that died before 6 hours.

* Difference

Relative risk

+ Cause-specific hazard ratio

Table S3. Protocol deviations summary

Protocol deviation – no./total no. (%)	**Vasopressor arm (N=)**	**Fluids arm (N=)**
Patient randomised but not eligible		
Inclusion criteria not met		
Blood pressure criteria not met	x/x (x.x)	x/x (x.x)
Lactate criteria not met	x/x (x.x)	x/x (x.x)
IV antimicrobial criteria not met	x/x (x.x)	x/x (x.x)
Exclusion criteria met		
Age < 18 years	x/x (x.x)	x/x (x.x)
Confirmed or suspected pregnancy	x/x (x.x)	x/x (x.x)
Transferred from another acute care facility	x/x (x.x)	x/x (x.x)
Hypotension suspected to be due to another cause	x/x (x.x)	x/x (x.x)
> 2 L IV fluid administered	x/x (x.x)	x/x (x.x)
> 6 hr since ED presentation or >2 hr since inclusion criteria met	x/x (x.x)	x/x (x.x)
One or both treatments not suitable or cannot be delivered	x/x (x.x)	x/x (x.x)
Underlying disease makes survival to 90 days unlikely	x/x (x.x)	x/x (x.x)
Death considered imminent or inevitable	x/x (x.x)	x/x (x.x)
Inability to follow patient up to day 90	x/x (x.x)	x/x (x.x)
Previous enrolment in this study	x/x (x.x)	x/x (x.x)
One or more boluses of 500 mL not administered for hypotension and/or hypoperfusion*	N/A	x/x (x.x)
Vasopressors not commenced for hypotension and/or hypoperfusion^	x/x (x.x)	N/A
Fluid boluses administered without specified indication as per study protocol^	x/x (x.x)	N/A
One or more fluid boluses > 250 mL administered^	x/x (x.x)	N/A

Plus-minus are mean ± SD. Ranges are median (Q1-Q3).

* Fluids arm only

^ Vasopressor arm only

Table S4. Protocol deviations list

Treatment group	Protocol deviation Reason

Table S5. Concomitant therapies during hospital admission

Therapy	Vasopressor arm (N=)	Fluids arm (N=)
Administered IV steroids for admission diagnosis of septic shock – no./total no. (%)	x/x (x.x)	x/x (x.x)
Time to administration of IV steroids – hr	x.x (x.x – x.x)	x.x (x.x – x.x)
Underwent surgery or a procedure for the presumed or known source of infection – no./total no. (%)	x/x (x.x)	x/x (x.x)
Time to initiation of surgery or a procedure for the presumed or known source of infection – hr	x.x (x.x – x.x)	x.x (x.x – x.x)
Received extra-corporeal membrane oxygenation – no./total no. (%)	x/x (x.x)	x/x (x.x)
Time to initiation of extra-corporeal membrane oxygenation – hr	x.x (x.x – x.x)	x.x (x.x – x.x)

Plus-minus are mean ± SD. Ranges are median (Q1-Q3).

Table S6. Laboratory tests and vital signs between 6 and 24 hours

Laboratory test or vital sign	Vasopressor arm (N=)	Missing (N)	Fluids arm (N=)	Missing (N)
Core temperature – °C				
6 hr	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
12 hr	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
18 hr	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
24 hr	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
Heart rate – beats/min				
6 hr (± 1 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
12 hr (± 2 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
18 hr (± 2 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
24 hr (± 4 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
MAP – mm Hg				
6 hr (± 1 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
12 hr (± 2 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
18 hr (± 2 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
24 hr (± 4 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
Respiratory rate – breaths/min				

6 hr (± 1 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
12 hr (± 2 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
18 hr (± 2 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
24 hr (± 4 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
SpO_2 – %				
6 hr (± 1 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
12 hr (± 2 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
18 hr (± 2 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
24 hr (± 4 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
Haemoglobin – g/dL				
6 hr (± 1 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
12 hr (± 2 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
18 hr (± 2 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
24 hr (± 4 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
Lactate – mg/dL				
6 hr (± 1 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
12 hr (± 2 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
18 hr (± 2 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
24 hr (± 4 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
PaO_2:FiO_2 ratio				
6 hr (± 1 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
12 hr (± 2 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
18 hr (± 2 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
24 hr (± 4 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
pH				
6 hr (± 1 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
12 hr (± 2 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
18 hr (± 2 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
24 hr (± 4 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
Bicarbonate – mmol/L				
6 hr (± 1 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
12 hr (± 2 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
18 hr (± 2 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x
24 hr (± 4 hr)	x.x (x.x – x.x)	x	x.x (x.x – x.x)	x

Plus-minus are mean ± SD. Ranges are median (Q1-Q3).

Table S7. Microbiology and antimicrobials

Microbiology or antimicrobial parameter	**Vasopressor arm (N=)**	**Fluids arm (N=)**
Time from ED presentation to first appropriate antimicrobial – hr	x.x (x.x – x.x)	x.x (x.x – x.x)
First antimicrobial therapy administered appropriate for the treatment of the infection – no./total no. (%)		
Yes	x/x (x.x)	x/x (x.x)

No	x/x (x.x)	x/x (x.x)
Unknown	x/x (x.x)	x/x (x.x)
Antimicrobial therapy administered in the first 72 hours from ED admission appropriate for the treatment of the infection – no./total no. (%)		
Yes	x/x (x.x)	x/x (x.x)
No	x/x (x.x)	x/x (x.x)
Unknown	x/x (x.x)	x/x (x.x)
Antimicrobials administered between ED presentation and 72 hr – no./total no. (%)		
Penicillins	x/x (x.x)	x/x (x.x)
Cephalosporins	x/x (x.x)	x/x (x.x)
Macrolides	x/x (x.x)	x/x (x.x)
Aminoglycosides	x/x (x.x)	x/x (x.x)
Carbapenems	x/x (x.x)	x/x (x.x)
Fluoroquinolones	x/x (x.x)	x/x (x.x)
Glycopeptides	x/x (x.x)	x/x (x.x)
Nitroimidazoles	x/x (x.x)	x/x (x.x)
Other	x/x (x.x)	x/x (x.x)
Time to initiation of antimicrobial censored at 72 hr – hr		
Penicillins	x.x (x.x – x.x)	x.x (x.x – x.x)
Cephalosporins	x.x (x.x – x.x)	x.x (x.x – x.x)
Macrolides	x.x (x.x – x.x)	x.x (x.x – x.x)
Aminoglycosides	x.x (x.x – x.x)	x.x (x.x – x.x)
Carbapenems	x.x (x.x – x.x)	x.x (x.x – x.x)
Fluoroquinolones	x.x (x.x – x.x)	x.x (x.x – x.x)
Glycopeptides	x.x (x.x – x.x)	x.x (x.x – x.x)
Nitroimidazoles	x.x (x.x – x.x)	x.x (x.x – x.x)
Other	x.x (x.x – x.x)	x.x (x.x – x.x)
At least one positive culture taken within 72 hr of ED presentation – no./total no. (%)	x/x (x.x)	x/x (x.x)
Positive culture by sample type/body site within 72 hr of ED presentation – no./total no. (%)*		
Respiratory	x/x (x.x)	x/x (x.x)
Blood	x/x (x.x)	x/x (x.x)
Urine	x/x (x.x)	x/x (x.x)
Soft tissue	x/x (x.x)	x/x (x.x)
Bone/joint	x/x (x.x)	x/x (x.x)
Other sterile site	x/x (x.x)	x/x (x.x)
Positive culture by organism within 72 hr of ED presentation – no./total no. (%)		
Gram positive	x/x (x.x)	x/x (x.x)
Gram negative	x/x (x.x)	x/x (x.x)
Viral	x/x (x.x)	x/x (x.x)
Fungal	x/x (x.x)	x/x (x.x)
Parasitic	x/x (x.x)	x/x (x.x)
Other	x/x (x.x)	x/x (x.x)

* Participants could have more than one positive culture

Table S8. Fluid and vasopressor administration from 0 hr to 24 hr post-randomisation by time period

Intervention	0 to 6 hr		6 to 12 hr		12 to 18 hr		18 to 24 hr	
	Vasopressor group (N=)	Fluids group (N =)	Vasopressor group (N=)	Fluids group (N =)	Vasopressor group (N=)	Fluids group (N =)	Vasopressor group (N=)	Fluids group (N =)
Fluid volume								
Total - ml	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)
Total - ml/kg^	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)
Crystalloid - ml	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)
Crystalloid - ml/kg[a]	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)
Colloid - ml	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)
Colloid - ml/kg	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)	x.x (x.x – x.x)
Vasopressor type[b]								

Norepinephrine - no./total no. (%)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)
Epinephrine - no./total no. (%)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)
Vasopressin - no./total no. (%)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)
Metaraminol - no./total no. (%)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)
Dopamine - no./total no. (%)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)
Phenylephrine - no./total no. (%)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)
Vasopressor route								
Peripheral venous - no./total no. (%)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)
Central venous - no./total no. (%)[c]	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)
Blood products								
Red cells - no./total no.	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)
Red cells - ml	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)

Platelets - no./total no.	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)
Platelets - ml	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)
Fresh frozen plasma - no./total no.	x/x 6x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)
Fresh frozen plasma - ml	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)
Cryoprecipitate - no./total no.	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)
Cryoprecipitate - ml	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)	x/x (x.x)

Values reported as mean ± standard deviation (SD) or median (interquartile range, IQR). Values indicated with no. are number of subjects.

[a] Weight refers to actual, estimated or documented in the patient's medical record.

[b] Type of vasopressor infusion was recorded at the end of each time period and patients may be in receipt of more than one vasopressor infusion.

[c] Central venous route refers to both central venous catheter and peripherally inserted central catheter.

Table S9. Complications related to the study intervention

Vascular access and complication parameter	Vasopressor arm (N=)	Fluids arm (N=)	Hazard ratio, or odds ratio (95% CI)
Complication related to the administration of vasopressors via a peripheral line – no./total no. (%)	x/x (x.x)	x/x (x.x)	x.xx (x.xx – x.xx)[#]
Tissue necrosis – no./total no. (%)	x/x (x.x)	x/x (x.x)	
Other – no./total no. (%)	x/x (x.x)	x/x (x.x)	
CVC or PICC complication related to the study intervention – no./total no. (%)	x/x (x.x)	x/x (x.x)	x.xx (x.xx – x.xx)[#]
Pneumothorax – no./total no. (%)	x/x (x.x)	x/x (x.x)	
Arterial puncture – no./total no. (%)	x/x (x.x)	x/x (x.x)	
CVC/PICC related infection – no./total no. (%)	x/x (x.x)	x/x (x.x)	
CVC/PICC related thrombosis – no./total no. (%)	x/x (x.x)	x/x (x.x)	
Other – no./total no. (%)	x/x (x.x)	x/x (x.x)	
Acute pulmonary oedema related to study intervention – no./total no. (%)	x/x (x.x)	x/x (x.x)	x.xx (x.xx – x.xx) [#]
Time to acute pulmonary oedema related to study intervention – hr	x.x (x.x – x.x)	x.x (x.x – x.x)	x.xx (x.xx – x.xx)[+]
Ischaemic complication related to study intervention – no./total no. (%)	x/x (x.x)	x/x (x.x)	x.xx (x.xx – x.xx) [#]
Ischaemic bowel – no./total no. (%)	x/x (x.x)	x/x (x.x)	
Ischaemic digits – no./total no. (%)	x/x (x.x)	x/x (x.x)	
Cardiac ischaemia – no./total no. (%)	x/x (x.x)	x/x (x.x)	
Other – no./total no. (%)	x/x (x.x)	x/x (x.x)	
Time to ischaemic complication related to study intervention – hr			x.xx (x.xx – x.xx)[+]
Ischaemic bowel – hr	x.x (x.x – x.x)	x.x (x.x – x.x)	
Ischaemic digits – hr	x.x (x.x – x.x)	x.x (x.x – x.x)	
Cardiac ischaemia – hr	x.x (x.x – x.x)	x.x (x.x – x.x)	
Other – hr	x.x (x.x – x.x)	x.x (x.x – x.x)	

Plus-minus are mean ± SD. Ranges are median (Q1-Q3). The analyses of complications related to treatment reported in this table were performed with mixed-effects logistic regression and Cox proportional hazard regression with treatment group as a fixed-effect and the study site as a random effect.

Odds ratio

+ Cause-specific hazard ratio

Table S10. Adverse events

Adverse event	Vasopressor arm (N=)	Fluids arm (N=)	P Value
No. of patients with event			
No. of events			
Type of event			

Comparisons between the number of adverse events by category were performed using the Fisher exact test.