Restricted or liberal fluid for haemodynamic resuscitation in sepsis

Protocol for an individual patient data meta-analysis of the ARISE FLUIDS, CLASSIC, CLOVERS and EVIS trials

Fluid **R**estricted r**E**suscitation in **S**epsis with **H**ypotension meta-ana**LY**sis (FRESHLY) Investigators

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Contents

1. INTRODUCTION

Sepsis has been identified as a global health priority by the World Health organisation [1], with an estimated annual incidence worldwide of 49 million cases and 11 million deaths [2]. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response, with septic shock defined as a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality [3].

The Surviving Sepsis Campaign recommends initial intravenous (IV) resuscitation with 30ml/kg of crystalloid fluid within the first three hours for patients with sepsis associated with hypotension and/or hypoperfusion [4]. These guidelines acknowledge a lack of evidence from randomised trials but cite support from a retrospective cohort study in which failure to deliver 30 ml/kg of IV fluid was associated with greater odds of mortality [5]. It is also recognised that in the three international trials of Early Goal Directed Therapy conducted in the past decade, fluid volumes of between 4 L and 5 L were administered in the first 24 hours in both intervention and control arms, demonstrating this is accepted standard practice [6]. Further, a recent Australian study reported an association between the volume of fluid administered in the first 24 hours of care and reduced adjusted odds of in-hospital mortality among patient admitted from the Emergency Department (ED) with infection, with the largest effect among those with septic shock admitted to an intensive care unit (ICU) [7].

There is currently a paucity of high-level evidence to inform the optimal haemodynamic resuscitation strategy in patients with septic shock, particularly during the initial phase of resuscitation which may take place in the ED or ward before admission to ICU. This equipoise is borne out in an observational study of 691 patients with sepsis and hypotension treated in 70 ED in Australia and New Zealand, where routine practice varied from a fluid-restrictive/early vasopressor strategy (<1500 ml IV fluid prior to vasopressors) to a liberal fluid strategy (>3000 ml IV fluid prior to vasopressors)[8].

Given the high mortality associated with septic shock, and the ubiquitous use of intravenous fluids and vasopressors in restoring perfusion, it is important that clinicians have high quality evidence on which to base treatment choices. Indeed, this question was identified as a high priority area for sepsis research [9]. Consequently, several large, multicentre clinical trials are currently in progress or planned.

This protocol describes a prospective, individual patient data meta-analysis (IPDMA) of four multicentre, open-label, randomised clinical trials of initial haemodynamic resuscitation in patients with septic shock. An IPDMA can overcome the limitations of a trial level meta-analyses of aggregate data which can arise due to heterogeneity. It also increases the power to detect differences in outcomes where mortality is low and among clinically important subgroups [10]. An IPDMA also allows for time-to-event analyses. Importantly, a prospectively planned IPDMA allows for harmonisation of data between trials and the publication of the outcomes and analysis plan prior to the analysis and reporting of any of the individual trial results which substantially strengthens validity of the IPDMA. This approach aims to provide high level evidence to address the question of whether a fluid-sparing/early vasopressor approach or a liberal fluid/later vasopressor approach to initial haemodynamic resuscitation in septic shock results in improved outcomes, including mortality.

2. OBJECTIVES

The primary objective of this IPDMA is to assess the effect on 90-day mortality of a resuscitation strategy based upon restriction of IV fluids compared to a conventional 'liberal' fluid strategy for haemodynamic resuscitation in adult patients with acute septic shock. Secondary objectives will assess the impact of the two resuscitation strategies on hospital and ICU length of stay, incidence and duration of organ failure (organ failure-free days) and safety.

Additional objectives include comparing the effect of the two haemodynamic resuscitation strategies on 90-day all-cause mortality on predetermined clinically important subgroups categorised according to patient characateristics and baseline fluid resuscitation.

3. PRIMARY OUTCOME

- All-cause mortality at 90 days post randomisation

4. SECONDARY OUTCOMES

- Time from randomisation to death
- Incidence of mechanical ventilation
- Incidence of acute renal replacement therapy
- Days alive free of organ support at 28 days post randomisation
- Duration of hospital and ICU stay
- Incidence of serious adverse events (SAE)

5. METHODS AND ANALYSIS

5.1 Included Studies

We will include four multicentre, open-label, randomised, clinical trials:

- Australasian Resuscitation in Sepsis Evaluation Fluids of Vasopressors in Emergency Department Sepsis (ARISE FLUIDS) trial conducted in Australia and New Zealand. ClinicalTrials.gov identifier NCT04569942
- Conservative versus Liberal Approach to fluid therapy of Septic Shock in intensive Care (CLASSIC) trial conducted in seven European countries. ClinicalTrials.gov identifier NCT03668236
- Crystalloid Liberal or Vasopressors Early (CLOVERS) trial conducted in the United States. ClinicalTrials.gov identifier NCT03434028
- Early Vasopressors in Sepsis (EVIS) trial conducted in the United Kingdom. ClinicalTrials.gov identifier NCT05179499

All four trials have all received relevant approval from a research ethics committee with a locally appropriate method of obtaining consent. These trials are prospectively chosen prior to the results of any individual trial being known because they are investigating the same broad question in patients with acute septic shock across several countries. The investigators of these trials collaborated to harmonise data and outcomes as far as possible across all trials to facilitate an IPDMA. This approach has successfully been used to analyse the three large international early goal-directed therapy trials in septic shock [11].

5.2 Participants

All trials include adult patients requiring resuscitation for hypotension or hypoperfusion due to suspected sepsis as defined in the original studies. Participants may be enrolled in the emergency department, acute care ward or intensive care unit.

All participants will have suspected or proven infection and meet one or more of the following criteria:

1) Systolic blood pressure (SBP) <100 mm Hg OR
   mean arterial pressure (MAP) <65 mm Hg

2) Lactate ≥ 2.0 mmol/L

3) Requirement for vasopressors to meet perfusion targets

5.3 Intervention and control groups

All four trials randomise to two treatment groups in a 1:1 ratio. Intervention arms are either:

- A haemodynamic resuscitation strategy based upon the restriction of IV fluids (by either volume or rate of infusion) with initiation or titration of vasopressors if required to meet perfusion targets or
- A strategy of resuscitation with intravenous fluids as the primary intervention to achieve perfusion targets with subsequent initiation or titration of vasopressors if required.

For the purposes of the IPDMA, the intervention is the group allocation within each trial regardless of actual fluid volume administered, or the timing or use of vasopressors.

5.4 Data Management

Prior to pooling of the data from the four trials, the clinical report forms, data dictionaries and study protocols for each trial will be compared and consensus definitions will be resolved by discussion between the trials teams to determine the final structure of the IPDMA dataset. Similar variables will be checked for consistency between the trials (analysis of distribution, range, and summary statistics) prior to being finally imported into the IPDMA database. Harmonisation of data will follow the principles used previously in the IPDMA of Early Goal Directed Therapy Trials in Sepsis [11].

5.5 Data synthesis

Baseline participant characteristics will be presented by treatment group and by trial. For continuous variables mean (and SD) or median (Q25, Q75) will be reported as appropriate. For categorical variables the absolute number and corresponding proportions (with 95% Confidence Intervals) will be presented. Patient characteristic across groups will be assessed using non-parametric Kruskal-Wallis tests for continuous variable and Chi-squared tests or Fisher's exact test for categorical variables as appropriate. Length of stay in hospital and ICU

will be reported for the overall population and for the subgroup who are alive at day 90 to account for the competing effect of early death.

5.6 Data analysis

A detailed statistical analysis plan will be developed and available prior to the closure of the last trial. The primary analysis will be undertaken in the intention to treat population with participants retained within their originally assigned treatment groups. The IPDMA will be a one stage, multi-level (patients nested in sites and nested in trials), mixed modelling. Heterogeneity between trials will be determined by fitting a fixed interaction term between treatment and trial, while overall treatment effect will be reported with trial treated as a fixed effect and site treated as a random effect. Additional sensitivity analyses will adjust for important baseline covariates including age, sex, illness severity, blood pressure and invasive mechanical ventilation.

Hospital (censored at 90 days) and 28-day mortality – binomial, mixed modelling reported as odds ratios with 95%CI.

Survival analysis – Cox proportional hazards regression reported as Hazards Ratio (95%CI)

Duration of stay in ED, ICU and hospital – assessed for normality, appropriate transformation reported as ratios of geometric means with 95% CI, accounting for impact of survivorship

Receipt of and duration of mechanical ventilation, vasopressor support and renal replacement therapy – binomial, mixed modelling reported as odds ratios with 95%CI

Where relevant, any assumptions underlying analyses will be detailed and reported. All results will be reported in tabular form and displayed using forest plots with 95%CI. All tests will be 2-sided and statistical significance will be defined as a p value of <0.05. No formal adjustment will be undertaken for multiple testing. However, given the number of outcomes and subgroups interpretation of p values beyond the primary outcome will be conservative.

5.7 Subgroup analyses

The following prespecified, clinically important, subgroups based on pre-randomisation variables will be analysed for the primary outcome as follows:

- Age

- Sex (M/F)
- Weight
- Blood lactate
- Source of infection (respiratory, urinary, abdominal/pelvic, other)
- IV fluid volume administration
- Mechanical ventilation
- Acute kidney injury (Y/N)
- Pre-existing congestive cardiac failure, chronic renal failure

5.8 Sample size considerations

Cumulatively, the included trials plan to enrol over 6000 participants.
Based on a relative reduction in 90-mortality of 20% and baseline mortality rate of 15%, this study will have >90% power (2 sided p-value of 0.05).
Should the baseline mortality rate be 20% or 25%, this study will have >95% power and >99% power respectively, to detect a 20% relative reduction (2 sided p-value of 0.05).

5.9 Confidentiality of data

Data will be transferred securely from each trial database to a central analysis centre following relevant approvals. All data will be stored securely according to existing protocols with access restricted by password to authorsised staff to ensure confidentiality. A Memorandum of Understanding between the trial groups will be established prior to the sharing of data. No identifying patient information will be transferred with pariticipants identified only by their unique study ID.

6. ETHICS AND DISSEMINATION

6.1 Ethics

All included trials received approval from Human Research Ethics Committee/Institutional Review Board and were conducted according to the regulatory requirements in each jurisdiction. Additionally, the IPDMA will be submitted for ethics approval.

6.2 Publication

The above analyses will be reported in a primary manuscript which will be submitted to an international journal. The authorship group will be identified as the FRESHLY Investigators and include representatives from all four trials on the writing committee.

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