A Pilot, Randomised, Unblinded, Feasibility, Safety and Biochemical and Physiological Efficacy Study of 20% vs 5% Human Albumin Solution for Fluid Bolus Therapy in Critically Ill Adults

Short title: Small volume resuscitation **W**ith albumin in **I**ntensive care: **P**hysiological **E**ffects (SWIPE)

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UK Protocol Mission Statement

This document describes the **S**mall volume resuscitation **W**ith albumin in **I**ntensive care: **P**hysiological **E**ffects (SWIPE) trial and provides information about procedures for entering patients into it. The protocol should not be used as a guide for the treatment of patients outside the trial. Every care was taken in drafting this protocol, but corrections or amendments may be necessary. Care must be taken to use the most up to date and approved version. This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) regulations 2004 and ICH Good Clinical Practice guidelines. The trial will be conducted in compliance with the protocol, the Data Protection Act (DPA Z6364106), the Declaration of Helsinki, Human Tissue Act (2004), the Research Governance Framework (2005) and other regulatory requirements as appropriate.

Principal Investigator

Dr Jonathan Bannard-Smith

Signature

Date

Sponsor Representative

Dr Lynne Webster

Signature

Date

UK Principal Investigator Statement

I Dr Jonathan Bannard-Smith, as Principal Investigator for the **S**mall volume resuscitation **W**ith albumin in **I**ntensive care: **P**hysiological **E**ffects trial to be conducted at CMFT, confirm that I will be responsible to ensure that all members of the local clinical trial team are appropriately trained on the trial protocol and have the relevant qualifications and experience to carry out their role in accordance with the trial protocol.

Signature

Date

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Lay Summary

Administration of fluids directly into a vein is commonly used to treat low blood pressure in critically ill patients. The aim of such so-called fluid resuscitation is to increase the circulating blood volume to improve the blood flow to body organs. Prolonged fluid resuscitation may, however, lead to fluid accumulation in the tissues, which contributes to organ damage and even increased mortality.

Albumin is a natural constituent of human blood with a high capacity of binding water. In the United Kingdom, two different albumin-containing solutions are widely and routinely used for fluid resuscitation; a 5% solution (containing 50 mg albumin per ml) and a concentrated 20% solution (containing 200 mg albumin per ml). Theoretically, the concentrated 20% albumin solution can accomplish the same volume expansion effect as the 5% solution using only one fifth of the administered volume. A reduced volume of fluid administered may ultimately attenuate the severity of organ damage, expedite recovery from the critical illness and reduce mortality.

This study is an investigator-initiated, multi-centre, open label, randomised-controlled trial. In the UK, the study has been determined to be a Clinical Trial of an Investigational Medicinal Product by the Competent Authority. The aim of this study is to test whether fluid resuscitation with the 20% albumin solution reduces fluid accumulation and organ damage in critically ill patients as compared to fluid resuscitation with the 5% albumin solution. The study will enrol a convenience sample of 400 adult participants. These patients will be recruited across three intensive care units in Melbourne and Adelaide, Australia and Manchester in the United Kingdom. We intend to publish aggregated findings in peer-reviewed critical care journals.

Background

Intravenous fluid administration is an integral part in the treatment of hemodynamic instability. The rationale for fluid therapy is to increase intravascular volume, venous return and cardiac output with the aim to improve perfusion and oxygen delivery to the organs. There is, however, considerable clinical controversy about the optimal use of fluids (type and extent) to achieve and maintain hemodynamic stability. Evidence from multiple observational studies, however, suggests that a prolonged and uncritical fluid therapy is, by causing fluid accumulation and tissue oedema, associated with the development and progression of organ failure and increased mortality in critically ill patients [1].

The choice of resuscitation fluid has important consequences for patient outcomes. The use of synthetic colloids, such as hydroxyethyl starches and gelatine solutions, has been largely abandoned in critically ill patients due to pronounced side-effect profiles including the ability to cause and aggravate acute kidney injury [2-5]. On the contrary, with the exception of patients suffering from traumatic brain injury [6], natural colloids, such as albumin solutions, appear safe for use in critically ill patients [7].

Albumin is present in human plasma at a concentration of 30-50 g/L and is the most important natural carrier of the colloid osmotic force. In addition, albumin has an important physiologic role as a transporter of biologically active molecules, as a drug binder, as a key component in maintaining the endothelial surface layer, and as a free radical scavenging antioxidant. A meta-analysis of 17 randomised trials demonstrated significantly lower mortality in septic patients resuscitated with albumin

as compared to other fluids (odds ratio 0.82, P = 0.047) [8]. This is consistent with the observed reduction in mortality associated with albumin use (pooled relative risk 0.92, P = 0.046) in a more recent meta-analysis of large-scale randomised trials [9].

In the United Kingdom, albumin is available in two preparations. The 5% albumin solution (Alburex 5®, CSL Behring, Marburg, Germany) contains sodium and chloride at concentrations of 140 mmol/L and 128 mmol/L respectively and is presented as 25 g albumin in 500 ml. The 20% solution (Alburex 20®, CSL Behring, Marburg, Germany) is presented as 20 g in 100 ml, contains only 20 mmol/L of chloride and 50-100 mmol/L of sodium. The volume expanding effect of the 5% solution is comparable to that of modern artificial colloids whereas the volume effect of the concentrated, 20% preparation is significantly higher. Small-volume resuscitation of critically ill patients with concentrated albumin offers a number of theoretical advantages, such as increased intravascular volume in excess of the volume of fluid administered and reduced interstitial oedema [10].

We recently found, in an observational study, that patients resuscitated with the diluted 5% albumin solution received five times more volume compared to patients resuscitated with the concentrated 20% albumin solution [11]. Despite this difference, a trend towards higher mean arterial blood pressure up to four hours after a bolus of 20% albumin (compared to a bolus of 5% albumin) was seen (P = 0.056, Figure 1). In addition, more patients receiving 5% albumin needed further fluid boluses within 24 hours as compared to patients receiving 20% albumin (58% versus 45%, P = 0.049). Finally, patients resuscitated with concentrated 20% albumin received approximately 30 times less chloride than those in the 5% albumin group. This is an important

finding since administration of chloride-rich solutions is associated with more complications, including severe renal failure requiring dialysis [12, 13].

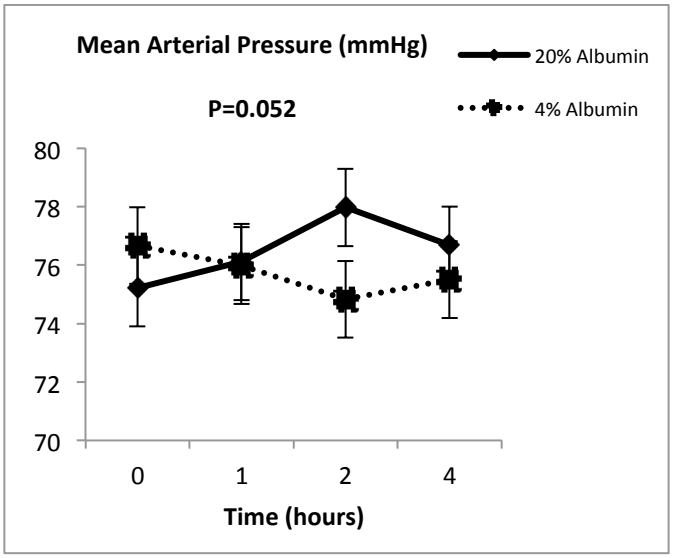

Figure 1. Mean arterial blood pressure over the first four hours following a fluid bolus of either 100 mL, 20% albumin solution or 500 mL, 5% albumin solution, including baseline values at 0 hours.

Aims

The aim of this study is to establish the feasibility, safety, biochemical and physiological efficacy of 20% albumin compared with 5% albumin for fluid bolus therapy in critically ill patients.

Specifically, we aim to study the effect of intravenous 20% albumin infusion compared to 5% albumin infusion on the following variables:

- Mean arterial blood pressure (first 4 hours)
- Central venous pressure (first 4 hours)
- Cardiac output (first 4 hours)
- Urinary output (first 4 hours)
- Serum biochemistry (first 4 hours)

- Volume of fluid administered over the first 4 hours and first 48 ICU hours following recruitment
- Use of vasoactive medications over the first 48 ICU hours following recruitment
- Serum chloride levels over the first 48 ICU hours following recruitment
- Serum albumin levels over the first 48 ICU hours following recruitment
- Renal function based on changes in serum creatinine and urine output in the first 48 ICU hours.
- Lung function based on arterial partial oxygen pressure (PaO_2)/fraction of inspired oxygen (FiO_2) ratio in the first 48 hours in ICU

Hypotheses

- We hypothesise that the administration of 20% albumin for fluid resuscitation in critically ill patients will be feasible and safe when compared to administration of 5% albumin
- We hypothesise that a lower volume of resuscitation fluid will be administered over the first 4 and 48 hours in ICU in patients receiving 20% albumin than in patients receiving 5% albumin.
- We hypothesise that the cumulative fluid balance over the first 48 hours in ICU will be significantly lower in patients receiving 20% albumin than in patients receiving 5% albumin.
- We hypothesise that the administration of 20% albumin will create a significantly greater increase in the hourly and mean arterial blood pressures over the study period compared to the 5% albumin.

- We hypothesise that the mean central venous pressure will be significantly lower in patients receiving 20% albumin than in those patients receiving 5% albumin.
- We hypothesise that patients receiving 20% albumin will require less vasoactive medications over the study period as compared to patients receiving 5% albumin.
- We hypothesise that the overall administration of chloride will be less in patients receiving 20% albumin than in patients receiving 5% albumin.
- We hypothesise that 20% albumin administration will significantly reduce peak serum creatinine in the first 48 hours following randomisation when compared to 5% albumin administration.
- Finally, we hypothesise that the administration of 20% albumin will significantly increase the PaO_2/FiO_2 ratio when compared to the administration of 5% albumin.

Relevance and Importance

- The association between fluid accumulation and poor patient outcomes has been established.
- Fluid resuscitation with 20% albumin may reduce the volume of fluid administration.
- A reduced volume of fluid administered during critical illness may achieve similar hemodynamic improvements without the need for additional volume administration

Methodology

Study design

The SWIPE study is an investigator-initiated, multi-centred, open label, randomised-controlled trial.

Participant recruitment and selection

All patients will be recruited if they meet the inclusion criteria and no exclusion criteria.

Inclusion criteria

- Admitted to the intensive care unit at participating sites for less than 24 hours.
- Age 18 years or greater
- Need for fluid bolus as determined by the treating clinician
- Presence of one or more of the following physiological states: systolic BP <90 mmHg, or MAP <65 mmHg, or increasing need for vasopressor drug infusion or pulse pressure variation >12 % or stroke volume variation >12%, or Cardiac index <2.2 L/min/m^2 or heart rate >100 or urinary output <20 ml/hr or either rising lactate levels or lactate levels >2 mmol/L or capillary refill time >3 seconds or central venous pressure <8 mmHg.

Exclusion criteria

- Confirmed or suspected pregnancy
- Patients with traumatic brain injury
- Active bleeding
- Haemoglobin level <70 g/L
- People who refuse blood products

- Patients in whom death is considered imminent (within 24 hours)

Sample size estimate

Given that in the first 48 hours the 5% albumin administered in the SAFE study [14] was a total of 1785ml (SD of 1865), we will aim to detect a decrease in fluid given to 1300ml (SD of 1368: proportionately the same as that seen in SAFE for a mean inout of 1785ml). This decrease of around 500ml in fluid input is considered of potential clinical value. To have a 90% power of detecting such a difference at an alpha level of 0.05, 195 patients will need to be randomised to each group. We have rounded this number up to 200 in each group to account for possible data loss.

Randomisation procedure

- Computer generated sets of random allocations will be produced by the Research Co-ordinator in advance of the study.
- Randomization will be by means of sealed envelopes with permuted blocks of variable size.
- Each envelope will contain a study arm allocation as well as a copy of a simplified version of the study protocol.
- Every patient who participates in any study related procedure will be assigned a unique patient number.

Intervention description

Patients will be randomised one of two arms:

- The **treatment arm** will receive an intravenous infusion of 20% albumin (Alburex 20®, CSL Behring, Marburg, Germany) every time the treating clinician decides

that a fluid bolus needs to be given during the first 48 hours in ICU. The treating clinician determines the volume and infusion rate of each fluid bolus.

- The **control arm** will receive an intravenous infusion of 5% albumin (Alburex 5®, CSL Behring, Marburg, Germany) every time the treating clinician decides that a fluid bolus needs to be given during the first 48 hours in ICU. The treating clinician determines the volume and infusion rate of each fluid bolus.

Randomised participants in this study will receive and infusion of 20% albumin (treatment group) or 5% albumin (control group) each time the treating physician decides that a fluid bolus needs to be given during the first 48 hours of ICU. The treating clinician determines the volume and infusion rate of each bolus. Other fluids (nutrition, drug infusions, blood products) are given as per the discretion of the treating clinician.

Blinding

Blinding in this trial is not possible as Alburex 20® comes in 100 mL glass bottles whereas Alburex 5® comes in 500 mL bottles.

Monitoring

- Routine clinical monitoring shall continue after recruitment to the study.
- Routine monitoring of critically ill patients admitted to the ICU includes:
    - Heart rate (HR)
    - Arterial blood pressure (ABP)
    - Central venous pressure (CVP)
    - Oxygen saturation (SpO_2)

- Urine output (UO)
- Respiratory rate (RR)
- Temperature
- Fluid intake
- Fluid output
- Ventilator settings
- Blood gas results
- Serum creatinine
- Serum albumin

Patient Care

- Participation in the study shall not affect patient treatment in any other way.
- All additional therapies shall be administered at the discretion of the treating clinician.
- These therapies include:
    - Oxygen therapy
    - Antibiotics
    - Radiological investigations
    - Surgical interventions

There will be no attempt to control any other treatment. In particular there will be no attempt to control vasopressor therapy, oxygen therapy, antibiotics, blood, blood products and surgical intervention.

Data collection

The case report form will collect the information detailed below. The electronic medical records and previous volumes of notes will be accessed to collect baseline data where appropriate. Laboratory data will be accessed to acquire the items detailed below. We will perform a data review after the first 20 patients to ensure our data capture strategy is appropriate.

Data will be collected on the following variables:

Patient data

- Code for patient, gender and age. Date of admission to ICU and to hospital.
- Reason for admission to intensive care (post-operative complication, sepsis, medical emergency, post-operative management, other) and urgency (planned, unplanned, emergency). If surgical, date and type of operation.
- Weight and height on admission, to be used for calculation of body surface area.

Clinical Data

- Haemodynamic data: HR, ABP, CVP will be measured hourly during the study period.
- Blood gas results: PaO_2, lactate concentration, pH/H+ concentration, bicarbonate concentration, sodium concentration, chloride concentration, creatinine concentration, haemoglobin concentration and base deficit/excess will be measured hourly during the study period.
- Fluid balance – Resuscitation fluids. Each fluid bolus will be recorded (type of resuscitation fluid, volume, infusion speed).
- Fluid balance – for each day or part there of.

- Baseline serum creatinine and urea pre-admission to ICU if available. Defined as a serum creatinine and urea taken in the six months pre-admission to hospital for this ICU event.
- Serum creatinine on admission, as indicated above, and as indicated clinically.
- Serum albumin on admission and as indicated clinically.
- Doses of furosemide administered (or rate of furosemide infusion).
- Doses of vasopressors and inotropes administered (or infusion rates).
- All other biochemical and haematological indices recorded as clinically indicated during the patient admission.

Outcome Data

- Primary efficacy outcome
    - Amount of resuscitation fluid (mL) administered over the first 48 hours in ICU.

- Secondary efficacy outcomes
    - The cumulative fluid balance after 48 hours in ICU.
    - The amount of vasoactive medication given over the first 4 hours after a fluid bolus and over the first 48 hours in ICU.
    - The total amount of fluids given over the first 4 hours after a fluid bolus, daily and over the first 48 hours in ICU.
    - The relative change in haemodynamic variables and blood gas results over the first 4 hours after a fluid bolus.
    - The relative change between baseline and peak creatinine in the first 48 hours after randomization.

- Patient-centred efficacy outcomes
    - Need for RRT
    - Renal status at 90 days
    - Hours on mechanical ventilation
    - ICU discharge status (alive or dead)
    - ICU length of stay
    - Hospital discharge status (alive or dead)
    - Hospital outcome (discharge destination – home, another hospital, advanced care institution)
    - Hospital length of stay (date of discharge)
    - Mortality status at 90 days.

- Feasibility and safety outcomes:
    - Distribution of values for primary and secondary outcome
    - Randomized / Screened patients ratio
    - Data completion rate
    - Loss to follow-up rate
    - Recruitment rate and duration
    - Separation in amount of fluid given

Safety outcomes

- Development of side-effects
- Episodes of hypotension
- Development of kidney failure

- Adverse changes in any of the physiological efficacy measures

Data analysis

Outcomes will be compared after log transformation where appropriate. Comparisons will be made using t-test and ANOVA for repeated-measures or Wilcoxon rank-signed test and Kruskall-Wallis according to the underlying distribution for continuous data and Chi-square for categorical data. A Kaplan-Meier curve with log-rank test will be performed to further compare in-hospital mortality and rate of discharge home. Logistic regression analysis will also be performed to adjust for baseline imbalances. Analysis will be an on intention-to-treat basis.

Risks and Benefits

Albumin solutions have been used for resuscitation since the 1940s. An investigation of the safety of albumin solutions showed that between 1998 and 2000, approximately 10^7 units of such albumin solutions were administered worldwide. Adverse effects that were directly associated with albumin were an extremely rare event during this observation period [15]. There are, however, more recent reports that the use of (20%) albumin is associated with increased mortality for patients with traumatic brain injury [6]. Accordingly, patients with traumatic brain injury will be excluded from the SWIPE study. Although albumin is prepared from pooled plasma, albumin preparations currently available are considered to be non-allergenic due to the manufacturing process.

Data handling, retention, storage and destruction

Data handling

The case report form (CRF) will be developed by the members of the investigator team as a paper CRF. All data will be collected by members of the investigator team as described in the CRFs from the source data. Information recorded in the CRF should accurately reflect the subject's medical/hospital notes and must be completed as soon as it is made available.

The intent of this process is to improve the quality of the clinical study by providing prompt feedback to the Investigators on the progress of the data submitted and to enhance the ability to collect early safety information in a more timely fashion to fully comply with the intent of GCP requirements. Completed CRFs will be stored within the Department of Intensive Care (Research office) of each participating site. Data from UK participants will be completely de-identified prior to its electronic encryption and sharing with the Chief Investigator in Australia for statistical analysis.

Data retention, storage and destruction

The data repository for this study will be stored electronically in password protected computers located within the ICU Research Office at participating sites, as appropriate. Paper data and study related documents used in this study will be de-identified and only a master log will be maintained to identify participants and their study data. The log will be locked in a protected office. All data for this trial will be retained for a period of fifteen years after which all electronic and paper data will be destroyed in accordance with hospital policy in place at the time.

Ethical Considerations

Guiding principles

This study is to be performed in accordance with the ethical principles of the Declaration of Helsinki; ICH Good Clinical Practice Guidelines., and NHMRC National Statement on Ethical Conduct in Research Involving Humans (June 1999). In the UK, the study will be conducted in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and statutory instrument 2006/2984. The study will also be conducted in accordance with the principles set down in the Research Governance Framework; the Data Protection Act (1998) and other regulatory requirements as appropriate.

Informed consent

The NHMRC National Statement on the Ethical Conduct in Human Research acknowledges in Chapter 4.4 that research involving patients who are heavily dependent on medical care, such as the patients in this study, is necessary to assess and improve the efficacy and safety of interventions used in their treatment.

Obtaining written and informed consent from patients who are highly dependent on medical care such as patients in ICU is difficult because these patients are often unconscious, sedated, intubated and too ill to understand information relating to clinical trial participation.

For patients that are highly dependent on medical care, such as patients in ICU, the preparation of consent documentation and associated consent procedure must adhere to the relevant local laws and guidelines.

A number of approaches to obtaining consent in this study have been developed from the guidelines in Chapter 4.4 of the National Statement and also from the ANZICS Clinical Trials Group Ethics Handbook for Researchers (2005). The National Statement provides guidance for such patients in sections 4.4.9 through to 4.4.14. In the UK; the informed consent procedure will be governed by the Medicines for Human Use (Clinical Trials) Regulations (2004); Schedule 1, part 5 and by The Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006, No. 2984.

Process of obtaining consent where the patients are highly dependent on medical care

Informed consent from participant

Where it is possible for a conscious and comprehending patient to give informed consent to take part in this study before project related activities are undertaken, the study will be explained verbally to that patient by the investigator and the patient will be given the opportunity to read the participant information sheet. After they have had their questions answered, had time to consider participation and if they are willing to take part in the study, they will be asked to sign the consent form in the presence of the Investigator, who will countersign the form. Intensive care physicians are highly experienced at caring for critically ill patients and also evaluating the competence of their patients to understand their illness and consent for therapeutic interventions. Where appropriate, a treating clinician who is not part of the study team will assess the competence of a potential participant to consent for

research. If the patient is deemed competent and consents to participate, they will be given a copy of the signed and dated consent form as well as the participant information sheet and any other documentation discussed through the consent process.

Informed consent from substitute decision maker

If a potential participant lacks the capacity to give consent then consent should be obtained from the participant's guardian, or person or organisation authorised by law before project related activities are undertaken (see 4.4.10 of **NHMRC National Statement on the Ethical Conduct in Human Research and Schedule 1 Part 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004**). For the purposes of this protocol, the descriptor "participant's legal representative" also known as the 'Person Responsible', describes the person who is legally allowed to give consent for the patient. In the UK, the legal representative will be defined as follows:

a person, other than a person involved in the conduct of the trial, who—

by virtue of their relationship with that adult or that minor, is suitable to act as their legal representative for the purposes of that trial, and is available and willing to so act for those purposes, or if there is no such person, a person, other than a person connected with the conduct of the clinical trial, who is the doctor primarily responsible for the medical treatment provided to that adult, or a person nominated by the relevant health care provider.

The procedure for obtaining consent from the legal representative must be approved by the local Independent Ethics Committee prior to use.

Delayed informed consent

Where it is not possible or practicable for the patient or their legal representative to consider the study and give consent, the patient may be enrolled into the study without prior consent, provided the procedure is in accord with the requirements of the Independent Ethics Committee and applicable legislation (In Australia, point 4.4.13 of NHMRC National Statement on the Ethical Conduct in Human Research and, in the UK, The Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006).

As soon as possible, the legal representative should be informed of the patient's participation in the study. In the UK, part 5 of Schedule 1 will then apply. The legal representative will be able to withdraw their consent for the patient to continue to participate in the study at any time. If they choose to withdraw the patient, permission will be asked to use the study-related data collected up to that time and for permission to collect and use outcome data.

If the patient dies before consent is gained and the legal representative cannot be contacted, the waiver of consent must be in accordance with the local Independent Ethics Committee requirements and applicable to local legislation.

Patients who recover sufficiently to understand the explanation of the study will be asked to consent to continue in the study procedures as soon as possible or be offered the chance to withdraw. If the patient chooses to withdraw from the study procedures, they will be asked for permission to use their study-related data and for permission to collect and use outcome data.

All interaction between research staff and potential or actual participants and their relatives will take into consideration the stress or emotional factors associated with critical illness and ensure that the dependency of potential participants and their relatives on medical personnel providing treatment does not compromise the freedom of decision making to participate (c.f. 4.4.11 **of** NHMRC National Statement on the Ethical Conduct in Human Research).

Where a researcher is also the treating health professional, another member of the research team independent of any responsibility for the clinical care of that patient, will be asked to make the initial approach and/or seek consent from participants or their legal representative.

The written informed consent form should be signed, name filled in and personally dated by the patient or by their legal representative and by the Investigator who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the patient and/or the legal representative.

Confidentiality of patient data

Participants will not be identified by name, and confidentiality of information in medical records will be preserved. All patients' details will be entered in coded format. The confidentiality of the participant will be maintained unless disclosure is required by law or other regulations.

Confidentiality

For consented patients; names, telephone numbers and addresses will be collected and stored in a locked filing cabinet for the duration of the study. After this time, the identifiable data will be destroyed. All non-identifiable data will be kept for 15 years as per the UK clinical trials regulations and Central Manchester University Hospitals guidelines. Only data which is pseudo-anonymised will be shared with the co-ordinating centre. The identifying key code will not be shared. The data of UK participants will be handled in accordance with the requirements of the Data Protection Act (1998).

Information and consent documents

Delayed next-of-kin (legal representative) and delayed patient information sheets, and consent forms have been developed based on Austin Health Human Research Ethics Committee requirements and state regulatory requirements. These have been adapted for use in the UK and are enclosed with this protocol.

Patient safety and adverse event report

Data safety management committee

This is an investigator-initiated study. There is no independent Data and Safety Monitoring Committee (DSMC) associated with the conduct of this study.

Adverse events (AEs)

AEs are defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational intervention and which does not necessarily have to have a causal relationship with this treatment.

It is recognised that the intensive care patient population will experience a number of common aberrations in laboratory values, signs and symptoms due to the severity of the underlying disease and the impact of standard therapies. These will not necessarily constitute an adverse event unless the event requires significant intervention or are considered to be of concern in the investigator's clinical judgement.

In all cases, the condition or disease underlying the symptom, sign or laboratory value should be reported e.g. renal failure rather than hyperkalaemia, and agitation rather than self-extubation.

Serious adverse events (SAEs)

SAEs are defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation

- Results in persistent or significant disability/incapacity
- Is a congenial anomaly/birth defect
- Is an important medical event which may require intervention to prevent one of the previously listed outcomes

Adverse reactions (ARs)

ARs are any untoward and unintended response in a study subject to the investigational medicinal product (IMP), which is related to any dose administered to that subject.

Suspected unexpected serious adverse reactions (SUSARs)

SUSARs are serious adverse reactions suspected to have occurred from administration of a medicinal product; but that are also “unexpected” in terms of the existing information and clinical experience of the medicinal product in question.

Reporting

AEs, SAEs, ARs and SUSARs events will be recorded on a separate case report form. All events will be reported and shared between investigators at all participating sites worldwide.

SAEs which occur from the time of of recruitment into the study to hospital discharge will be collected and reported to the study sponsor within 24 hours of study staff becoming aware of the event. The sponsor will ensure they are reported annually to the appropriate ethics committees and the MHRA.

SUSARs which are either fatal or life-threatening will be reported to the MHRA within 7 days of the sponsor being aware of their occurrence. Any SUSARs that are not fatal, nor considered life threatening will be reported to the MHRA within 15 days of the sponsor becoming aware of them.

Minimum information to report will include:

• Patient initials and study number

• Nature of the event

• Commencement and cessation of the event

• An investigator's opinion of the relationship between study treatment and the event (unrelated, possibly, probably or definitely related).

• Whether treatment was required for the event and what treatment was administered.

Study Conduct

Protocol amendments

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant, will be reviewed and approved by the sponsor and CI prior to submission in writing to the REC, MHRA and local R&D for approval prior to enrolment into an amended protocol.

Protocol deviations and serious breaches

The Regulations and guidance state that no deviation must be made from an approved trial protocol, unless it is an urgent safety measure taken to protect a participant from immediate harm. The trial investigators are encouraged to contact the sponsor if a potential protocol deviation has occurred (or if an event has occurred and it is unclear whether it should be classified as a deviation) and the sponsor will advise as to what information and actions are required.

For Clinical Trials of Investigational Medicinal Products (CTIMPs), there is a legal requirement to report serious breaches of Good Clinical Practice (GCP) or the trial protocol to the MHRA and REC within a defined timeframe. If a major deviation on a CTIMP meets the criteria for a serious breach, it will be notified immediately to the Sponsor and reported to the REC and the MHRA within 7 days of confirmation. Complete investigations of breaches will be fully documented, filed in the Trial Master File and a copy sent to the sponsor.

End of Trial

The UK Chief Investigator and/or the sponsor have the right at any time to terminate the trial for clinical or administrative reasons.

The end of trial in the UK will be the date of the last data collection from the last patient. An end of trial notification will be submitted to the REC and MHRA within 90 days of this date. An end of the trial notification will be submitted to the REC and MHRA within 15 days if the trial is terminated prematurely. Investigators will inform participants of any premature termination of the trial and ensure that the appropriate follow up is arranged for all involved. A summary report of the trial will be provided to the REC and MHRA within 12 months of the end of trial notification.

Ethics and regulatory approvals

The UK Chief Investigator will ensure access to source data and documents for trial-related monitoring, audits, REC review, and regulatory inspection.

The trial will be conducted in accordance with the principles of GCP.

The sponsor will ensure that the trial protocol, participant information sheet, consent form, GP letter and submitted supporting documents have been approved by a research ethics committee prior to any participant recruitment. The protocol and all

agreed substantial protocol amendments, will be documented and submitted for ethical and regulatory approval prior to implementation. Annual reports will be submitted to the REC and the Competent Authority (the MHRA). The UK CI and sponsor will ensure that the REC and the MHRA are notified that the trial has finished (either as expected or prematurely) within required timeframes with summary reports to be provided as required.

Funding and insurance

For patients recruited in Australia:

Funding is provided by the Austin Hospital Special Purpose Fund (Y8016) *Anaesthesia Intensive Care Trust Fund* (AICTF) for the development and completion of this project. Top-up funding is being sought via a competitive grant application. As an investigator-initiated study performed in an Australian public hospital, indemnity insurance will be provided by the public hospital (Austin Health).

For patients recruited in the United Kingdom:

Funding is provided by CSL Behring in the form of an unrestricted grant. Central Manchester University Hospitals NHS Foundation Trust will act as the sponsor for UK patients and will provide NHS indemnity.

Trial registration

This study is registered with the Australian New Zealand Clinical Trial Registry (ACTRN12615000349549) and the European Medicines Agency (EudraCT No: 2016-001940-20). Prior to commencement in the UK, this study will be registered with the ISRCTN registry. These are public access registries. All pending trial registration numbers will be provided to the HREC when the registration is completed.

Publication

The study will be published in the name of the of the study investigators. The chief investigator will be listed as the first author and other members of the management committee will be listed alphabetically. Funding bodies will be acknowledged in the publication.

Following completion of the study and data analysis the study results will be published in a peer-reviewed critical care journal and presented at local and national intensive care conferences. In addition, we will provide a summary of the study and its findings to the staff of the two study sites.

Study findings will not be provided to trial participants as:

1. The physiological findings will be of a pilot investigation in nature.

2. The implications of the findings are uncertain beyond those of the main study and only aim to assist clinicians' in perhaps understating more clearly possible impact behind differences in fluid choice that might become apparent from the findings of the study.

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