The Plasma-Lyte 148 v Saline (PLUS) study protocol: a multicentre, randomised controlled trial of the effect of intensive care fluid therapy on mortality

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ABSTRACT

Background: 0.9% sodium chloride (saline) is the most commonly administered resuscitation fluid on a global basis but emerging evidence suggests that its high chloride content may have important adverse effects.

Objective: To describe the study protocol for the Plasma-Lyte 148 v Saline study, which will test the hypothesis that in critically ill adult patients the use of Plasma-Lyte 148 (a buffered crystalloid solution) for fluid therapy results in different 90-day all-cause mortality when compared with saline.

Design and setting: We will conduct this multicentre, blinded, randomised controlled trial in approximately 50 intensive care units in Australia and New Zealand. We will randomly assign 8800 patients to either Plasma-Lyte 148 or saline for all resuscitation fluid, maintenance fluid and compatible drug dilution therapy while in the ICU for up to 90 days after randomisation.

Outcome measures: The primary outcome is 90-day all-cause mortality; secondary outcomes include mean and peak creatinine concentration, incidence of renal replacement therapy, incidence and duration of vasoactive drug treatment, duration of mechanical ventilation, ICU and hospital length of stay, and quality of life and health services use at 6 months.

Results and conclusions: The PLUS study will provide high-quality data on the comparative safety and efficacy of Plasma-Lyte 148 compared with saline for resuscitation and compatible crystalloid fluid therapy in critically ill adult patients.

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Background and rationale

Fluid resuscitation is an important and common intervention in the management of critically ill patients, but the choice of fluid remains an issue of debate.[1] Worldwide, 0.9% sodium chloride (saline) has been the most widely used resuscitation fluid,[2] but its use is increasingly being challenged by evidence that suggests the high chloride content may have important adverse effects and that resuscitation with "balanced" or "buffered" crystalloids may offer patients better outcomes.[3-12]

In a study in an Australian intensive care unit where fluids with high chloride content were removed, a significant reduction in acute kidney injury (AKI) and need for renal replacement therapy (RRT) was observed in comparison to historical controls. Furthermore, the observed hospital mortality was reduced from 14.9% to 12.7%, a reduction in relative risk (RR) of 14.7% ($P = 0.08$).[5,6] A meta-analysis of high-chloride fluid resuscitation versus low-chloride fluid resuscitation in perioperative and critical care patients reported that saline was associated with an increased risk of developing AKI, metabolic acidosis, receiving a blood transfusion and an increased duration of mechanical ventilation.[13]

The highest quality evidence to date comparing the use of a buffered salt solution (Plasma-Lyte 148) with saline comes from a randomised, blinded, cluster cross-over trial conducted in four New Zealand ICUs (the Saline v Plasma-Lyte 148 for Intensive Care Unit Fluid Therapy [SPLIT] study). No difference in the primary outcome of the incidence of AKI was observed between groups (RR, 1.04 [95% CI, 0.80–1.36]; $P = 0.77$) nor in the secondary outcomes of RRT use and mortality. The observed risk of in-hospital death was 12.8% lower in patients assigned to Plasma-Lyte 148, but the 95% CIs did not exclude the possibility of a clinically important decrease or increase in mortality risk with the use of Plasma-Lyte 148 instead of saline.[14] A criticism of the SPLIT study is that the small volume of study fluid administered to patients (median, 2.0 L) may have been too low to cause detectable renal toxicity.[15,16]

In another pilot, cluster-randomised, multiple cross-over trial (the Isotonic Solution Administration Logistical Testing [SALT] study) comparing saline to buffered crystalloid solutions (lactated Ringer's solution or Plasma-Lyte A) in a single adult ICU, no difference in the overall incidence of AKI or major adverse kidney events was found (median volume of study fluid, 1.5 L). However, in patients who received larger volumes of saline, there was a reported increase in major adverse kidney events, suggesting a dose–response relationship.[16]

Recent observational data have shown that buffered salt solutions have gained popularity and are now the most commonly administered crystalloid solutions for fluid resuscitation in Australian and New Zealand ICUs, as well as in other geographic regions.[17-20] Given the limitations of current evidence and the increased use of buffered salt solutions,[15,21] we are conducting the Plasma-Lyte v Saline (PLUS) study to provide an accurate and reliable estimate of the comparative risks and benefits of the use of a buffered salt solution (Plasma-Lyte 148) v saline in critically ill patients. The trial is registered with ClinicalTrials.gov (NCT02721654) and the World Health Organization (UTN U1111-1178-8334).

Study design

The PLUS study is a prospective, multicentre, parallel-group, concealed, blinded, randomised controlled trial with a planned sample size of 8800 patients enrolled in approximately 50 ICUs in Australia and New Zealand. Participants will be randomly assigned to receive either Plasma-Lyte 148 or saline for all resuscitation fluid, maintenance fluid and drug dilution therapy (when fluids are compatible) while in the ICU, for up to 90 days after randomisation.

Participants

The inclusion and exclusion criteria (listed in Table 1) are designed to enrol a population of critically ill patients whose severity of illness places them at a high risk of death and who are likely to receive a substantial volume of crystalloid fluid. These criteria have been adapted from those used successfully in the Normoglycemia in Intensive Care Evaluation — Survival Using Glucose Algorithm Regulation (NICE SUGAR)[22] study, and the volume of fluid they are likely to receive has been estimated by examination of the Crystalloid v Hydroxyethyl Starch Trial (CHEST)[23] database. The criteria are designed to enrol a population with a 90-day mortality rate of around 23%, and an average ICU length of stay of 6 days, during which they are expected to receive an average of 12 L of crystalloid fluid.

Study treatments

After randomisation, study participants will receive either Plasma-Lyte 148 or saline for all resuscitation episodes, maintenance fluid and drug dilution therapy (when fluids are compatible) while in the ICU for up to 90 days. Other crystalloid fluids may be used as carrier fluids for the infusion of any drug for which either Plasma-Lyte 148 or saline is considered incompatible or when mandated by local drug administration protocols. Both study fluids are

Table 1. Inclusion and exclusion criteria for the PLUS study

Inclusion criteria

- The patient will receive fluid resuscitation defined as a bolus of fluid prescribed to be administered over 1 hour or less to increase or maintain intravascular volume that is in addition to maintenance fluids, or specific fluids used to replace non-physiological fluid losses
- The patient is expected to be in the ICU the day after tomorrow
- The patient is not expected to be well enough to be eating tomorrow
- An arterial or central venous catheter is in situ, or placement is imminent as part of routine management
- Plasma-Lyte 148 and 0.9% saline are considered equally appropriate for the patient
- The requirement for fluid resuscitation is supported by at least one of seven pre-specified clinical signs:
  - heart rate > 90 beats per minute
  - systolic blood pressure < 100 mmHg or mean arterial pressure < 75 mmHg
  - central venous pressure < 10 mmHg
  - pulmonary artery wedge pressure < 12 mmHg
  - capillary refill time > 1 second
  - urine output < 0.5 mL/kg for at least 1 hour

Exclusion criteria

- Age less than 18 years
- Patients who have previously received fluid resuscitation (as defined above) prescribed in the ICU during this current ICU admission
- Patients transferred directly from another ICU who have received fluid resuscitation (as defined above) during that ICU admission
- Contraindication to either study fluid, eg, previous allergic reaction to Plasma-Lyte 148
- Patients admitted to the ICU with specific fluid requirements: the treatment of burns; following liver transplantation surgery; for correction of specific electrolyte abnormalities
- Patients with traumatic brain injury or those considered at risk of developing cerebral oedema
- Patients in whom death is deemed imminent and inevitable
- Patients with an underlying disease process with a life expectancy of < 90 days
- Patients in whom it is unlikely the primary outcome can be ascertained
- Known or suspected pregnancy
- Patients who have previously been enrolled in the PLUS study

PLUS = Plasma-Lyte 148 versus saline. ICU = intensive care unit.

manufactured by Baxter Healthcare and will be labelled, packed and distributed by the company directly to the study sites. Study fluid will be coded and labelled in compliance with applicable regulations, and in a manner that protects the blinding. Both fluids are clear, colourless solutions and macroscopically indistinguishable, and they will be supplied in identical 1000 mL bags.

Study outcomes

The primary outcome is mortality from all causes at 90 days after randomisation; Table 2 lists the primary and secondary outcomes and the proposed pre-defined subgroups. The study outcomes are pragmatic, patient-centred and, with the exception of the quality-of-life assessment, free from risk of ascertainment bias. In addition to examination of outcomes for the overall population, outcomes will also be examined for four subgroups, defined by the following baseline patient characteristics:

- with or without kidney injury (defined as baseline creatinine concentration at least 1.5 times above the upper limit of normal for the local laboratory)
- with or without sepsis (defined using the 2016 Sequential Organ Failure Assessment [SOFA]-based criteria[24,25])
- admitted to the ICU directly after surgery or not
- and low v high severity of illness (defined by Acute Physiology and Chronic Health Evaluation [APACHE] II[26] score < 25 or ≥ 25, respectively).

Randomisation and allocation concealment

We will conduct permuted block randomisation with variable block sizes, stratified by site, using a password-protected, secure website. Each patient will be allocated a unique patient study number and, after randomisation, will be assigned to receive either Plasma-Lyte 148 or saline (blinded study treatment).

Data collection and management

The George Institute for Global Health will manage the data. The principal means of data collection and data processing will be electronic, via a password-protected website. All computerised forms will be electronically signed by authorised study staff and all changes made after electronic signing will have an electronic audit trail with a signature and date. We will keep a screening log to monitor recruitment and report the size of the patient population from which eligible patients have been recruited.

Data will be collected by trained staff and entered into a secure online electronic case report form (eCRF) (see Table 3 for full details of information to be collected). The information to be collected includes eligibility criteria at randomisation, patient demographic data, admission diagnosis and clinical information (eg, APACHE II[26] score). These data will be collected to assess baseline balance between each treatment group and to categorise patients into the pre-specified subgroups of interest.

Daily clinical information and laboratory data will be recorded while the patient is in the ICU for up to 90 days after randomisation, to document the response to treatment and to monitor safety. Follow up for the primary outcome will be until death or 90 days after randomisation, whichever is the earliest. At Day 90, vital status, length of stay in the ICU, length of stay in hospital, date and cause of death (if appropriate) will be recorded.[27] Follow up at 6 months will assess vital status, quality of life and functional capacity, using the EQ-5D-5L

Table 2. Primary outcomes, secondary outcomes and pre-specified subgroups for the PLUS study

Primary outcomes

- Death from all causes 90 days after randomisation

Secondary outcomes

- Mean and peak serum creatinine concentration during the first 7 days
- Maximum post-randomisation increase in serum creatinine in ICU during the index hospital admission
- Proportion of patients newly treated with renal replacement therapy up to 90 days after randomisation
- Proportion of patients treated with and duration of treatment with vasoactive drugs
- Duration of mechanical ventilation in the ICU
- Length of stay and all-cause mortality at ICU discharge
- Length of stay and all-cause mortality at 28 days
- Length of stay and all-cause mortality at hospital discharge
- Quality-adjusted life years gained assessed at 6 months after randomisation
- Health services use during the 6 months after randomisation

Pre-specified subgroups for primary and secondary outcome analyses

- Patients with or without kidney injury (defined as baseline creatinine concentration at least 1.5 times above the upper limit of normal for the local laboratory)
- Patients with or without sepsis (defined using 2016 SOFA-based criteria[20,21])
- Patients admitted to the ICU directly after surgery or not
- Low versus high severity of illness (defined by APACHE II[22] score, < 25 or ≥ 25)

PLUS = Plasma-Lyte 148 versus saline. ICU = intensive care unit.

Table 3. Data to be collected

Period of study	Data
Randomisation	Patient identifier, sex, date of birth, inclusion and exclusion criteria, date and time of randomisation, treatment allocation
Baseline information	Hospital and ICU admission date and time
	ICU admission diagnosis (operative v non-operative), source of ICU admission, readmission to the ICU
	Pre-defined subgroups: with/without sepsis (defined by 2016 SOFA-based criteria[20,21]), with/without kidney injury (defined by threshold creatinine concentration), admitted to the ICU directly after surgery or not, low v high severity of illness (defined by APACHE II[22] score < 25 or ≥ 25)
	Clinical data: weight, HR, MAP, CVP, pH, base excess; serum lactate, potassium, chloride and haemoglobin levels; mechanical ventilation
	Organ dysfunction: SOFA[21] score for cardiovascular and respiratory domains, highest creatinine and bilirubin levels, lowest platelet count, worst non-sedated GCS, APACHE II[22] score
	Volume of fluid received within 24 h before randomisation: 0.9% saline, hypertonic saline, Plasma-Lyte 148, Hartmann's solution, gelatin-based fluids, starch-based fluids, albumin
Days 1–14	Daily total volumes of: study fluid, non-study fluid administered as bolus, maintenance and other fluids, gelatin-based fluids, starch-based fluids, albumin, blood products (packed cells, whole blood, fresh frozen plasma, platelets, cryoprecipitate)
	Organ dysfunction (SOFA[21] score domains)
	Clinical data: HR, MAP, CVP, pH, base excess; serum lactate, potassium, chloride and haemoglobin levels; mechanical ventilation, RRT, net fluid balance (total fluid input and output), urine output
Day 15–90	Mechanical ventilation, RRT, organ dysfunction (SOFA[21] score for cardiovascular domain, highest creatinine level), daily volume of study fluid
90-day summary	Vital status at Day 90
	date and cause of death
	ICU discharge date and readmissions to ICU
	Hospital discharge date and readmissions to hospital
	RRT in ICU and indication
	RRT outside ICU
	Reason for discontinuation of study treatment
	Type of consent obtained
6 months after randomisation	Vital status at 6 months, date and cause of death, EQ-5D-5L,[24] linkage to health services data (economic evaluation)
Up to 6 months after randomisation	Adverse reactions: description, timing and resolution of any non-serious or serious drug reactions thought to be study treatment-related, collected from randomisation to Day 90
	Protocol deviations (eg, randomisation of ineligible patient; incorrect treatment pack used; non-study fluid administered as bolus, resuscitation or maintenance fluid; other deviations): collected from randomisation to end of study (6 months)

ICU = intensive care unit. SOFA = sequential organ failure assessment. APACHE = Acute Physiology and Chronic Health Evaluation. HR = heart rate. MAP = mean arterial pressure. CVP = central venous pressure. GCS = Glasgow Coma Score. RRT = renal replacement therapy.

quality-of-life questionnaire (www.euroqol.org/home.html). On completion of the 6-month follow up, we will link the records to routinely collected health data, when possible, to assess longer term outcomes and for cost-effectiveness comparisons (see Figure 1).

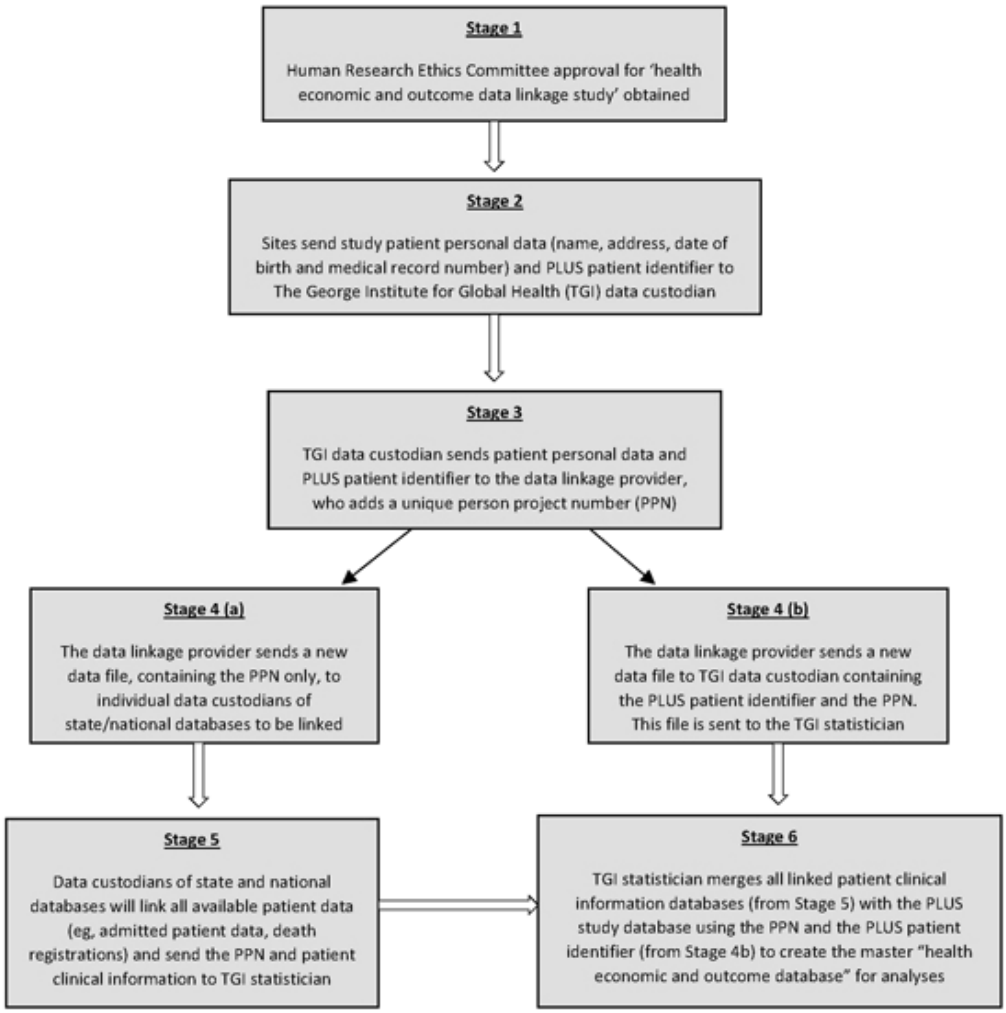
Study fluid distribution and logistics

We will coordinate the study fluid distribution using the study website. This system will track which treatment packs have been distributed to each of the participating centres and the allocation of these treatment packs to each patient. The web-based platform will enable the coordinating centre to monitor the supplies of fluid at each of the study sites and ensure timely re-supply as required.

Ethics

The relevant human research ethics and site governance approvals will be obtained before each participating site commences patient enrolment. All participating centres in Australia have approval to use the following consent hierarchy (based on the National Health and Medical Research Council national statement[28]): if it is not possible to obtain prior informed consent from the patient or their substitute decision maker in a timely manner to allow

Figure 1. Proposed multijurisdictional data linkage for economic evaluation



resuscitation with the study treatment, patients will be entered into the study and then consent to continue will be obtained, as soon as practically possible, from either the patient or their legal substitute decision maker. The patient or their legal substitute decision maker may also withdraw consent for study participation at any time.

In New Zealand, the approach used will be consistent with section 7.4 of the Code of Health and Disability Services Consumers' Rights, which outline the framework for providing treatment to patients who are unable to consent for themselves, and the New Zealand Guideline on Ethics in Health Research.[29,30]

Sample size and statistical power

The planned sample size is 8800 patients. The largest dataset available indicates the possibility of a 3.2% absolute decrease in mortality with buffered fluids compared with saline in critically ill patients.[14] The population to be included in the PLUS study is based on the population recruited to the NICE SUGAR study.[22] The control group in that study included over 90% of patients who were mechanically ventilated at randomisation and who had a 90-day mortality rate of 24.9%. Allowing for a 2% secular reduction of interval mortality from 2008 to 2015, we estimate a mortality rate of 23% in patients assigned to saline resuscitation (control). Data from the SPLIT trial, with similar inclusion criteria to the PLUS study, confirms a reduction in RR of 12.5%; this is consistent across subgroups.[15] Thus, we have designed the study to provide 90% power to detect a 2.9% reduction in 90-day mortality in the study population, which is less than the reduction in mortality reported in database studies.[3,11] A study of 8596 patients would provide 90% power to detect a 2.9% absolute decrease in mortality with the use of Plasma-Lyte 148, representing a 12.5% reduction in RR. However, allowing for about 2% loss to follow up at 90 days, we plan to include an additional 172 patients.

Rounding up, the study plan is to include 8800 patients to achieve a 90% power to detect the hypothesised difference at an alpha of 0.05.

Statistical analysis

We will conduct the main analyses on an intention-to-treat basis, using standard statistical methods for categorical and continuous data. The primary analysis of 90-day mortality will be performed using a χ^2 test. Analyses will also be conducted in pre-defined subgroup pairs. We will prepare and publish a detailed statistical analysis plan before the first interim analysis and we summarise it as follows.

The primary outcome (90-day all-cause mortality) will be compared between the two treatment groups using RRs and 95% CIs. Survival times will be compared using the log-rank test and presented as Kaplan–Meier curves without adjustment for baseline covariates. For the pre-specified subgroups, the primary outcome will be assessed using similar methods as for the main analysis.

An independent statistician will conduct at least one blinded interim analyses when we have completed the 90-day follow up for 2933 patients (one-third of the planned recruitment cohort). The purpose of this interim analysis is to test for the difference in the effect on mortality of the two study fluids, identify any potential safety issues and test for early efficacy. These data will be submitted to the independent data and safety monitoring committee (DSMC).

We will conduct a cost-effectiveness analysis comparing costs and quality-adjusted life-years gained between the treatment arms, based on data collected up to 6 months after randomisation. Depending on the primary outcome of the trial, further analyses may include a longer term cohort study and a modelled economic evaluation. All economic analyses will adopt a health care payer perspective in order to capture relevant costs and consequences of treatment assignment to the health system. The methodology will reflect the pragmatic approach adopted in the CHEST cost-effectiveness analysis.[23,31] The PLUS cost-effectiveness analysis will be informed by a separate statistical analysis plan.

Data safety and monitoring

We will report all adverse events thought to be related to study treatment to the coordinating centre, the George Institute for Global Health. These will be assessed and recorded in the study database. This information will be submitted to the DSMC. The DSMC will be independent from the coordinating centre and investigators, and will perform an ongoing review of predefined safety parameters, study outcomes and overall study conduct. The DSMC is comprised of experts in clinical trials, fluid therapy, statistics and intensive care medicine. The primary responsibility of the DSMC is to review interim analyses of outcome data and to recommend to the study management committee whether they consider that the study needs to be changed, unblinded or terminated, based on these analyses. A detailed DSMC charter outlining roles, responsibilities, processes of trial-stopping rules, reporting, and communication has been signed by the chairperson and all members of the DSMC.

The DSMC will reveal the unblinded results to the PLUS study management committee if, taking into account both statistical and clinical issues and exercising their best clinical and statistical judgement, the un-blinded results provide sufficient evidence that the trial treatment is, on balance, beneficial or harmful for all, or for a particular category of patients. Stopping rules will be based on the following:

- The DSMC will inform investigators if, at any time, the randomised comparisons provides evidence "beyond reasonable doubt" of a difference between randomised groups in total (all cause) mortality.
- The DSMC will inform investigators if there is evidence that is likely to lead many clinicians conversant with the available evidence to change their practice relating to the choice of fluids for intravenous fluid therapy in critically ill adults.
- A three standard deviation difference in mortality will constitute such evidence, unless the DSMC members decide that other evidence constitutes evidence beyond reasonable doubt.
- Additionally, while the primary focus of the DSMC will be on all-cause mortality, this will not preclude the committee recommending termination of the study (or some modification to its design) if evidence emerges of an important difference in some other major outcome (such as cause-specific mortality).

The coordinating centre is responsible for taking all reasonable steps to ensure the proper conduct of the clinical trial protocol. The George Institute for Global Health will be the overarching coordinating centre, providing all aspects of trial management, operations and monitoring. The Medical Research Institute of New Zealand will be acting as the local coordinating centre in New Zealand and will provide local trial management, operations and monitoring.

Funding and support

Our study is funded by the Australian National Health and Medical Research Council (Project Grant 1101765) and the Health Research Council of New Zealand. Baxter Healthcare will provide the blinded study fluids for the trial and will manage the warehousing and distribution of the fluids. The data will be managed, analysed and reported independent of Baxter Healthcare and the funding agencies.

Data sharing and collaboration with the Brazilian Research in Intensive Care Network

The investigators and The George Institute for Global Health (the study sponsor and coordinating centre) recognise that there is potential value in clinical trial data being made available to external researchers for additional analyses and to generate new hypotheses. In response, the Institute has formulated a data-sharing policy and requires all trials for which it is the coordinating centre to have a written data-sharing plan that accords with that policy. The data-sharing plan will be approved by the study management committee and the Institute before the first planned interim analysis.

In addition, trial processes (protocol, intervention, eCRF, data collection and statistical analysis) have been prospectively harmonised with the Balanced Solution v Saline in Intensive Care Study (BaSICS), a similar randomised trial being conducted by the Brazilian Research in Intensive Care Network (BRICNet).[32] AFter publication of the results of the PLUS and BaSICS trials, the data from the two trials will be combined in a patient-level meta-analysis. This will provide greater power to examine pre-specified subgroup effects and allow a comparison of the treatment effects in two very different health care environments.

Summary

The administration of intravenous fluid for resuscitation is a common intervention in critically ill patients. There is now substantive evidence to inform clinicians on the type of fluids that are safe and effective for resuscitation, with crystalloid fluids recommended as the first-line treatment in most circumstances. Although saline has been the most commonly used resuscitation fluid, emerging data suggests that it may be harmful when compared with buffered salt solutions. With the increased use of buffered salt solutions and considering the limited prospective evidence to support their superiority, the PLUS study will provide high-quality data on the comparative safety and efficacy of these commonly used crystalloid solutions.

Competing interests

None declared.

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