Individual patient data comparative analysis of hydroxyethyl starch 130/0.4 v 4% albumin for fluid resuscitation in critically ill patients: statistical analysis plan

Naomi E Hammond, Laurent Billot, Simon Finfer and John Myburgh

There are currently no randomised controlled trials (RCTs) directly comparing iso-oncotic albumin to hydroxyethyl starch (HES) (130/0.4) in critically ill patients with sufficient statistical power to examine effects on important patient-centred outcomes. Two large-scale, high-quality, pragmatic RCTs of fluid resuscitation in intensive care patients (the Saline v Albumin Fluid Evaluation [SAFE]1 and Crystalloid v Hydroxyethyl Starch Trial [CHEST]2 studies) have been published. This means there is a unique opportunity to combine individual patient-level data to compare the effects of 4% albumin with 6% HES (130/0.4) on death-from-all-causes and other outcomes 28 days after randomisation in critically ill patients. On behalf of the SAFE and CHEST investigators, we present the statistical analysis plan (SAP) for an individual patient data comparative analysis to increase internal validity and minimise bias. Publishing a preplanned SAP is consistent with best research practice3–4 and will enable transparency of the study design.5–7 Human research ethics committee approval was received (protocol x12-0345 and LNR/12/RPAH/526).

Overview

The SAFE study was a multicentre, blinded RCT of 6997 patients, conducted in 16 Australian and New Zealand intensive care units between November 2001 and June 2003, that compared the effects of 0.9% saline and 4% albumin on 28-day all-cause mortality in a heterogeneous ICU patient population.1 No significant difference in 28-day all-cause mortality between patients resuscitated with 0.9% saline or 4% albumin (relative risk [RR], 0.99; 95% CI, 0.91–1.09; \( P = 0.87 \)) was observed. Long-term mortality was significantly increased in patients with severe traumatic brain injury who received 4% albumin (RR, 1.63; 95% CI, 1.17–2.26; \( P = 0.003 \)).8 In contrast, patients with severe sepsis assigned to receive 4% albumin had a reduced adjusted risk of death (odds ratio [OR], 0.71; 95% CI, 0.52–0.97; \( P = 0.03 \)).9

The CHEST study was also a multicentre, blinded RCT of 7000 patients, modelled on the design of the SAFE study. The CHEST study was conducted in 32 Australian and New Zealand ICUs between December 2009 and January 2012 and compared the effects of 6% HES (130/0.4) and 0.9% saline on 90-day mortality in a heterogeneous ICU patient population.2 No significant difference in 90-day mortality between patients assigned to receive 6% HES (130/0.4) or 0.9% saline was observed (RR, 1.06; 95% CI, 0.96–1.18; \( P = 0.26 \)). Mortality at 28 days was assessed as a tertiary outcome with no significant difference in mortality between groups reported (RR, 1.05; 95% CI, 0.93–1.19; \( P = 0.40 \)). At 90 days, there was a significant increase in the use of renal replacement therapy (RRT) in patients who received 6% HES (130/0.4) compared with those receiving 0.9% saline (RR, 1.21; 95% CI, 1.00–1.45; \( P = 0.04 \)).

ABSTRACT

Background: Recent randomised controlled trials have compared the effects of albumin and hydroxyethyl starch (HES) v crystalloids on patient-centred outcomes in critically ill patients. The Saline v Albumin Fluid Evaluation (SAFE) trial reported patient-centred outcomes at 28 days in 6933 patients assigned to fluid resuscitation with either 4% albumin or 0.9% saline; the Crystalloid v Hydroxyethyl Starch Trial (CHEST) reported patient-centred outcomes at 28 days in 6644 patients assigned to fluid resuscitation with either 6% HES (130/0.4) or 0.9% saline. As the two trials used a common reference fluid (0.9% saline) and had most trial methods and data collection points harmonised, a comparison of 4% albumin and 6% HES (130/0.4) on patient-centred outcomes at 28 days in critically ill patients using the individual patient data from the two trials is feasible.

Objectives: To prepublish the statistical analysis plan (SAP) of an individual patient data comparative analysis of the SAFE and CHEST studies.

Methods: The statistical analyses are described in detail with the appropriate statistical analysis specified.

Results: The planned statistical analyses are described in detail for the SAFE and CHEST individual patient data comparative analysis. We outline the proposed statistical analysis for the baseline characteristics, processes of care and the outcomes. Subgroups are defined with statistical comparisons between the fluid groups and in each subgroup explained.

Conclusion: We have developed a SAP for the SAFE/CHEST individual patient data comparative analysis to increase the internal validity of the study and minimise bias.
Table 1. Inclusion and exclusion criteria of the CHEST and SAFE trial

<table>
<thead>
<tr>
<th>Criteria</th>
<th>SAFE</th>
<th>CHEST</th>
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<tbody>
<tr>
<td><strong>Inclusion criteria</strong></td>
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<tr>
<td>• Written informed consent has been obtained or if not possible, the procedure for obtaining delayed informed consent has been approved by the ethics committee before randomisation</td>
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<td>• Fluid resuscitation is required to increase or maintain intravascular volume that is in addition to maintenance fluids, enteral and parenteral nutrition, blood products and specific replacement fluids to replace ongoing insensible or fluid losses from other sites (eg, fistula losses from the gastrointestinal tract, urinary losses from diabetes insipidus or the polyuric phase of acute renal failure, or to correct metabolic derangements)</td>
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<tr>
<td>• The ICU clinician considers that 4% albumin (SAFE), 6% hydroxyethyl starch (130/0.4) (CHEST) and 0.9% saline are equally appropriate for the patient and that no specific indication or contraindication for any exists</td>
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<td>• The requirement for fluid resuscitation must be supported by at least one of the following clinical signs:</td>
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<td>➢ heart rate &gt; 90 beats/minute</td>
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<td>➢ systolic blood pressure &lt; 100 mmHg, or mean arterial pressure &lt; 75 mmHg, or ≥ 40 mmHg decrease in systolic or mean arterial pressure from the baseline recording</td>
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<td>➢ central venous pressure &lt; 10 mmHg</td>
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<td>➢ pulmonary artery wedge pressure &lt; 12 mmHg</td>
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<td>➢ respiratory variation in systolic or mean arterial pressure &gt; 5 mmHg</td>
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<td>➢ capillary refill time &gt; 1 second</td>
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<td>➢ urine output &lt; 0.5 mL/kg for 1 hour</td>
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<td><strong>Exclusion criteria</strong></td>
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<td>• Age &lt; 18 years</td>
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<td>• Past known allergic reaction to a human albumin solution (SAFE) or a hydroxyethyl starch solution (CHEST)</td>
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<td>• Religious objection to the administration of human blood products (eg, if patient was a Jehovah’s Witness)</td>
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<td>• Patient is to undergo plasmapheresis during the ICU admission</td>
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<tr>
<td>• Primary non-traumatic intracranial haemorrhage or severe traumatic intracranial haemorrhage (mass lesion of &gt; 25 mL, seen on cranial computed tomographic scan)</td>
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<tr>
<td>• Patient is undergoing RRT or the ICU clinician considers RRT is imminent (ie, RRT will start in 6 hours)</td>
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<td>• Undocumented serum creatinine level &gt; 350 μmol/L and urine output averaging ≤ 10 mL/hour over 12 hours</td>
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<td>• Severe hypernatraemia (serum sodium &gt; 160 mmol/L)</td>
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<td>• Severe hyperchloraemia (serum chloride &gt; 130 mmol/L)</td>
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<td>• Woman is of child-bearing age (18–49 years), unless there is documented evidence of menopause, hysterectomy, surgical sterilisation or a negative pregnancy test before randomisation</td>
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<td>• Woman is breastfeeding</td>
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<td>• Patient has received hydroxyethyl starch &gt; 1000 mL outside the ICU within 24 hours before randomisation</td>
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<td>• Patient was admitted to the ICU after cardiac surgery</td>
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<td>• Patient was admitted to the ICU for treatment of burns or after liver transplantation surgery</td>
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<tr>
<td>• Death is deemed imminent and inevitable or the patient has an underlying disease and a life expectancy &lt; 90 days</td>
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<tr>
<td>• A limitation-of-therapy order has been documented restricting implementation of the study protocol or the treating clinician deems aggressive care unsuitable</td>
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<tr>
<td>• Patient has previously been enrolled in the SAFE or CHEST study</td>
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<tr>
<td>• Patient has previously received fluid resuscitation that was prescribed within the study ICU during this current ICU admission (this allows inclusion of patients who arrive in the ICU with fluid running)</td>
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<tr>
<td>• Patient has been transferred to the study ICU from another ICU and received fluid resuscitation for the treatment of volume depletion in that other ICU</td>
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CHEST = Crystalloid v Hydroxyethyl Starch Trial. SAFE = Saline v Albumin Fluid Evaluation. ICU = intensive care unit. RRT = renal replacement therapy.
Patient population

The primary inclusion criterion for the CHEST and SAFE studies was patients 18 years or older who had been admitted into an ICU and the treating clinician believed the patient needed fluid for resuscitation to increase or maintain intravascular volume. This decision was supported by at least one clinical criterion being present.

The main differences in the patient populations between the trials were the exclusion of patients with a primary non-traumatic intracranial haemorrhage or traumatic intracranial haemorrhage (mass lesion > 25 mL) and the exclusion of patients receiving, or about to receive, RRT in the CHEST study. Table 1 outlines the full inclusion and exclusion criteria of the CHEST and SAFE studies.

Objectives

The principal objective of our study is to compare the effects of resuscitation with 4% albumin or 6% HES (130/0.4) on 28-day all-cause mortality in a heterogeneous ICU patient population. This and other selected outcomes will also be assessed in predefined subgroups (patients with sepsis, acute kidney injury, operative and non-operative patients and disease severity), cardiovascular measurements (HR, MAP and CVP), MV and pre-ICU albumin or HES use.

Definition of efficacy variables

Primary outcome

The primary outcome is all-cause mortality at 28 days. This was the primary outcome for the SAFE study and a tertiary outcome for the CHEST study.

Secondary outcomes

Secondary outcomes will be the proportions of patients treated with RRT, and days alive and free of RRT; and the proportions of patients treated with mechanical ventilation (MV), and days alive and free of MV within 28 days.

Tertiary outcomes and process measures

These include:

- ICU and hospital mortality within 28 days
- new organ failure, defined by sequential organ failure assessment (SOFA) scores of 0, 1 or 2 in any individual score at baseline, followed by an increase in the score to 3 or 4 in the same system within 28 days
- ICU and hospital length-of-stay
- daily volume of study or non-study fluid given in the first 4 days and total volume by Day 28
- daily volume of transfusion requirements given in the first 7 days and total volume by Day 28
- positive fluid balance daily for the first 7 days and total by Day 7
- physiological effects (central venous pressure, mean arterial pressure and heart rate) in the first 7 days.

Statistical methods

Analysis principles

All analyses will be conducted on an intention-to-treat basis. P values of < 0.05 will be considered statistically significant unless otherwise stated. No imputation for missing values will be made unless otherwise specified. The number of observations used in the analysis will be reported.

Data preparation

Table 2 lists the data available in the SAFE and CHEST studies that will be used in our comparative analysis.

Assessment of trial heterogeneity

We will examine potential sources of heterogeneity of the comparative treatment effects. As recommended by the Australian Government Pharmaceutical Benefits Advisory Committee indirect comparisons working group report, the following factors will be considered:

- confounding factors related to the included participant population (patient baseline characteristics, eg, age, sex and severity of illness).
confounding factors related to the trial circumstances (eg, participating hospitals, geographical circumstances and date of trials)
• differing treatment in the common reference group and the intervention group (eg, dose, timing and duration of treatment)
• differing outcome measures and statistical analysis methods (eg, definitions, scoring tools used and frequency of measurement).

Pooled data analysis
After exclusion of patients (as outlined under Patient population and in Figure 1), the individual patient data from the SAFE and CHEST studies will be merged into one master dataset. All patients will be analysed with appropriate adjustments for heterogeneity at the individual patient level, using a combination of multivariate analysis and propensity score methods. All analyses and covariate adjustments will only be conducted using this pooled dataset. Table 2 outlines the summary and time schedule of the data to be retrieved from the SAFE and CHEST databases. The numbers of patients included in the different levels of analysis will be shown in a study flow diagram (Figure 1).

Statistical analysis of baseline characteristics
The common comparator between the SAFE and CHEST studies is 0.9% saline. The saline groups in the two trials will be compared using common baseline variables to determine variations between the two cohorts.
A description of the baseline characteristics of patients assigned to receive saline in the SAFE and CHEST studies, and the respective study fluids, will be presented. Discrete variables will be summarised using numbers and percentages that will be calculated from the number of patients for whom data are available. Where values are missing, the denominator will be stated in the text or in a footnote in the corresponding summary table. Continuous variables, including durations, will be summarised using standard measures of central tendency and dispersion (means and SDs or medians and interquartile ranges) (Table 3 and Table 4).

Baseline variables that have different distributions between the two studies will be included as covariates in

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**Table 3. Baseline characteristics available for comparative analysis**

- Age*
- Sex
- Source of admission to ICU (ED, hospital ward, another ICU, another hospital, OT after emergency surgery, OT after elective surgery or readmission to the same ICU during the same hospitalisation)
- Time from ICU admission to randomisation*
- Operative ICU admission diagnosis (cardiovascular, gastrointestinal, gynaecological, neurological, orthopaedic, renal, respiratory, trauma or other postoperative diagnosis)
- Non-operative ICU admission diagnosis (cardiovascular, gastrointestinal, haematological, metabolic, neurological, other medical, renal, respiratory, sepsis or trauma)
- Sepsis at baseline (a defined focus of infection [yes/no], two or more SIRS15 criteria [yes/no] and source of infection)
- Severe sepsis at baseline (sepsis plus one or more organ failures, as defined by two or more points on any SOFA score10 component, except in the cardiovascular score which will include a SOFA score of 1, 3 or 4)
- SOFA score10 (cardiovascular, respiratory, renal, hepatic and haematological components)
- Cardiovascular measurements (heart rate [beats/min],* mean arterial pressure [mmHg],* central venous pressure [mmHg]* and mechanical ventilation before randomisation)
- Pre-ICU albumin or hydroxyethyl starch (yes/no)
- APACHE II score*11

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**Table 4. Process and outcome measures available for comparative analysis**

**Day 0 to Day 28**
- Cardiovascular measurements indicating response to fluid resuscitation (heart rate, mean arterial pressure, central venous pressure)
- Daily transfusion requirements (mL) over time
- Daily amount of study fluid (mL) over time
- Renal replacement therapy (daily)
- Mechanical ventilation requirements (daily)
- SOFA score10 (daily to Day 7, then every 3rd day)
- Time on study treatment (days)
- Time from cessation of study treatment to (last) discharge from ICU
- Daily fluid balance (mL) over time
- Average over time from randomisation to time study treatment stopped (if treatment is stopped and then restarted, all episodes on study treatment will be used to calculate the mean)*
- Time of ICU discharge
- Time of index hospital discharge
- Date of death

SOFA = sequential organ failure assessment. ICU = intensive care unit.
* Ordinal and continuous data will be reported as mean with SD, or median with interquartile range. Dichotomous variables will be reported as number of patients and percentage with data available.
the multivariate models comparing the individual patient data of the albumin and HES groups. The difference in the distributions between baseline variables will be assessed using the standardised differences.\textsuperscript{13,15,16}

Missing data
If more than 5\% of data are missing for a variable, an “unknown” category will be created. If the variable is continuous, it will be categorised.

Additional covariates for primary and subgroup analysis
In addition to baseline characteristics for which differences between the two groups are shown, covariates that are predictors of mortality or predictors of fluid use will be included in an adjusted analysis. Baseline and additional covariates to be included are:
- acute kidney injury (AKI) score (measured by the renal domain of the sequential organ failure assessment [SOFA] score)\textsuperscript{10}
- age
- Acute Physiology and Chronic Health Evaluation (APACHE) II\textsuperscript{11} score
- central venous pressure
- sex
- heart rate
- individual SOFA scores\textsuperscript{10}
- mean arterial pressure
- MV
- non-operative patients
- operative (emergency) patients
- operative (elective) patients
- sepsis
- severe sepsis
- source of admission.

Propensity score
Propensity scores will be calculated to adjust for imbalances between the HES and albumin groups.\textsuperscript{17,18} The propensity score will first be used as an additional covariate in the multivariate analysis; second, to create a matched sample; and third, to calculate inverse probability treatment weights (IPTW). The propensity score will be modelled on the probability of being treated in the CHEST v the SAFE studies.

Baseline variables that are common to the two studies will be included in the logistic regression analysis model to calculate the propensity score. First-order interactions that have a resulting $\chi^2 \ P<0.5$ will be included in the model. After the propensity score is generated, the distribution of scores between the two treatment groups will be assessed for adequate overlap so as to allow comparability.\textsuperscript{17} The covariate distribution will be compared for differences by using the standardised differences.\textsuperscript{13,16}

Analysis methods

Multivariate analysis
We will undertake a multivariate adjusted analysis, using logistic or linear regression, to analyse the primary, secondary and tertiary outcomes and process measures. Univariate analyses will be conducted using the baseline variables identified in the comparison of the common reference groups, plus any additional covariates as outlined above under Additional covariates for primary and subgroup analysis. The covariate analyses with $P<0.2$ will be included in the multivariate analysis. Missing values will be treated as described above under Missing data. The multivariate analysis will be conducted with and without the propensity score added as a covariate.

Matched analysis with propensity score
In addition to the multivariate analysis, we will create matched samples using propensity scoring. We will match individual patients between the SAFE study treatment group (albumin) and the CHEST treatment (HES) group using the optimal matching technique that is most likely to create adequately matched pairs for enough patients,\textsuperscript{7} and we will assess the quality of the matching using the...
standardised difference.\textsuperscript{7,17,19} We will use logistic or linear regression with generalised estimating equations to model the correlation within each matched pair,\textsuperscript{13,20} and this method will be considered as the primary analysis from all proposed analysis methods.

**Analysis with IPTWs**
We will use the propensity score to weight individual data using IPTWs. The formula for estimating the IPTW is:

\[
    w_{i} = \frac{z_{i}}{\epsilon_{i}} + \left(1 - \frac{z_{i}}{(1 - \epsilon_{i})}\right)
\]

in which \(w_{i}\) is the IPTW, \(z_{i}\) will be equal 1 for CHEST or 0 for SAFE, and \(\epsilon_{i}\) is the propensity score. The weight given to each patient is equal to the inverse of the probability of receiving the treatment that the patient actually received.\textsuperscript{19} For extreme weight values, stabilisation techniques will be used.\textsuperscript{21} The quality of the weighting will be tested using standardised difference.\textsuperscript{7}

**Aggregate data indirect comparison**
We will use the model of Bucher and colleagues\textsuperscript{22} as a reference for the traditional, common, reference-based indirect comparison. We will only use this approach on the primary outcome (28-day mortality) and the secondary outcome of RRT and MV use. The approach will consist of calculating the following odds ratios:
- comparing albumin with saline in the SAFE study (\(OR_{ALB/SAL}\))
- comparing HES with saline in the CHEST study (\(OR_{HES/SAL}\)).

Following Bucher and colleagues, the effect of HES compared with albumin will be estimated as:

\[
    \log(OR_{HES/ALB}) = \log(OR_{HES/SAL}) - \log(OR_{ALB/SAL})
\]

and its variance as:

\[
    \text{var}(\log(OR_{HES/ALB})) = \text{var}(\log(OR_{HES/SAL})) + \text{var}(\log(OR_{ALB/SAL})).
\]

**Analysis models**
We will analyse binary outcomes using logistic regression (ICU and hospital mortality and SOFA score [respiratory, coagulation, liver, and cardiovascular failure]), and will present treatment effects as unadjusted and adjusted odds ratios and 95% CIs.

For continuous outcomes, we will use linear regression (daily volume of study fluid given, daily transfusion requirements, fluid balance and length of stay). We will report the summary statistics as mean and SD per arm, and mean difference with 95% CI.

To account for the matched nature of the data after optimal matching (described above under Matched analysis with propensity score), we will use generalised estimating equations that model the within-matched pair correlation.\textsuperscript{20}

**Subgroup analysis**
We will conduct subgroup analyses on the following a priori baseline characteristics applied to the primary outcome measure of 28-day mortality and secondary outcomes of RRT and MV use. We will conduct adjusted analyses using logistic regression and in each subgroup, treatment effect will be assessed using odds ratios with 95% CIs. To assess heterogeneity, we will conduct a test of interaction between the subgroup variable and the treatment arm. We will conduct the subgroup analyses using the matched sample (described under Matched analysis with propensity score) and IPTW (described under Analysis with IPTWs).

The four baseline characteristics that will define subgroups are sepsis, AKI, operative and non-operative patients, and disease severity.

**Sepsis**
This subgroup will consist of two levels: sepsis and severe sepsis. Patients with sepsis includes patients with a defined focus of infection and two or more systemic inflammatory response syndrome criteria. Patients with severe sepsis includes patients with sepsis and one or more organ failures. Organ failure is to be defined as 2 or more points in any SOFA score component at baseline, except for the cardiovascular score which will include a SOFA score of 1, 3 or 4.

**Acute kidney injury**
AKI will be defined as 2 or more points in the renal component of the SOFA score\textsuperscript{10} (creatinine > 170 μmol/L or < 500 mL total urine output in the 24 hours before randomisation)

**Operative and non-operative patients**
This subgroup will consist of three levels: operative (emergency surgical and elective surgical) and non-operative (medical) patients. Operative patients will be defined as patients who have been admitted from the operating room or the recovery room (either elective or emergency surgery) before randomisation. All other patients will be classified as medical patients.

**Disease severity**
We will compare low disease severity with high disease severity. High disease severity is defined as an APACHE II\textsuperscript{11} score ≥ 25.

**Tables and figure shells**
Tables will include baseline characteristics of patients assigned to receive saline in the SAFE and CHEST studies, and patients assigned to 4% albumin and 6% HES, along with process measures, volume of study fluid given, outcomes and subgroup analyses.

Planned tables and figures include:
- baseline characteristics (saline groups, plus albumin and HES groups)
• results from logistic and linear regression using multivariate analysis, matching, IPTW and indirect comparison as described by Bucher and colleagues\(^2\)
• study fluid administration and physiological effects of treatment
• flow diagram of available patients (data completeness) for SAFE and CHEST studies
• distribution of propensity scores
• plot of standardised difference of means of baseline covariates
• forest plot of subgroup analyses using matching and IPTWs.

Discussion
This is the SAP for an individual patient data comparative analysis study comparing 4% albumin with 6% HES (130/0.4). This study will use the individual patient data of the CHEST and SAFE studies to compare the effects of resuscitation between two colloids (4% albumin to 6% HES (130/0.4)) on 28-day all-cause mortality in a heterogeneous ICU patient population, along with prespecified subgroups.

In the absence of RCTs directly comparing HES with albumin, the proposed individual patient data comparison will provide the best possible evidence. This study is unique, as the individual patient data from two high-quality, large-scale randomised trials, conducted by the same group of investigators, is available to the authors, enabling a comparative analysis using a combination of statistical methods. In addition to undertaking a traditional common reference-based indirect comparison, we will use propensity scores to balance the two trials and assess the sensitivity of the results to various methods. Limitations include the facts that the trials were conducted almost 10 years apart, they had different primary outcomes, and they contained different patient acuities.

Our comparative analysis will not only use available statistical methods in a novel approach, but will give new evidence in the comparison of two commonly used colloids for resuscitation in critically ill adult patients.

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Competing interests
None declared.

Author details
Naomi E Hammond, Research Fellow,\(^1\) Intensive Care Research Manager,\(^2\) PhD Candidate,\(^3\) and Conjoint Senior Lecturer\(^4\)

Laurent Billot, Associate Professor,\(^4\) and Director\(^5\)
Simon Finfer, Professorial Fellow,\(^1\) Senior Staff Specialist in Intensive Care,\(^7\) and Professor\(^4\)
John Myburgh, Director,\(^1\) Professor of Critical Care,\(^9\) and Senior Staff Specialist in Intensive Care\(^6\)
1 Critical Care and Trauma Division, The George Institute for Global Health, Sydney, NSW, Australia.
2 Malcolm Fisher Department of Intensive Care, Royal North Shore Hospital, Sydney, NSW, Australia.
3 St George Clinical School, University of New South Wales, Sydney, NSW, Australia.
4 Sydney Medical School, University of Sydney, Sydney, NSW, Australia.
6 Department of Intensive Care, St George Hospital, Sydney, NSW, Australia.

Correspondence: nhammond@georgeinstitute.org.au

References
5 Thomas L, Peterson ED. The value of statistical analysis plans in observational research: defining high-quality research from the start. \(JAMA\) 2012; 308: 773-4.
12 Report of the Indirect Comparisons Working Group to the Pharmaceutical Benefits Advisory Committee: assessing indirect compari-


