

Statistical analysis plan for the Crystalloid Versus Hydroxyethyl Starch Trial (CHEST)

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on behalf of the Crystalloid Versus Hydroxyethyl Starch Trial
(CHEST) Management Committee

To avoid or minimise analysis bias in clinical trials, a predetermined statistical analysis plan is recommended before completion of data collection.¹ The investigators of two large-scale randomised controlled trials, the Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) Study² and the RENAL (Randomized Evaluation of Normal versus Augmented Level) Replacement Therapy Study³ have previously published statistical analysis plans for the aforementioned trials.^{4,5}

The Crystalloid Versus Hydroxyethyl Starch Trial (CHEST) is a large-scale randomised controlled trial comparing the effects of fluid resuscitation with 6% hydroxyethyl starch (130/0.4) in normal saline to normal saline alone in intensive care patients on all-cause mortality at 90 days.

The trial design was closely modelled on the Saline Versus Albumin Fluid Evaluation (SAFE) study, which compared 4% albumin in saline to normal saline in a similar population of patients.^{6,7}

This statistical analysis plan was developed by the chief investigators and senior statisticians at the George Institute for Global Health before completion of patient recruitment and data collection. All authors were blind to treatment allocation and to the unblinded data produced for interim analyses conducted by an independent Data Safety and Monitoring Board (DSMB).

Study overview

Trial design

CHEST is a prospective, multicentre, blinded, concealed, randomised controlled trial comparing two intravenous fluid resuscitation therapies for the management of fluid resuscitation in critically ill patients.

The trial has been registered with the Australian New Zealand Clinical Trials Registry (ACTRN12609000245291) and ClinicalTrials.gov (NCT00935168). It has been endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group.

The full study protocol has been published previously in *Intensive Care Medicine*.⁸

ABSTRACT

Background: The Crystalloid Versus Hydroxyethyl Starch Trial (CHEST) is a 7000-patient, multicentre, randomised controlled trial comparing the effects of 6% hydroxyethyl starch (130/0.4) to normal saline for fluid resuscitation in intensive care patients. The trial design is based on the Saline Versus Albumin Fluid Evaluation (SAFE) study and will be the largest fluid resuscitation trial conducted to date.

Objective: In accordance with two other trials conducted by the investigators, a predetermined statistical analysis plan (SAP) has been described and made public before completion of patient recruitment and data collection. The SAP will be adhered to for the final data analysis of this trial to avoid analysis bias arising from knowledge of study findings.

Methods: The SAP was designed by the chief investigators and statisticians and approved by the CHEST Management Committee. All authors were blind to treatment allocation and to the unblinded data produced during two interim analyses conducted by the Data Safety and Monitoring Board. The data shells were produced from a previously published protocol. Statistical analyses are described in broad detail. Specifically, information relevant to baseline characteristics and processes of care were defined, and statistically relevant descriptive elements described, with appropriate comparisons between groups. Trial outcomes were selected, categorised into primary, secondary and tertiary outcomes, and appropriate statistical comparisons between groups were planned and described.

Results: A standard SAP for CHEST was developed. A trial profile outline and list of mock tables were produced. Descriptions of analyses of baseline characteristics, processes of care, measures of efficacy and outcomes were described. Six prespecified subgroups were defined and statistical comparisons between groups in these subgroups were described. In addition, analyses of tertiary outcomes, including health economic and functional outcome assessment, were described.

Conclusion: We have developed a predetermined SAP for CHEST. This plan accords with high-quality standards of internal validity to minimise analysis bias.

Funding statement

CHEST is funded by the National Health and Medical Research Council (project grant no. 632503), the New South Wales Department of Health (unrestricted grant), and Fresenius Kabi (unrestricted grant through the University of Sydney to the George Institute and logistic support for study fluid acquisition, blinding and distribution). The funders had no input into the design and conduct of the trial or into the statistical analysis plan.

Study population

A total of 7000 patients were enrolled in this study at 32 study centres in Australia and New Zealand. Recruitment was completed on 23 January 2012. Patients were screened according to inclusion and exclusion criteria. Eligible patients were randomised to receive either 6% hydroxyethyl starch (130/0.4) in 0.9% sodium chloride solution or 0.9% sodium chloride (normal saline) alone for intravenous fluid resuscitation.

For all patients, information was collected at randomisation, each day while in the intensive care unit, 28 days, 90 days, and 6 months after randomisation.

To allow for cost-effectiveness analysis, quality of life at 6 months will be assessed using the EuroQol-5D (EQ-5D) questionnaire,⁹ and use of health services after discharge from hospital will be assessed in a subset of participants recruited in NSW.

Additionally, patients with traumatic brain injury (TBI) will have additional follow-up 6 months after randomisation to ascertain measures of functional survival using the Glasgow Outcome Scale.^{10,11}

Inclusion criteria

Patients treated in the ICU were eligible for inclusion in the study if all of the following requirements were met:

- written informed consent was obtained, or if not possible, the procedure for obtaining delayed informed consent before randomisation was approved by the ethics committee;
- fluid resuscitation was required to increase or maintain intravascular volume that was 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;
- the intensive care clinician considered that the use of 6% hydroxyethyl starch (130/0.4) and saline were equally appropriate for fluid resuscitation for the patient, and that no specific indication or contraindication for either existed; and

- the requirement for fluid resuscitation was supported by at least one of the following clinical signs
 - heart rate >90 beats/min;
 - systolic blood pressure (SBP) <100 mmHg or mean arterial pressure (MAP) <75mmHg, or \geq 40 mmHg decrease in SBP or MAP from the baseline recording;
 - central venous pressure <10 mmHg;
 - pulmonary artery wedge pressure <12 mmHg;
 - respiratory variation in systolic or MAP of >5 mmHg;
 - capillary refill time >1 second; or
 - urine output <0.5 mL/kg for 1 hour.

Exclusion criteria

Patients were excluded from the study if one or more of the following were present:

- age less than 18 years;
- known previous allergic reaction to hydroxyethyl starch solutions;
- primary non-traumatic intracranial haemorrhage or severe traumatic intracranial haemorrhage (mass lesion >25 mL);
- patient was receiving renal replacement therapy or the intensive care clinician considered renal replacement therapy imminent (ie, will start within 6 hours);
- documented serum creatinine concentration \geq 350 μ mol/L and urine output averaging \leq 10 mL/hour over 12 hours;
- severe hypernatraemia (serum sodium level >160 mmol/L);
- severe hyperchloraemia (serum chloride level >130 mmol/L);
- possibility of pregnancy — women of childbearing age (18–49 years), unless evidence of documented menopause, hysterectomy or surgical sterilisation or negative pregnancy test before randomisation or if breastfeeding;
- patient had received >1000 mL of hydroxyethyl starch outside the ICU in the 24 hours before randomisation;
- admitted to the ICU after cardiac surgery, treatment of burns or after liver transplantation surgery;
- death was deemed imminent and inevitable, or the patient had an underlying disease process with a life expectancy of <90 days;
- a limitation-of-therapy order was documented, restricting implementation of the study protocol, or the treating clinician deemed aggressive care unsuitable;
- patient was previously enrolled in CHEST;
- patient previously received fluid resuscitation that was prescribed within the study ICU during this current ICU admission (this allowed inclusion of patients who arrive in the ICU with fluid running); or
- patient was transferred to the study ICU from another ICU and received fluid resuscitation for the treatment of volume depletion in the other ICU.

Aims

Primary aim

The primary aim is to determine whether intravenous fluid resuscitation with 6% hydroxyethyl starch (130/0.4) in 0.9% sodium chloride solution in a heterogeneous population of critically ill adults results in different 90-day all-cause mortality compared with intravenous fluid resuscitation with 0.9% sodium chloride (normal saline) alone. The null hypothesis assumes no difference in all-cause mortality between patients given 6% hydroxyethyl starch (130/0.4) compared with patients given saline for fluid resuscitation.

Secondary aims

- To determine whether there is any difference in the incidence of acute renal injury or failure between patients randomised to intravenous fluid resuscitation with 6% hydroxyethyl starch (130/0.4) and those receiving 0.9% sodium chloride (normal saline) alone.
- To determine whether there are any differences in mortality within six predefined subgroups: patients admitted for trauma with TBI, patients admitted for trauma without TBI, patients with severe sepsis, patients with pre-existing renal failure in the absence of oliguria or anuria, patients with an Acute Physiology and Chronic Health Evaluation (APACHE) II score¹² >25, and patients who received hydroxyethyl starch for resuscitation before randomisation.
- To determine the cost-effectiveness of 6% hydroxyethyl starch (130/0.4) compared with saline.

Definition of the efficacy variables

Primary outcome

The primary outcome measure for the study is death from all causes at 90 days.

Secondary outcomes

- Incidence of acute renal injury or acute renal failure (measured using daily RIFLE [Risk, Injury, Failure, Loss, End-stage kidney disease] criteria for the diagnosis of acute kidney injury,¹³ Sequential Organ Failure Assessment [SOFA] score,¹⁴ and requirement and duration of renal replacement therapy).
- Duration of mechanical ventilation.
- Organ failure defined by SOFA score for cardiovascular, liver, coagulation and respiratory function.¹⁴
- Survival times from randomisation to Day 90.
- Hospital mortality.
- Cause-specific mortality within the 90-day follow-up period with primary cause of death categorised as
 - cardiovascular — distributive shock;

- cardiovascular — cardiogenic shock;
- cardiovascular — hypovolaemic shock;
- cardiovascular — primary arrhythmia;
- anoxic respiratory failure;
- neurological — TBI with brain death;
- neurological — TBI without brain death;
- metabolic; or
- other.

Tertiary outcomes

- Mortality and determination of functional outcomes at 6 months in patients admitted with TBI (measured using the Glasgow Outcome Scale).¹¹
- Length of stay in ICU (Day 90 summary).
- Length of stay in hospital (Day 90 summary).
- ICU mortality.
- 28-day mortality.
- Quality-of-life assessment (measured using EQ-5D) at 6 months.
- Linkage to health services utilisation data for cost-effectiveness 6 months after randomisation.

Analysis principles

All analyses will be conducted on an intention-to-treat basis. All tests are two-sided and the nominal level of α will be 5%. All statistical analyses will be unadjusted except where indicated.

Subgroup analyses will be carried out irrespective of whether there is a significant effect of treatment on the primary outcome.

There will be no imputation for missing values unless specified otherwise. Where there are missing observations, we will report the number of observations used in the analysis. Last observations will not be carried forward for continuous outcomes.

P will not be adjusted for multiplicity. However, the outcomes are clearly categorised by degree of importance.

Design issues

Data collection follow-up

Table 1 provides a summary and time schedule of the data to be collected in the trial electronic case report form.

Treatment allocation

Eligible patients who require intravenous fluid to expand or maintain intravascular volume in the ICU will be randomised to receive either:

- 6% hydroxyethyl starch (130/0.4) in 0.9% sodium chloride solution, or
- 0.9% sodium chloride (normal saline) alone.

Table 1. Summary and time schedule of the data to be collected in the trial electronic case report form

Period of study	Data collection
Randomisation	Patient demographics; eligibility criteria; admission diagnosis of trauma/non-trauma
Baseline information	Source and date of admission to intensive care unit; weight; ICU admission diagnosis; subgroup categories into "sepsis", "trauma", and "traumatic brain injury" patients; previous hydroxyethyl starch administration; APACHE II score; ¹² RIFLE criteria for acute renal injury at the time of randomisation; ¹³ data to derive SOFA scores ¹⁴ for each organ system at the time of randomisation; ⁴ cardiovascular measurements; mechanical ventilation; urine output
Days 1–90	While in ICU only: RIFLE criteria for acute renal injury (including urine output) (Days 0–7 only); data to derive SOFA scores for each organ system (Days 0–28 only); use of renal replacement therapy or mechanical ventilation; cardiovascular measurements indicating response to fluid resuscitation; daily blood products; study fluid and other fluid input and output
Day 90 summary	Vital status at Day 28 and Day 90; length of stay in ICU; length of stay in hospital; place and cause of death; type of consent obtained; reasons for discontinuation of study fluid; use of renal replacement therapy after ICU discharge
Serious unexpected suspected adverse reactions	Description, timing and resolution of any serious unexpected adverse events thought to be related to study treatment from randomisation to 90 days after randomisation
Other treatment-related adverse events	Description, timing and resolution of any other reportable adverse events from randomisation to 90 days after randomisation
Protocol violations	
Six months after randomisation	Vital status; Glasgow Outcome Scale score in patients with traumatic brain injury; EQ-5D and linkage to health services data (for cost-effectiveness analysis)

APACHE = Acute Physiology and Chronic Health Evaluation. EQ-5D = EuroQol-5D. RIFLE = Risk, Injury, Failure, Loss, End-stage kidney disease. SIRS = systemic inflammatory response syndrome. SOFA = Sequential Organ Failure Assessment.

Randomisation was stratified according to participating institution and to whether there is an admission diagnosis of trauma.

Randomisation was achieved using a minimisation algorithm via a secure, password-protected, encrypted, interactive internet-based randomisation system, with backup service through a 24-hour on-call service provided by the project team at the George Institute.

Power

A study population of 7000 patients will provide 90% power at a two-sided significance level to detect an absolute difference in risk (either an increase or decrease) in 90-day mortality between the 6% hydroxyethyl starch (130/0.4) and saline groups of 3.5%. This detected difference in absolute risk would be considered clinically important and likely to influence practice. The sample size for this study has been calculated based on a 28-day mortality of 21% in patients treated with saline from the SAFE study;⁷ extrapolating this to assume the 90-day all-cause mortality in patients treated with saline will be about 26% (based on other studies of critically ill patients).^{2,15}

In addition, although renal failure or injury is a secondary outcome, 7000 patients would also provide sufficient power (90%, $\alpha=0.05$) to detect an increase in the risk of renal failure by 1.5 (estimated from the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis [VISEP]

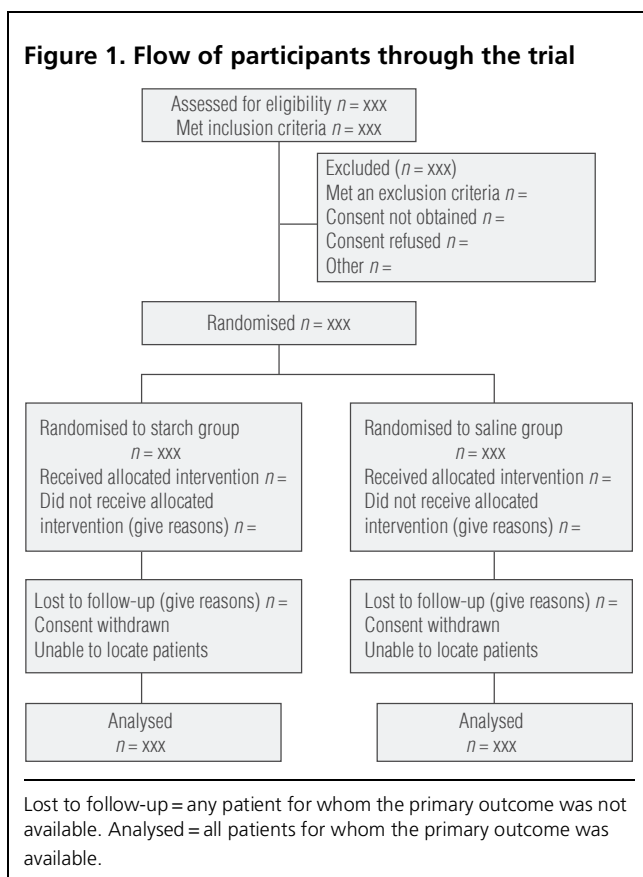
Trial¹⁶) from a baseline incidence of renal failure in the study population of 6%.

An independent DSMB reviewed unblinded data on patient characteristics, treatment compliance and study outcomes. An initial interim analysis was conducted when 2000 patients were followed up for 90 days. The purpose of this interim analysis was to test for the difference in mortality between the two study fluids to check for potential safety issues and to assess early efficacy. To maintain the type I error rate (ie, α), group sequential tests will be used with the $\alpha \times t^2$ spending function, which is less conservative than the O'Brien–Fleming function in terms of early stopping, with negligible loss in power.

A second interim analysis was conducted after 4000 patients were followed up for 90 days.

Stopping rules were based on the following:

- A responsibility to inform investigators if at any time the randomised comparisons provided
 - evidence "beyond reasonable doubt" of a difference between randomised groups in all-cause mortality or the requirement for renal replacement therapy; or
 - evidence that is likely to lead many clinicians conversant with the available evidence to change their practice with regard to the choice of fluids for intravascular volume expansion.
- Additionally, although the primary focus of the committee was on all-cause mortality, this did not preclude the



committee recommending termination of the study (or some modification to its design) if there was evidence of an important difference in some other major outcome (such as cause-specific mortality).

With 2000 patients and assuming a reference mortality rate of 26%, there will be about 14% power to detect an absolute decrease in mortality of 3.5%. Statistical significance will be declared if *P* is less than 0.004 (equivalent to *z* score larger than 2.872). In addition, incident renal failure as measured by the need for renal replacement therapy will be reported to the DSMB.

In terms of non-inferiority, this means that, at the time of the interim analysis, there would be 80% power to declare non-inferiority of 6% hydroxyethyl starch (130/0.4) with a margin of 1.21 (equivalent to a mortality rate of 31.5%). This assumes a mortality rate of 26% in both arms.

The DSMB also reviewed summaries of all suspected unexpected adverse reactions and deaths that occur during the study.

Data and consent-related issues

Data will be queried so that no missing values remain. Due to the nature of the study, informed prior consent was not always possible and a patient or their legal surrogate would

be asked for delayed consent. Two important situations can lead to the cessation of study treatment — a patient, next of kin or legal surrogate may withdraw consent, or they may refuse continuation of study treatment when delayed consent is sought (as opposed to withdrawing existing consent).

In both cases, the study treatment was ceased and the patient received fluid administration as prescribed by their treating clinicians. In this situation, specific consent was sought to continue study follow-up procedures and to use study data. If consent for use of data was withheld, that patient’s data was removed from the analysis except for data related to consent. Censoring dates will only occur in case of “real” loss to follow-up (ie, discharged patients with no information beyond some point in time). In that case, the date of censoring will be the last day of contact or the date of hospital discharge if no other information is available.

Permanent discontinuations

The data of patients who withdraw or withhold consent to continue study treatment but consent to the use of their data will remain in the analysed dataset and will be analysed on an intention-to-treat basis.

Vital status at 28 or 90 days will not be imputed if this information is missing.

Statistical analysis

Trial profile

Flow of patients through the study will be displayed in a CONSORT (Consolidated Standards of Reporting Trials) diagram (Figure 1). We will report number of screened patients who met study inclusion criteria and number included. Reporting of reasons for exclusion of non-included patients and information are detailed below.

Characteristics of patients and baseline comparisons

Description of the following baseline characteristics will be presented by treatment group. Discrete variables will be summarised as number (%). Percentages will be calculated according to the number of patients for whom data are available. Where values are missing, the denominator (which will be less than the number of patients assigned to the treatment group) will be stated in the body or a footnote in the corresponding summary table. Number (%) of patients will be reported for the categories indicated in Box 1.

Continuous variables will be summarised by use of standard measures of central tendency and dispersion, either mean (SD) or median (interquartile range [IQR]), as indicated in Box 1. Median (IQR) will be added as summary measures.

Box 1. Baseline characteristics and process measures to be recorded for the Crystalloid Versus Hydroxyethyl Starch Trial (CHEST)

<p>Baseline characteristics</p> <p>1. Age*</p> <p>2. Sex</p> <p>3. Weight*</p> <p>4. Source of admission to ICU (ED, hospital ward, another ICU, another hospital, OT after emergency surgery, OT after elective surgery, readmission to the same ICU during the same hospitalisation)</p> <p>5. Time from ICU admission to randomisation*</p> <p>6. Operative versus non-operative ICU admission diagnoses:</p> <p>a. Operative admission diagnosis</p> <p>i. Cardiovascular</p> <p>ii. Gastrointestinal</p> <p>iii. Gynaecological</p> <p>iv. Neurological</p> <p>v. Orthopaedic</p> <p>vi. Renal</p> <p>vii. Respiratory</p> <p>viii. Trauma</p> <p>ix. Other postoperative</p> <p>b. Non-operative admission diagnosis</p> <p>i. Cardiovascular</p> <p>ii. Gastrointestinal</p> <p>iii. Haematological</p> <p>iv. Metabolic</p> <p>v. Neurological</p> <p>vi. Other medical diseases</p> <p>vii. Renal</p> <p>viii. Respiratory</p> <p>ix. Sepsis</p> <p>x. Trauma</p> <p>7. Sepsis at baseline</p> <p>a. First site of infection</p> <p>i. organism for the first site of infection</p> <p>b. Second site of infection</p> <p>i. organism for second site of infection</p> <p>c. SIRS criteria¹⁷ 2 out of 4 (yes/no)</p>	<p>8. Trauma with or without brain injury at baseline</p> <p>9. TBI as primary cause for hospital admission</p> <p>10. Glasgow Coma Scale score¹⁸ for patients with TBI</p> <p>a. Best eye-opening response[†]</p> <p>b. Best verbal response[†]</p> <p>c. Best motor response[†]</p> <p>d. Received sedation at time of assessment (yes/no)</p> <p>e. Received neuromuscular blocker at time of assessment (yes/no)</p> <p>11. SOFA score¹⁴</p> <p>a. Cardiovascular component</p> <p>b. Respiratory component</p> <p>c. Renal component</p> <p>d. Hepatic component</p> <p>e. Haematological component</p> <p>12. RIFLE criteria for acute renal injury¹³</p> <p>a. Urine output 6 h before randomisation*</p> <p>b. Urine output 12 h before randomisation*</p> <p>c. Urine output 24 h before randomisation*</p> <p>d. Normal creatinine level before admission in past 12 months*</p> <p>e. Serum creatinine level (µmol/L) before randomisation*</p> <p>f. RIFLE criteria for the diagnosis of acute kidney injury, where:</p> <p>i. RIFLE R: Increased serum creatinine level × 1.5, or GFR decrease > 25%, or UO < 0.5 mL/kg/h × 6 h</p> <p>ii. RIFLE I: Increased serum creatinine level × 2, or GFR decrease > 50%, or UO < 0.5 mL/kg/h × 12 h</p> <p>iii. RIFLE F: Increased serum creatinine level × 3, or GFR decrease 75%, or serum creatinine level ≥ 350 µmol/L in the setting of an acute increase of ≥ 44 µmol/L, or UO < 0.3 mL/kg/h × 24 h, or anuria × 12 h</p> <p>iv. RIFLE L: persistent ARF — complete loss of kidney function > 4 weeks</p> <p>v. RIFLE E: end-stage kidney disease > 3 months</p>	<p>13. Cardiovascular measurements</p> <p>a. Heart rate (beats/min)*</p> <p>b. Central venous pressure (mmHg)*</p> <p>c. Mean arterial pressure (mmHg)*</p> <p>d. Lactate level (mmol/L)*</p> <p>e. Mechanical ventilation before randomisation</p> <p>14. Previous hydroxyethyl starch fluid received</p> <p>a. Hydroxyethyl starch received before randomisation (yes/no)</p> <p>b. Volume of hydroxyethyl starch received before randomisation (mL)*</p> <p>15. APACHE II score*¹²</p> <p>Process measures</p> <p>1. Day 1 to Day 90</p> <p>a. Cardiovascular measurements indicating response to fluid resuscitation (heart rate, mean arterial pressure, central venous pressure, arterial lactate), study fluid and other fluid input and output</p> <p>b. Mean hourly blood products over time</p> <p>c. Daily amount of study fluid (mL) over time</p> <p>d. Daily amount and type of non-study fluid (mL) over time</p> <p>e. Urine output (daily)</p> <p>f. Renal replacement therapy (daily)</p> <p>g. SOFA score (daily to Day 28)</p> <p>h. Time on study treatment (days)</p> <p>i. Time from cessation of study treatment to (last) discharge from ICU</p> <p>j. Averaged over time from randomisation to time study treatment stopped (if study treatment is stopped and then restarted, all episodes on study treatment will be used to calculate the mean)*</p> <p>2. Six-month follow-up:</p> <p>a. Quality-of-life questionnaire: EQ-5D scores</p> <p>b. Glasgow Outcome Scale score for patients with TBI</p>
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APACHE = Acute Physiology and Chronic Health Evaluation. ARF = acute renal failure. ED = emergency department. EQ-5D = EuroQol-5D. GFR = glomerular filtration rate. ICU = intensive care unit. OT = operating theatre. RIFLE = Risk, Injury, Failure, Loss, End-stage kidney disease. SIRS = systemic inflammatory response syndrome. SOFA = Sequential Organ Failure Assessment. TBI = traumatic brain injury. UO = urine output.

* Reported as mean (SD). † Reported as median (interquartile range).

Concomitant treatments

Aside from the study treatment, patient management was otherwise unaffected and the treating clinicians were free to provide whatever other medical care was deemed necessary for the patient.

No interactions between the study treatment and any particular drugs or nutritional products are known to date.

Limitation of treatment

Treatment limitation refers to:

- withdrawing a treatment that might otherwise prolong life as it is no longer considered appropriate for that individual (ie, stopping of a previously provided treatment); or
- withholding treatment that might otherwise prolong life as it is not considered appropriate for that individual (ie, not commencing a treatment).

Each of these will have been authorised by a treating clinician independent of the study and documented in the medical record. The specific treatments limited or withdrawn will not be reported.

The study will report:

- Patients for whom there was limitation of treatment.
- Patients for whom treatment limited or withheld.
- Time from randomisation to first treatment limitation order.

Consent and permanent discontinuation of study treatment

- Consent (no. [%] in categories a–f):
 - a. Prior informed consent from patient.
 - b. Prior informed consent from a legal surrogate.
 - c. Delayed informed consent from patient.
 - d. Delayed informed consent from a legal surrogate.
 - e. Consent from other legal body before or after patient's death.
 - f. No consent obtained — data withdrawn.
- Patients for whom study treatment permanently discontinued (no. [%] in categories a–g):
 - a. Patients for whom informed consent withdrawn.
 - b. Patients for whom delayed informed consent withheld.
 - c. Study treatment discontinued by treating clinician (not due to serious adverse event or palliative care).
 - d. Study treatment discontinued due to adverse drug reaction.
 - e. Study treatment discontinued as focus of treatment changed to palliative care.
 - f. Study treatment discontinued for other reason.
 - g. Development of acute renal dysfunction or failure requiring renal replacement therapy.

Description of analyses

Primary outcome: A standard χ^2 test will be used as the primary test of statistical significance of the effect of treatment allocation on 90-day all-cause mortality. Number (%) per arm and relative risks measuring the treatment effect and their 95% confidence intervals (CIs) will be reported. An adjusted analysis for sensitivity purposes will be considered, using multivariate logistic regression analysis adjusted for strata used in minimisation and the following predictors: age, ICU admission source, APACHE II score and

baseline creatinine level. A sensitivity analysis will also be considered if more than 5% of the 90-day mortality data are missing.

Secondary outcomes: A standard χ^2 test will be used to assess the effect of treatment on binary or categorical outcomes (ie, incidence of acute renal injury/acute renal failure, 28-day all-cause mortality, ICU mortality, incidence of organ failure). Frequencies and percentages per arm, relative risks measuring the treatment effect and their 95% CIs will also be reported along with *P* for the χ^2 test. In addition, the number of new organ failures will be tabulated per treatment arm — frequencies and percentages for all new organ failures (0–4).

Survival time from randomisation to Day 90 will be analysed using log-rank test. *P* and a hazard ratio (95% CI) obtained from a Cox proportional hazards model will also be presented. The proportional hazard assumption across treatment arms will be checked graphically using a log-cumulative hazard plot or the addition of a time-dependent covariate to the model. Probability of survival by treatment group will also be presented as Kaplan–Meier curves.

Length of stay will be calculated from randomisation to discharge, death or Day 90, whichever comes first. Summary statistics will include the median and the interquartile range computed separately for each treatment arm. The effect of treatment allocation will be tested using a two-sample *t* test or Wilcoxon rank-sum test, as appropriate.

Organ failures (respiratory, cardiovascular, coagulation and hepatic) will be analysed using χ^2 test at 90 days. Frequencies and percentages per arm and an odds ratio (95% CI) measuring the treatment effect will also be reported.

Analyses adjusted for the same predictors as the primary outcome will also be done for the secondary outcomes as subsidiary analyses. They will be based on a linear, logistic or Cox regression as appropriate, depending on the type of outcome.

Parameters of efficacy

Mechanical ventilation and renal replacement therapy are resource-consumption measures and treatments that are not performed on all patients. They will be summarised in two ways: number (%) of patients per arm who received such a therapy and mean (SD) duration in days per treatment arm. If patients were still being treated with mechanical ventilation or renal replacement therapy at the end of the study, their data will be censored. The effect of treatment allocation will be tested using two-sample *t* tests or Wilcoxon rank-sum tests, as appropriate.

SOFA scores for each organ system will be described daily up to Day 28. EQ-5D quality-of-life score will be compared using two-sample tests or Wilcoxon rank-sum tests depend-

Box 2. Crystalloid Versus Hydroxyethyl Starch Trial (CHEST) sites and principal investigators

Auckland City Hospital, New Zealand: Shay McGuinness
 Austin Hospital, Victoria: Rinaldo Bellomo
 Bendigo Hospital, VIC: Jason Fletcher
 Blacktown Hospital, New South Wales: Latesh Poojara
 Calvary Mater Newcastle, NSW: Katrina Ellem
 Canberra Hospital, Australian Capital Territory: Imogen Mitchell
 Christchurch Hospital, New Zealand: Seton Henderson
 Concord Hospital, NSW: David Milliss
 Epworth Richmond, VIC: Benno Ihle
 Frankston Hospital, VIC: Kavi Haji
 Fremantle Hospital, Western Australia: Bart de Keulenaer
 Geelong Hospital, VIC: Claire Cattigan
 John Hunter Hospital, NSW: Peter Harrigan
 Liverpool Hospital, NSW: Michael Parr
 Mater Health Services, Queensland: Jeffrey Presneill
 Nepean Hospital, NSW: Ian Seppelt
 North Shore Hospital, New Zealand: Janet Liang
 Northern Hospital, VIC: Graeme Duke
 Prince of Wales Hospital, NSW: Yahya Shehabi
 Royal Brisbane and Women's Hospital, QLD: Robert Boots
 Royal Hobart Hospital, Tasmania: David Cooper
 Royal North Shore Hospital, NSW: Simon Finfer
 Royal Prince Alfred Hospital, NSW: David Gattas
 St George Hospital, NSW: John Myburgh
 St Vincent's Hospital Melbourne, VIC: John Santamaria
 Tauranga Hospital, New Zealand: Troy Browne
 Waikato Hospital, New Zealand: Frank van Haren
 Wellington Hospital, New Zealand: Richard Dinsdale
 Wesley Hospital, QLD: Bala Venkatesh
 Western Hospital, VIC: Forbes McGain
 Westmead Hospital, NSW: Edward Stachowski

Box 3. Crystalloid Versus Hydroxyethyl Starch Trial (CHEST) Management Committee

John Myburgh, Chair (George Institute for Global Health, University of New South Wales, St George Hospital, Sydney)
 Julie Harland, Senior Project Manager (George Institute)
 Rinaldo Bellomo (George Institute, University of Melbourne, Austin Hospital, Melbourne)
 Alan Cass (George Institute, University of Sydney)
 Maryam Correa (George Institute)
 Simon Finfer (George Institute, University of Sydney, Royal North Shore Hospital, Sydney)
 David Gattas (Royal Prince Alfred Hospital, Sydney)
 Parisa Glass (George Institute)
 Joanne Lee (George Institute)
 Jeffrey Lipman (University of Queensland, Royal Brisbane and Women's Hospital)
 Bette Liu (George Institute, University of Sydney)
 Colin McArthur (Australian and New Zealand Intensive Care Society Clinical Trials Group, Melbourne)
 Shay McGuinness (Auckland Cardiovascular Hospital, New Zealand)
 Dorrilyn Rajbhandari (George Institute)
 Colman Taylor (George Institute, University of Sydney)
 Steve Webb (Australian and New Zealand Intensive Care Society Clinical Trials Group)
 Lynsey Willenberg (George Institute)

- Patients with an admission diagnosis of trauma without an associated TBI.
- Patients with a pre-randomisation APACHE II score of > 25.
- Patients who received hydroxyethyl starch for resuscitation pre-randomisation will be analysed for the presence of acute renal injury and mortality.

Control of type I error for multiple looks

To maintain the type I error rate (ie, α), group sequential tests will be used with the $\alpha \times t^2$ spending function, which is less conservative than the O'Brien–Fleming function in terms of early stopping. Although part of the level is lost at the two interim analyses, the final level will not be corrected as this loss is negligible with such a stopping rule.

Tables and figures

Tables include baseline characteristics of the participants, process measures, volume of study fluid given, volume of non-study fluid for fluid resuscitation, outcomes and subgroup analyses.

Planned mock tables are:

- Table 1. Randomisation by country and centre.
- Table 2. Available data (data completeness).
- Table 3. Baseline characteristics.
- Table 4. Daily amount of study fluid (mL) over time.

ing on distribution. Glasgow Outcome Scale score will also be calculated in descriptive tables by treatment groups.

Subgroup analyses

The primary outcome for planned subgroup analyses will be the same as in the main analysis (ie, 90-day all-cause mortality). Subgroup analyses will be exploratory and aim at generating new hypotheses.

P will be reported unadjusted, but the number of declared subgroup analyses will be specified in all publications.

Six pre-identified subgroup analyses will be performed:

- Patients fulfilling RIFLE criteria (Risk or Injury) for the presence of acute kidney injury at randomisation.
- Patients with an admission diagnosis of sepsis.
- Patients with an admission diagnosis of trauma with an associated TBI.

- Table 5. Daily amount of non-study fluid (mL) over time.
 - Table 6. Daily amount of blood products (mL) over time.
 - Table 7. SOFA scores over time.
 - Table 8. Primary and secondary outcomes.
 - Table 9. Summary of adverse drug reactions.
 - Table 10. Protocol violations.
- Planned figures are:
- Figure 1. CONSORT diagram illustrating flow of patients through the study.
 - Figure 2. Daily amount of study fluid (mL) over time.
 - Figure 3. Daily amount of blood products (mL) over time.
 - Figure 4. Kaplan–Meier estimates of the probability of survival for all-cause mortality censored at 90 days.
 - Figure 5. Forest plots of odds ratios for death at 90 days for all patients and for prespecified subgroups.

CHEST study sites, principal investigators and Management Committee

The CHEST principal investigators and sites are shown in Box 2. The CHEST Management Committee members are shown in Box 3.

Competing interests

The authors approved the final manuscript and declare no conflict of interest in relation to this manuscript. John Myburgh and Simon Finfer have received speaker and travel expenses from Fresenius Kabi.

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