Study protocol for the Balanced Solution versus Saline in Intensive Care Study (BaSICS): a factorial randomised trial

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ABSTRACT

Background: The effectiveness and safety of balanced crystalloid fluids compared with saline (0.9% sodium chloride) as a fluid of choice in critically ill patients remain unclear. The effects of different fluid infusion rates on outcomes are also unknown.

Objectives: To test the hypothesis that a balanced crystalloid solution, compared with saline, decreases 90-day all-cause mortality among critically ill patients; and to test the hypothesis that slow, compared with rapid, infusion rate decreases 90-day mortality in this population of patients.

Methods: The Balanced Solution versus Saline in Intensive Care Study (BaSICS) is a pragmatic, 2 × 2 factorial, randomised controlled trial. A total of 11 000 patients will be recruited from at least 100 Brazilian intensive care units. Patients will be randomised to receive Plasma-Lyte 148 or saline, and to rapid infusion (999 mL/h) or slow infusion (333 mL/h). Study fluids will be used for resuscitation episodes (at rapid or slow infusion rates), dilution of compatible medications and maintenance solutions. Patients, health care providers and investigators will be blinded to the solutions being tested. The rate of bolus infusion will not be blinded.

Outcomes: The primary outcome is 90-day all-cause mortality. Secondary outcomes are: incidence of renal failure requiring renal replacement therapy within 90 days, incidence of acute kidney injury (Kidney Disease: Improving Global Outcomes stages 2 and 3), incidence of non-renal organ dysfunction assessed by Sepsis-related Organ Failure Assessment score at Days 3 and 7, and number of mechanical ventilation-free days within the first 28 days after randomisation.

Results and conclusions: The BaSICS trial will provide robust evidence on whether a balanced crystalloid, compared with saline, improves important patient outcomes in critically ill patients. BaSICS will also provide relevant information on whether bolus infusion rate affects outcomes in this population.

Trial registration: ClinicalTrials.gov NCT02875873.

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The administration of intravenous (IV) fluids to restore intravascular volume is one of the most common interventions in the intensive care unit. Saline (0.9% sodium chloride) is the most widely used crystalloid fluid worldwide.[1] Nevertheless, experimental and clinical studies show that saline has deleterious effects on the kidneys, acid–base balance, electrolyte homoeostasis, tissue perfusion, the inflammatory response and coagulation parameters.[2-5]

Plasma-Lyte 148 is a balanced crystalloid fluid with osmolality closer to human plasma and lower sodium and chloride concentrations compared with saline. Observational and small randomised studies suggest that balanced crystalloid fluids might be preferable to saline in critically ill patients.[4-6] One of the putative mechanisms for the benefit of balanced solutions is their lower potential to cause hyperchloraemia, which, in turn, could be associated with increased inflammation and acute kidney injury (AKI).[7,8] Recently, the safety and efficacy of volume expansion with Plasma-Lyte 148 compared with saline were assessed in an exploratory, double-blind, cluster-randomised, double-crossover trial (the 0.9% Saline v Plasma-Lyte 148 for ICU Fluid Therapy [SPLIT] study).[9] In this study, a median infusion of 2 L of Plasma-Lyte 148 or saline did not affect the risk of AKI (risk ratio [RR], 1.04; 95% CI, 0.80–1.36; $P = 0.77$), the need for renal replacement therapy (RRT) (RR, 0.96; 95% CI, 0.62–1.50; $P = 0.91$) or in-hospital mortality (RR, 0.88; 95% CI, 0.67–1.17; $P = 0.40$). However, the SPLIT trial used a very low dose of study fluid (2 L over the ICU stay), did not select fluid used specifically for resuscitation and studied a relatively low-risk population (mean Acute Physiology and Chronic Health Evaluation [APACHE] II score, 14; overall AKI rate, 9%).

In addition to the type of fluid, there are wide regional variations in infusion rates and volumes prescribed as fluid boluses. The multicentre Fluid Challenges in Intensive Care study showed that crystalloid fluids represent the most common type of fluids used in a fluid challenge, typically administered as a bolus of 500 mL in less than 30 minutes.[1] Nevertheless, it has been suggested that fluid bolus infusion rate, a neglected aspect of fluid management, may have important effects on physiological and clinical outcomes in ICU patients.[10]

A prospective, randomised study in African children with severe infection showed that fluid boluses of saline or 5% albumin increased mortality compared with standard therapy without boluses.[10] Interestingly, most of the excess mortality with rapid fluid resuscitation was attributed to cardiovascular

collapse.[11] A rapid fluid bolus may abruptly reduce the adrenergic tone and/or worsen myocardial compliance, leading to or aggravating haemodynamic instability.[12] Despite increasing cardiac output, a fluid bolus (500 mL in 30 minutes) may decrease arterial elastance, compromising arterial blood pressure. In contrast, resuscitation protocols based on slower infusion rates and involving reduction of fluid infusion seem to be safe in specific populations of critically ill patients.[10,13,14] Therefore, one crucial issue to be addressed is whether the fluid bolus infusion rate affects the outcomes of critically ill adult patients.

We describe a protocol for a multicentre, randomised, factorial, clinical trial that will assess the effects of Plasma-Lyte 148 versus saline as the fluid of choice in critically ill patients, as well as the effects of rapid and slow fluid challenge infusion rates on important patient outcomes.

Methods

Aims

We aim to determine whether a balanced crystalloid solution (Plasma-Lyte 148) used for fluid resuscitation reduces 90-day mortality compared with saline in critically ill patients. We also aim to determine the effect of rapid administration (999 mL/h) versus slow administration (333 mL/h) of crystalloid solution on 90-day mortality in critically ill patients at high risk of renal injury.

Study design and setting

The Balanced Solution versus Saline in Intensive Care Study (BaSICS) is a pragmatic, multicentre, 2 × 2 factorial, randomised controlled trial. Patients will be randomised to receive Plasma-Lyte 148 or saline, and to rapid (999 mL/h) or slow (333 mL/h) infusion rates.

Patients, health care providers and study investigators will be blinded to the solutions being tested but not to the rate of bolus infusion. Study fluids will be used for resuscitation episodes (at rapid or slow infusion rates). These same fluids will be used for dilution of compatible medications and maintenance fluids, but only patients who are determined to require fluid boluses (Table 1) will be enrolled. The primary outcome is 90-day mortality. We will recruit about 11 000 patients in at least 100 Brazilian ICUs (see Appendix 1, online at cicm.org.au/Resources/Publications/Journal). Patients will be enrolled after ICU admission.

Eligibility

Inclusion criteria

To be randomised, patients must meet all the following inclusion criteria:

- Need for fluid resuscitation or plasma expansion (Table 1), and the clinician considers that either Plasma-Lyte 148 or saline is equally appropriate for patients, with no specific indications or contraindications for any of the fluids or for rapid or slow infusion.
- Not expected to be discharged on the day after admission.
- At least one of the following risk factors for acute kidney injury:
  - age ≥ 65 years
  - hypotension (mean arterial pressure [MAP] < 65 mmHg or systolic blood pressure [SBP] < 90 mmHg) or use of vasopressors
  - sepsis
  - use of invasive mechanical ventilation or continuous non-invasive mechanical ventilation (including high-flow nasal cannula) for > 12 h
  - oliguria (< 0.5 mL/kg/h for ≥ 3 h)
  - serum creatinine level ≥ 1.2 mg/dL (women) or ≥ 1.4 mg/dL (men)
  - liver cirrhosis or acute liver failure.

Table 1. Guidelines for volume expansion (fluid challenge) during the study period

These criteria suggest the need for volume expansion (item 1 plus item 2)

1. At least one sign of hypoperfusion:

a. Heart rate > 120 beats/min

b. SBP < 90 mmHg or MAP < 65 mmHg or decrease in SBP of > 40 mmHg from baseline

c. Capillary refill time > 1 s

d. Mottling score ≥ 2

e. Lactate level > 2 mmol/L (> 18 mg/dL)

f. $Scvo_2$ < 70%

g. Urinary output < 0.5 mL/kg in past hour

2. At least one sign of responsiveness to fluid therapy or absence of signs of hypervolaemia:

a. Pulse pressure variation > 13%

b. Increase in pulse pressure > 5% after an expiratory pause of 15 s

c. Passive leg elevation leads to increased cardiac index (> 10%) or pulse pressure (> 11%) or MAP (> 5%)

c. Respiratory variation in CVP > 1 mmHg

d. Echocardiographic signs of hypovolaemia

e. CVP ≤ 10 mmHg

f. Absence of clinical signs of hypervolaemia when data for above symptoms not available

SBP = systolic blood pressure. MAP = mean arterial pressure. $Scvo_2$ = central venous oxygen saturation. CVP = central venous pressure.

Exclusion criteria

We will apply the following exclusion criteria:

- age < 18 years

- acute renal failure treated with RRT or expected to require RRT within the next 6 hours
- severe electrolyte disturbance (serum sodium level ≤ 120 mmol/L or ≥ 160 mmol/L, serum potassium level ≥ 5.5 mmol/L)
- death considered imminent and inevitable within 24 hours
- patients with suspected or confirmed brain death
- patients receiving palliative care only
- patients previously enrolled in BaSICS.

Interventions

Patients will receive Plasma-Lyte 148 or saline during their ICU stay (limited to 90 days), by random assignment. When fluid expansion is indicated, it will be provided according to the randomisation group (rates of infusion of 999 mL/h or 333 mL/h) during the ICU stay (limited to 90 days) (Figure 1). Whenever possible, the assigned study fluid and rate should be adhered to during investigations and procedures performed while the patient is temporarily outside the ICU. The volumes and frequency of administration will be determined by the primary physician (Figure 2), but guidelines suggesting triggers for fluid infusion will be provided to the study centres (Table 1). Adherence to study fluids and infusion rate will be assessed on Days 1 to 3 after randomisation and on Day 7.

The study fluids will also be used when crystalloid solutions are indicated to maintain volume status. Infusion rates for maintenance solutions are at the discretion of health care providers. Medications and solutions with ingredients that are compatible with saline and Plasma-Lyte 148 (eg, sedative drugs, vasopressors and antibiotics) should be infused using the study fluids (Figure 2). A list of medications compatible with both study fluids will be sent to the participating centres (Appendix 2).

In some scenarios (eg, extreme electrolyte disturbances [Table 2]), study fluids should not be used; in these scenarios, the physician will be prompted to resume using study fluids as soon as the contraindication for the fluid no longer exists. In imminently life-threatening situations (Table 3), patients may receive rapid infusion boluses (999 mL/h) regardless of the infusion rate to which they have been randomly assigned.

We will suggest that investigators consider the late-strategy criteria of the AKIKI trial to indicate starting RRT (Table 4),[15] because there is no consensus on whether early or late RRT is the most appropriate for critically ill patients. We will remind the centres that RRT should not be delayed if the late-strategy criteria in AKIKI are met.

Figure 1. Study design

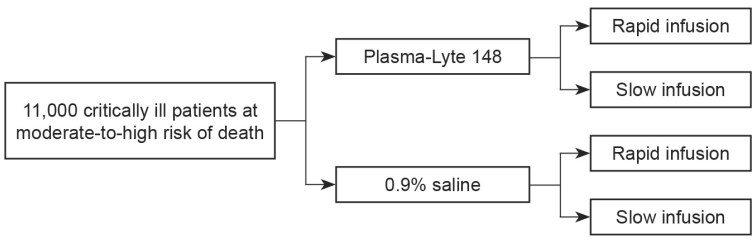
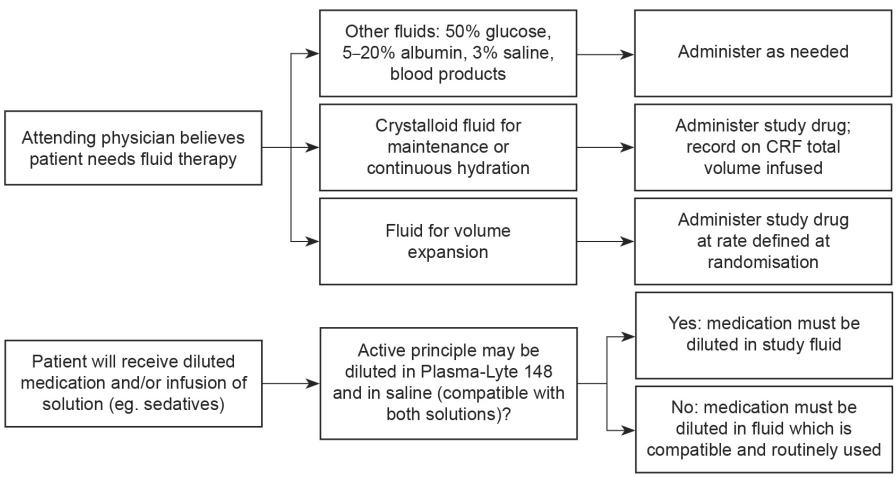


Figure 2. Treatment algorithm for fluid administration for patients who fulfilled inclusion criteria, including need for initial fluid expansion



CRF = case report form.

Table 2. Specific situations in which the assigned study fluid must not be administered

Situation	Recommended alternative fluid
Severe hyperchloraemia (chloride level ≥ 120 mmol/L)	Plasma-Lyte 148 or Ringer's lactate
Severe hypernatraemia (sodium level ≥ 160 mmol/L)	Plasma-Lyte 148 or Ringer's lactate (if fluid resuscitation is needed)
Severe hyponatraemia (sodium level ≤120 mmol/L)	Normal or hypertonic saline
Hyperkalaemia (potassium level ≥ 5.5 mmol/L)	Normal saline

Table 3. Specific situations in which study fluids may be administered at rapid infusion rate (999 mL/h), regardless of randomised assignment

Situation 1: severe arterial hypotension (SBP < 80 mmHg or MAP < 50 mmHg)
or
Situation 2: diagnosis of haemorrhagic shock with active bleeding requiring aggressive volume replacement

SBP = systolic blood pressure. MAP = mean arterial pressure.

Table 4. Indications for starting renal replacement therapy

Renal failure (KDIGO stage 2 or 3) combined with one of the following:
■ Serum potassium level > 6 mEq/L
■ pH < 7.15, in a context of pure metabolic acidosis or mixed acidosis with $Paco_2$ > 50 mmHg and no possibility of increasing minute volume
■ Hypervolaemia with respiratory impairment requiring oxygen delivery > 5 L/min (for patients on spontaneous ventilation) or inspired oxygen fraction > 50% (for patients receiving invasive mechanical ventilation or non-invasive ventilation)
■ Serum urea level > 240 mg/dL

KDIGO = Kidney Disease: Improving Global Outcomes.

Outcomes

Outcomes are similar for both factors in BaSICS (saline versus Plasma-Lyte 148, and rapid versus slow infusion speed).

Primary outcome

The primary outcome is 90-day all-cause mortality.

Secondary outcomes

Secondary outcomes are:

- Renal failure requiring RRT within 90 days
- AKI (classified as Kidney Disease: Improving Global Outcomes [KDIGO] stage ≥ 2 at Days 3 and 7 after randomisation).[16] For diagnosis of AKI, serum creatinine level and urine output will be assessed using the following criteria: twofold or higher increase in serum creatinine level from reference level, or urine output level < 0.5 mL/kg/h for ≥ 12 hours. The reference creatinine level will be the lowest of the randomisation creatinine and previous creatinine levels (the most recent value available in the previous 6 months and before current admission). If no previous creatinine value is available, it will be estimated using the Modification of Diet in Renal Disease equation:

  $$\text{Creatinine level} = 75/(186 \times [\text{age} - 0.203] \times F \times B) - 0.887$$

  in which F = 0.742 (female patients) and B = 1.21 (black patients). If a patient is classified as having a KDIGO score of 2 at randomisation, they will be excluded from the sample for the evaluation of this outcome.
- New respiratory, hepatic, cardiac, neurological and coagulation dysfunction, assessed by Sepsis-related Organ Failure Assessment scores at Days 3 and 7.[17]
- Mechanical ventilation-free days at 28 days after randomisation.

Tertiary outcomes

Tertiary outcomes are:

- ICU and in-hospital mortality due to any cause
- length of ICU stay
- length of hospital stay.

Other exploratory outcomes

- Comparison of serum chloride levels between the four study groups over time.
- Quality of life (utility) assessment after 6 months, through the EuroQol five dimensions health state (EQ-5D) questionnaire, which will be administered to a selected subsample of about 1100 patients.

Randomisation

We will allocate patients in a 1:1:1:1 ratio to receive Plasma-Lyte 148 as slow infusion, Plasma-Lyte 148 as rapid infusion, saline as slow infusion or saline as rapid infusion. The randomisation list will be generated with online software using random permuted blocks, stratified by centre according to fluid type (A to F) and infusion speed. Therefore, each block will have 12 patients. Block size will not be disclosed to research personnel.

Research personnel will randomise patients via a web-based central, automated randomisation system, available 24 hours per day, maintained by the Research Institute HCor, São Paulo, Brazil. The assigned study group will only be disclosed after patients have been registered in the web-based randomisation system.

Blinding

Patients, health care providers, data collectors, outcome assessors and statisticians will be blinded to the study fluids (Plasma-Lyte 148 or saline). Plasma-Lyte 148 and saline will be macroscopically identical and will be available in identical plastic containers of 500 mL, identified with codes A, B, C, D, E and F. Blinding to fluid bolus infusion rate is not feasible. Thus, this intervention will remain open to those involved in patient care.

Timeline, data collection and management

Trained research personnel at the sites will collect data in a web-based case report form. Data will be collected and analysed independent of adherence to the study protocol to allow intention-to-treat analyses. Data will be collected on: the day of randomisation (Day 0), Days 1 to 3, Day 7, ICU discharge and hospital discharge. Investigators will telephone the patient or relatives to obtain 90-day follow-up data. They will also collect 180-day follow-up data on vital status and health-related quality of life from the subsample of about 1100 patients.

We will use the following procedures to ensure data quality:

- Investigators will attend a training session before the beginning of the study to standardise procedures, including data collection.
- Investigators will be able to contact the coordinating centre to resolve problems that may arise.
- Data cleaning will be applied continuously to identify inconsistencies and missing data. The centres will be notified of any inconsistencies and missing data and prompted to resolve them.
- The coordinating centre will review detailed reports on screening, inclusion, follow-up and data consistency and completeness, on a weekly basis. The coordinating centre will take immediate action to resolve any problems.
- Centres will be monitored throughout the study and onsite visits will take place, if there is a need, from the recruiting centre. A trained professional will be appointed by the coordinating centre to monitor the participating centres. During the monitoring visits, all information will be considered strictly confidential. We do not intend to conduct audits at the participating centres except for usual monitoring.

Statistical methods

Sample size

We will enrol 11 000 patients in the trial. We estimate that there will be a mortality rate of 35% within 90 days in the control groups (saline or rapid infusion), based on the eligibility criteria applied to the databases of two Brazilian multicentre studies.[18,19] The study will have a statistical power of 89% to detect a hazard ratio of 0.90 or less for 90-day mortality, with an alpha level of 0.05.

We do not expect a significant interaction between the two interventions (Plasma-Lyte 148 versus saline and slow versus rapid infusion rate). Nevertheless, if such interaction exists, the study will have a power of 80% to detect a positive hazard ratio of 0.835, considering that Plasma-Lyte 148 and slow infusion speed will result in lower mortality.

Statistical analysis

We will prepare a detailed statistical analysis plan before patient enrolment begins, which is intended to be published or made available electronically. All analysis will be conducted on the intention-to-treat principle. The effect of type of fluid (Plasma-Lyte 148 v saline) and the infusion rate (rapid v slow infusion) on the primary outcome will be assessed with Cox proportional hazards regression and Kaplan–Meier curves, and will be presented as hazard ratios with 95% confidence intervals and *P* values. Binary secondary outcomes will be compared using χ^2 tests and presented as risk ratios with 95% CI and *P* values. Results for continuous outcomes will be expressed as mean differences, 95% CIs and *P* values, calculated with the independent *t* test, or Wilcoxon rank sum test in the case of non-normal distribution. We will analyse the available dataset for secondary and tertiary outcomes.

Subgroup analysis

The effect of the type of fluid (Plasma-Lyte 148 v saline) and infusion speed on the primary outcome will be assessed using Cox proportional hazards regression in the subgroups of patients with and without the following characteristics at baseline:

- sepsis
- AKI KDIGO Stage 1
- admitted from the surgical block
- traumatic brain injury
- APACHE II score ≥ 25
- patients receiving > 1.0 L of saline in the 24 hours before randomisation.

We will infer a subgroup effect if the *P* value for homogeneity of treatment effects is < 0.05.

As exploratory analysis, we will assess the subgroup of patients who received at least 6 L of fluid in the first 3 days after ICU admission. We will also perform a dose-response analysis to assess whether there is a minimum volume to be infused to obtain a positive association between balanced solution used and outcome. This analysis is sustained by previous research suggesting that the potential benefit from balanced solutions may only occur in aggressively resuscitated patients,[5] but will be considered strictly exploratory.

Interim analyses and data monitoring committee

We have set up a data monitoring committee (DMC) with the primary aim of helping to ensure the safety of patients in the trial by protecting them from avoidable harm. A group of independent experts has been appointed to the DMC: Gordon Guyatt (Chair), methodologist and trialist; Niall Ferguson, triallist and intensivist; and Stephen Walter, statistician. All have extensive experience in trial methodology.

The DMC will initially prepare a charter specifying details of the committee, its operation, meeting schedule and the trial stopping rules. The rules will be based on the principles listed below. We will conduct interim analyses after recruitment of about 25%, 50% and 75% of the study cohort. Based on the interim analyses and occasionally on external evidence, the DMC will decide whether there is evidence beyond reasonable doubt to support that the experimental treatment (Plasma-Lyte 148 v saline; and slow v rapid infusion rate) increases 90-day mortality, with $P < 0.01$. The members of the DMC may consider requesting to continue the study for an additional 3 months to confirm such effects (especially if P is between 0.01 and 0.001). If the safety criterion is met in one of the factors analysed in the study, the corresponding factorial arm will be stopped and the study will continue with the remaining one.

In the case of evidence of superiority of Plasma-Lyte 148 over saline, or of slow infusion over rapid infusion, with $P < 0.001$ in the interim analysis conducted after the recruitment of 50% or more patients, the DMC may also consider stopping the study. However, the DMC will request to continue the study for an additional 3 months and for the analyses to be repeated to confirm the difference between the treatments and to allow stabilisation of estimated effect.

In accordance with the DMC, we decided that the study will not be discontinued because of a benefit in the first interim analysis (after the recruitment of 25% of the sample). The reasons for this decision were:

- Early discontinuation of randomised trials because of a benefit tends to produce biased estimates of effect (overestimation of the true effect), which may lead to erroneous medical guidelines and decisions, especially with a small number of events.[20]
- According to the ethical principle of non-maleficence, a new treatment should not be used until there is clear, objective evidence that it is beneficial.
- Clinical practice does not usually change unless there is convincing evidence of the advantages of the new treatment, which will be undermined if the study is discontinued early due to a benefit.[21]

Recruitment strategy

Recruiting 11 000 critically ill patients is clearly challenging. We anticipate that we should recruit this sample size within 48 months in 100 ICUs. We will use several strategies to ensure adequate recruitment:

- Submission to all ethics committees will be supported by staff at the Research Institute HCor, with the aim of shortening time to study approval.
- Adequate training will be provided to sites in investigator meetings and during site initiation visits.
- Study procedures will be kept as simple as possible and we will foster a culture of embedding study activities in the routines of participating ICUs.
- Sites will receive study fluids and reimbursement for patient inclusion.
- Investigators will be acknowledged in all publications and will be offered the opportunity to lead substudies.
- We will prioritise promotion of patients' enrolment using several strategies (phone contacts, emails, newsletters, weekly enrolment reports and others) in the daily activities of the Research Institute HCor.
- We will act according to the 12 components for marketing clinical trials proposed by Francis and colleagues.[22]

Trial organisation and funding

The Research Institute HCor is the sponsor and coordinator of the study, in association with the Brazilian Research in Intensive Care Network (BRICNet). The trial structure includes the following groups: the coordinating centres, investigators, steering committee and DMC.

The study will be conducted as part of and funded by the Program to Support Institutional Development of the Universal Health System from the Brazilian Ministry of Health. Baxter Latin America will provide the fluids and transport logistics used in the trial. Baxter will not be involved in any aspects of trial design, execution, analysis or interpretation of the results.

Safety

All unexpected serious adverse events related to the study interventions must be reported to the Research Institute HCor within 24 hours. An unexpected serious adverse event directly related to the study is defined as any event meeting these two criteria:

- any fatal or life-threatening event (immediate risk of death), or any event that causes sequelae or permanent disability, or that extends hospitalisation
- the attending physician believes the event is related to the patient's inclusion in the BaSICS trial.

Serious adverse events will be considered as "related to the study" if the attending physician believes that the event was probably caused by the fluid and/or the rate of infusion used in the study and follows a plausible time sequence after the administration of the fluid.

Ethics and dissemination

Ethics approval and registration

This study protocol, version 1.5, from August 2016, has been approved by the Research Ethics Committee of the Coordinating Centre (Hospital do Coração/Associação do Sanatório Sírio) (CAAE: 57395816.6.1001.0060). The study will not begin at the participating centres until approval has been obtained from the responsible local internal review board for each participating ICU. All amendments to the protocol must be approved by the internal review

board of each participating centre. This protocol conforms to the Standard Protocol Items: Recommendations for Interventional Trials recommendations,[23] and has been registered in ClinicalTrials.gov (NCT02875873).

Informed consent

Whenever possible, prospective written informed consent will be requested before randomisation from all eligible patients, or from their legal representatives when the patients are unable to provide consent due to communication or cognitive limitations. If no legal representative is available at the time, the patient will be randomised, and written consent from the patient or legal representative will be sought as soon as possible afterwards (deferred consent).

Confidentiality

Each patient and research centre will be identified by a unique number in the electronic case report form. Information obtained from medical records must be handled as confidential data by the research centres; it must be kept in restricted access locations, and anonymity must be ensured on interim and final reports.

Data sharing

We intend to make the study database available to other researchers. In the first 2 years after the publication of the main manuscript, the investigators will perform analyses for substudies proposed by investigators from the BaSICS collaborative group. In this phase, the database will be kept in conditions of restricted access by the study coordinators, and third parties will have access to it only with previous authorisation of the BaSICS steering committee, which will analyse each research proposal and statistical analysis plan. The steering committee will provide the requested data if the proposal does not conflict with future or ongoing substudies of investigators from the collaborative group. After 2 years, all data collected during the BaSICS trial will be publicly available on a free-access platform. We emphasise that specific data that may identify a patient, such as initials or date of birth, will not be made publicly available. Each individual requesting access to the database must formally commit to notifying the steering committee of the study in the event that any database information identifying a patient is found.

An individual patient data meta-analysis grouping the data from this study and the Plasma-Lyte 148 versus Saline Study (NCT02721654) is planned.

Dissemination

The BaSICS steering committee will publish the study findings, whatever they are. The main manuscript will be submitted by the writing committee on behalf of the research group (BaSICS investigators and the BRICNet). The names of other trial committees and all collaborators will be listed after the text.

Conclusions

The BaSICS trial will provide robust evidence as to whether the use of a balanced crystalloid fluid reduces 90-day mortality compared with saline in critically ill patients receiving fluid resuscitation. BaSICS will also provide relevant information on whether the fluid bolus infusion rate affects outcomes in this population of patients.

Competing interests

We declare that Baxter Latin America will donate fluids and provide distribution logistics for the BaSICS trial. Baxter will not be involved in any aspect of the study design, analysis or decision to publish the results. Luciano Azevedo and Murillo de Assunção received personal grants for the advisory board from Baxter Brazil. Otavio Berwanger has received research grants for investigator-initiated clinical trials from AstraZeneca, Amgen, Boehringer-Ingelheim, Roche and Bayer, which are unrelated to the topic of this study.

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Appendix

This appendix was part of the submitted manuscript and has been peer reviewed. It is posted as supplied by the authors.

Study protocol for the Balanced Solution vs. Saline in Intensive Care Study (BaSICS): a factorial randomized trial assessing balanced crystalloid versus 0,9% sodium chloride and rapid versus slow infusion rate in critically ill patients

ELECTRONIC APPENDIX

Appendix 1 – List of Participating Centers (in alphabetical order of site investigator)

Hospital	Site Investigator
Hospital Municipal Vila Santa Catarina	Airton Leonardo Manoel de Oliveira
Instituto Nacional De Cardiologia	Alexandre Rouge Felipe
Hospital Universitário Regional de Maringá - HUM	Almir Germano
Hospital do Trabalhador	Álvaro Rea Neto
Hospital Marcelino Champagnat	Álvaro Rea Neto
Hospital Universitário Cajuru	Álvaro Rea Neto
Instituto de Neurologia de Curitiba	Álvaro Rea Neto
Hospital Vita Batel	Álvaro Rea Neto
Hospital Municipal Moysés Deutsch	Ana Helena Vicente Andrade
Hospital do Servidor Público Municipal de Sâo Paulo	Ana Helenir Benaglia
Hospital Primavera	André Luis Veiga de Oliveira
Hospital da Cidade	André Luiz Nunes Gobatto
Hospital Guilherme Alvaro	André Scazufka Ribeiro
Hospital HOME	Antonio Aurélio de Paiva Fagundes Jr.
Hospital Estadual Roberto Chabo	Astor Bruno Ferreira de Mello
Hospital da Luz	Bruno Adler Maccagnan Pinheiro Besen
Hospital Universitário - Universidade Federal de Juiz de Fora	Bruno do Valle Pinheiro
Hospital Samaritano	Bruno Franco Mazza
Hospital Estadual Getúlio Vargas	Bruno Gonçalves

Hospital Anchieta	Bruno Jardim Grossi
Instituto Estadual do Cérebro Paulo Niemeyer	Cássia Righy Shinotsuka
Hospital Moinhos de Vento	Cassiano Teixeira
Hospital Paulistano	Cesar Biselli Ferreira
Hospital Universitário Regional do Norte do Paraná - UEL	Cintia Magalhães Carvalho Grion
Hospital Nossa Senhora das Neves	Ciro Leite Mendes
Hospital Samaritano João Pessoa	Ciro Leite Mendes
Hospital Unimed João Pessoa	Ciro Leite Mendes
Vitória Apart Hospital	Claudio Piras
Hospital Regional de Mato Grosso do Sul Rosa Pedrossian	Claudnei Menezes de Rezende
Hospital Municipal Irmã Dulce	Daniela Boni
Instituto de Infectologia Emilio Ribas II - Fundação do ABC	Daniela Boni
Prevent Senior Instituto Prevent Senior - IPS	Daniella Cabral de Freitas
Hospital das Clínicas da Universidade Federal de Goiás	Denise Milioli Ferreira
Fundação Amaral Carvalho	Éderson Roberto de Mattos
Hospital Adventista de Belém	Edgar Brito Sobrinho
Hospital do Coração de São Paulo	Edson Romano
Hospital São Francisco da Santa Casa de Porto Alegre	Eraldo de Azevedo Lúcio
Sociedade Literária e Caritativa Santo Agostinho – Hospital São José	Felipe Dal Pizzol
Hospital Alemão Oswaldo Cruz	Fernando Godinho Zampieri
Hospital São Paulo, Universidade de São Paulo	Flávia Ribeiro Machado
Hospital SEPACO	Flávio Geraldo Rezende de Freitas
Hospital Geral De Vitória Da Conquista	Geovani Moreno Santos Junior
Santa Casa de Misericórdia de Vitória da Conquista	Geovani Moreno Santos Júnior
Hospital Universitário São Francisco na Providência de Deus	Giovana Colozza Mecatti
Centro Hospitalar Unimed	Glauco Adrieno Westphal
Hospital de Ilhéus	Heitor Portela Póvoas Filho
Hospital São Paulo UNIFESP	Hélio Penna Guimarães
UTI - Moléstias Infecciosas - HCFMUSP	Ho Yeh Li
Hospital Nereu Ramos	Israel Silva Maia
Hospital Santa Paula	Joao Geraldo Simoes Houly
Hospital do Servidor Público Estadual	João Manoel Silva Junior
Santa Casa de Misericórdia de São João Del Rei	Jorge Luiz da Rocha Paranhos
Hospital Sírio Libanês	José Mauro Vieira Junior

Hospital das Clinicas da Faculdade de Medicina de Botucatu	Laercio Martins De Stefano
Hospital Distrital Evandro Ayres De Moura	Lanese Medeiros Figueiredo
Hospital Quinta D´Or	Laura Brasil Herranz
UTI Pronto Socorro - HCFMUSP	Leandro Utino Taniguchi
Hospital Geral de Palmas	Leonardo Guimarães Castro Boa Sorte
Hospital de Clínicas de Uberlândia	Liliane Barbosa da Silva Passos
Hospital Geral Cleriston Andrade	Lúcio Couto de Oliveira Junior
Unidade de Apoio Cirúrgico - HCFMUSP	Luiz Marcelo Sá Malbouisson
Hospital Monte Klinikum	Marcelo Jorge Jacó Rocha
Hospital Universitário Evangélico de Curitiba	Marcelo Oliveira Santos
Hospital Municipal Evandro Freire	Márcio Duarte Viçoso Barcellos
Hospital São João de Deus - Fundação Geraldo Correa	Marcone Lisboa Simões da Rocha
Casa de Saúde Pinheiro Machado	Marcus Alexandre da Silva Bezerra
Hospital Municipal Dr Mário Gatti	Marcus Vinicius Pereira
Hospital Evangélico Cachoeiro do Itapemirim	Marlus Muri Thompson
Hosp Providência de Apucarana	Mateus Dias de Moura
Hospital e Maternidade São Vicente	Meton Soares de Alencar Filho
Hospital das Clínicas - UFPE	Michele Maria Gonçalves de Godoy
Hospital SAMUR	Miquéias Martins Lima Silva
Hospital Universitáio Cassiano Antônio Moraes - UFES	Paula Frizera Vassalo
Complexo Hospitalar de Mangabeira Governador Tarcísio Burity	Paulo Cesar Gottardo
Santa Casa de Maringá	Paulo Roberto Aranha Torres
AC Camargo Cancer Center	Pedro Caruso
Hospital do Câncer - UOPECCAN	Péricles Duarte
Hospital Universitário de Cascavel - HU do Oeste do Parana	Péricles Duarte
Hospital Estadual Jayme dos Santos Neves	Priscilla de Aquino Martins
Hospital Santa Cruz	Rafael Botelho Foernges
Hospital de Clinicas – Universidade Estadual de Campinas	Renan Alves da Cruz
Hospital Nossa Senhora dos Prazeres	Ricardo Rath de Oliveira Gargioni
Conjunto Hospitalar do Mandaqui	Roberto Camargo Narciso
Hospital Municipal Souza Aguiar	Roberto Seabra Lannes
Hospital Maternidade São José - UNESC - Fundação Social Rural de Colatina	Rodrigo Cruvinel Figueiredo
Hospital São Lucas - PUCRS	Sergio Baldisserotto

Hospital Geral do Grajaú	Sergio Elia Mataloun
Hospital Norte D'Or	Sergio Teixeira Sant'Anna Junior
Fundação Faculdade Regional de Medicina de São José do Rio Preto	Suzana Margareth Ajeje Lobo
Irmandade Santa Casa de Porto Alegre	Thiago Costa Lisboa
Hospital Albert Einstein	Thiago Domingos Correa
Hospital das Clínicas Universidade Federal de Minas Gerais	Vandack Alencar Nobre Junior
Real e Benemérita Associação Portuguesa de Beneficência	Viviane Cordeiro Veiga
Hospital Novo Atibaia	Walter Carlos Girardelli Baptista
Hospital e Pronto Socorro 28 de Agosto	Wilson de Oliveira Filho
Hospital das Clínicas Ribeirão Preto - FMUSPRP	Wilson José Lovato

Appendix 2 – Medications compatible with both saline and Plasma-Lyte148

Drug	**Manufacturer**	**Concentration**
Aciclovir	Hospira	25 mg/ml
Adrenaline	Aspen	12 mg/100 ml
Amikacin	DBL	40 mg/ml
Atracurium	DBL	0.5 mg/ml
Atropine	Pfizer	0.4 mg/ml
Benzylpenicillin	CSL	2400 mg/50 ml
Calcium Chloride	Baxter	40 mg/ml
Calcium Gluconate	Baxter	40 mg/ml
Caspofungin	MSD	70 mg/100 ml
Cefoxitin	Hospira	20 mg/ml
Ceftazidime	Hospira	100 mg/ml
Cephazolin	Hospira	2000 mg/50 ml
Ciprofloxacin	Bayer	2 mg/ml
Clindamycin	Pfizer	900 mg/50 ml
Clonidine	Boehringer Ingelheim	20 mcg/ml
Cloxacillin	Teva	100 mg/ml
Cyclophosphamide	Baxter	8 mg/ml
Dexamethasone	Aspen	4 mg/ml
Digoxin	Aspen	0.25 mg/ml
Dobutamine	Hospira	5 mg/ml
Dopamine	Hospira	3.2 mg/ml
Ephedrine	Hospira	5 mg/ml
Ergometrine	Hospira	200 mcg/5 ml
Esmolol	Phebra	10 mg/ml
Esomeprazole	Astra Zeneca	0.4 mg/ml

Fentanyl	Hospira	10 mcg/ml
Flucloxacillin	Hospira	40 mg/ml
Fluconazole	Pfizer	200 mg/100 ml
Foscarnet	Clinect	24 mg/ml
Frusemide	Sandoz	10 mg/ml
Gentamicin	Pfizer	10 mg/ml
Glyceryl Trinitrate	Hospira	30 mg/50 ml
Glycopyrrolate	Aspen	0.2 mg/ml
Granisetron	Hospira	0.05 mg/ml
Heparin	Pfizer	1000 units/ml
Hydralazine	Link	2 mg/ml
Hydrocortisone	Pfizer	100 mg/2 ml
Hydromorphone	Mundipharma	2 mg/ml
Imipenem/Cilastatin	MSD	5 mg/ml
Isoprenaline	Hospira	1 mg/100 ml
Ketamine	Hospira	2 mg/ml
Labetalol	Sandoz Canada	5 mg/ml
Lignocaine Hydrochloride	Pfizer	8 mg/ml
Lincomycin	Pfizer	2 mg/ml
Magnesium Sulfate	Baxter	0.4 mmol/ml
Meropenem	Hospira	40 mg/ml
Metarminol	Montrose	0.2 mg/ml
Metoclopramide	iNova	5 mg/ml
Metoprolol	AstraZeneca	1 mg/ml
Metronidazole	Hospira	5 mg/ml
Midazolam	Pfizer	1 mg/ml
Milrinone	Sanofi	300 mcg/ml

Morphine Sulfate	Hospira	1 mg/ml
Moxifloxacin	Bayer	1.6 mg/ml
Naloxone	Hospira	0.4 mg/ml
Neostigmine	AstraZeneca	0.5 mg/ml
Noradrenaline	Hospira	16 mg/100 ml
NovoRapid insulin	Novo Nordisk	1 unit/ml
Ondansetron	GSK	1 mg/ml
Oxytocin	Aspen	1 unit/ml
Pancuronium	AstraZeneca	2 mg/ml
Paracetamol	Pfizer	10 mg/ml
Parecoxib	Pfizer	40 mg/2 ml
Pethidine	Hospira	10 mg/ml
Piperacillin/Tazobactam	Pfizer	4500 mg/50 ml
Potassium Chloride	Baxter	0.5 mmol/ml
Potassium Dihydrogen Phosphate	Baxter	0.5 mmol/ml
Protamine	Sanofi	10 mg/ml
Rocuronium	Hospira	10 mg/ml
Salbutamol	GSK	0.05 mg/ml
Sodium Nitroprusside	Hospira	0.6 mg/ml
Sugammadex	MSD	25 mg/ml
Suxamthonium	AstraZeneca	2 mg/ml
Syntometrine	Novartis	1 mL/4 mL
Thiopentone	Link	50 mg/ml
Tramadol	Sandoz	50 mg/ml
Tranexamic acid	Pfizer	100 mg/ml
Trimethoprim/Sulfamethoxazole	Hospira	1 mg/25 ml
Vancomycin	Hospira	20 mg/ml

Verapamil	Abbott	2.5 mg/ml
Voriconazole	Pfizer	5 mg/ml