In critically ill patients with impaired circulation, fluid resuscitation is the cornerstone of the initial treatment in the intensive care unit. Colloids are frequently used, and hydroxyethyl starch (HES) is the most commonly used colloid, worldwide. The efficacy and safety of HES use in critically ill patients has been evaluated in high-quality randomised controlled trials (RCTs), including the Crystalloid versus Hydroxyethyl Starch Trial (CHEST) and the Scandinavian Starch in Severe Sepsis/Septic Shock Trial (6S). These trials compared 6% HES solutions (with a molecular weight of 130 kD and molar substitution ratio of between 0.4 and 0.42) with their respective carrier crystalloid solutions in a general population of critically ill patients and patients with severe sepsis, and assessed their effect on all-cause 90-day mortality and the use of renal replacement therapy (RRT). Both trials raised safety concerns about the use of HES in these patients, by showing an increase in the relative risk (RR) of death in the 6S trial, and an increase in the use of RRT in both trials.

Before the trials were completed and published, the investigators agreed to conduct an individual patient data meta-analysis (IPDMA) of patients with severe sepsis in order to facilitate a preplanned individual patient data meta-analysis (IPDMA) of patients with severe sepsis. Data collection was harmonised between the two trials in order to facilitate a preplanned individual patient data meta-analysis (IPDMA) of patients with severe sepsis.

Objectives and rationale: To publish a statistical analysis plan (SAP) for an IPDMA of patients with severe sepsis enrolled in the 6S trial and the CHEST.

Methods and outcomes: The SAP is described in broad detail with specific information regarding baseline characteristics and process of care. The outcomes for the trial have been described and are presented as primary, secondary and exploratory outcomes with appropriate comparisons between groups detailed. Subgroups have been defined based on pre-randomisation variables.

Conclusion: We developed a preanalysis SAP to combine data on patients with severe sepsis from the 6S trial and the CHEST. Pre-publication of our SAP will reduce the risk of bias in the reporting of the results and improve confidence in the estimates of effects, allowing comparisons with conventional meta-analyses and assisting in the translation of research findings into clinical practice.
observed, compared with patients who were assigned to receive Ringer’s acetate.

CHEST was a multicentre, blinded RCT of 7000 patients conducted in 32 Australian and New Zealand ICUs between December 2009 and January 2012. CHEST compared the effect of 6% HES (130/0.4) (Voluven [Fresenius Kabi]) and 0.9% saline on 90-day mortality in a heterogeneous ICU patient population.2 No significant difference in 90-day

<table>
<thead>
<tr>
<th>Table 1. Inclusion and exclusion criteria of the CHEST and 6S trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Criteria</strong></td>
</tr>
<tr>
<td>Inclusion criteria</td>
</tr>
<tr>
<td>Written, informed consent obtained or, if not possible, procedure for obtaining delayed, informed consent approved by ethics committee before randomisation</td>
</tr>
<tr>
<td>Fluid resuscitation required to increase or maintain intravascular volume, in addition to maintenance fluids, enteral and parenteral nutrition, blood products and specific replacement fluids to replace ongoing insensible or other fluid losses</td>
</tr>
<tr>
<td>ICU clinician considers that 6% hydroxyethyl starch (130/0.4)* and 0.9% saline are equally appropriate for the patient and no specific indication or contraindication for either exists</td>
</tr>
<tr>
<td>Requirement for fluid resuscitation supported by at least one of the following clinical signs:</td>
</tr>
<tr>
<td>1. heart rate &gt;90 beats per minute</td>
</tr>
<tr>
<td>2. systolic blood pressure &lt; 100 mmHg, or mean arterial pressure &lt; 75 mmHg, or at least 40 mmHg decrease in systolic or mean arterial pressure from baseline recording</td>
</tr>
<tr>
<td>3. central venous pressure &lt; 10 mmHg</td>
</tr>
<tr>
<td>4. pulmonary artery wedge pressure &lt; 12 mmHg</td>
</tr>
<tr>
<td>5. respiratory variation in systolic or mean arterial pressure &gt; 5 mmHg</td>
</tr>
<tr>
<td>6. capillary refill time &gt; 1 second</td>
</tr>
<tr>
<td>7. urine output &lt; 0.5 ml/kg for 1 hour</td>
</tr>
<tr>
<td>Patient fulfils criteria for severe sepsis within the previous 24 hours, according to the SCCM/ACCP definitions</td>
</tr>
<tr>
<td>Exclusion criteria</td>
</tr>
<tr>
<td>Age &lt; 18 years</td>
</tr>
<tr>
<td>Known previous allergic reaction to hydroxyethyl starch solutions or malic acid†</td>
</tr>
<tr>
<td>Primary non-traumatic intracranial haemorrhage* or severe traumatic intracranial haemorrhage (mass lesion on cranial computerised tomographic scan &gt; 25 ml)*</td>
</tr>
<tr>
<td>Receiving RRT* or ICU clinician considers RRT is imminent (ie, RRT will start in 6 hours)*</td>
</tr>
<tr>
<td>Documented serum creatinine level &gt; 350 μmol/L, and urine output average is ≤ 10 ml/hour over 12 hours</td>
</tr>
<tr>
<td>Severe hypernatraemia (serum sodium &gt; 160 mmol/L)</td>
</tr>
<tr>
<td>Severe hyperchloreaemia (serum chloride &gt; 130 mmol/L)</td>
</tr>
<tr>
<td>Severe hyperkalaemia (plasma potassium &gt; 6 mmol/L)</td>
</tr>
<tr>
<td>Woman is of child-bearing age (18–49 years old), unless documented evidence of menopause, hysterectomy, surgical sterilisation or negative pregnancy test before randomisation</td>
</tr>
<tr>
<td>Woman is breastfeeding</td>
</tr>
<tr>
<td>Received &gt; 1000 ml hydroxyethyl starch* or any synthetic colloid† within 24 hours before randomisation</td>
</tr>
<tr>
<td>Patient admitted to the ICU after cardiac surgery</td>
</tr>
<tr>
<td>Patient admitted to the ICU for treatment of burns or after liver* or kidney† transplantation surgery</td>
</tr>
<tr>
<td>Death is deemed imminent and inevitable* or the patient has an underlying disease process with a life expectancy of &lt; 90 days*</td>
</tr>
<tr>
<td>Limitation of therapy order is documented restricting implementation of study protocol, or treating clinician deems aggressive care unsuitable</td>
</tr>
<tr>
<td>Previous enrolment in the CHEST or 6S trial</td>
</tr>
<tr>
<td>Patient 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>
</tr>
<tr>
<td>Patient was transferred to the study ICU from another ICU and received fluid resuscitation for the treatment of volume depletion in that other ICU</td>
</tr>
<tr>
<td>Enrolment into another ICU trial of drugs with potential action on circulation, renal function or coagulation</td>
</tr>
</tbody>
</table>

CHEST=Crystalloid versus Hydroxyethyl Starch Trial. 6S=Scandinavian Starch in Severe Sepsis/Septic Shock. ICU=intensive care unit. SCCM/ACCP=Society of Critical Care Medicine/American College of Chest Physicians. RRT=renal replacement therapy. *CHEST. †6S.
mortality between patients assigned to receive 6% HES (130/0.4) and 0.9% saline was observed (RR, 1.06; 95% CI, 0.96–1.18; \(P = 0.26\)) although there was a significant increase in the use of RRT in patients assigned to receive 6% HES (130/0.4) compared with 0.9% saline (RR, 1.21; 95% CI, 1.00–1.45; \(P = 0.04\)).

**Objective**

The primary objective of our IPDMA is to determine whether fluid resuscitation with 6% HES (130/0.4) or 6% HES (130/0.42) versus normal saline or Ringer’s acetate affects the risk of death at 90 days, use of RRT, or the development of acute kidney injury (AKI) in patients with severe sepsis. We will conduct adjusted analyses to identify risk factors for all outcomes and to determine whether the influence of type of resuscitation fluid on the outcomes persists as an independent risk factor.

Outcomes will also be determined in the following predefined patient subgroups: with and without septic shock, with and without acute kidney failure, with and without the administration of 6% HES before randomisation, operative versus non-operative, and high versus low severity of illness.

**Population**

**Patient selection**

Table 1 outlines the inclusion and exclusion criteria of the 6S trial and CHEST. All patients from the 6S trial will be included in the IPDMA. CHEST patients with sepsis and severe sepsis will be included according to the following definitions:

- Sepsis: a source of infection and two systemic inflammatory response syndrome criteria
- Severe sepsis: sepsis plus at least one organ failure, defined as a Sequential Organ Failure Assessment (SOFA) score of 2 or more for the organ in question, except in the case of the cardiovascular score which will include a SOFA score of 1, 3 or 4.

Definitions of organ failures derived from the SOFA score are:

- Glasgow coma score < 13
- \(\text{PaO}_2/\text{FiO}_2\) ratio < 300 mmHg in the 24 hours before randomisation
- Mean arterial pressure < 70 mmHg, or requirement for vasopressors or inotropic treatment (any of the following: noradrenaline, adrenaline, dopamine \(\geq 5.1 \mu g/kg/min\), vasopressin, metaraminol, phenylephrine)
- Creatinine > 170 \(\mu g/L\) or < 500 mL total urine output in the 24 hours before randomisation
- Platelet count < 100 \(\times 10^9/\text{L}\) in the 24 hours before randomisation
- Bilirubin > 32 \(\mu g/dL\) in the 24 hours before randomisation.

**Efficacy variables**

**Primary outcomes**

The primary outcome will be 90-day mortality (any cause).

**Secondary outcomes**

The secondary outcomes will be:

- The use of RRT 90 days after randomisation
- Creatinine criteria from the RIFLE score:
  - RIFLE-R: a 1.5 times increase in creatinine from the baseline level (last creatinine measured before randomisation [CHEST] and preadmission creatinine before randomisation [6S trial])
  - RIFLE-I: creatinine double that of the baseline level
  - RIFLE-F: creatinine triple that of the baseline level, or an acute rise of \(\geq 44 \mu g/L\), from baseline creatinine, and creatinine \(\geq 350 \mu g/L\)
- Days alive and not requiring RRT in the 90-day follow-up period (the patient is considered dependent on RRT from the date RRT is started to the last date of RRT treatment)
- 28-day mortality (any cause).

**Exploratory outcomes and process measures**

Other outcomes and measures to be evaluated include:

- Days alive and free of mechanical ventilation in the 90-day period
- Days alive and out of ICU in the 90-day period
- Days alive and out of hospital in the 90-day period
- Total and daily volume received of study and non-study fluids in the first 7 days
- Total and daily volume of blood products received for the first 7 days (combined and split into packed red cells, fresh frozen plasma and platelets)
- Total and daily fluid balance in the first 7 days
- New organ failure in the first 5 days, as defined by the SOFA score of 0 or 1 in any individual score at baseline, followed by an increase in the score to 2, 3, or 4 in the same system within 5 days.

**Subgroup and covariates analyses**

We will examine the effect of treatment allocation in patient subgroups and test for heterogeneity in effects between subgroups. The same variables will also be used as covariates in multivariate models to identify factors that may be related to the outcomes.
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Table 2. Summary and schedule of data to be retrieved from the CHEST and 6S trial databases

<table>
<thead>
<tr>
<th>Period of study</th>
<th>Data collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomisation</td>
<td>Date of birth, sex, date of randomisation, treatment allocation, ICU admission diagnosis (surgical v non-surgical), weight</td>
</tr>
<tr>
<td>Baseline</td>
<td>Focus of infection (lung, abdomen, urinary tract, soft tissue or skin, other), data to derive SOFA score (including subscores), APACHE II score (CHEST), SAPS II score (6S), renal and circulatory parameters, treatment with hydroxyethyl starch prior to randomisation</td>
</tr>
<tr>
<td>Days 1–89</td>
<td>While in the ICU only: study fluid (mL/kg), non-study fluid for resuscitation (mL/kg), blood products (mL/kg), fluid balances (mL/kg) (Days 1–7 only), data to derive SOFA score including subscores (renal subscore Days 1–89, other subscores Days 1–5 only), RRT, MV</td>
</tr>
<tr>
<td>Day 90 summary</td>
<td>Vital status at Day 28 and Day 90, length of stay in ICU and hospital, total use of RRT and MV*</td>
</tr>
</tbody>
</table>

CHEST=Crystalloid versus Hydroxyethyl Starch Trial. 6S=Scandinavian Starch in Severe Sepsis/Septic Shock. SOFA=sequential organ failure assessment. APACHE=Acute Physiology and Chronic Health Evaluation. SAPS=Simplified Acute Physiology Score. RRT=renal replacement therapy. MV=mechanical ventilation. ICU=intensive care unit. *Data on MV in 6S trial, and on RRT in both trials, were collected for 90 days; CHEST registered MV until discharge from the index ICU admission.

Subgroups
Predefined subgroups will be created based on baseline characteristics using the definitions used in CHEST and the 6S trial.

Septic shock at randomisation
Septic shock will be defined according to the criteria of the 6S trial:
- mean arterial pressure < 70 mmHg (after initial fluid resuscitation), or
- requirement for ongoing vasopressor or inotropic treatment (as defined above under Patient selection), or
- arterial or venous lactate > 4 mmol/L.

AKI at randomisation
AKI will be defined as two or more points in the renal component of the SOFA score (creatinine > 170 μmol/L, or < 500 mL total urine output in the 24 hours before randomisation).

Prerandomisation HES
Both trials allowed 1000 mL of 6% HES (130/0.4 or 0.42) to be administered before randomisation. The subgroup analysis will compare patients who did not receive any HES versus patients who received 1–1000 mL of HES before randomisation.

Operative versus non-operative patients
Analysis will be undertaken for three groups: non-operative, elective surgical and emergency surgical patients, and comparisons will be made between the groups. Operative patients will be defined as patients needing emergency or elective surgery before ICU admission.

High versus low disease severity
High disease severity will be defined as an Acute Physiology and Chronic Health Evaluation (APACHE) II14 score of ≥ 24 for CHEST patients, or a Simplified Acute Physiology Score (SAPS) II15 of ≥ 53 in 6S trial patients (both these values correspond to an adjusted inhospital mortality of 53% for patients with an admission diagnosis of cardiovascular insufficiency due to sepsis).

Since there is no validated method for converting SAPS II scores to APACHE II scores, we will not use these scores as a continuous covariate for adjustment.

Additional baseline covariates
Additional baseline covariates for the adjusted analyses will include:
- age
- abdominal infection (intra-abdominal and gut)
- respiratory infection.

Statistical analysis
Analysis principles include the following:
- All analyses will be conducted on an intention-to-treat basis.
- All tests will be two-sided and the nominal level of alpha will be 5%.
- We will conduct unadjusted and fully adjusted analyses for all outcomes (see below under Adjusted analyses).
- Subgroups and covariates are defined at the patient level.
- Subgroup and covariate analyses will be carried out irrespective of whether there is a significant effect of treatment allocation on the outcome of interest.
- We will not impute missing values unless otherwise specified.
- We will report the number of observations used in the analyses.
- All the analyses will be conducted in SAS (SAS Institute), Stata (StataCorp) and R (R Development Core Team).

Meta-analysis steps
The meta-analysis will follow a hierarchical process. First, we will analyse each trial separately to check the feasibility
of analyses and ensure that data have not been altered in the process of combining the databases. Second, we will analyse the data from the two trials together to conduct the main analyses. Table 2 outlines the summary and time schedule of the data to be retrieved from the CHEST and 6S trial databases.
**Analysis of each trial**
We will begin by analysing primary and secondary outcomes for each trial separately, as a way to assess the feasibility of the analyses at the trial level and to ensure consistency with the original, previously published, trial-specific analyses. No subgroup analysis or covariate adjustment will be done at the trial level.

**Analysis of heterogeneity**
For each primary and secondary outcome, the assumption of homogeneity between the treatment effects in the two trials will be tested with the Cochran Q test. The assumption of homogeneity will be rejected at P < 0.1. The inconsistency factor (I²) statistics will be used to estimate the proportion of total variation in trial effect estimates that is due to between-trial variation.

**Pooled data analysis**
For the main analyses, the individual patient data from each trial will be pooled into one master dataset. All the patients will be analysed together, with appropriate heterogeneity adjustments at the individual patient level. Subgroup analyses and covariate adjustments will only be done using this pooled dataset.

**Baseline characteristics**
We will describe baseline characteristics for each trial by randomised treatment group (6% HES [130/0.4–0.42] versus crystalloid) and overall. Discrete variables will be summarised using frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available, as shown in Table 3. Continuous variables, including durations, will be summarised using standard measures of central tendency and dispersion, ie, mean and standard deviation (SD), or median and interquartile range (IQR), as shown in Table 3.

**Primary outcome analyses: 90-day mortality**
For the primary outcome analyses, we will use the dataset combining the individual patient data from each trial as described above under Pooled data analysis. Missing data will not be imputed, but the number available and missing will be reported.

**Primary analysis**
We will do the primary analysis for all-cause mortality 90 days after randomisation using log-binomial regressions, which will allow direct estimation of risks and risk ratios (relative risks). After having pooled the individual patient data from the two trials, we will compute the difference in proportion of patients who fulfil the outcome definition between the two groups (6% HES [130/0.4–0.42] versus crystalloid) using all available data. We will test the treatment effect by using a log-binomial regression with a random study effect and random study-by-treatment interaction (ie, a random intercept and a random treatment effect for each study).

In case of convergence problems with the log-binomial regression, in particular with the subgroup and adjusted analyses, we will use robust Poisson regression as a backup. 17

**Subgroup analyses**
We will repeat the analysis of the primary outcome for each subgroup of patients, ie, those:
- with septic shock
- with AKI at randomisation
- who received HES before randomisation
- who needed elective surgery versus emergency surgery versus non-operative treatment
- with high versus low disease severity.

For each subgroup variable, we will use a separate model to which we will add two fixed effects:
- the subgroup variable alone
- the interaction between the subgroup variable and the randomised treatment.

We will use a forest plot to report relative risks and P values for tests of heterogeneity between the randomised treatment and the subgroup variable.

**Adjusted analyses**
The relationship between each subgroup variable and the primary outcome will be tested using a univariate log-binomial regression (or robust Poisson). Every covariate with a univariate P < 20% will be retained for a multivariate analysis. In case of strong collinearity between two covariates, ie, a Pearson correlation coefficient > 0.80, the variable with the smallest univariate P value will be kept for the multivariate model. Similarly, we will test first-order interactions and include those with a P value < 20% in the multivariate model. Covariates with missing values will be imputed using multiple imputation methods.

**Secondary and exploratory outcomes**

**Binary outcomes**
Binary outcomes will include:
- any RRT in the 90 days after randomisation
- creatinine-based RIFLE criteria (as defined above under Secondary outcomes)
- 28-day mortality (any cause)
• new organ failure in the first 5 days, as defined by a SOFA score of 2 or more in any organ system (further defined above under Exploratory outcomes and process measures).

For the above outcomes, we will replicate the analysis outlined above under Primary analysis. We will perform adjusted analyses following the strategy highlighted above under Adjusted analyses, but no subgroup analysis will be done.

**Continuous outcomes**
Continuous outcomes will include:

• days alive and free from RRT in the 90-day follow-up period (the patient is considered dependent on RRT from the date RRT is started to the last date of RRT treatment)
• days alive and free of ventilation
• days alive and out of the ICU
• days alive and out of hospital
• daily volume of study and non-study fluid received in the first 7 days
• daily volume of blood products received in the first 7 days (combined and split into packed cells, fresh frozen plasma, and platelets)
• daily fluid balance in the first 7 days
• total volume of study and non-study fluid received in the first 7 days
• total volume of blood products received in the first 7 days (combined and split into packed cells, fresh frozen plasma, and platelets)
• total fluid balance in the first 7 days.

The indexed hospital admission will be used to calculate the days out of the ICU and out of hospital. Readmissions into the ICU or hospital subsequent to the indexed hospital admission will not be included.

Continuous outcomes will be analysed using linear regression instead of log-binomial regression. All other analyses will remain as described above under Primary analysis and Adjusted analyses, but no subgroup analysis will be done. Daily volume data will only be analysed descriptively, and reported as mean and SD, or median and IQR.

**Tables and figures**
Planned tables will include baseline characteristics of 6S trial and CHEST participants who had sepsis, overall and by randomised treatment, and tables showing the results of the analyses of outcomes, process measures and subgroups analyses. Planned tables and figures include:

• Table 1: baseline characteristics by trial and assigned treatment
• Table 2: primary, secondary and exploratory outcomes
• Table 3: summary of follow-up data by trial and assigned treatment

**Conclusion**
This is our SAP for a prospectively planned IPDMA comparing the effects of 6% HES (130/0.4–0.42), 0.9% saline or Ringer’s acetate on the risk of death, the use of RRT and the development of AKI in patients with severe sepsis 90 days after randomisation. The patient data will be from the 6S trial and the CHEST, which have had inclusion and exclusion criteria and outcome measures harmonised to enable this analysis. Not all definitions were the same for some data points between the trials, and some data fields were not collected in both trials, therefore not all data will be combined.

The results of our IPDMA will allow comparison with other recently published systematic reviews and meta-analyses on this topic and facilitate the translation of research findings into clinical practice.

**Competing interests**
None declared.

**Author details**
Naomi E Hammond, Research Fellow,1 Research Manager,2 and Conjoint Senior Lecturer3
Nicolai Haase, Medical Doctor4
Laurent Billot, Associate Professor,3 and Director5
Jørn Wetterslev, Chief Physician6
Manoj K Saxena, Research Fellow,7 and Staff Specialist7
Simon Finfer, Professorial Fellow,1 Senior Staff Specialist,2 and Professor3
Anders Perner, Senior Staff Specialist and Professor4
John Myburgh, Director,1 Senior Staff Specialist,7 and Professor of Critical Care8

1 Critical Care and Trauma Division, The George Institute for Global Health, Sydney, NSW, Australia.
2 Malcolm Fisher Department of Intensive Care Medicine, Royal North Shore Hospital, Sydney, NSW, Australia.
3 Sydney Medical School, University of Sydney, Sydney, NSW, Australia.
4 Department of Intensive Care, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark.
6 Copenhagen Trial Unit, Center for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark.
Original Articles

7 Department of Intensive Care, St George Hospital, Sydney, NSW, Australia.
8 St George Clinical School, University of New South Wales, Sydney, NSW, Australia.

Correspondence: nhammond@georgeinstitute.org.au

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