Individual patient data meta-analysis of hydroxyethyl starch 130/0.4–0.42 versus crystalloid for fluid resuscitation in patients with severe sepsis: a statistical analysis plan

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ABSTRACT

Background: The Crystalloid versus Hydroxyethyl Starch Trial (CHEST) and the Scandinavian Starch in Severe Sepsis/Septic Shock (6S) trial reported that 6% hydroxyethyl starch (HES) is associated with increased use of renal replacement therapy and death in critically ill patients. 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. Prepublication 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.

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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.[1] 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).[2,3] 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.[2,3]

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 improve the precision of estimate of effects and to increase statistical power.[4] Inclusion and exclusion criteria and the primary outcome measure were prospectively harmonised to facilitate this analysis. We therefore publish the statistical analysis plan (SAP) for this IPDMA to reduce the risk of bias[5-7] and to be consistent with best practice.[8,9]

Overview

Rationale for IPDMA

The advantages of using individual patient data rather than aggregated data for a meta-analysis include the provision of more information than is available in an aggregate data meta-analysis, increased precision of estimates and increased statistical power, the ability to conduct survival analyses and multivariate analyses, flexibility in the categorisation of subgroups, and ensuring consistency of individual patient data according to standard protocols.[10,11]

Overview of the 6S trial and CHEST

The 6S trial was a multicentre, blinded RCT of 804 patients conducted in Scandinavian ICUs between December 2009 and November 2011, that compared the effect of 6% HES (130/0.42) (Tetraspan [B Braun]) with Ringer's acetate on 90-day mortality and dialysis-dependent acute kidney failure in ICU patients with severe sepsis.[3] In patients assigned to receive 6% HES (130/0.42), a significant increase in 90-day mortality (RR, 1.17; 95% CI, 1.01–1.36; $P = 0.03$) and use of RRT (RR, 1.35; 95% CI, 1.01–1.80; $P = 0.04$) was

Table 1. Inclusion and exclusion criteria of the CHEST and 6S trial

Criteria	6S	CHEST
Inclusion criteria		
Written, informed consent obtained or, if not possible, procedure for obtaining delayed, informed consent approved by ethics committee before randomisation	Yes	Yes
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	Yes	Yes
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		Yes
Requirement for fluid resuscitation supported by at least one of the following clinical signs:		Yes
➢ heart rate >90 beats per minute		
➢ systolic blood pressure <100 mmHg, or mean arterial pressure <75 mmHg, or at least 40 mmHg decrease in systolic or mean arterial pressure from baseline recording		
➢ central venous pressure <10 mmHg		
➢ pulmonary artery wedge pressure <12 mmHg		
➢ respiratory variation in systolic or mean arterial pressure >5 mmHg		
➢ capillary refill time >1 second		
➢ urine output <0.5 mL/kg for 1 hour		
Patient fulfils criteria for severe sepsis within the previous 24 hours, according to the SCCM/ACCP definitions	Yes	
Exclusion criteria		
Age <18 years	Yes	Yes
Known previous allergic reaction to hydroxyethyl starch solutions or malic acid†	Yes	Yes
Primary non-traumatic intracranial haemorrhage*† or severe traumatic intracranial haemorrhage (mass lesion on cranial computerised tomographic scan >25 mL)*	Yes	Yes
Receiving RRT*† or ICU clinician considers RRT is imminent (ie, RRT will start in 6 hours)*	Yes	Yes
Documented serum creatinine level >350 μmol/L, and urine output average is ⩽ 10 mL/hour over 12 hours		Yes
Severe hypernatraemia (serum sodium >160 mmol/L)		Yes
Severe hyperchloraemia (serum chloride >130 mmol/L)		Yes
Severe hyperkalaemia (plasma potassium >6 mmol/L)	Yes	
Woman is of child-bearing age (18–49 years old), unless documented evidence of menopause, hysterectomy, surgical sterilisation or negative pregnancy test before randomisation		Yes
Woman is breastfeeding		Yes
Received >1000 mL hydroxyethyl starch* or any synthetic colloid† within 24 hours before randomisation	Yes	Yes
Patient admitted to the ICU after cardiac surgery		Yes
Patient admitted to the ICU for treatment of burns or after liver*† or kidney† transplantation surgery	Yes	Yes
Death is deemed imminent and inevitable*† or the patient has an underlying disease process with a life expectancy of <90 days*	Yes	Yes
Limitation of therapy order is documented restricting implementation of study protocol, or treating clinician deems aggressive care unsuitable		Yes
Previous enrolment in the CHEST or 6S trial	Yes	Yes
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)		Yes
Patient was transferred to the study ICU from another ICU and received fluid resuscitation for the treatment of volume depletion in that other ICU		Yes
Enrolment into another ICU trial of drugs with potential action on circulation, renal function or coagulation	Yes	

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.

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

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)[12] 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
- Pa_{O_2}/F_{IO_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 (⩾ 5.1 μg/kg/minute), vasopressin, metaraminol, phenylephrine)
- creatinine > 170 μmol/L or < 500 mL total urine output in the 24 hours before randomisation
- platelet count $< 100 \times 10^9$/L in the 24 hours before randomisation
- bilirubin > 32 μmol/L 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[13] 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 ⩾ 44 mmol/L, from baseline creatinine, and creatinine ⩾ 350 mmol/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.

Table 2. Summary and schedule of data to be retrieved from the CHEST and 6S trial databases

Period of study	Data collection
Randomisation	Date of birth, sex, date of randomisation, treatment allocation, ICU admission diagnosis (surgical v non-surgical), weight
Baseline	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
Days 1–89	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
Day 90 summary	Vital status at Day 28 and Day 90, length of stay in ICU and hospital, total use of RRT and MV*

CHEST = Crystalloid versus Hydroxyethyl Starch Trial. 6S = Scandinavian Starch in Severe Sepsis/Septic Shock. SOFA = sequential organ failure assessment.[12] APACHE = Acute Physiology and Chronic Health Evaluation.[14] SAPS = Simplified Acute Physiology Score.[15] 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) II[14] score of ⩾ 24 for CHEST patients, or a Simplified Acute Physiology Score (SAPS) II[15] 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

Table 3. Baseline characteristics, process measures and outcomes reported for the Crystalloid versus Hydroxyethyl Starch Trial (CHEST) and Scandinavian Starch in Severe Sepsis/Septic Shock (6S) trial*

Baseline characterisitics	Process and outcome measures (maximum follow-up, 90 days)
Date of randomisation	Fluid volumes and transfusions while in the ICU (Days 1–7)
Treatment allocation	Study fluid (mL/kg)
Sex	Non-study fluid for resuscitation (mL/kg)
Age	Red blood cells (mL/kg)
Weight	Fresh frozen plasma (mL/kg)
Operative v non-operative diagnosis	Platelets (mL/kg)
Admitted to the ICU from OT or recovery after emergency surgery†	Total fluid input (mL/kg)
Admitted to the ICU from OT or recovery after elective surgery†	Total fluid output (mL/kg)
Emergency surgery during index admission and before ICU admission‡	SOFA score while in the ICU (renal component, Days 1–90; others, Day 1–5)
Elective surgery during index admission and before ICU admission†	Most deranged cardiovascular score
Focus of Infection	Lowest PaO_2/FiO_2 ratio
Lungs	Mechanical ventilation with the above ratio
Abdomen (including intra-abdominal and gut)	Urine output
Urinary tract	Highest creatinine
Soft tissue or skin	Lowest platelet count
Other	Highest bilirubin
Disease severity	Renal replacement therapy (daily, until 90 days)
Acute Physiology and Chronic Health Evaluation II score†[14]	Mechanical ventilation (daily, until 90 days)
Simplified Acute Physiology Score II‡[15]	Time of last ICU discharge
Shock at randomisation	Time of index hospital discharge
Mean arterial pressure < 70 mmHg (yes/no)	Date of death
Ongoing vasopressor treatment (yes/no)	
Arterial or venous lactate > 4 mmol/L (yes/no)	
Baseline creatinine	
Last creatinine measured before randomisation†	
Pre-hospital admission creatinine‡	
Highest creatinine in the previous 24 hours‡	
Glasgow coma score < 13 (yes/no)	
Sequential Organ Failure Assessment score§[12]	
Most deranged cardiovascular score	
Lowest PaO_2/FiO_2 ratio	
Mechanical ventilation with the above ratio (yes/no)	
Urine output in the previous 24 hours	
Highest creatinine	
Lowest platelet count	
Highest bilirubin	
Previous hydroxyethyl starch received	
During index hospital admission†	
In the 24 hours before randomisation‡	

ICU = intensive care unit. OT = operating theatre. * Ordinal and continuous data will be reported as mean with standard deviations or as medians with interquartile ranges; dichotomous variables will be reported as number of patients and percentage of those with data available. † CHEST. ‡ 6S trial. § Modified, and does not include cerebral failure.

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[16] (I^2) 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 back-up.[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
- Figure 1: algorithm of available patient data (data completeness) for patients with sepsis in the 6S trial and CHEST
- Figure 2: forest plot of subgroup analyses of the primary outcome
- Figure 3: treatment received by trial over the first 7 days (study and non-study fluid, blood products [total and split into packed cells, fresh frozen plasma, and platelets] and fluid balance by trial and day).

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.

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