Protocols and Summary of Changes

Submission Bundle

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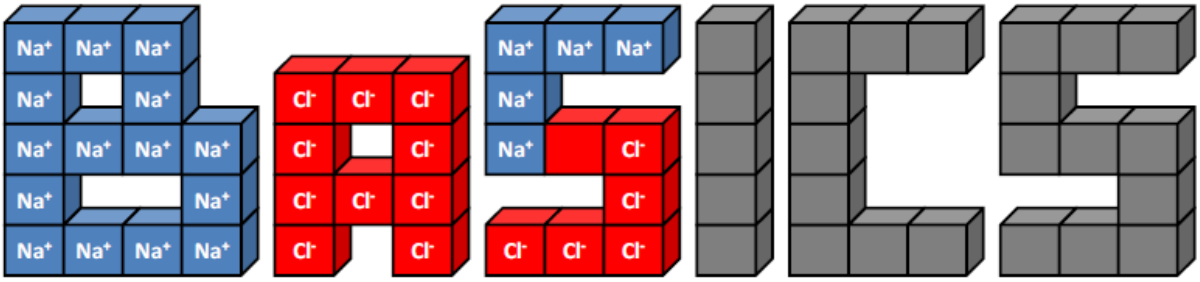
Protocol v1.2.2



BaSICS

Balanced Solution versus Saline in Intensive Care Study

Randomized, 2x2 factorial study to evaluate the effect of a balanced crystalloid solution compared to 0.9% sodium chloride, and rapid versus slow infusion, on the clinical outcomes of seriously ill patients

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Synopsis

Title	**Randomized, 2x2 factorial study to evaluate the effect of a balanced crystalloid solution compared to 0.9% sodium chloride, and rapid versus slow infusion, on the clinical outcomes of seriously ill patients**
Outline	Randomized, pragmatic, multicenter, 2x2 factorial, data recording-based study. Serious ICU patients, of moderate to high risk for acute kidney injury, will be randomly assigned to receive a balanced crystalloid solution (Plasma-Lyte®) or 0.9% sodium chloride, and to receive rapid bolus crystalloids (999 ml/h) versus slowly (333 ml/h), when plasma expansion is required.
Bias control	Secrecy of assignment with web-based randomization. Intent to treat analysis. Blinding of patients and healthcare professionals to crystalloid solutions (balanced solution or 0.9% sodium chloride).
Primary objectives	To determine whether, compared to 0.9% sodium chloride, a balanced crystalloid solution (Plasma-Lyte®) used for plasma expansion can decrease mortality and risk of kidney injury with need of renal replacement therapy in seriously ill patients and those at high risk of kidney injury within 90 days. To determine the effect of rapid (999 ml/h) versus slow (333 ml/h) administration of crystalloid solution on 90-day mortality in seriously ill patients.
Inclusion criteria	The criteria below must be present: 1. Need for plasma expansion and the clinician considers that Plasma-Lyte® or saline is equally appropriate for patients, with no specific indications or contraindications for any of the fluids, or for fast or slow speed. 2. Prediction of stay at the ICU for over 24 hours. 3. At least one of the following risk factors for acute kidney injury: a. Age ≥ 65 years b. Hypotension (MBP < 65mmHg or SBP < 90mmHg) or use of vasopressors c. Sepsis d. Use of invasive mechanical ventilation; or non-invasive (including high-flow nasal cannula) continuous> 12 hours e. Oliguria (<0.5 ml/kg/hour for ≥ 3 hours) f. Serum creatinine ≥ 1.2 mg/dl for women or ≥ 1.4 mg/dl for men g. Liver cirrhosis or acute liver failure
Exclusion criteria	1. Age < 18 years 2. Kidney failure under renal replacement therapy or with expectation of requiring renal replacement therapy in the next six hours 3. Severe hyponatremia (serum Na ≤ 120 mmol/L) 4. Severe hypernatremia (serum Na ≥ 160 mmol/L) 5. Hyperkalemia (serum K ≥ 5.5 mmol/L) 6. Death considered imminent and inevitable within 24 hours 7. Patients with suspected or confirmed brain death 8. Patients under exclusive palliative cares 9. Patient previously included in the BaSICS study
Study treatments	The treatments to be compared in the study are Plasma-Lyte® and 0.9% sodium chloride (both have identical appearance and will be packed in identical bottles), and fast (999 ml/h) versus slow (333 ml/h) infusion of these fluids.

Study endpoints – Plasma-Lyte® versus 0.9% sodium chloride	Co-Primary endpoints: • Death in 90 days • Kidney failure requiring renal replacement therapy in 90 days Secondary endpoints: • Incidental kidney injury (KDIGO ≥ 2) on days 3 and 5 • Incidental hepatic, cardiac, neurological, coagulation and respiratory dysfunctions (using SOFA) on days 3 and 5 • Mechanical ventilation-free days in 28 days Tertiary endpoints (exploratory): • Death by any cause at the ICU and hospital • Length of stay at the ICU • Duration of hospitalization
Slow versus fast infusion study endpoints	Primary endpoint: • Death in 90 days Secondary endpoints: • Kidney failure requiring renal replacement therapy in 90 days • Incidental kidney injury (KDIGO ≥ 2) on days 3 and 5 • Incidental hepatic, cardiac, neurological, coagulation and respiratory dysfunctions (using SOFA) on days 3 and 5 • Mechanical ventilation-free days in 28 days Tertiary endpoints (exploratory): • Death by any cause at the ICU and hospital • Length of stay at the ICU • Duration of hospitalization
Data management	We will use data collected routinely from patients admitted to the ICU using a digital database accessible through the Internet. Data quality assurance will be done through central verification, aiming at complete and consistent data. The sites will receive periodic reports for the adequacy of potentially inconsistent or incomplete data.
Sample size	Sample of 11,000 patients. Plasma-Lyte® versus 0.9% Sodium chloride: The study will have 82% power to detect a 15% relative reduction in the risk of kidney injury with need of dialysis in 90 days considering a 15% risk of the outcome in the 0.9% sodium chloride group. And will have 83% power to detect a 10% relative reduction in the risk of death in 90 days, considering a 35% risk in the 0.9% sodium chloride group. In both cases the α level is 0.025, considering the execution of Bonferroni-corrected hypothesis tests for the two primary endpoints, maintaining an overall α by 0.05. Fast vs slow infusion: The study will have 89% power to detect a 10% relative reduction in the risk of hospital death, considering a 25% risk in the 0.9% sodium chloride group, with α of 0.05.
Statistical analysis	All analyses will follow the intent to treat principle. We will evaluate the effect of Plasma-Lyte® compared to 0.9% sodium chloride and the effect of the two infusion rates on the primary endpoints will be compared through a hazard ratio with a 95% confidence interval and comparison of Kaplan-Meier curves (using the log rank test). The P-value for the two co-primary endpoints will be adjusted by the Bonferroni equation. For binary secondary endpoints we will perform the comparison using relative risks, 95% confidence intervals and chi-square tests. For continuous outcomes with normal distribution, we will present the medical difference, 95% confidence interval and P value calculated by t test. For continuous endpoints with asymmetric distribution, we will perform the Wilcoxon test.

Summary

Introduction

The administration of fluids in order to restore intravascular blood volume in critically ill patients is one of the most common interventions in intensive care medicine (1, 2). Currently, different types of fluids are available at the bedside for the treatment of seriously ill patients, to be chosen by care teams (2). However, there is a growing body of evidence demonstrating that the type, quantity and time of fluid administration can influence the outcome of patients (3-5).

The biggest controversy in relation to fluids in intensive care concerns the different types of fluids to be used in critically ill patients, especially with regard to the comparison between colloids and crystalloids (6). However, evidence obtained from large randomized controlled trials (RCT) has shown that there are no clear advantages of protein colloids over crystalloids as in the case of albumin (7), or in the case of synthetic non-protein colloids that are harmful (8). Thus, recently, researchers' attention has shifted from focus to comparisons between different types of crystalloid solutions (9-11).

0.9% sodium chloride (0.9% saline) is the most widely available and used crystalloid worldwide (2). 0.9% saline is an isotonic crystalloid, that is, with osmolality close to that of unbalanced human plasma, which contains equal concentrations of sodium and chloride (154 mmol/L, each). Due to this proportion of ions, 0.9% sodium chloride has a strong ion difference (SID) equal to zero (Table 1). Experimental (12-14), clinical (15, 16) and meta-analyzes (3, 5) studies suggest that resuscitation with 0.9% saline is harmful for the kidneys, for acid-base balance, for electrolyte homeostasis (hyperchloremic metabolic acidosis), in addition to compromising tissue perfusion (17), inflammatory response (14) and coagulation (18).

Table 1. Composition of the main balanced and unbalanced solutions available.

Composition / properties	Human plasma	Solutions					
		0.9% Saline	Ringer Solution	Hartmann Solution	Ringer Lactate	Ringer Acetate	Plasma-Lyte
pH	7.35 - 7.45	5.5	6.0	6.5	6.5	6.7	7.4
Osmolarity (mOsm/L)	291	308	310	279	273	270	294
Sodium (mmol/L)	135 - 145	154	147	131	130	131	140
Potassium (mmol/L)	4.5 - 5.5		4	5	4	4	5
Calcium (mmol/L)	2.2 - 2.6		2.2	2	1.5	2	
Magnesium (mmol/L)	0.8 - 1.0					1	1.5
Chlorine (mmol/L)	94 - 111	154	156	111	109	110	98
Bicarbonate (mmol/L)	23 - 27						
Lactate (mmol/L)	1.0 - 2.0			29	28		
Acetate (mmol/L)						30	27
Gluconate (mmol/L)							23

Hyperchloremia negatively affects renal function (19). Intrarenal (renal artery) infusion of chloride-containing solutions, such as 0.9% saline or ammonium chloride (NH4Cl), produces vasoconstriction and, therefore, reduces blood flow in the renal artery and reduces the glomerular filtration rate in the kidneys isolated from healthy dogs (20). Intravascular expansion with solutions containing supraphysiological concentrations of chloride, such as 0.9% saline, produces an increase in the supply of chloride to cells located in the dense macula of distal nephrons (19). As a result, several mediators, such as adenosine, are released by the cells of the dense macula to the renal circulation (tubuloglomerular feedback) (21). Adenosine has a strong vasoconstrictor effect on the afferent renal arteriole, compromising renal blood flow, glomerular filtration rate and, ultimately, renal function (19).

Balanced crystalloids have been proposed as an alternative to unbalanced solutions, in order to minimize or prevent the deleterious effects of these solutions (2). Plasma-Lyte® is a balanced crystalloid, with an osmolarity of 294 mOsm/L, and with sodium and chlorine

concentrations of 140 mmol/L and 98 mmol/L, respectively. Plasma-Lyte® also has potassium, magnesium, acetate and gluconate in its composition (Table 1). Considering the adverse events related to saline described above, it has been postulated that balanced crystalloids may be the ideal fluids for resuscitation of critically ill patients (2-5).

Most experimental studies that compared Plasma-Lyte® with 0.9% saline were performed in animal models of hemorrhagic shock or abdominal sepsis (12-14, 22). While resuscitation of hemorrhagic shock with 0.9% saline solution, but not with Plasma-Lyte®, produced hyperchloremic metabolic acidosis (13, 22), renal blood flow and renal oxygen consumption were higher with Plasma-Lyte® (13). In another experimental animal study, rats were randomized to be resuscitated with Plasma-Lyte® or 0.9% saline, subcutaneously, eighteen hours after induction of sepsis by cecal ligation and puncture (14). Plasma-Lyte® resuscitation was associated with maintenance of plasma chlorine levels and arterial pH, lower serum creatinine, lower urinary cystatin-C, lower plasma levels of NGAL (neutrophil gelatinase-associated lipocalin) and interleukin-6 (IL-6), lower incidence and severity of acute kidney injury and longer survival than animals resuscitated with 0.9% saline. Serum potassium levels, one of the main concerns related to resuscitation with balanced solutions containing potassium, such as Plasma-Lyte®, did not differ between groups (14).

The impact of Plasma-Lyte® infusion compared to 0.9% saline on acid-base balance, electrolyte disturbances and renal blood flow was assessed in a randomized, controlled, cross-over, double-blind study involving twelve healthy volunteers (23). In this study, Plasma-Lyte® and 0.9% saline produced similar effects on intravascular expansion. However, the use of 0.9% saline produced sustained hyperchloremia, reduced SID, increased extravascular volume (edema) and reduced diuresis compared to Plasma-Lyte®. In addition, the speed of blood flow in the renal artery and renal cortical perfusion assessed by nuclear magnetic resonance were significantly lower in healthy volunteers after infusion of 0.9% saline than after infusion of Plasma-Lyte® (23).

Several small randomized studies including up to 90 patients compared balanced crystalloid solutions with unbalanced crystalloid solutions in severe clinical and surgical patients (Table 2) (15, 16, 18, 24-27). Together, these studies demonstrate that the resuscitation of critically ill patients with 0.9% saline, compared to Plasma-Lyte®, is associated with a higher incidence of acid-base and electrolyte balance disorders (Table 2).

Table 2: Summary of randomized and controlled studies comparing Plasma-Lyte® with 0.9% saline solution in severe clinical and surgical patients.

Author year	N	Patients	Comparison*	Main findings of the study
McFarlane 1994	30	Open abdominal surgery	0.9% Saline Plasma-Lyte®	Acidosis and hyperchloremia with 0.9% saline
Young 2014	46	Trauma	0.9% Saline Plasma-Lyte®	Acidosis and hyperchloremia with 0.9% saline
Smith 2015	18	Trauma	0.9% Saline Plasma-Lyte®	Acidosis with 0.9% saline. Formation of thrombi faster with Plasma-Lyte® Metabolic acidosis
Hadimioglu 2008	90	Kidney transplantation	0.9% Saline Ringer lactate Plasma-Lyte®	Hyperchloremia with 0.9% saline. Increase of lactate with ringer lactate. Potassium not modified in the three groups.
Kim 2013	60	Kidney transplantation	0.9% Saline Plasma-Lyte®	Acidosis and hyperchloremia with 0.9% saline
Mahler 2012	45	Diabetic ketoacidosis	0.9% Saline Plasma-Lyte®	Metabolic acidosis and hyperchloremia with 0.9% saline.
Hasman 2012	90	Moderate or severe dehydration	0.9% Saline Ringer lactate Plasma-Lyte®	Accentuated acidosis with 0.9% saline.

A liberal strategy for administering crystalloid solutions containing chloride versus a restrictive strategy for chloride, that is, solutions without chloride in critically ill patients, was compared in a before-after study (28). In a six-month control period (liberal period), 760 patients received fluids containing chloride (0.9% saline, 4% gelatin solution or 4% albumin) according to the preference of the medical assistance team. After an interval of 6 months, 773 patients received only fluids poor in chloride (Hartmann's solution, Plasma-Lyte® or 20% albumin). The authors demonstrated a significant reduction in the incidence of acute kidney injury and kidney failure (from 14.0% to 8.4%; p <0.001) according to the RIFLE criterion (Risk, Injury, Failure, Loss, and End-Stage) , and the need for renal replacement therapy (RRT) (from 10.0% to 6.3%; p = 0.005). There were no differences in hospital mortality or other clinical outcomes (28).

Raghunathan et al. Demonstrated in a retrospective cohort study including 53,448 septic patients that resuscitation with balanced crystalloid solutions (mainly Ringer's lactate), but not with unbalanced solutions (mainly 0.9% saline), was associated with reduced risk of death hospital (relative risk, 0.86; 95% confidence interval, 0.78 to 0.94; p = 0.001) (9). However, no significant differences were observed in the incidence of acute kidney injury, need for RRT and length of stay in the ICU and hospital.

In a large cohort of patients undergoing open abdominal surgery, Shaw and colleagues matched, according to the propensity score, 926 patients who received Plasma-Lyte® versus 2,778 patients who received 0.9% saline (29). Major complications were significantly less common in patients who received Plasma-Lyte® (odds ratio, 0.80; 95% confidence interval, 0.66 to 0.97). In addition, the incidence of infections, the need for RRT, the need for transfusion of blood components and days of mechanical ventilation were significantly lower in patients treated with Plasma-Lyte®.

A cohort study involving 3116 patients with systemic inflammatory response syndrome (SIRS) demonstrated that balanced crystalloid solutions, such as Plasma-Lyte®, compared to 0.9% saline, were associated with a lower rate of major complications (atrial fibrillation, congestive heart failure, acute respiratory failure, pneumonia, sepsis and coagulopathy), less frequency of electrolyte disturbances and hyperchloremic acidosis, shorter hospital stay, less need for hospital readmission and lower hospital mortality. However, the incidence of acute kidney injury did not differ between the groups studied (11).

More recently, the safety and efficacy of plasma expansion with Plasma-Lyte® 148, compared to 0.9% saline, were evaluated in an exploratory, blind, double-crossover, cluster randomization study (30). In this study involving 2278 critically ill patients, a median infusion of 2 liters of Plasma-Lyte® 148 or 0.9% saline did not affect the risk of acute kidney injury according to the RIFLE criterion (relative risk, 1.04; confidence interval of 95%, 0.80 to 1.36; p = 0.77), the need for TRS (relative risk, 0.96; 95% confidence interval, 0.62 to 1.50; p = 0.91), ICU mortality (relative risk, 0.92; 95% confidence interval, 0.68 to 1.24; p = 0.62) and hospital mortality (relative risk, 0.88; confidence interval 95%, 0.67 to 1.17; p = 0.40). However, acid-base and electrolyte parameters were not presented by the authors, which makes it impossible for us to infer how much physiological differentiation there was in fact between the two groups studied.

The effect of intravascular expansion with crystalloid solutions containing little chloride (Plasma-Lyte®, Ringer lactate or Hartmann's solution) compared to solutions containing a lot of chloride (0.9% saline) in critically ill clinical or surgical patients has recently been evaluated in a meta-analysis (3). Twenty-one studies (15 randomized controlled trials) with 6253 patients were included. Although crystalloids with a high chloride content do not affect mortality, they increased the risk of hyperchloremia and metabolic acidosis (relative risk, 2.87; 95% confidence interval, 1.95 to 4.21; p <0.001) and the risk of acute kidney injury (relative risk, 1.64; 95% confidence interval, 1.27 to 2.13; p <0.001). Finally, there was a

greater need for transfusion of blood components after resuscitation with 0.9% saline compared to crystalloids containing little chloride.

Another meta-analysis including fourteen studies with 18916 adult septic patients suggested that resuscitation with balanced crystalloids, compared to 0.9% saline, may be associated with lower mortality (odds ratio, 0.78; 95% confidence interval, 0.58 to 1.05) (5). More recently, another meta-analysis including ten randomized controlled trials with 6664 septic patients showed no significant difference in the need for RRT between balanced crystalloids and 0.9% saline (odds ratio of 0.9%, 0.85; 95% credibility range , 0.56 to 1.30) (4).

In summary, the current literature suggests that resuscitation of critically ill patients with 0.9% saline is associated with a higher incidence of acid-base balance disorders and electrolyte disturbances. Weak evidence suggests that resuscitation with 0.9% saline may still be associated with a higher incidence of acute renal failure, increased need for RRT and increased mortality. Therefore, in light of the inconclusive nature of the available literature, it is not possible to make a definitive recommendation as to which crystalloid solution is the most suitable for resuscitating critically ill patients.

Additional aspects of the use of fluids should also be highlighted, since the fluid challenge is not restricted to the type of fluid used. Various infusion volumes and speeds are applied in intensive care, with great variability between sites and countries. The recent FENICE study suggested that a typical water challenge in intensive care involves infusing 500 ml of crystalloid in approximately 30 minutes, but with wide variability (31). In fact, the interquartile range of the infusion rate applied in the FENICE study was 500-1,333 ml/h. The value of 500 mL in thirty minutes is apparently the most common and has been used previously by clinical studies (32). However, consensus on resuscitation and management of critically ill patients is vague when defining the speed that should be used during a plasma expansion test (33).

The use of large aliquots infused over short periods of time is capable of promoting relevant physiological changes even in healthy volunteers, such as pulmonary edema (34, 35), an effect that also depends on the type of solution to be used (36). This accumulation of fluids does not appear to be harmless, and may be associated with a reduction in exercise tolerance (37). In addition, the higher the rate of infusion, the more the fluid will alter the acid-base balance (inducing chlorine changes, for example) since its immediate dilution will be by plasma and not by total body water (38) . Rapid infusion rates (up to 30 mL / kg / h) of 0.9% saline are associated with the occurrence of hyperchloremic acidosis during the intraoperative period (39). In experimental models, the slow infusion of saline is associated with greater natriuresis than the rapid infusion, suggesting that there is a pathophysiological mechanism that can justify variations in the rhythm of diuresis for the same fluid depending only on its infusion speed (40). As the pace of diuresis is part of the diagnostic criteria for

acute kidney injury, the bolus fluid infusion rate cannot be ignored as a possible contributor to the occurrence of kidney injury (41).

A recent prospective randomized study in African children with severe infection demonstrated that the use of fluid boluses (saline or albumin) was associated with higher mortality when compared to standard therapy (without bolus) (42). Interestingly, the cause of higher mortality in the bolus group was not volume overload, but shock (43). Although the reasons for these findings are not clear, it is possible that the rapid infusion of fluid abruptly reduces adrenergic tone or worsens myocardial compliance, leading to hemodynamic decompensation. Infusion of fluid can, for example, reduce arterial elastance and lead to a drop in blood pressure even in situations where cardiac output is increased (44). There are also concerns about the occurrence of intracranial hypertension, an effect that has already been demonstrated in animals (45). Such deleterious effects could be mitigated if the rate of infusion were reduced. Resuscitation protocols based on slower fluid infusions have been shown to be safe in some subpopulations of adult patients, such as those with malaria (46). It is possible that the acute hemodynamic effects of slower plasma expansion are less pronounced. However, recent literature shows that even when fast infusion speeds are used, the hemodynamic benefit of the fluid bolus is rapid and transient (47, 48). Thus, one of the fundamental questions to be assessed is whether, together with the composition, the speed of fluid infusion can change the outcome in critically ill patients.

Given the widespread use of 0.9% saline in national ICUs and their potential deleterious effects, the safety and efficacy of balanced solutions (Plasma-Lyte® or Ringer Lactate) compared to saline solution for resuscitation of critically ill patients evaluated in a randomized, multicentre, pragmatic clinical trial. Additionally, it is imperative that the effect of using faster infusion speeds is compared to slower speeds.

Objectives

This is a study that aims to assess the clinical effects of two interventions through a factorial study, namely:

1. To compare 0.9% saline solution with Plasma-Lyte®

2. To compare a faster infusion rate (999 ml/h) with a slower rate (333 ml/h) during volume tests.

Primary objectives

0.9% saline solution versus Plasma-Lyte® Comparison

To determine whether, when compared with 0.9% sodium chloride, a balanced crystalloid solution (Plasma-Lyte®) used for plasma expansion can decrease mortality and occurrence of kidney injury with need of renal replacement therapy in 90 days in seriously ill patients with high risk for acute kidney injury.

Comparison of slow infusion versus fast infusion

To determine the effect of rapid (999 ml/h) versus slow (333 ml/h) administration of crystalloid solution on 90-day mortality in seriously ill patients.

Secondary and tertiary (exploratory) objectives

For the speed of infusion, the occurrence of renal injury requiring renal replacement within 90 days is a secondary endpoint.

Additional secondary objectives for both interventions include assessing the impact of interventions at the incidence of KDIGO stage 2 or 3 acute kidney injury at 3 and 5 days after randomization; incidence of liver, cardiac, neurological, coagulation and respiratory system dysfunction (using SOFA score) on days 3 and 5 after randomization and days without mechanical ventilation on the 28 days after the patient entered the study.

As tertiary objectives, we will assess mortality in the ICU, length of stay in the ICU and in the hospital.

Methods

Outline

The BaSICS study (*Balanced Solution in Intensive Care Study*) is a randomized, pragmatic, multicenter, 2x2 factorial, data recording-based and patient- and healthcare staff-blinded study. The study will compare two resuscitation therapies with fluids in a factorial manner in critically ill patients admitted to Intensive Care Units (ICUs). The study is expected to recruit about 11,000 patients in at least 70 Brazilian ICUs for 16 months. Eligible patients must be randomized to receive 0.9% saline or balanced solution (Plasma-Lyte®) and factorially for infusion speeds of 999 ml/h or 333 ml/h and will be evaluated during their stay at the hospital.

The protocol of this study follows the recommendations of the *SPIRIT 2013 Statement*.

Study sites

The participation of at least 70 Brazilian ICUs will be necessary, including at least 16 patients per month for 16 months to recruit this sample size.

Eligibility

Inclusion Criteria

Patients admitted to the ICU who have an indication of receiving intravenous fluids for expansion or maintenance of intravascular volume will be included. To be randomized for the study, patients must meet the following three inclusion criteria concurrently:

A. Need for volume expansion as defined by the attending physician, with no specific indications or contraindications for any of the fluids, or for fast or slow speed.
B. Expectation of stay at the ICU greater than 24 hours.

C. At least one of the following risk factors for acute kidney injury:

i. Age > 65 years
ii. Hypotension (MBP < 65mmHg or SBP < 90mmHg) or use of vasopressors
iii. Sepsis, defined by the SEPSIS criteria 3 (49).
iv. Use of invasive mechanical ventilation for any period or non-invasive (including high-flow nasal cannula) continuous for more than 12 hours.
v. Oliguria (< 0.5 ml/kg/hour for ≥ 3 hours)
vi. Creatinine ≥ 1.2 mg/dl (women) or ≥ 1.4 mg/dl (men)
vii. Liver cirrhosis or failure

Exclusion Criteria

The following exclusion criteria will be applied:

1. Age < 18 years

2. Kidney failure under renal replacement therapy or with expectation of requiring renal replacement therapy in the next six hours

3. Severe hyponatremia (serum Na ≤ 120 mmol/L)

4. Severe hypernatremia (serum Na ≥ 160 mmol/L)

5. Hyperkalemia (serum K ≥ 5.5 mmol/L)

6. Death considered imminent and inevitable within 24 hours

7. Patients with suspected or confirmed brain death

8. Patients under exclusive palliative cares

9. Patient previously included in the BaSICS study

Interventions

Eligible patients who require volume replacement therapy will receive the study fluid, Plasma-Lyte® or 0.9% saline at infusion speeds of 999 ml/h or 333 ml/h, according to randomization, in quantity and frequency of administration determined by the attending physician (Figure 1). In the case of infusion of maintenance serum, the study drug should be used at the speed typically applied for this purpose (40-120 ml/h, depending on the service). Anyway, guidelines will be proposed to investigators to indicate fluid infusion (Chart 3).

The type of therapy (type of fluid and speed) to which the patient is allocated will be used in all episodes of fluid resuscitation during his stay in the ICU. As much as possible, volume replacement therapy with crystalloid solution during investigations and procedures performed outside the ICU will be with the designated study fluid. However, clinicians should be aware of special situations in which Plasma-Lyte® or 0.9% saline solution is contraindicated, in which the study fluid should not be used (Chart 4). In situations of imminent risk (Chart 5), the patient will be able to receive fluids at rapid flow (999 ml/h) regardless of the speed group to which he is randomized.

Figure 1. Administration of intravenous fluids during the BaSICS study.

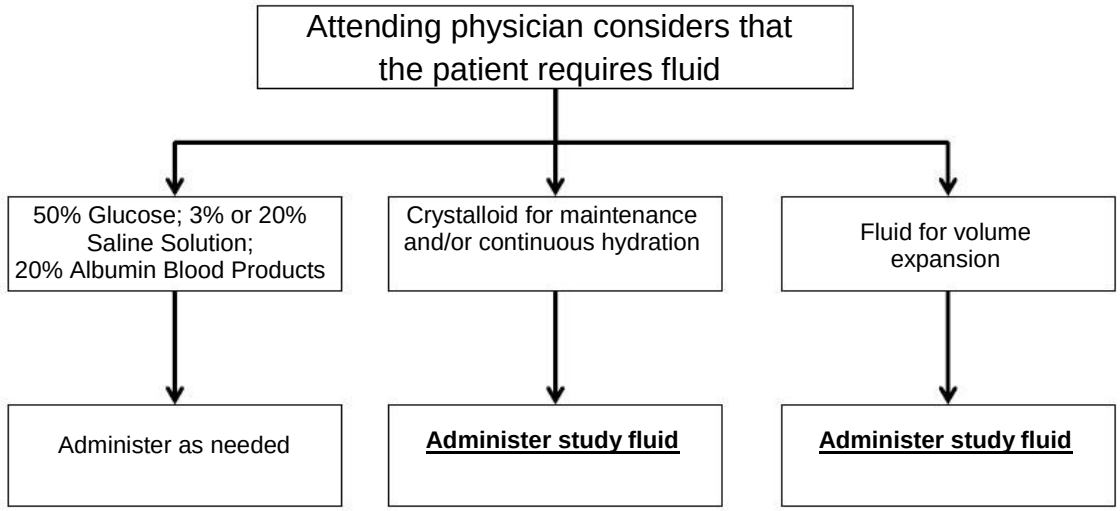

Chart 3. Guidelines for indicating plasma expansion by fluid infusion
Volume replacement is indicated in the presence of the following criteria:

1. **AT LEAST** a sign of **hypoperfusion**:
   - Heart rate> 120 bpm
   - SBP < 90 mmHg or MBP < 65 mmHg or SBP drop of at least 40 mmHg in relation to baseline levels
   - Capillary filling time> 1s
   - Mottling score ≥ 2
   - Lactate > 2mmol/L (> 18 mg/dl)
   - ScvO2 <70%
   - Drop in urine output, with <0.5 ml/kg in the last hour
2. **AND AT LEAST** a sign of **fluid responsiveness or no signs of hypervolemia:**
   - Pulse pressure variation> 13%
   - Pulse pressure increase> 5% after 15s expiratory pause
   - Passive elevation of the lower limbs leads to an increase in the cardiac index (> 10%), pulse pressure (> 11%) or mean arterial pressure (> 5%)
   - Respiratory variation of central venous pressure > 1 mmHg
   - Echocardiographic signs of hypovolemia
   - Central venous pressure ≤8 mmHg
   - Absence of clinical signs of hypervolemia when the above signs are not available

Chart 4. Situations in which the study fluids should not be administered:

Contraindication to the study fluids:	**Action:**
Severe hyperchloremia (Cl ≥ 120 mmol/L)	Avoid 0.9% NaCl
Severe hypernatremia (Na ≥ 160 mmol/L)	Avoid 0.9% NaCl
Severe hyponatremia (Na ≤ 120 mmol/L)	Avoid Plasma-Lyte®
Hyperkalemia (K ≥ 5.5 mmol/L)	Avoid Plasma-Lyte®

Chart 5. Situations where the fluids could be administered rapidly (999 ml/h):

Situation 1

Severe hypotension (systolic pressure below 80 mmHg or mean arterial pressure below 50 mmHg)

OR

Situation 2

Diagnosis of hemorrhagic shock with active bleeding requiring aggressive fluid replacement

The indication of the beginning of renal replacement therapy will be in charge of each site. However, we will suggest to sites that consider criteria (Chart 6) as indicative of the need to

start renal replacement therapy. The mode of therapy and its intensity will also be at the discretion of the site.

Chart 6. Indications for starting renal replacement therapy (adapted from (50)):

Indications of Start of Renal Replacement
Kidney failure KDIGO 2 or 3 (41), together with one of the following: • Serum potassium above 6 mEq/L • pH <7.15 in the context of pure metabolic acidosis or mixed acidosis with (PaCO2 above 50 mmHg without the possibility of an increase in minute volume) • Hypervolemia with respiratory impairment, requiring oxygen supply of more than 5 L/min (patients on spontaneous ventilation) or inspired oxygen fraction above 50% (for patients on mechanical or non-invasive ventilation) • Serum urea above 240 mg/dl

It is important to note that both interventions that will be tested by the present study are commonplace in clinical practice. As previously mentioned, balanced (such as Plasma-Lyte®) and unbalanced (such as NaCl 0.9%) fluids are routinely used in critical medicine, with variations in use largely due to availability and local preferences. Likewise, the fluid infusion rate also shows great variability. Thus, although this study evaluates two relevant issues, it does not represent any significant deviation from the usual practice of intensive care units.

We plan to evaluate the evolution of serum chlorine values in a convenience sample among the patients included in the study, considering data only from sites that collect routine serum chlorine in their ICU. We estimate a size of approximately 1000 patients within this convenience sample.

Endpoints

Plasma-Lyte® versus 0.9% NaCl Comparison

Co-Primary endpoints:

- Death in 90 days
- Kidney failure requiring renal replacement therapy in 90 days

Secondary endpoints:

- Kidney injury KDIGO ≥ 2 (50) on days 3 and 5 after randomization based only on serum creatinine: stage 2 (serum creatinine ≥ 2.0 x baseline values or more) or 3 (serum creatinine ≥ 3.0 times baseline values or increase in serum creatinine to

values ≥ 4.0 mg/dl more). For determination of the KDIGO criterion, we will define baseline creatinine as the lowest serum creatinine value available in patients' hospital records up to six months before the current ICU admission.
- New respiratory, hepatic, cardiac, neurological and coagulation dysfunction (using SOFA score) on days 3 and 5 (51).
- Mechanical ventilation-free days during the first 28 days after randomization.

Tertiary endpoints (exploratory):
- Death by any cause at the ICU and hospital
- Length of stay at the ICU
- Duration of hospitalization

Comparison of slow versus fast crystalloid infusion

Primary endpoint:

- Death in 90 days

Secondary endpoints:

- Kidney failure requiring renal replacement therapy in 90 days
- Kidney injury KDIGO > 2 (41) on days 3 and 5 after randomization based only on serum creatinine: stage 2 (serum creatinine ≥ 2.0 x baseline values or more) or 3 (serum creatinine ≥ 3.0 times baseline values or increase in serum creatinine to values ≥ 4.0 mg/dl more). For determination of the KDIGO criterion, we will define baseline creatinine as the lowest serum creatinine value available in patients' hospital records up to six months before the current ICU admission.
- New respiratory, hepatic, cardiac, neurological and coagulation dysfunction (using SOFA score) on days 3 and 5 (51).
- Mechanical ventilation-free days during the first 28 days after randomization.

Tertiary endpoints:

- Death by any cause at the ICU and hospital
- Length of stay at the ICU
- Duration of hospitalization

Evaluation of serum chlorine in convenience sample

Exploratory endpoint:

- Comparison of serum chlorine values between the four possible study groups over time (admission, first day and fifth day).

Time sequence

The study visits and the variables collected at each visit are described below:

Day 0: Tracking, randomization and baseline data

- Verification of inclusion and exclusion criteria
- Obtainment of the ICF
- Randomization
- Reason for non-randomization of eligible patients
- Time between ICU admission and randomization
- Quantity and type of fluids administered 24 hours before randomization
- Date of birth
- Gender
- Weight (checked with balance)
- Height
- Origin of the patient (operating room [elective and emergency surgery], emergency room, ward, another hospital (excluding other ICU), other ICU)
- Comorbidities (APACHE II variables)
- APACHE II score
- SOFA score (51)
- Creatinine on admission to the ICU
- Serum chlorine and other laboratory tests, if available
- Dose of vasopressors (mcg / Kg / min) administered at randomization
- Inotropic dose (mcg / Kg / min) administered at randomization
- Mode of ventilation support at the time of randomization

Daily data from Day 1 to Day 5

- Quantity, type and speed of infusion of fluids administered.
- Fluid balance
- Diuresis
- Only on Day 1: Serum chlorine, if available, only in sites that routinely collect the serum chlorine level
- Acute renal failure requiring renal replacement therapy
- Use of red blood cell concentrate

Day 3 specific data

- SOFA score, broken down by component (51)
- Serum creatinine

Day 5 specific data

- Serum creatinine

- Serum chlorine, if available, only in sites that routinely collect serum chlorine level

Data at ICU discharge

- Date of discharge from the ICU (or death)
- Vital status at discharge from the ICU

Hospital discharge

- Date of hospital discharge (or death)
- Vital status at hospital discharge
- Reasons (based on Table 6) to initiate renal replacement therapy
- Number of days on mechanical ventilation during hospital stay

90-day data:

- Vital state in 90 days
- Use of renal replacement therapy (dialysis) in the period

The 90-day data will be collected by a single telephone exchange that will contact the patient, his legal representative or family member.

Randomization

The randomization list will be generated electronically using appropriate software. Randomization will be carried out in blocks (blocks of 4 patients) stratified by site and will be factorial for the two interventions performed.

The confidentiality of the randomization list will be maintained through a centralized, automated, internet-based randomization system, available 24 hours a day, developed by a team of programmers and researchers from the Research Institute of Hospital do Coração (IP-HCor).

The group to which the patient will be allocated will only be released after registration of the information in the electronic system, which prevents the investigator and the assistant team from predicting which of the treatment groups the patient will be allocated to. To include the patient in the study, the researcher simply has to access the IP-HCor website (https://servicos.hcor.com.br/iep/estudoclinico) and fill out a simple clinical form.

Blinding

Regarding the type of fluid to be used, there will be complete blinding (double-blind in patients, health teams, researchers, data collectors, outcome validators and statisticians responsible for the analysis of the results). For technical reasons, it is impossible to carry out blinding at the rate of infusion at which the patient will be randomized, so that this intervention will remain open to those involved with the care of the patient.

For blinding the fluid solution, the treatments available in this study (Plasma-Lyte® and 0.9% saline) will be macroscopically similar and will be available in identical 500 ml plastic containers. These containers will be manufactured blinded.

Data collection and management:

We will use data collected routinely in the intensive care unit through a digital database, with easy access via the Internet. This strategy reduces the burden on care teams at participating sites, since data are already collected routinely, and minimizes costs related to data collection (52).

Several procedures will guarantee the quality of the data, including:

1) All researchers will participate in a training session before the start of the study to ensure consistency of the study procedures, including data collection;
2) Researchers will be able to call the study's Coordinating Site to resolve issues or problems that may arise;
3) Data cleansing to identify inconsistencies will be conducted periodically (approximately every fifteen days). The sites will be notified of inconsistencies in order to provide correction;
4) Statistical techniques for identifying fraud will be performed throughout the study;
5) The Coordinating Site will review detailed reports on screening, inclusion, follow-up, consistencies and data completeness on a monthly basis. It will immediately take action to resolve any problems.
6) Monitoring at the sites will be carried out during the conduct of the study to sample the sites, particularly if there are special needs due to the accumulation of inconsistencies or missing data. A trained professional will be appointed by the Coordinating Site to monitor participating sites. All information during the monitoring visits will be treated in a strictly confidential manner.

Monitoring

Data monitoring

A Data Monitoring Committee (DMC) will be formed by epidemiologists and interventionists independent of the study's investigators.

The DMC is responsible for providing guidance to the Steering Committee on continuing the study as planned or stopping recruitment based on evidence that the intervention of the experimental group results in increased mortality compared to control. At the beginning of its activities, the DMC must prepare a booklet specifying the details of the

formation of the DMC, its operation, meetings and interruption rules. In any case, the rules of the booklet should be guided by the principles described below.

Interim analyzes will be performed after approximately 25%, 50% and 75% of the sample size has been recruited. In the light of these interim analyzes and, eventually, external evidence, the Data Monitoring Committee should assess whether there is evidence beyond reasonable doubt that one of the interventions is clearly contraindicated for all patients, or for any subgroup.

The criterion of evidence beyond reasonable doubt is an increase in mortality or incidence of acute kidney injury requiring renal replacement therapy in the Plasma-Lyte® group compared to the 0.9% sodium chloride group, with a P <0 , 01 or an increase in mortality in the slow versus fast group with p <0.01. Data Monitoring Committee members may consider requesting a continuation of the study for an additional three months to confirm the effect (particularly if P value between 0.01 and 0.001). If the safety criterion is reached in one of the factors analyzed in the study, the corresponding factor arm will be stopped and the study will continue with the remaining factor arm.

If there is evidence of superiority of Plasma-Lyte® compared to sodium chloride, or slow infusion compared to fast, with a P value <0.001 after an interim evaluation of 50% or more patients, DMC may also consider interrupting the study. However, you must request continuation for another three months and repeat the analyzes to confirm the difference between treatments and, mainly, allow stabilization of the effect estimates (aiming to avoid an estimate of the effect at a “random high” moment).

The study should not be interrupted for benefit in the first interim analysis (with 25% of patients). The reasons for this decision are: 1) The early interruption of randomized studies for benefit tends to produce biased effect estimates (overestimating the true effect), and may lead medical guidelines and decision makers to error, particularly with low numbers of events. (53); 2) Following the ethical principle of non-maleficence, a new treatment should not be used until there is clear objective evidence that it is beneficial; 3) Clinical practice does not usually change unless there is sufficiently convincing evidence of the advantages of the new treatment, which would be weakened if the study is stopped early for benefit (54).

Safety

Unexpected serious adverse events directly related to the study should be reported. Unexpected serious adverse events directly related to the study are defined as adverse events that meet the following two criteria:

1) Any fatal or life-threatening event (immediate risk of death) or that leaves a sequel or permanent disability or that prolongs hospitalization; AND

2) The attending physician believes that the event is related to inclusion in the BaSICS study. Serious adverse events will be considered “study related” if the attending physician judges that the event was probably caused by the study fluid and / or infusion rate and follows a plausible time sequence since the administration of the study fluid

Audit

We do not foresee carrying out an audit of the participating sites beyond the usual monitoring of the sites.

Statistical methods

Sample size and recruitment strategies

We will include 11,000 patients. We estimated 35% day mortality and acute kidney injury requiring renal replacement therapy around 15% in the control group by applying the eligibility criteria of our study to the ORCHESTRA study database (55) and based on data from the CHECKLIST study (56).

Regarding the type of fluid, the study will have 82% statistical power to detect a 15% relative risk reduction of kidney injury requiring renal replacement therapy considering an incidence of 15% in the control group and a power of 83% for detect a reduction in the relative risk of mortality in 90 days of 10% considering a mortality in 90 days of 30%, both with type α error of 0.025 (considering analysis of two co-primary endpoints). Regarding the rate of infusion, the study will have 89% power to detect a 10% relative reduction in the risk of death in 90 days, considering an incidence of 35% in the 0.9% sodium chloride group, with α of 0.05.

We do not foresee interaction between the effects of the study's factorial arms, however, if there is an interaction, the study will have an 88% power to detect an interaction of up to 30% between the interventions.

We plan to recalculate the sample size value after including the first 500 patients in order to adjust the number of patients to be included according to the incidence of events in our population.

Statistical analysis

Detailed statistical analysis plan will be drawn up before the inclusion of patients begins. The fundamental characteristics of the statistical analysis plan are described below.

All analyses will follow the intent to treat principle. We will evaluate the effect of Plasma-Lyte® compared to 0.9% sodium chloride and the effect of the two infusion rates on the primary endpoints will be compared through a hazard ratio with a 95% confidence

interval and comparison of Kaplan-Meier curves (using the log rank test). The P-value for the two co-primary endpoints will be adjusted by the Bonferroni equation. For binary secondary endpoints we will perform the comparison using relative risks, 95% confidence intervals and chi-square tests. For continuous outcomes with normal distribution, we will present the medical difference, 95% confidence interval and P value calculated by *t* test. For continuous endpoints with asymmetric distribution, we will perform the Wilcoxon test.

We will analyze the effect of the fluids under study on primary outcomes according to the following subgroups:

- Sepsis patients (49).
- Patients with acute kidney injury (KIDGO Stage 1)
- Surgical patients
- Patients with cranioencephalic trauma
- APACHE II $\geq$ 25 or < 25 points
- Patients that received > 1000 ml of sodium chloride in 24 hours prior to randomization versus ≤ 1000 ml

We will also evaluate the effect of Plasma-Lyte® versus sodium chloride in patients who have received> 6,000ml of fluids during the first 5 days. This analysis will be considered merely exploratory, once these subgroups cannot be defined initially (at the moment of randomization).

Ethics and dissemination

Ethics committee approval

Before beginning the study, the investigator must forward a copy of the protocol, the informed consent form and other requested statements, to the Local Ethics Committee of his Institution (LEC). A protocolized referral letter and the LEC approval letter, when approved, must be sent to the Study Coordinating Site.

Amendments

All eventual amendments to the protocol must be approved by the LEC of each participating site

Consent

Written consent will be requested from all eligible patients or their legal/family representative when the patient's clinical conditions such as cognitive impairments or communication limitations (e.g. patient on mechanical ventilation) do not allow for direct obtaining (mechanical ventilation) , sedation).

Regarding the process of obtaining the consent form for this study, we consider that: 1) the study intervention, volume expansion with crystalloid for seriously ill patients, is administered on an emergency basis in almost all cases, with no possibility of delays. 2) in most Brazilian ICUs, family members remain in the unit for limited periods of time (1 to 2 times a day), therefore, they are not immediately available for the consent process. 3) Plasma-Lyte® and 0.9% saline solution are routinely used in clinical practice with exactly the same indications and without robust evidence of differences in clinical effect. 4) the fluid prescription standard worldwide is very variable and reflects regional preferences because there is no good clinical evidence (e.g. 60% of expansions with crystalloids in Brazil are carried out with 0.9% saline solution and the remainder with balanced solutions, while more than half of the time balanced solutions are used in other countries). 5) there is no consensus on the speed of infusion that should be used in critically ill patients or data that justify or refute any of the chosen speeds 6) the national resolution 466 of 2012, in section III, subsection 2, item “g”, provides obtaining the consent form a posteriori in special cases. In view of the above, we reinforce that the process of obtaining consent will be carried out in all cases, without exception. Investigators in the BaSICS study are committed to obtaining the consent form before the patient's inclusion in the study, whenever possible. However, we understand that in several cases it is fully justified and it will only be possible to obtain consent a posteriori. If the patient is unable to consent to his participation, the term will be obtained as quickly as possible, either through his family member / legal representative or the patient himself, when able to consent.

The consent request and the pertinent study information provided to the legal representative must be conducted by the principal investigator, co-investigator or the study coordinator. The patient's legal representative and the research professional assigned to obtain the consent must date and sign two copies of the informed consent form, one copy of which must be delivered to the patient's legal representative and one copy must be filed with the other study documents. It will be clearly exposed to the patients' legal representatives that their participation is voluntary and may withdraw from the study at any time without any implication in the quality and conduct of the subsequent medical treatment. The ICF proposed by the study must be evaluated by each research site and, if there is a need for changes, these must be approved by the Study Coordinating Site before submission to LEC.

Confidentiality

No patient identification data will be sent to the Study Coordinating Site. The electronic data collection form will identify the patient and the investigating site by the corresponding number. The data obtained from the medical record must be kept confidential by the

research sites, in cabinets with restricted access and the guarantee of anonymity of all data in provisional and definitive reports will be ensured.

Statements of interests

The members of the Steering Committee declare that it does not present conflicts of interest.

Database sharing

We intend to open access to the study database for other researchers. In the first two years after the publication of the main manuscript, researchers will dedicate themselves to conduct analyzes for sub-studies proposed by researchers in the collaborative group. In this phase, the database will be kept under the guardianship of the study coordinators, and its access will be allowed to third parties only by express authorization of the BaSICS Study Steering Committee after the proposal evaluation accompanied by a statistical analysis plan. The Steering Committee should grant access to the requested data as long as the proposal does not conflict with planned or ongoing sub-studies by researchers from the BaSICS collaborative group. After a period of two years, all data collected by the BaSICS study will be made available to the public on a free platform. We emphasize that no data that allows the future identification of the patient such as initials, date of birth, among others, will be publicly available after the period of two years. Each individual who requests access to the database must formally undertake to notify the study's steering committee of any information that allows the patient to be identified in the database.

Dissemination policies

The BaSICS Study Steering Committee undertakes to publish its results, whatever they may be. As it is a large-scale collaborative randomized study, we aim to send the main publications to high impact journals.

We intend to submit two main manuscripts, one on the effects of Plasma-Lyte® compared to 0.9% sodium chloride, and the other on the effects of slow infusion versus rapid infusion of fluids.

Both manuscripts will be submitted on behalf of the research group (BaSICS Investigators) and this is the name that should appear on the title page of the manuscript when it is published. The research group for each of the studies will be composed of the main Steering Committee of the BaSICS study plus the researchers from the sites that recruit the greatest number of patients. Researchers from all participating sites (two to three per institution) who have included at least 30 patients will be listed at the end of publications or in supplementary material, depending on the editorial policy of each journal. The listing will occur in alphabetical order of the sites.

Suggestions of topics for sub-studies and secondary publications, as well as the inclusion of individual data for meta-analyzes, should be sent by the researchers to the Steering Committee, which will evaluate the proposal and may approve it, suggest improvements or reject it. The evaluation will be conducted based on scientific merit and the participation of researchers for the success of the main study.

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Protocol v3.0

BaSICS

Balanced solution versus Saline in Intensive Care Study

Randomized, 2x2 factorial study to evaluate the effect of a balanced crystalloid solution compared to 0.9% sodium chloride, and rapid versus slow infusion, on the clinical outcomes of seriously ill patients

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Funding	PROADI-SUS – Programa de Apoio ao Desenvolvimento Institucional do SUS Baxter Hospitalar
Version	3.0 de March 2020
Study Registry	NCT02875873

Version History

Version 1.2. - Initial

Version 1.4.1

This version presents the following changes:

- Unification of endpoints for the two interventions to be tested
- Change of the date of definition of secondary endpoints from days 3 and 5 to 3 and 7
- Change of days of collection of information
- Clarification of the definitions of acute kidney injury
- Recalculation of the study's power
- Adjustment in the guidelines for use of the study fluid
- Inclusion of quality of life analysis in 180 days in a sub-sample of 1,100 patients
- Change in the number of individuals by randomization block

Version 1.5

This version does NOT bring any change in inclusion and exclusion criteria, endpoints or definitions of the study. The only proposed changes are:

1. Addition of the registration number in ClinicalTrials.gov
2. Addition of an appendix with the list of drugs that can be diluted in Plasma-Lyte® for aid of the sites.

Version 2.0
This version presents as changes the exclusion of the exclusion criterion referring to hyperkalemia and some text adjustments and team updates.

Version 3.0
This version presents as changes the alteration of quality of life assessment through EQ-5D-3L questionnaire in six months and some text adjustments and team updates.

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Synopsis

Title	Randomized, 2x2 factorial study to evaluate the effect of a balanced crystalloid solution compared to 0.9% sodium chloride, and rapid versus slow infusion, on the clinical outcomes of seriously ill patients
Outline	Randomized, pragmatic, multicenter, 2x2 factorial, data recording-based study. Serious ICU patients, of moderate to high risk for acute kidney injury, will be randomly assigned to receive a balanced crystalloid solution (Plasma-Lyte®) or 0.9% sodium chloride, and to receive rapid bolus crystalloids (999 ml/h) versus slowly (333 ml/h), when plasma expansion is required.
Biascontrol	Secrecy of assignment with web-based randomization. Intent to treat analysis. Blinding of patients and healthcare professionals to crystalloid solutions (balanced solution or 0.9% sodium chloride).
Primary objectives	To determine whether, compared to 0.9% sodium chloride, a balanced crystalloid solution (Plasma-Lyte®) used for plasma expansion can decrease mortality in seriously ill patients and those at high risk of kidney injury within 90 days. To determine the effect of rapid (999 ml/h) versus slow (333 ml/h) administration of crystalloid solution on 90-day mortality in seriously ill patients.
Inclusion criteria	The criteria below must be present: 1. Need for plasma expansion and the clinician considers that Plasma-Lyte® or saline is equally appropriate for patients, with no specific indications or contraindications for any of the fluids, or for fast or slow speed. 2. Patients with no discharge plan on the day following admission. 3. At least one of the following risk factors for acute kidney injury: a. Age ≥ 65 years b. Hypotension (MBP < 65mmHg or SBP < 90mmHg) or use of vasopressors c.Sepsis d. Use of invasive mechanical ventilation; or non-invasive (including high-flow nasal cannula) continuous > 12 hours e. Oliguria (< 0.5 ml/kg/hour for ≥ 3 hours) f. Serum creatinine ≥ 1.2 mg/dl for women or ≥ 1.4 mg/dl for men g. Liver cirrhosis or acute liver failure
Exclusion criteria	1. Age < 18 years 2. Kidney failure under renal replacement therapy or with expectation of requiring renal replacement therapy in the next six hours 3. Severe hyponatremia (serum Na ≤ 120 mmol/L) 4. Severe hypernatremia (serum Na ≥ 160 mmol/L) 5. Death considered imminent and inevitable within 24 hours 6. Patients with suspected or confirmed brain death 7. Patients under exclusive palliative cares 8. Patient previously included in the BaSICS study
Study treatments	The treatments to be compared in the study are Plasma-Lyte® and 0.9% sodium chloride (both have identical appearance and will be packed in identical bottles), and fast (999 ml/h) versus slow (333 ml/h) infusion of these fluids.

Study endpoints: Plasma-Lyte® versus 0.9% sodium chloride	Primary endpoint: – Death in 90 days Secondary endpoints: – Kidney failure requiring renal replacement therapy in 90 days – Incidental kidney injury (KDIGO ≥ 2) on days 3 and 7 – Incidental hepatic, cardiac, neurological, coagulation and respiratory dysfunctions (using SOFA) on days 3 and 7 – Mechanical ventilation-free days in 28 days Tertiary endpoints (exploratory): – Death by any cause at the ICU and hospital – Length of stay at the ICU – Duration of hospitalization
Study endpoints: Slow versus fast infusion	Primary endpoint: – Death in 90 days Secondary endpoints: – Kidney failure requiring renal replacement therapy in 90 days – Incidental kidney injury (KDIGO ≥ 2) on days 3 and 7 – Incidental hepatic, cardiac, neurological, coagulation and respiratory dysfunctions (using SOFA) on days 3 and 7 – Mechanical ventilation-free days in 28 days Tertiary endpoints (exploratory): – Death by any causeat the ICU and hospital – Length of stay at the ICU – Duration of hospitalization
Data management	We will use data collected routinely from patients admitted to the ICU using a digital database accessible through the Internet. Data quality assurance will be done through central verification, aiming at complete and consistent data. The sites will receive periodic reports for the adequacy of potentially inconsistent or incomplete data.
Sample size	Sample of 11,000 patients. Plasma-Lyte® versus 0.9% Sodium chloride: The study will have 89% power to detect a 10% relative reduction in the risk of death in 90 days, considering a 35% risk in the 0.9% sodium chloride group. Fast vs slow infusion: The study will have 89% power to detect a 10% relative reduction in the risk of death in 90 days, considering a 35% risk in the 0.9% sodium chloride group, with α of 0.05. Interaction: We do not consider a priori the existence of interactions between interventions. Regardless, we will have an 80% power to detect a risk ratio of 0.835 between interventions
Statistical analysis	All analyses will follow the intent to treat principle. We will evaluate the effect of Plasma-Lyte® compared to 0.9% sodium chloride and the effect of the two infusion rates on the primary outcome using a hazard ratio with a 95% confidence interval and comparison of Kaplan-Meier curves (using the log rank test). For binary

	secondary endpoints we will perform the comparison using relative risks, 95% confidence intervals and chi-square tests. For continuous outcomes with normal distribution, we will present the medical difference, 95% confidence interval and P value calculated by t test. For continuous endpoints with asymmetric distribution, we will perform the Wilcoxon test. We do not foresee interaction between the effects of the study's factorial arms, however, if there is an interaction, the study will have an 88% power to detect an interaction of up to 30% between the interventions.
Subgroups defined a *priori*	– Patients with sepsis. – Patients with baseline acute kidney injury (KDIGO Stage 1) – Surgical patients – Patients with cranioencephalic trauma – APACHE II $\geq$ 25 or < 25 points – Patients that received > 1000 ml of sodium chloride in 24 hours prior to randomization versus ≤ 1000 ml – Patients who have received > 6,000 ml of fluids during the first 3 days. This analysis will be considered merely exploratory, once these subgroups cannot be defined initially (at the moment of randomization).

Summary

Introduction

The administration of fluids in order to restore intravascular blood volume in critically ill patients is one of the most common interventions in intensive care medicine (1, 2). Currently, different types of fluids are available at the bedside for the treatment of seriously ill patients, to be chosen by care teams (2). However, there is a growing body of evidence demonstrating that the type, quantity and time of fluid administration can influence the outcome of patients (3-5).

The biggest controversy in relation to fluids in intensive care concerns the different types of fluids to be used in critically ill patients, especially with regard to the comparison between colloids and crystalloids (6). However, evidence obtained from large randomized controlled trials (RCT) has shown that there are no clear advantages of protein colloids over crystalloids as in the case of albumin (7), or in the case of synthetic non-protein colloids that are harmful (8). Thus, recently, researchers' attention has shiftedfrom focus to comparisons between different types of crystalloid solutions (9-11).

0.9% sodium chloride (0.9% saline) is the most widely available and used crystalloid worldwide (2). 0.9% saline is an isotonic crystalloid, that is, with osmolality close to that of unbalanced human plasma, which contains equal concentrations of sodium and chloride (154 mmol/L, each). Due to this proportion of ions, 0.9% sodium chloride has a strong ion difference (SID) equal to zero (Table 1). Experimental (12-14), clinical (15, 16) and meta-analyzes (3, 5) studies suggest that resuscitation with 0.9% saline is harmful for the kidneys, for acid-base balance, for electrolyte homeostasis (hyperchloremic metabolic acidosis), in addition to compromising tissue perfusion (17), inflammatory response (14) and coagulation (18).

Table 1. Composition of the main balanced and unbalanced solutions available.

		Solutions					
Composition / properties	**Human plasma**	**0.9% Saline**	**Ringer Solution**	**Hartmann Solution**	**Ringer Lactate**	**Ringer Acetate**	**Plasma-Lyte**
pH	7.35 - 7.45	5.5	6.0	6.5	6.5	6.7	7.4
Osmolarity (mOsm/L)	291	308	310	279	273	270	294
Sodium (mmol/L)	135 - 145	154	147	131	130	131	140
Potassium (mmol/L)	4.5 - 5.5		4	5	4	4	5
Calcium (mmol/L)	2.2 - 2.6		2.2	2	1.5	2	
Magnesium (mmol/L)	0.8 - 1.0					1	1.5
Chlorine (mmol/L)	94 - 111	154	156	111	109	110	98
Bicarbonate (mmol/L)	23 - 27						
Lactate (mmol/L)	1.0 - 2.0			29	28		
Acetate (mmol/L)						30	27
Gluconate (mmol/L)							23

Hyperchloremia negatively affects renal function (19). Intrarenal (renal artery) infusion of chloride-containing solutions, such as 0.9% saline or ammonium chloride (NH4Cl), produces vasoconstriction and, therefore, reduces blood flow in the renal artery and reduces the glomerular filtration rate in the kidneys isolated from healthy dogs (20). Intravascular expansion with solutions containing supraphysiological concentrations of chloride, such as 0.9% saline, produces an increase in the supply of chloride to cells located in the dense macula of distal nephrons (19). As a result, several mediators, such as adenosine, are released by the cells of the dense macula to the renal circulation (tubuloglomerular *feedback*) (21). Adenosine has a strong vasoconstrictor effect on the afferent renal arteriole, compromising renal blood flow, glomerular filtration rate and, ultimately, renal function (19).

Balanced crystalloids have been proposed as an alternative to unbalanced solutions, in order to minimize or prevent the deleterious effects of these solutions (2). Plasma-Lyte® is a balanced crystalloid, with an osmolarity of 294 mOsm/L, and with sodium and chlorine concentrations of 140 mmol/L and 98 mmol/L, respectively. Plasma-Lyte® also has potassium, magnesium, acetate and gluconate in its composition (Table 1). Considering the adverse events related to saline described above, it has been postulated that balanced crystalloids may be the ideal fluids for resuscitation of critically ill patients (2-5).

Most experimental studies that compared Plasma-Lyte® with 0.9% saline were performed in animal models of hemorrhagic shock or abdominal sepsis (12-14, 22). While resuscitation of hemorrhagic shock with 0.9% saline solution, but not with Plasma-Lyte®, produced hyperchloremic metabolic acidosis (13, 22), renal blood flow and renal oxygen consumption were higher with Plasma-Lyte® (13). In another experimental animal study, rats were randomized to be resuscitated with Plasma-Lyte® or 0.9% saline, subcutaneously, eighteen hours after induction of sepsis by cecal ligation and puncture (14). Plasma-Lyte® resuscitation was associated with maintenance of plasma chlorine levels and arterial pH, lower serum creatinine, lower urinary cystatin-C, lower plasma levels of NGAL (neutrophil gelatinase-associated lipocalin) and interleukin-6 (IL-6), lower incidence and severity of acute kidney injury and longer survival than animals resuscitated with 0.9% saline. Serum potassium

levels, one of the main concerns related to resuscitation with balanced solutions containing potassium, such as Plasma-Lyte®, did not differ between groups (14).

The impact of Plasma-Lyte® infusion compared to 0.9% saline on acid-base balance, electrolyte disturbances and renal blood flow was assessed in a randomized, controlled, *cross-over*, double-blind study involving twelve healthy volunteers (23). In this study, Plasma-Lyte® and 0.9% saline produced similar effects on intravascular expansion. However, the use of 0.9% saline produced sustained hyperchloremia, reduced SID, increased extravascular volume (edema) and reduced diuresis compared to Plasma-Lyte®. In addition, the speed of blood flow in the renal artery and renal cortical perfusion assessed by nuclear magnetic resonance were significantly lower in healthy volunteers after infusion of 0.9% saline than after infusion of Plasma-Lyte® (23).

Several small randomized studies including up to 90 patients compared balanced crystalloid solutions with unbalanced crystalloid solutions in severe clinical and surgical patients (Table 2) (15, 16, 18, 24-27). Together, these studies demonstrate that the resuscitation of critically ill patients with 0.9% saline, compared to Plasma-Lyte®, is associated with a higher incidence of acid-base and electrolyte balance disorders (Table 2).

Table 2: Summary of randomized and controlled studies comparing Plasma-Lyte® with 0.9% saline solution in severe clinical and surgical patients.

Author Year	**N**	**Patients**	**Comparison***	**Main findings of the study**
McFarlane 1994	30	Abdominal surgery open	0.9% Saline Plasma-Lyte®	Acidosis and hyperchloremia with 0.9% saline
Young 2014	46	Trauma	0.9% Saline Plasma-Lyte®	Acidosis and hyperchloremia with 0.9% saline
Smith	18	Trauma	0.9% Saline	Acidosis with 0.9% saline.

2015			Plasma-Lyte®	Formation of thrombi faster with Plasma-Lyte®
Hadimioglu 2008	90	Kidney transplantation	0.9% Saline Ringer lactate Plasma-Lyte®	Metabolic acidosis Hyperchloremia with 0.9% saline. Increase of lactate with ringer lactate. Potassium not modified in the three groups.
Kim 2013	60	Kidney transplantation	0.9% Saline Plasma-Lyte®	Acidosis and hyperchloremia with 0.9% saline
Mahler 2012	45	Diabetic ketoacidosis	0.9% Saline Plasma-Lyte® 0.9% Saline	Hyperchloremic metabolic acidosis with 0.9% saline.
Hasman 2012	90	Dehydration moderate or severe	Ringer lactate Plasma-Lyte®	Accentuated acidosis with 0.9% saline.

A liberal strategy for administering crystalloid solutions containing chloride versus a restrictive strategy for chloride, that is, solutions without chloride in critically ill patients, was compared in a before-after study (28). In a six-month control period (liberal period), 760 patients received fluids containing chloride (0.9% saline, 4% gelatin solution or 4% albumin) according to the preference of the medical assistance team. After an interval of 6 months, 773 patients received only fluids poor in chloride (Hartmann's solution, Plasma-Lyte® or 20% albumin). The authors demonstrated a significant reduction in the incidence of acute kidney injury and kidney failure (from 14.0% to 8.4%; p <0.001) according to the RIFLE criterion (*Risk, Injury, Failure, Loss, and End-Stage*) , and the need for renal replacement therapy (RRT) (from 10.0% to 6.3%; p = 0.005). There were no differences in hospital mortality or other clinical outcomes (28).

Raghunathan et al. Demonstrated in a retrospective cohort study including 53,448 septic patients that resuscitation with balanced crystalloid solutions (mainly Ringer's lactate), but not with unbalanced solutions (mainly 0.9% saline), was associated with reduced risk of death hospital

(relative risk, 0.86; 95% confidence interval, 0.78 to 0.94; p = 0.001) (9). However, no significant differences were observed in the incidence of acute kidney injury, need for RRT and length of stay in the ICU and hospital.

In a large cohort of patients undergoing open abdominal surgery, Shaw and colleagues matched, according to the propensity score, 926 patients who received Plasma-Lyte® versus 2,778 patients who received 0.9% saline (29). Major complications were significantly less common in patients who received Plasma-Lyte® (odds ratio, 0.80; 95% confidence interval, 0.66 to 0.97). In addition, the incidence of infections, the need for RRT, the need for transfusion of blood components and days of mechanical ventilation were significantly lower in patients treated with Plasma-Lyte®.

A cohort study involving 3116 patients with systemic inflammatory response syndrome (SIRS) demonstrated that balanced crystalloid solutions, such as Plasma-Lyte®, compared to 0.9% saline, were associated with a lower rate of major complications (atrial fibrillation, congestive heart failure, acute respiratory failure, pneumonia, sepsis and coagulopathy), less frequency of electrolyte disturbances and hyperchloremic acidosis, shorter hospital stay, less need for hospital readmission and lower hospital mortality. However, the incidence of acute kidney injury did not differ between the groups studied (11).

More recently, the safety and efficacy of plasma expansion with Plasma-Lyte® 148, compared to 0.9% saline, were evaluated in an exploratory, blind, double-*crossover*, cluster randomization study (30). In this study involving 2278 critically ill patients, a median infusion of 2 liters of Plasma-Lyte® 148 or 0.9% saline did not affect the risk of acute kidney injury according to the RIFLE criterion (relative risk, 1.04; confidence interval of 95%, 0.80 to 1.36; p = 0.77), the need for TRS (relative risk, 0.96; 95% confidence interval, 0.62 to 1.50; p = 0.91), ICU mortality (relative risk, 0.92; 95% confidence interval, 0.68 to 1.24; p = 0.62) and hospital mortality (relative risk, 0.88; confidence interval 95%, 0.67 to 1.17; p = 0.40). However, acid-base and electrolyte parameters were not presented by the authors, which makes it impossible for us to infer how much physiological differentiation there was in fact between the two groups studied.

The effect of intravascular expansion with crystalloid solutions containing little chloride (Plasma-Lyte®, Ringer lactate or Hartmann's solution) compared to solutions containing a lot of chloride (0.9% saline) in critically ill clinical or surgical patients has recently been evaluated in a meta-analysis. (3). Twenty-one studies (15 randomized controlled trials) with 6253 patients were included. Although crystalloids with a high chloride content do not affect mortality, they increased the risk of hyperchloremia and metabolic acidosis (relative risk, 2.87; 95% confidence interval, 1.95 to 4.21; p <0.001) and the risk of acute kidney injury (relative risk, 1.64; 95% confidence interval, 1.27 to 2.13; p <0.001). Finally, there was a greater need for transfusion of blood components after resuscitation with 0.9% saline compared to crystalloids containing little chloride.

Another meta-analysis including fourteen studies with 18916 adult septic patients suggested that resuscitation with balanced crystalloids, compared to 0.9% saline, may be associated with lower mortality (odds ratio, 0.78; 95% confidence interval, 0.58 to 1.05) (5). More recently, another meta-analysis including ten randomized controlled trials with 6664 septic patients showed no significant difference in the need for RRT between balanced crystalloids and 0.9% saline (odds ratio of 0.9%, 0.85; 95% credibility range , 0.56 to 1.30) (4).

In summary, the current literature suggests that resuscitation of critically ill patients with 0.9% saline is associated with a higher incidence of acid-base balance disorders and electrolyte disturbances. Weak evidence suggests that resuscitation with 0.9% saline may still be associated with a higher incidence of acute renal failure, increased need for RRT and increased mortality. Therefore, in light of the inconclusive nature of the available literature, it is not possible to make a definitive recommendation as to which crystalloid solution is the most suitable for resuscitating critically ill patients.

Additional aspects of the use of fluids should also be highlighted, since the fluid challenge is not restricted to the type of fluid used. Various infusion volumes and speeds are applied in intensive care, with great variability between sites and countries. The recent FENICE study suggested that a typical

water challenge in intensive care involves infusing 500 ml of crystalloid in approximately 30 minutes, but with wide variability . (31). In fact, the interquartile range of the infusion rate applied in the FENICE study was 500-1,333 ml/h. The value of 500 mL in thirty minutes is apparently the most common and has been used previously by clinical studies (32). However, consensus on resuscitation and management of critically ill patients is vague when defining the speed that should be used during a plasma expansion test (33).

The use of large aliquots infused over short periods of time is capable of promoting relevant physiological changes even in healthy volunteers, such as pulmonary edema (34, 35), an effect that also depends on the type of solution to be used (36). This accumulation of fluids does not appear to be harmless, and may be associated with a reduction in exercise tolerance (37). In addition, the higher the rate of infusion, the more the fluid will alter the acid-base balance (inducing chlorine changes, for example) since its immediate dilution will be by plasma and not by total body water (38) . Rapid infusion rates (up to 30 mL/kg/h) of 0.9% saline are associated with the occurrence of hyperchloremic acidosis during the intraoperative period (39). In experimental models, the slow infusion of saline is associated with greater natriuresis than the rapid infusion, suggesting that there is a pathophysiological mechanism that can justify variations in the rhythm of diuresis for the same fluid depending only on its infusion speed (40). As the pace of diuresis is part of the diagnostic criteria for acute kidney injury, the bolus fluid infusion rate cannot be ignored as a possible contributor to the occurrence of kidney injury . (41).

A recent prospective randomized study in African children with severe infection demonstrated that the use of fluid *boluses* (saline or albumin) was associated with higher mortality when compared to standard therapy (without bolus) (42). Interestingly, the cause of higher mortality in the *bolus* group was not volume overload, but shock (43). Although the reasons for these findings are not clear, it is possible that the rapid infusion of fluid abruptly reduces adrenergic tone or worsens myocardial compliance, leading to hemodynamic decompensation. Infusion of fluid can, for example, reduce arterial elastance and lead to a drop in blood pressure even in situations where cardiac output is

increased (44). There are also concerns about the occurrence of intracranial hypertension, an effect that has already been demonstrated in animals (45). Such deleterious effects could be mitigated if the rate of infusion were reduced. Resuscitation protocols based on slower fluid infusions have been shown to be safe in some subpopulations of adult patients, such as those with malaria (46). It is possible that the acute hemodynamic effects of slower plasma expansion are less pronounced. However, recent literature shows that even when fast infusion speeds are used, the hemodynamic benefit of the fluid *bolus* is rapid and transient (47, 48). Thus, one of the fundamental questions to be assessed is whether, together with the composition, the speed of fluid infusion can change the outcome in critically ill patients.

Given the widespread use of 0.9% saline in national ICUs and their potential deleterious effects, the safety and efficacy of balanced solutions (Plasma-Lyte® or Ringer Lactate) compared to saline solution for resuscitation of critically ill patients evaluated in a randomized, multicentric, pragmatic clinical trial. Additionally, it is imperative that the effect of using faster infusion speeds is compared to slower speeds.

Objectives

This is a study that aims to assess the clinical effects of two interventions through a factorial study, namely:

1. To compare 0.9% saline solution with Plasma-Lyte®
2. To compare a faster infusion rate (999 ml/h) with a slower rate (333 ml/h) during volume tests.

Primary Objectives

0,9%saline solution versus Plasma-Lyte® Comparison

To determine whether, when compared with 0.9% sodium chloride, the use of a balanced crystalloid solution (Plasma-Lyte®) can decrease mortality in 90 days in seriously ill patients with high risk for acute kidney injury.

Comparison of slow infusion versus fast infusion

To determine the effect of rapid (999 ml/h) versus slow (333 ml/h) administration of crystalloid solution para volume expansion on mortality in 90 days of seriously ill patients.

Secondary and tertiary (exploratory) objectives

Additional secondary objectives for both interventions include assessing the impact of interventions on the occurrence of kidney damage requiring kidney replacement within 90 days; the incidence of KDIGO stage 2 or 3 acute kidney injury at 3 and 7 days after randomization; incidence of liver, cardiac, neurological, coagulation and respiratory system dysfunction (using SOFA score) on days 3 and 7 after randomization and days without mechanical ventilation on the 28 days after the patient entered the study.

As tertiary objectives, we will assess mortality in the ICU, length of stay in the ICU and in the hospital.

Additionally, we will assess quality of life six months after discharge from the ICU in a sample equivalent to 10% of the total number of patients included through the EQ-5D-3L questionnaire (49).

Methods

Outline

The BaSICS study (*Balanced Solution in Intensive Care Study*) is a randomized, pragmatic, multicenter, 2x2 factorial, data recording-based and patient- and healthcare staff-blinded study. The study will compare two resuscitation therapies with fluids in a factorial manner in critically ill patients admitted to Intensive Care Units (ICUs). The study is expected to recruit about 11,000 patients in at least 70 Brazilian ICUs for 36 months. Eligible patients must be randomized to receive 0.9% saline or balanced solution (Plasma-Lyte®) and factorially for infusion speeds of 999 ml/h or 333 ml/h and will be evaluated during 90 days after randomization .

The protocol for this study follows the recommendations of the *SPIRIT 2013 Statement.*

Study Sites

The participation of at least 70 Brazilian ICUs will be necessary, including at least 16 patients per month for 36 months to recruit this sample size.

Eligibility

Inclusion Criteria

Patients admitted to the ICU who have an indication of receiving intravenous fluids for expansion or maintenance of intravascular volume will be included. To be randomized for the study, patients must meet the following three inclusion criteria concurrently:

1. A. Need for volume expansion as defined by the attending physician, with no specific indications or contraindications for any of the fluids, or for fast or slow speed.
2. Patients with no discharge plan on the day following admission.
3. At least one of the following risk factors for acute kidney injury:

a. Age > 65 years

b. Hypotension (MBP < 65mmHg or SBP < 90mmHg) or use of vasopressors

c. Sepsis, defined by the SEPSIS criteria 3 (50)

d. Use of invasive mechanical ventilation for any period **or** non-invasive (including high-flow nasal cannula) continuous for more than 12 hours.

e. Oliguria (< 0.5 ml/kg/hour for ≥ 3 hours)

f. Creatinine ≥ 1.2 mg/dl (women) or ≥ 1.4 mg/dl (men)

g. Liver cirrhosis or failure

Exclusion Criteria

The following exclusion criteria will be applied:

1. Age < 18 years

2. Kidney failure under renal replacement therapy or with expectation of requiring renal replacement therapy in the next six hours

3. Severe hyponatremia (serum Na ≤ 120 mmol/L)

4. Severe hypernatremia (serum Na ≥ 160 mmol/L)

5. Death considered imminent and inevitable within 24 hours

6. Patients with suspected or confirmed brain death

7. Patients under exclusive palliative cares

8. Patient previously included in the BaSICS study

Interventions

Eligible patients who require volume replacement therapy will receive the study fluid, Plasma-Lyte® or 0.9% saline at infusion speeds of 999 ml/h or 333 ml/h, according to randomization, in quantity and frequency of administration determined by the attending physician (Figure 1). In the case of infusion of maintenance serum, the study drug should be used at the speed typically applied for this purpose (40-120 ml/h, depending on the service). When possible, medications and solutions whose active ingredient is also compatible with 0.9% saline or Plasma-Lyte® (for example, sedative drugs, vasopressors and antibiotics) will be infused according to the study group (Figure 1). Guidelines will be proposed to investigators to indicate fluid infusion (Chart 3). A list of drugs compatible with Plasma-Lyte® is given in Appendix 1. Appendix 2 suggests medications that can be safely diluted in both Plasma-Lyte® and saline solution, and these medications should be diluted in the study fluid whenever possible.

The type of therapy (type of fluid and speed) to which the patient is allocated will be used in all episodes of fluid resuscitation during his stay in the ICU. As much as possible, volume replacement therapy with crystalloid solution during investigations and procedures performed outside the ICU will be with the designated study fluid. However, clinicians should be aware of special situations in which Plasma-Lyte® or 0.9% saline solution is contraindicated, in which the study fluid should not be used (Chart 4). In addition, regarding the use of study fluids, a list of medications compatible with both solutions will be provided to the sites so that their dilution is carried out according to the randomization group. In situations of imminent risk (Chart 5), the patient will be able to receive fluids at rapid flow (999 ml/h) regardless of the speed group to which he is randomized.

Figure 1. Administration of intravenous fluids during the BaSICS study.

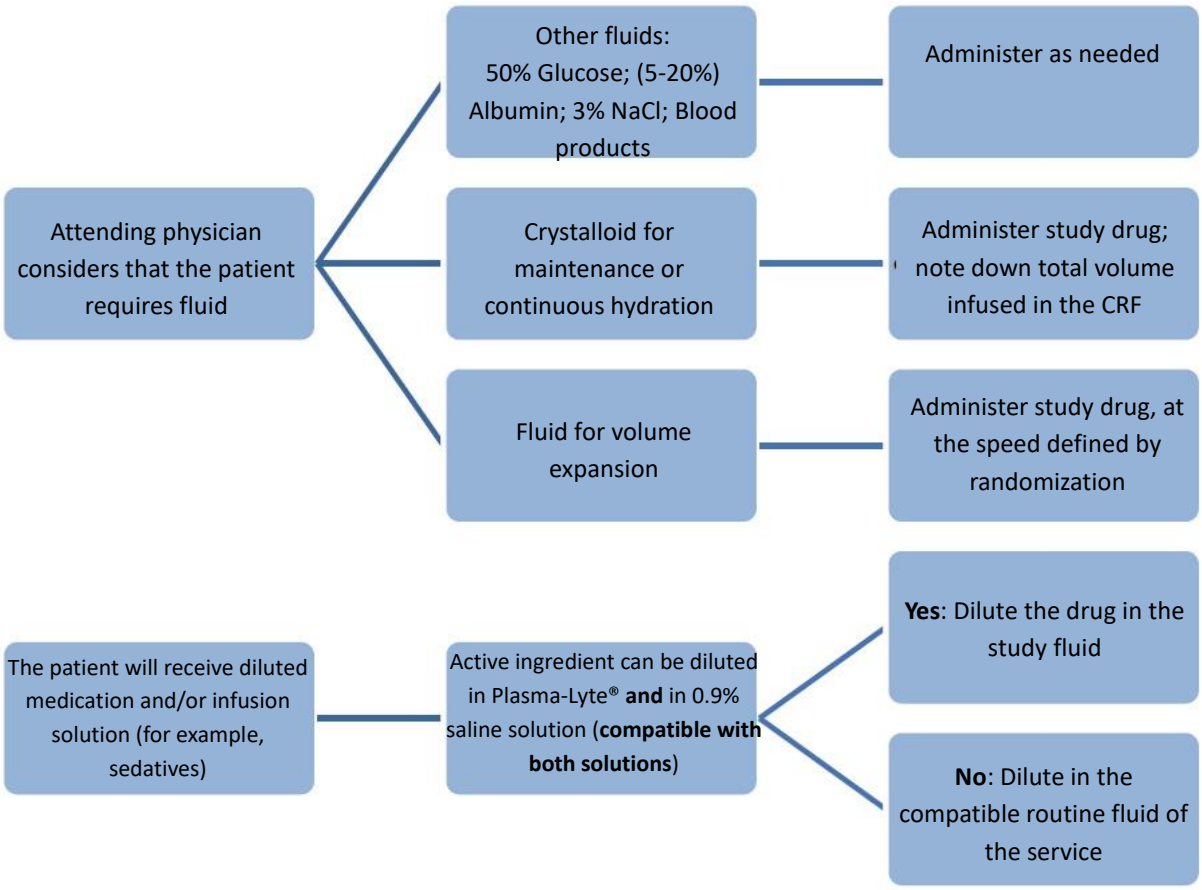

Chart 3. Guidelines for indicating plasma expansion by fluid infusion

Volume replacement is suggested in the presence of the following criteria:

1. At least a sign of hypoperfusion:
   - Heart rate > 120 bpm
   - SBP < 90 mmHg or MBP < 65 mmHg or SBP drop of at least 40 mmHg in relation to baseline levels
   - Capillary filling time> 1s
   - Mottling score ≥ 2
   - Lactate > 2mmol/L (> 18 mg/dl)
   - ScvO2 <70%
   - Drop in urine output, with <0.5 ml/kg in the last hour

2. And at least a sign of fluid responsiveness or no signs of hypervolemia:
   - Pulse pressure variation> 13%
   - Pulse pressure increase> 5% after 15s expiratory pause
   - Passive elevation of the lower limbs leads to an increase in the cardiac index (> 10%), pulse pressure (> 11%) or mean arterial pressure (> 5%)
   - Respiratory variation of central venous pressure > 1 mmHg
   - Echocardiographic signs of hypovolemia
   - Central venous pressure ≤ 8 mmHg
   - Absence of clinical signs of hypervolemia when the above signs are not available

Chart 4. Situations in which the study fluids should not be administered:

Severe hyperchloremia (Cl ≥ 120 mmol/L)
Severe hypernatremia (Na ≥ 160 mmol/L)
Severe hyponatremia (Na ≤ 120 mmol/L)

Chart 5. Situations where the fluids could be administered rapidly (999 ml/h):

Situation 1
Severe hypotension (systolic pressure below 80 mmHg or mean arterial pressure below 50 mmHg)
OR
Situation 2
Diagnosis of hemorrhagic shock with active bleeding requiring aggressive fluid replacement

The indication of the beginning of renal replacement therapy will be in charge of each site. However, we will suggest to sites that consider criteria (Chart 6) as indicative of the need to start renal replacement therapy. The mode of therapy and its intensity will also be at the discretion of the site.

Chart 6. Indications for starting renal replacement therapy (adapted from (51)):

Kidney failure KDIGO 2 or 3 (41), together with one of the following:

- Serum potassium above 6 mEq/L
- pH < 7.15 in the context of pure metabolic acidosis or mixed acidosis with (PaCO2 above 50 mmHg without the possibility of an increase in minute volume)
- Hypervolemia with respiratory impairment, requiring oxygen supply of more than 5 L/min (patients on spontaneous ventilation) or inspired oxygen fraction above 50% (for patients on mechanical or non-invasive ventilation)
- Serum urea above 240 mg/dl

It is important to note that both interventions that will be tested by the present study are commonplace in clinical practice. As previously mentioned, balanced (such as Plasma-Lyte®) and unbalanced (such as NaCl 0.9%) fluids are routinely used in critical medicine, with variations in use largely due to availability and local preferences. Likewise, the fluid infusion rate also shows great variability. Thus, although this study evaluates two relevant issues, it does not represent any significant deviation from the usual practice of intensive care units.

We plan to evaluate the evolution of serum chlorine values in a convenience sample among the patients included in the study, considering data only from sites that collect routine serum chlorine in their ICU. We estimate a size of approximately 1000 patients within this convenience sample.

Endpoints

The outcomes for both factorial arms of the study (Plasma-Lyte® versus 0.9% NaCl and slow versus fast crystalloid infusion) are identical:

Primary endpoint:

- Death in 90 days

Secondary endpoints:

- Kidney failure requiring renal replacement therapy in 90 days
- Kidney injury KDIGO > 2 (51) on days 3 and 7 after randomization. For the diagnosis of kidney injury we will consider serum creatinine and diuresis: Serum creatinine ≥ 2.0 times the reference values or diuresis below 0.5 ml/kg/h on daily average. In case diuresis value isn't available, creatinine value will be used. The reference creatinine will be the lowest between randomization creatinine and previous creatinine (the oldest available in the last six months and prior to current admission). If there is no previous creatinine available, we will estimate its value using the MDMR equation:

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

Where F= 0,742 (female patients) and N = 1,21 for black patients

- If, at the time of randomization, the patient already has KDIGO 2 criteria, it will not be counted as part of the sample to assess this outcome.
- New respiratory, hepatic, cardiac, neurological and coagulation dysfunction (using SOFA score) on days 3 and 7 (52).
- Mechanical ventilation-free days during the first 28 days after randomization.

Tertiary endpoints (exploratory):

- Death by any cause at the ICU and hospital
- Length of stay at the ICU
- Duration of hospitalization

Other exploratory endpoints:

- Comparison of serum chlorine values between the four possible study groups over time.
- Quality of life assessment through EQ-5D-3L questionnaire in six months, to be conducted in sample of approximately 10% of the patients, obtained randomly

Time sequence

The study visits and the variables collected at each visit are described below:

Day 0: Tracking, randomization and baseline data

- Verification of inclusion and exclusion criteria
- Obtainment of the ICF
- Randomization
- Reason for non-randomization of eligible patients
- Time between ICU admission and randomization
- Quantity and type of fluids administered 24 hours before randomization
- Date of birth
- Gender
- Weight (checked with balance)
- Height
- Origin of the patient (operating room [elective and emergency surgery], emergency room, ward, another hospital (excluding other ICU), other ICU)
- Comorbidities (APACHE II variables)
- APACHE II score
- SOFA score (52)
- Creatinine on admission to the ICU
- Serum chlorine and other laboratory tests, if available
- Dose of vasopressors (mcg/Kg/min) administered at randomization
- Inotropic dose (mcg/Kg/min) administered at randomization
- Mode of ventilation support at the time of randomization

Daily data from Day 1 to Day 3 and on Day 7

- Quantity and speed of infusion of administered study fluids
- Total fluid volume infused during the day
- Fluid balance
- Diuresis
- Serum creatinine
- Serum chlorine, if available, only in sites that routinely collect serum chlorine level
- Use of red blood cell concentrate
- SOFA score, broken down by component (52)

Data at ICU discharge

- Date of discharge from the ICU (or death)
- Vital status at discharge from the ICU

Hospital discharge

- Date of hospital discharge (or death)
- Vital status at hospital discharge
- Reasons (based on Table 6) to initiate renal replacement therapy
- Number of days on mechanical ventilation during hospital stay

90-day data:

- Vital state in 90 days
- Use of renal replacement therapy (dialysis) in the period

The 90-day data will be collected by a single telephone exchange that will contact the patient, his legal representative or family member.

Data in six months:

- – Short quality of life assessment, through EQ-5D-3L questionnaire (in 10% of the total patient sample)

Randomization

The randomization list will be generated electronically using appropriate software. Randomization will be carried out in blocks (blocks of 12 patients) stratified by center and will be factorial for the two interventions performed.

The confidentiality of the randomization list will be maintained through a centralized, automated, internet-based randomization system, available 24 hours a day, developed by a team of programmers and researchers from the Research Institute of Hospital do Coração (IP-HCor).

The group to which the patient will be allocated will only be released after registration of the information in the electronic system, which prevents the investigator and the assistant team from predicting which of the treatment groups the patient will be allocated to. To include the patient in the study, the researcher simply has to access the study website (https:// http://basics.hcor.novatela.com.br/Entrar/Login) and fill out a simple clinical form.

Blinding

Regarding the type of fluid to be used, there will be complete blinding (double-blind in patients, health teams, researchers, data collectors, outcome validators and statisticians responsible for the analysis of the results). For technical reasons, it is impossible to carry out blinding at the rate of infusion at which the patient will be randomized, so that this intervention will remain open to those involved with the care of the patient.

For blinding the fluid solution, the treatments available in this study (Plasma-Lyte® and 0.9% saline) will be macroscopically similar and will be available in identical 500 ml plastic containers. These containers will be manufactured blinded.

Data collection and management

We will use data collected routinely in the intensive care unit through a digital database, with easy access via the Internet. This strategy reduces the burden on care teams at participating sites, since data are already collected routinely, and minimizes costs related to data collection (53).

Several procedures will guarantee the quality of the data, including:

1) All researchers will participate in a training session before the start of the study to ensure consistency of the study procedures, including data collection;

2) Researchers will be able to call the study's Coordinating Site to resolve issues or problems that may arise;

3) Data cleansing to identify inconsistencies will be conducted periodically (approximately every fifteen days). The sites will be notified of inconsistencies in order to provide correction;

4) Statistical techniques for identifying fraud will be performed throughout the study;

5) The Coordinating Site will review detailed reports on screening, inclusion, follow-up, consistencies and data completeness on a monthly basis. It will immediately take action to resolve any problems.

6) Monitoring at the sites will be carried out during the conduct of the study to sample the sites, particularly if there are special needs due to the accumulation of inconsistencies or missing data. A trained professional will be appointed by the Coordinating Site to monitor participating sites. All information during the monitoring visits will be treated in a strictly confidential manner.

Monitoring

Data monitoring

A Data Monitoring Committee (DMC) will be formed by epidemiologists and interventionists independent of the study's investigators.

The DMC is responsible for providing guidance to the Steering Committee on continuing the study as planned or stopping recruitment based on evidence that the intervention of the experimental group results in increased mortality compared to control. At the beginning of its activities, the DMC must prepare a booklet specifying the details of the formation of the DMC, its operation, meetings and interruption rules. In any case, the rules of the booklet should be guided by the principles described below.

Interim analyzes will be performed after approximately 25%, 50% and 75% of the sample size has been recruited. In the light of these interim analyzes and, eventually, external evidence, the Data Monitoring Committee should assess whether there is evidence beyond reasonable doubt that one of the interventions is clearly contraindicated for all patients, or for any subgroup.

The criterion of evidence beyond reasonable doubt is an increase in mortality or incidence of acute kidney injury requiring renal replacement therapy in the Plasma-Lyte® group compared to the 0.9% sodium chloride group, with a P <0 , 01 or an increase in mortality in the slow versus fast group with p <0.01. Data Monitoring Committee members may consider requesting a continuation of the study for an additional three months to confirm the effect (particularly if P value between 0.01 and 0.001). If the safety criterion is reached in one of the factors analyzed in the study, the corresponding factor arm will be stopped and the study will continue with the remaining factor arm.

If there is evidence of superiority of Plasma-Lyte® compared to sodium chloride, or slow infusion compared to fast, with a P value <0.001 after an interim evaluation of 50% or more patients, DMC may also consider interrupting the study. However, you must request continuation for another three months and repeat the analyzes to confirm the difference between treatments and, mainly, allow stabilization of the effect estimates (aiming to avoid an estimate of the effect at a *"random high"* moment).

The study should not be interrupted for benefit in the first interim analysis (with 25% of patients). The reasons for this decision are: 1) The early interruption of randomized studies for benefit tends to produce biased effect estimates (overestimating the true effect), and may lead medical guidelines and decision makers to error, particularly with low numbers of events. (54); 2) Following the ethical principle of non-maleficence, a new treatment should not be used until there is clear

objective evidence that it is beneficial; 3) Clinical practice does not usually change unless there is sufficiently convincing evidence of the advantages of the new treatment, which would be weakened if the study is stopped early for benefit (55).

Safety

Unexpected serious adverse events directly related to the study should be reported. Unexpected serious adverse events directly related to the study are defined as adverse events that meet the following two criteria:

1) Any fatal or life-threatening event (immediate risk of death) or that leaves a sequel or permanent disability or that prolongs hospitalization; **AND**

2) The attending physician believes that the event is related to inclusion in the BaSICS study.

Serious adverse events will be considered "study related" if the attending physician judges that the event was probably caused by the study fluid and / or infusion rate and follows a plausible time sequence since the administration of the study fluid

Audit

We do not foresee carrying out an audit of the participating sites beyond the usual monitoring of the sites.

Statistical methods

Sample size and recruitment strategies

We will include 11,000 patients. We estimated 35% day mortality and acute kidney injury requiring renal replacement therapy around 15% in the control group by applying the eligibility criteria of our study to the ORCHESTRA study database (56) and based on data from the CHECKLIST study (57).

With regard to the type of fluid, the study will have a statistical power of 89% to detect a 10% reduction in the relative risk of mortality in 90 days, considering a 90% mortality in 35 days. Regarding the rate of infusion, the study will have 89% power to detect a 10% relative reduction in the risk of death in 90 days, considering an incidence of 35% in the 0.9% sodium chloride group. Both α are 0.05.

We do not foresee interaction between the effects of the study's factorial arms, however, if there is an interaction, we will have a power of 80% to detect a risk ratio of 0.835 between interventions and a power of 90% to detect a risk ratio of 0.80 (i.e. twice the estimated effect for the main interactions). We plan to recalculate the sample size value after including the first 1000 patients in order to adjust the number of patients to be included according to the incidence of events in our population.

Statistical analysis

Detailed statistical analysis plan will be drawn up before the inclusion of patients begins. The fundamental characteristics of the statistical analysis plan are described below.

All analyses will follow the intent to treat principle. We will evaluate the effect of Plasma-Lyte® compared to 0.9% sodium chloride and the effect of the two infusion rates on the primary outcome using a *hazard ratio* with a 95% confidence interval and comparison of Kaplan-Meier curves (using the log rank test). For binary secondary endpoints we will perform the comparison using relative risks, 95% confidence intervals and chi-square tests. For continuous outcomes with normal distribution, we will present the medical difference, 95% confidence interval and P value calculated by *t* test. For continuous endpoints with asymmetric distribution, we will perform the Wilcoxon test.

We will analyze the effect of the fluids under study on primary outcomes according to the following subgroups:

- Sepsis patients (50).
- Patients with baseline acute kidney injury (KDIGO Stage 1)
- Surgical patients
- Patients with cranioencephalic trauma
- APACHE II $\geq$ 25 or < 25 points
- Patients that received > 1000 ml of sodium chloride in 24 hours prior to randomization versus ≤ 1000 ml

- – We will also evaluate the effect of Plasma-Lyte® versus sodium chloride in patients who have received> 6,000ml of fluids during the first 3 days. This analysis will be considered merely exploratory, once these subgroups cannot be defined initially (at the moment of randomization).

Ethics and dissemination

Ethics committee approval

Before beginning the study, the investigator must forward a copy of the protocol, the informed consent form and other requested statements, to the Local Ethics Committee of his Institution (LEC). A protocolized referral letter and the LEC approval letter, when approved, must be sent to the Study Coordinating Site.

Amendments

All eventual amendments to the protocol must be approved by the LEC of each participating site

Consent

Written consent will be requested from all eligible patients or their legal/family representative when the patient's clinical conditions such as cognitive impairments or communication limitations (e.g. patient on mechanical ventilation) do not allow for direct obtaining (mechanical ventilation, sedation).

Regarding the process of obtaining the consent form for this study, we consider that: 1) the study intervention, volume expansion with crystalloid for seriously ill patients, is administered on an emergency basis in almost all cases, with no possibility of delays. 2) in most Brazilian ICUs, family members remain in the unit for limited periods of time (1 to 2 times a day), therefore, they are not immediately available for the consent process. 3) Plasma-Lyte® and 0.9% saline solution are routinely used in clinical practice with exactly the same indications and without robust evidence of differences in clinical effect. 4) the fluid prescription standard worldwide is very variable and reflects regional preferences because there is no good clinical evidence (e.g. 60% of expansions with crystalloids in Brazil are carried out with 0.9% saline solution and the remainder with balanced solutions, while more than half of the time balanced solutions are used in other countries). 5) there is no consensus

on the speed of infusion that should be used in critically ill patients or data that justify or refute any of the chosen speeds 6) the national resolution 466 of 2012, in section III, subsection 2, item “g”, provides "*to obtain the free and clarified consent of the research patient and/or his legal representative, even in cases of researches that, for its nature, may imply justifiably, in consent a posteriori;”* In view of the above, we reinforce that the process of obtaining consent will be carried out in all cases, without exception. Investigators in the BaSICS study are committed to obtaining the consent form before the patient's inclusion in the study, whenever possible. However, we understand that in several cases it is fully justified and it will only be possible to obtain consent *a posteriori.* If the patient is unable to consent to his participation, the term will be obtained as quickly as possible, either through his family member / legal representative or the patient himself, when able to consent.

The consent request and the pertinent study information provided to the legal representative must be conducted by the principal investigator, co-investigator or the study coordinator. The patient's legal representative and the research professional assigned to obtain the consent must date and sign two copies of the informed consent form, one copy of which must be delivered to the patient's legal representative and one copy must be filed with the other study documents. It will be clearly exposed to the patients' legal representatives that their participation is voluntary and may withdraw from the study at any time without any implication in the quality and conduct of the subsequent medical treatment. The ICF proposed by the study must be evaluated by each research site and, if there is a need for changes, these must be approved by the Study Coordinating Site before submission to LEC.

Confidentiality

Only the data necessary to perform the follow-up after 90 days of discharge will be made available to the Study Coordinating Center, such as name and phone number, the rest of the information is confidential and will be kept confidential by the participating center. The electronic data collection form will identify the patient and the investigating site by the corresponding number. The data obtained from the medical record must be kept confidential by the research sites, in cabinets with restricted access and the guarantee of anonymity of all data in provisional and definitive reports will be ensured.

Statements of interests

The members of the Steering Committee declare that it does not present conflicts of interest.

Database sharing

We intend to open access to the study database for other researchers. In the first two years after the publication of the main manuscript, researchers will dedicate themselves to conduct analyzes for sub-studies proposed by researchers in the collaborative group. In this phase, the database will be kept under the guardianship of the study coordinators, and its access will be allowed to third parties only by express authorization of the BaSICS Study Steering Committee after the proposal evaluation accompanied by a statistical analysis plan. The Steering Committee should grant access to the requested data as long as the proposal does not conflict with planned or ongoing sub-studies by researchers from the BaSICS collaborative group. After a period of two years, all data collected by the BaSICS study will be made available to the public on a free platform. We emphasize that no data that allows the future identification of the patient such as initials, date of birth, among others, will be publicly available after the period of two years. Each individual who requests access to the database must formally undertake to notify the study's steering committee of any information that allows the patient to be identified in the database.

Dissemination policies

The BaSICS Study Steering Committee undertakes to publish its results, whatever they may be. As it is a large-scale collaborative randomized study, we aim to send the main publications to high impact journals.

We intend to submit two main manuscripts, one on the effects of Plasma-Lyte® compared to 0.9% sodium chloride, and the other on the effects of slow infusion versus rapid infusion of fluids.

Both manuscripts will be submitted on behalf of the research group (BaSICS Investigators) and this is the name that should appear on the title page of the manuscript when it is published. The research group for each of the studies will be composed of the main Steering Committee of the BaSICS study plus the researchers from the sites that recruit the greatest number of patients. Researchers from all participating sites (two to three per institution) who have included at least 30 patients will

be listed at the end of publications or in supplementary material, depending on the editorial policy of each journal. The listing will occur in alphabetical order of the sites.

Suggestions of topics for sub-studies and secondary publications, as well as the inclusion of individual data for meta-analyzes, should be sent by the researchers to the Steering Committee, which will evaluate the proposal and may approve it, suggest improvements or reject it. The evaluation will be conducted based on scientific merit and the participation of researchers for the success of the main study.

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Appendix 1 - List of compatibility with Plasma-Lyte®:

This list of compatibility of Plasma-Lyte® is a literal translation of the document obtained by the investigators of the Study PLUS (ANZICS) that evaluated the compatibility of Plasma-Lyte® with a series of drugs for routine use at the intensive care unit.

The solution:

Plasma-Lyte® 148 pH 7.4 is a crystalloid solution composed of various electrolytes, including *buffers*; consult the composition below[1]:

Component	Na_+ mEq/L	K_+ mEq/L	Cl_- mEq/L	Mg_{2+} mEq/L	$C_2H_3CO_2$ Acetate mEq/L	$C_6H_{12}O_7$ Gluconate mEq/L
mEq/L	140	5	98	3	27	23
mmol/l	140	5	98	1.5	27	23

Plasma-Lyte® 148 pH 7.4 is indicated as source of water and electrolytes or as alkalizing agent1. During the administration of Plasma-Lyte® 148 pH 7.4, it may be necessary to administer different drugs through Y infusion. Baxter ordered a study aiming to evaluate the physical compatibility of Plasma-Lyte 148 pH 7.4, with range of drugs commonly used in the surgical block/center and in intensive cares. The study was conducted by an independent agency in facilities audited by the Food and Drug Administration (FDA), a North American food and drug control department, and by the Therapeutic Goods Administration (TGA), an Australian regulatory agency, in order to comply with the global quality standards.

The study:

Plasma-Lyte® 148 pH 7.4 was tested with 87 drugs in terms of physical compatibility (appearance and turbidity) immediately after being mixed and also 1 and 4 hours after mixing. Plasma-Lyte® 148 pH 7.4 was mixed in a 1: 1 ratio with each tested drug to stimulate Y^2 administration.

Compatibility was determined by:

1. Visual examinations performed in the laboratory with normal diffused fluorescent light.

2. Turbidity measured with high intensity unidirectional light using a portable turbidimeter model 2100P (Hach).

Definition of compatibility

Previous studies by Lawrence Trissel et al. indicated that incompatibility can be defined by the visible particulate material, opacity or change in turbidity in relation to control solutions[3]. An increase in turbidity of 0.5 nephelometric turbidity units (NTU) or more in relation to baseline values was previously identified as an incompatibility criterion[4].

Results:

The study results indicate that the following drugs are compatible, based on visual observation and on turbidity.

Drug	Manufacturer	Tested Concentration
Acyclovir	Hospira	25 mg/ml
Tranexamic acid	Pfizer	100 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
Caspofungin	MSD	70 mg/100 ml
Cefazolin	Hospira	2000 mg/50 ml
Cefoxitin	Hospira	20 mg/ml
Ceftazidime	Hospira	100 mg/ml
Cyclophosphamide	Baxter	8 mg/ml
Ciprofloxacin	Bayer	2 mg/ml

Drug	Manufacturer	Tested Concentration
Clindamycin	Pfizer	900 mg/50 ml
Clonidine	Boehringer Ingelheim	20 mcg/ml
Calcium Chloride	Baxter	40 mg/ml
Potassium Chloride	Baxter	0.5 mmol/ml
Lidocaine Hydrochloride	Pfizer	8 mg/ml
Cloxacillin	Teva	100 mg/ml
Dexamethasone	Aspen	4 mg/ml
Digoxin	Aspen	0.25 mg/ml
Potassium dihydrogen phosphate	Baxter	0.5 mmol/ml
Dobutamine	Hospira	5 mg/ml
Dopamine	Hospira	3.2 mg/ml
Ephedrine	Hospira	5 mg/ml
Ergometrine	Hospira	200 mcg/5ml
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
Furosemide	Sandoz	10 mg/ml
Gentamicin	Pfizer	10 mg/ml

Drug	Manufacturer	Tested Concentration
Glycopyrrolate	Aspen	0.2 mg/ml
Calcium Gluconate	Baxter	40 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
NovoRapid Insulin	Novo Nordisk	1 units/ml
Isoprenaline	Hospira	1 mg/100 ml
Labetalol	Sandoz Canada	5 mg/ml
Lincomycin	Pfizer	2 mg/ml
Meropenem	Hospira	40 mg/ml
Metaraminol	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
Moxifloxacin	Bayer	1.6 mg/ml
Naloxone	Hospira	0.4 mg/ml
Neostigmin	AstraZeneca	0.5 mg/ml

Drug	Manufacturer	Tested Concentration
Sodium Nitroprusside	Hospira	0.6 mg/ml
Noradrenaline	Hospira	16 mg/100 ml
Oxytocin	Aspen	1 units/ml
Ondansetron	GSK	1 mg/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
Protamine	Sanofi	10 mg/ml
Ketamine	Hospira	2 mg/ml
Rocuronium	Hospira	10 mg/ml
Salbutamol	GSK	0.05 mg/ml
Syntometrine	Novartis	1 ml/4 ml
Sugammadex	MSD	25 mg/ml
Magnesium Sulfate	Baxter	0.4 mmol/ml
Morphine Sulfate	Hospira	1 mg/ml
Suxamethonium	AstraZeneca	2 mg/ml
Thiopentone	Link	50 mg/ml
Tramadol	Sandoz	50 mg/ml
Trimethoprim/Sulfamethoxazole	Hospira	1 mg/25 ml
Glyceryl Trinitrate	Hospira	30 mg/50 ml

Drug	Manufacturer	Tested Concentration
Vancomycin	Hospira	20 mg/ml
Verapamil	Abbott	2.5 mg/ml
Voriconazole	Pfizer	5 mg/ml

It was observed visually that the following drugs were clear and colorless fluids, but turbidity increased by more than 0.5 NTU in relation to the moment immediately after mixing (baseline value).

Drug	Manufacturer	Tested Concentration	Observation
Pantoprazole	Sandoz	800 mcg/ml	0.68 NTU immediately after mixing, 0.86 NTU after 1 hour and 1.50 NTU after 4 hours
Phenytoin	Hospira	50 mg/ml	0.18 NTU immediately after mixing, 0.19 NTU after 1 hour and 0.72 NTU after 4 hours

It was observed visually that the following drugs underwent changes when mixed, but there was a change by less than 0.5 NTU in turbidity in relation to the moment immediately after mixing (baseline value).

Drug	Manufacturer	Tested Concentration	Observation
Amiodarone	Sanofi	9 mg/ml	Foam on the top part of the clear and colorless fluid immediately after mixing and 1 hour afterwards. Less foam after 4 hours.

Cyclosporine	Sandoz	2.5 mg/ml	Clear and colorless fluid, formation of bubbles inside the solution with the addition of physiological serum. The bubbles continued after 1 and 4 hours.

Changes were observed in visual appearance of the following drugs immediately after mixing and an increase in turbidity by more than 0.5 NTU in relation to the moment immediately after mixing (baseline value).

Drug	Manufacturer	Tested Concentration	Observation
Mofetil Mycophenolate	Roche	6 mg/ml	White and turbid fluid immediately, 1 hour and 4 hours after mixing. 640 NTU immediately after mixing, > 1000 NTU after 1 hour and 809 NTU after 4 hours.
Propofol	Sandoz	10 mg/ml	Milky fluid immediately, 1 hour and 4 hours after mixing. Number of NTU above the normal range immediately, 1 hour and 4 hours after mixing.

References

1Plasma-Lyte 148 SPC, ANZ

2 Allen LV, Levinson RS, Phisutsinthop D. Compatibility of various admixtures with secondary additives at Y- injection sites of intravenous administration sets. Am J Hosp Pharm. 1977; 34:939-943

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4Trissel LA, Martinex JF. Compatibility of pipercillin sodium plus Tazobactam with selected drugs during simulated Y-site injection. Am J Hosp Pharm. 1994; 51:672-678

Appendix 2 – Simplified list of drugs compatible with Plasma-Lyte® and Saline Solution and that can be diluted in the study fluid, together with its maximum concentration:

Sedative and Analgesic Drugs	Antibiotic and Antimicrobial Drugs
Midazolam 1 mg/ml	Vancomycin 20 mg/ml
Fentanyl 10 mcg/ml	Piperacillin/Tazobactam 4500 mg/50 ml
Ketamine 2 mg/ml	Meropenem 40 mg/ml
Thiopentone 50 mg/ml	Imipenem 5 mg/ml
Morphine Sulfate 1 mg/ml	Amikacin 40 mg/ml
Vasopressors and Vasodilators	Gentamicin 10 mg/ml
Norepinephrine 16 mg/100 ml	Cefazolin 2000 mg/50 ml
Dobutamine 5 mg/ml	Ceftazidime 100 mg/ml
Dopamine 3.2 mg/ml	Ciprofloxacin 2 mg/ml
Epinephrine 12 mg/100 ml	Moxifloxacin 1.6 mg/ml
Sodium Nitroprusside 0.6 mg/ml	Trimethoprim/Sulfamethoxazole 1 mg/25 ml
Milrinone 300 mcg/ml	Fluconazole 200 mg/100 ml
Esmolol 10 mg/ml	Voriconazole 5 mg/ml
Clonidine 20 mcg/ml	Clindamycin 900 mg/50 ml
Symptomatic Corticosteroids	**and others**
Dexamethasone 4 mg/ml	Ondansetron 1 mg/ml
Hydrocortisone 100 mg/2 ml	Metoclopramide 5 mg/ml
Anticoagulants	Esomeprazole 0.4 mg/ml
Heparin 1000 units/ml	Tramadol 50 mg/ml

For the BaSICS study, we recommend not to dilute anticonvulsants (except sedatives), antiarrhythmic or immunosuppressant drugs in the study fluid

Summary of changes between all protocol versions

Version Comparison – BASICS – Versions 1.2.2 to 1.4.1

PREVIOUS CONTENT		ALTERED CONTENT		Justification
Version 1.2.2		**Version 1.4.1**		**Justification**
Version Date: June, 2016		**Version Date: August, 2016**		
Synopsis				
Title	**Randomized, 2x2 factorial study to evaluate the effect of a balanced crystalloid solution compared to 0.9% sodium chloride, and rapid versus slow infusion, on the clinical outcomes of seriously ill patients**	Title	Randomized, 2x2 factorial study to evaluate the effect of a balanced crystalloid solution compared to 0.9% sodium chloride, and rapid versus slow infusion, on the clinical outcomes of seriously ill patients	Synopsis updated accordingly to protocol's new version
Outline	Randomized, pragmatic, multicenter, 2x2 factorial, data recording-based study. Serious ICU patients, of moderate to high risk for acute kidney injury, will be randomly assigned to receive a balanced crystalloid solution (Plasma-Lyte®) or 0.9% sodium chloride, and to receive rapid bolus crystalloids (999 ml/h) versus slowly (333 ml/h), when plasma expansion is required.	Outline	Randomized, pragmatic, multicentric, 2x2 factorial, data recording-based study. Serious ICU patients, of moderate to high risk for acute kidney injury, will be randomly assigned to receive a balanced crystalloid solution (Plasma-Lyte®) or 0.9% sodium chloride, and to receive rapid bolus crystalloids (999 ml/h) versus slowly (333 ml/h), when plasma expansion is required.	
Bias control	Secrecy of assignment with web-based randomization. Intent to treat analysis. Blinding of			

Version Comparison – BASICS – Versions 1.2.2 to 1.4.1

PREVIOUS CONTENT		ALTERED CONTENT		Justification
Version 1.2.2		**Version 1.4.1**		
Version Date: June, 2016		**Version Date: August, 2016**		
	patients and healthcare professionals to crystalloid solutions (balanced solution or 0.9% sodium chloride).	Biascontrol	Secrecy of assignment with web-based randomization. Intent to treat analysis. Blinding of patients and healthcare professionals to crystalloid solutions (balanced solution or 0.9% sodium chloride).	
Primary objectives	To determine whether, compared to 0.9% sodium chloride, a balanced crystalloid solution (Plasma-Lyte®) used for plasma expansion can decrease mortality and risk of kidney injury with need of renal replacement therapy in seriously ill patients and those at high risk of kidney injury within 90 days. To determine the effect of rapid (999 ml/h) versus slow (333 ml/h) administration of crystalloid solution on 90-day mortality in seriously ill patients.	Primary objectives	To determine whether, compared to 0.9% sodium chloride, a balanced crystalloid solution (Plasma-Lyte®) used for plasma expansion can decrease mortality in seriously ill patients and those at high risk of kidney injury within 90 days. To determine the effect of rapid (999 ml/h) versus slow (333 ml/h) administration of crystalloid solution on 90-day mortality in seriously ill patients.	
Inclusion criteria	The criteria below must be present: 1. Need for plasma expansion and the clinician considers that Plasma-Lyte® or saline is	Inclusion criteria	The criteria below must be	

Version Comparison – BASICS – Versions 1.2.2 to 1.4.1

PREVIOUS CONTENT **Version 1.2.2** **Version Date: June, 2016**	ALTERED CONTENT **Version 1.4.1** **Version Date: August, 2016**	Justification
equally appropriate for patients, with no specific indications or contraindications for any of the fluids, or for fast or slow speed. 2. Prediction of stay at the ICU for over 24 hours. 3. At least one of the following risk factors for acute kidney injury: a. Age ≥ 65 years b. Hypotension (MBP < 65mmHg or SBP < 90mmHg) or use of vasopressors c. Sepsis d. Use of invasive mechanical ventilation; or non-invasive (including high-flow nasal cannula) continuous> 12 hours	present: 4. Need for plasma expansion and the clinician considers that Plasma-Lyte® or saline is equally appropriate for patients, with no specific indications or contraindications for any of the fluids, or for fast or slow speed. 5. Patients with no discharge plan on the day following admission. 6. At least one of the following risk factors for acute kidney injury: h. Age ≥ 65 years i. Hypotension (MBP < 65mmHg or SBP < 90mmHg) or use of vasopressors j. Sepsis	

Version Comparison – BASICS – Versions 1.2.2 to 1.4.1

PREVIOUS CONTENT **Version 1.2.2** **Version Date: June, 2016**		ALTERED CONTENT **Version 1.4.1** **Version Date: August, 2016**		**Justification**
	e. Oliguria (<0.5 ml/kg/hour for ≥ 3 hours) f. Serum creatinine ≥ 1.2 mg/dl for women or ≥ 1.4 mg/dl for men g. Liver cirrhosis or acute liver failure		k. Use of invasive mechanical ventilation; or non-invasive (including high-flow nasal cannula) continuous > 12 hours l. Oliguria (<0.5 ml/kg/hour for ≥ 3 hours) m. Serum creatinine ≥ 1.2 mg/dl for women or ≥ 1.4 mg/dl for men n. Liver cirrhosis or acute liver failure	
Exclusion criteria	1. Age < 18 years 2. Kidney failure under renal replacement therapy or with expectation of requiring renal replacement therapy in the next six hours 3. Severe hyponatremia (serum Na ≤ 120 mmol/L) 4. Severe hypernatremia (serum Na ≥ 160 mmol/L) 5. Hyperkalemia (serum K ≥ 5.5 mmol/L) 6. Death considered imminent	Exclusion criteria	10. Age < 18 years 11. Kidney failure under renal replacement therapy or with expectation of requiring renal replacement therapy in the	

Version Comparison – BASICS – Versions 1.2.2 to 1.4.1

PREVIOUS CONTENT **Version 1.2.2** **Version Date: June, 2016**		ALTERED CONTENT **Version 1.4.1** **Version Date: August, 2016**	Justification
	and inevitable within 24 hours 7. Patients with suspected or confirmed brain death 8. Patients under exclusive palliative cares 9. Patient previously included in the BaSICS study	next six hours 12. Severe hyponatremia (serum Na ≤ 120 mmol/L) 13. Severe hypernatremia (serum Na ≥ 160 mmol/L) 14. Hyperkalemia (serum K ≥ 5.5 mmol/L) 15. Death considered imminent and inevitable within 24 hours 16. Patients with suspected or confirmed brain death 17. Patients under exclusive palliative cares 18. Patient previously included in the BaSICS study	
Study treatments	The treatments to be compared in the study are Plasma-Lyte® and 0.9% sodium chloride (both have identical appearance and will be packed in identical bottles), and fast (999 ml/h) versus slow (333 ml/h) infusion of these fluids.		
Study endpoints – Plasma-Lyte® versus 0.9%	Co-Primary endpoints: • Death in 90 days • Kidney failure requiring renal replacement therapy in 90 days Secondary endpoints: • Incidental kidney injury		
		Study treatments: The treatments to be compared in the study are Plasma-Lyte® and 0.9%	

Version Comparison – BASICS – Versions 1.2.2 to 1.4.1

PREVIOUS CONTENT Version 1.2.2 Version Date: June, 2016		ALTERED CONTENT Version 1.4.1 Version Date: August, 2016		Justification
sodium chloride	(KDIGO ≥ 2) on days 3 and 5 • Incidental hepatic, cardiac, neurological, coagulation and respiratory dysfunctions (using SOFA) on days 3 and 5 • Mechanical ventilation-free days in 28 days Tertiary endpoints (exploratory): • Death by any cause at the ICU and hospital • Length of stay at the ICU • Duration of hospitalization		sodium chloride (both have identical appearance and will be packed in identical bottles), and fast (999 ml/h) versus slow (333 ml/h) infusion of these fluids.	
Slow versus fast infusion study endpoints	Primary endpoint: • Death in 90 days Secondary endpoints: • Kidney failure requiring renal replacement therapy in 90 days • Incidental kidney injury (KDIGO ≥ 2) on days 3 and 5 • Incidental hepatic, cardiac, neurological, coagulation and respiratory dysfunctions (using SOFA) on days 3 and	Study endpoints: Plasma-Lyte® versus 0.9% sodium chloride	Primary endpoint: • Death in 90 days Secondary endpoints: • Kidney failure requiring renal replacement therapy in 90 days • Incidental kidney injury (KDIGO ≥ 2) on days 3 and 7 • Incidental hepatic, cardiac, neurological, coagulation and respiratory dysfunctions	

Version Comparison – BASICS – Versions 1.2.2 to 1.4.1

PREVIOUS CONTENT **Version 1.2.2** **Version Date: June, 2016**		ALTERED CONTENT **Version 1.4.1** **Version Date: August, 2016**	Justification
	5 • Mechanical ventilation-free days in 28 days Tertiary endpoints (exploratory): • Death by any cause at the ICU and hospital • Length of stay at the ICU • Duration of hospitalization	(using SOFA) on days 3 and 7 • Mechanical ventilation-free days in 28 days Tertiary endpoints (exploratory): • Death by any causeat the ICU and hospital • Length of stay at the ICU • Duration of hospitalization	
Data management	We will use data collected routinely from patients admitted to the ICU using a digital database accessible through the Internet. Data quality assurance will be done through central verification, aiming at complete and consistent data. The sites will receive periodic reports for the adequacy of potentially inconsistent or incomplete data.		
Sample size	Sample of 11,000 patients. Plasma-Lyte® versus 0.9% Sodium chloride: The study will have 82% power to detect a 15%	Study endpoints: Slow versus fast infusion Primary endpoint: • Death in 90 days Secondary endpoints: • Kidney failure requiring renal replacement therapy in 90 days • Incidental kidney injury (KDIGO ≥ 2) on days 3	

Version Comparison – BASICS – Versions 1.2.2 to 1.4.1

PREVIOUS CONTENT **Version 1.2.2** **Version Date: June, 2016**		ALTERED CONTENT **Version 1.4.1** **Version Date: August, 2016**		Justification
	relative reduction in the risk of kidney injury with need of dialysis in 90 days considering a 15% risk of the outcome in the 0.9% sodium chloride group. And will have 83% power to detect a 10% relative reduction in the risk of death in 90 days, considering a 35% risk in the 0.9% sodium chloride group. In both cases the α level is 0.025, considering the execution of Bonferroni-corrected hypothesis tests for the two primary endpoints, maintaining an overall α by 0.05. Fast vs slow infusion: The study will have 89% power to detect a 10% relative reduction in the risk of hospital death, considering a 25% risk in the 0.9% sodium chloride group, with α of 0.05.		and 7 • Incidental hepatic, cardiac, neurological, coagulation and respiratory dysfunctions (using SOFA) on days 3 and 7 • Mechanical ventilation-free days in 28 days Tertiary endpoints (exploratory): • Death by any cause at the ICU and hospital • Length of stay at the ICU • Duration of hospitalization	
Statistical analysis	All analyses will follow the intent to treat principle. We will evaluate the effect of Plasma-Lyte® compared to 0.9% sodium	Data management	We will use data collected routinely from patients admitted to the ICU using a digital database accessible	

Version Comparison – BASICS – Versions 1.2.2 to 1.4.1

PREVIOUS CONTENT Version 1.2.2 Version Date: June, 2016	ALTERED CONTENT Version 1.4.1 Version Date: August, 2016	Justification
chloride and the effect of the two infusion rates on the primary endpoints will be compared through a hazard ratio with a 95% confidence interval and comparison of Kaplan-Meier curves (using the log rank test). The P-value for the two co-primary endpoints will be adjusted by the Bonferroni equation. For binary secondary endpoints we will perform the comparison using relative risks, 95% confidence intervals and chi-square tests. For continuous outcomes with normal distribution, we will present the medical difference, 95% confidence interval and P value calculated by t test. For continuous endpoints with asymmetric distribution, we will perform the Wilcoxon test.	through the Internet. Data quality assurance will be done through central verification, aiming at complete and consistent data. The sites will receive periodic reports for the adequacy of potentially inconsistent or incomplete data. Sample size Sample of 11,000 patients. Plasma-Lyte® versus 0.9% Sodium chloride: The study will have 89% power to detect a 10% relative reduction in the risk of death in 90 days, considering a 35% risk in the 0.9% sodium chloride group. Fast vs slow infusion: The study will have 89% power to detect a 10% relative reduction in the risk of death, in 90 days, considering a 35% risk in the 0.9% sodium	

Version Comparison – BASICS – Versions 1.2.2 to 1.4.1

PREVIOUS CONTENT		ALTERED CONTENT		Justification
Version 1.2.2		**Version 1.4.1**		**Justification**
Version Date: June, 2016		**Version Date: August, 2016**		
			chloride group, with α of 0.05. Interaction: We do not consider a priori the existence of interactions between interventions. Regardless, we will have an 80% power to detect a risk ratio of 0.835 between interventions	
		Statistical analysis	All analyses will follow the intent to treat principle. We will evaluate the effect of Plasma-Lyte® compared to 0.9% sodium chloride and the effect of the two infusion rates on the primary outcome using a hazard ratio with a 95% confidence interval and comparison of Kaplan-Meier curves (using the log rank test). For binary secondary endpoints we will perform the comparison using relative risks, 95% confidence intervals and chi-square tests. For continuous outcomes with	

Version Comparison – BASICS – Versions 1.2.2 to 1.4.1

PREVIOUS CONTENT **Version 1.2.2** **Version Date: June, 2016**	ALTERED CONTENT **Version 1.4.1** **Version Date: August, 2016**	Justification
	points - Patients that received > 1000 ml of sodium chloride in 24 hours prior to randomization versus ≤ 1000 ml - Patients who have received > 6,000 ml of fluids during the first 3 days. This analysis will be considered merely exploratory, once these subgroups cannot be defined initially (at the moment of randomization).	
Page 16 Primary Objectives Section		
0.9% saline solution versus Plasma-Lyte® Comparison To determine whether, when compared with 0.9% sodium chloride, a balanced crystalloid solution (Plasma-Lyte®) used for plasma expansion can decrease	0.9% saline solution versus Plasma-Lyte® Comparison To determine whether, when compared with 0.9% sodium chloride, the use of a balanced crystalloid solution (Plasma-Lyte®) can decrease mortality in 90 days in seriously ill	BASICS is a 2x2 factorial trial. Previously, primary outcomes to type of fluid and infusion speed were different on the fact that for the type of fluid the need for renal replacement were coprimary outcome along with mortality. In this amendment to simplify factorial study analysis and taking in

Version Comparison – BASICS – Versions 1.2.2 to 1.4.1

PREVIOUS CONTENT **Version 1.2.2** **Version Date: June, 2016**	ALTERED CONTENT **Version 1.4.1** **Version Date: August, 2016**	**Justification**
mortality and occurrence of kidney injury with need of renal replacement therapy in 90 days in seriously ill patients with high risk for acute kidney injury.	patients with high risk for acute kidney injury.	consideration that mortality is a robust outcome with more interest, we'll keep 90 days mortality as the only primary outcome to both interventions.
Page 16 Primary Objectives Section		
Secondary and tertiary (exploratory) objectives For the speed of infusion, the occurrence of renal injury requiring renal replacement within 90 days is a secondary endpoint. Additional secondary objectives for both interventions include assessing the impact of interventions on the incidence of KDIGO stage 2 or 3 acute kidney injury at 3 and 5 days after randomization; incidence of hepatic, cardiac, neurological, coagulation and respiratory system dysfunctions (using SOFA score) on days 3 and 5 after randomization and mechanical ventilation-free days on the 28 days after the patient's enrollment in the study. As tertiary objectives, we will assess	Secondary and tertiary (exploratory) objectives Additional secondary objectives for both interventions include assessing the impact of interventions on the occurrence of kidney damage requiring kidney replacement within 90 days; the incidence of KDIGO stage 2 or 3 acute kidney injury at 3 and 7 days after randomization; incidence of liver, cardiac, neurological, coagulation and respiratory system dysfunction (using SOFA score) on days 3 and 7 after randomization and days without mechanical ventilation on the 28 days after the patient entered the study. As tertiary objectives, we will assess mortality in the ICU, length of stay in the ICU and in the hospital. Additionally, we will assess quality of life six months after discharge from the ICU in a	BASICS' secondary outcomes are now identical for both factorial groups. In the initial protocol, we planned to measure secondary outcome occurrence at days 3 and 5. However, we understand that this period was short. Therefore, we will evaluate organic damage outcomes (KDIGO 2 kidney injury and other organic damages) at days 3 and 7.

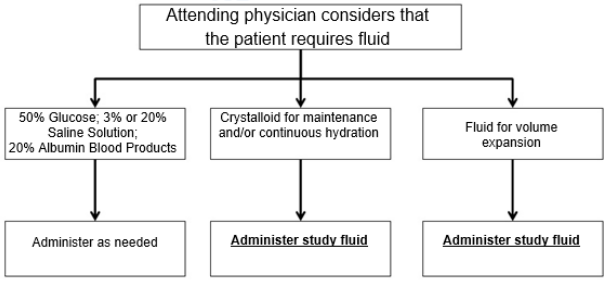
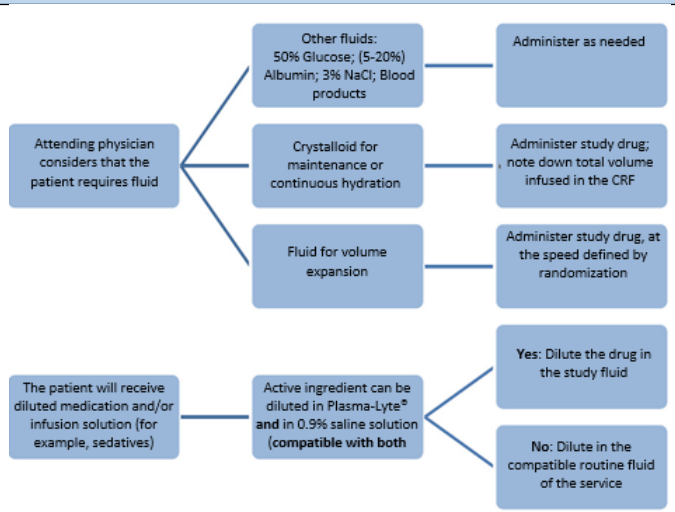
Version Comparison – BASICS – Versions 1.2.2 to 1.4.1

PREVIOUS CONTENT **Version 1.2.2** **Version Date: June, 2016**	ALTERED CONTENT **Version 1.4.1** **Version Date: August, 2016**	**Justification**
mortality in the ICU, length of stay in the ICU and in the hospital.	sample equivalent to 10% of the total number of patients included through the EQ-5D-5L questionnaire (49).	
Page 18 Interventions Section		
Eligible patients who require volume replacement therapy will receive the study fluid, Plasma-Lyte® or 0.9% saline at infusion speeds of 999 ml/h or 333 ml/h, according to randomization, in quantity and frequency of administration determined by the attending physician (Figure 1). In the case of infusion of maintenance serum, the study drug should be used at the speed typically applied for this purpose (40-120 ml/h, depending on the service). Anyway, guidelines will be proposed to investigators to indicate fluid infusion (Chart 3). The type of therapy (type of fluid and speed) to which the patient is allocated	Eligible patients who require volume replacement therapy will receive the study fluid, Plasma-Lyte® or 0.9% saline at infusion speeds of 999 ml/h or 333 ml/h, according to randomization, in quantity and frequency of administration determined by the attending physician (Figure 1). In the case of infusion of maintenance serum, the study drug should be used at the speed typically applied for this purpose (40-120 ml/h, depending on the service). When possible, medications and solutions whose active ingredient is also compatible with 0.9% saline or Plasma-Lyte® (for example, sedative drugs, vasopressors and antibiotics) will be infused according to the study group (Figure 1). Guidelines will be proposed to investigators to indicate fluid infusion (Chart 3).	Study fluid will always be used for volume replacement therapy in the absence of contraindications mentioned on the protocol. We also suggest in the initial protocol version that study fluid should be used whenever possible for maintenance infusions. However, study protocol did not mention which fluid should be used for medication infusion, which could make sites doubtful. This first amendment fulfils this deficiency, we highlight that medications can be diluted in saline or Plasma-Lyte®, according to the randomized intervention. A list with forementioned medications is available to assure adherence.

Version Comparison – BASICS – Versions 1.2.2 to 1.4.1

PREVIOUS CONTENT **Version 1.2.2** **Version Date: June, 2016**	ALTERED CONTENT **Version 1.4.1** **Version Date: August, 2016**	**Justification**
will be used in all episodes of fluid resuscitation during his stay in the ICU. As much as possible, volume replacement therapy with crystalloid solution during investigations and procedures performed outside the ICU will be with the designated study fluid. However, clinicians should be aware of special situations in which Plasma-Lyte® or 0.9% saline solution is contraindicated, in which the study fluid should not be used (Chart 4). In situations of imminent risk (Chart 5), the patient will be able to receive fluids at rapid flow (999 ml/h) regardless of the speed group to which he is randomized. Figure 1. Administration of intravenous fluids during the BaSICS study.	The type of therapy (type of fluid and speed) to which the patient is allocated will be used in all episodes of fluid resuscitation during his stay in the ICU. As much as possible, volume replacement therapy with crystalloid solution during investigations and procedures performed outside the ICU will be with the designated study fluid. However, clinicians should be awareof special situations in which Plasma-Lyte® or 0.9% saline solution is contraindicated, in which the study fluid should not be used (Chart 4). In addition, regarding the use of study fluids, a list of medications compatible with both solutions will be provided to the sites so that their dilution is carried out according to the randomization group. In situations of imminent risk (Chart 5), the patient will be able to receive fluids at rapid flow (999 ml/h) regardless of the speed group to which he is randomized. Figure 1. Administration of intravenous fluids during the BaSICS study.	

Version Comparison – BASICS – Versions 1.2.2 to 1.4.1

PREVIOUS CONTENT **Version 1.2.2** **Version Date: June, 2016**	ALTERED CONTENT **Version 1.4.1** **Version Date: August, 2016**	**Justification**
		
Page 21 Endpoints Section		
Plasma-Lyte® versus 0.9% NaCl Comparison <u>Co-Primary endpoints:</u> • Death in 90 days • Kidney failure requiring renal replacement therapy in 90 days <u>Secondary endpoints:</u>	The outcomes for both factorial arms of the study (Plasma-Lyte® versus 0.9% NaCl and slow versus fast crystalloid infusion) are identical: Primary endpoint: • Death in 90 days Secondary endpoints: • Kidney failure requiring renal replacement therapy in 90 days	BASICS' secondary outcomes are now identical for both factorial groups. In the initial protocol, we planned to measure secondary outcome occurrence at days 3 and 5. However, we understand that this period was short. Therefore, we will evaluate organic damage outcomes (KDIGO 2 kidney injury and other organic damages) at days 3 and 7.

Version Comparison – BASICS – Versions 1.2.2 to 1.4.1

PREVIOUS CONTENT **Version 1.2.2** **Version Date: June, 2016**	ALTERED CONTENT **Version 1.4.1** **Version Date: August, 2016**	Justification
• Kidney injury KDIGO ≥ 2 (50) on days 3 and 5 after randomization based only on serum creatinine: stage 2 (serum creatinine ≥ 2.0 x baseline values or more) or 3 (serum creatinine ≥ 3.0 times baseline values or increase in serum creatinine to values ≥ 4.0 mg/dl more). To determine the KDIGO criterion, we will define baseline creatinine as the lowest serum creatinine value available in patients' hospital records up to six months before the current ICU admission. • New respiratory, hepatic, cardiac, neurological and coagulation dysfunction (using SOFA score) on days 3 and 5 (51). • Mechanical ventilation-free days during the first 28 days after randomization.	• Kidney injury KDIGO ≥ 2 (51) on days 3 and 7 after randomization. For the diagnosis of kidney injury we will consider serum creatinine and diuresis: Serum creatinine ≥ 2.0 times the reference values or diuresis below 0.5 ml/kg/h for more than 12 hours. The reference creatinine will be the lowest between randomization creatinine and previous creatinine (the oldest available in the last six months and prior to current admission). If there is no previous creatinine available, we will estimate its value using the MDMR equation: Creatinine = (75 / [186x (age-0.203) x F x N] -0.887 Where F = 0.742 (female patients) and N = 1.21 for black patients If, at the time of randomization, the patient already has KDIGO 2 criteria, it will not be counted as part of the sample to assess this outcome. • New respiratory, hepatic, cardiac, neurological and coagulation	According to change on organic damage occurrence evaluation, time sequence data collection was updated. Initially these data would be collected on days 1, 2, 3, 4 and 5 after randomization. In this amendment, we updated data collection days to 1, 2, 3 and 7 after randomization. We added some information that will clarify acute kidney injury definition (according to KDIGO classification), including how patient baseline creatinine will be estimated.

Version Comparison – BASICS – Versions 1.2.2 to 1.4.1

PREVIOUS CONTENT **Version 1.2.2** **Version Date: June, 2016**	ALTERED CONTENT **Version 1.4.1** **Version Date: August, 2016**	Justification
Tertiary endpoints (exploratory): • Death by any cause at the ICU and hospital • Length of stay at the ICU • Duration of hospitalization Comparison of slow versus fast crystalloid infusion Primary endpoint: • Death in 90 days Secondary endpoints: • Kidney failure requiring renal replacement therapy in 90 days • Kidney injury KDIGO > 2 (41) on days 3 and 5 after randomization based only on serum creatinine: stage 2 (serum creatinine ≥ 2.0 x baseline values or more) or 3 (serum creatinine ≥ 3.0 times baseline values or increase in serum creatinine to values ≥ 4.0 mg/dl more). To determine the	dysfunction (using SOFA score) on days 3 and 7 (52). • Mechanical ventilation-free days during the first 28 days after randomization. Tertiary endpoints (exploratory): • Death by any cause at the ICU and hospital • Length of stay at the ICU • Duration of hospitalization **Other exploratory endpoints:** - Comparison of serum chlorine values between the four possible study groups over time. - Quality of life assessment through EQ-5D-5L questionnaire in six months, to be conducted in sample of approximately 10% of the patients, obtained randomly	

Version Comparison – BASICS – Versions 1.2.2 to 1.4.1

PREVIOUS CONTENT **Version 1.2.2** **Version Date: June, 2016**	ALTERED CONTENT **Version 1.4.1** **Version Date: August, 2016**	Justification
KDIGO criterion, we will define baseline creatinine as the lowest serum creatinine value available in patients' hospital records up to six months before the current ICU admission. • New respiratory, hepatic, cardiac, neurological and coagulation dysfunction (using SOFA score) on days 3 and 5 (51). • Mechanical ventilation-free days during the first 28 days after randomization. Tertiary endpoints: • Death by any cause at the ICU and hospital • Length of stay at the ICU • Duration of hospitalization Evaluation of serum chlorine in convenience sample Exploratory endpoint:	o **Time sequence** The study visits and the variables collected at each visit are described below: Day 0: Tracking, randomization and baseline data - Verification of inclusion and exclusion criteria - Obtainment of the ICF - Randomization - Reason for non-randomization of eligible patients - Time between ICU admission and randomization - Quantity and type of fluids administered 24 hours before randomization - Date of birth - Gender - Weight (checked with balance)	

Version Comparison – BASICS – Versions 1.2.2 to 1.4.1

PREVIOUS CONTENT **Version 1.2.2** **Version Date: June, 2016**	ALTERED CONTENT **Version 1.4.1** **Version Date: August, 2016**	Justification
- Comparison of serum chlorine values between the four possible study groups over time (admission, first day and fifth day). o Time sequence The study visits and the variables collected at each visit are described below: Day 0: Tracking, randomization and baseline data - Verification of inclusion and exclusion criteria - Obtainment of the ICF - Randomization - Reason for non-randomization of eligible patients - Time between ICU admission and randomization - Quantity and type of fluids administered 24 hours before	- Height - Origin of the patient (operating room [elective and emergency surgery], emergency room, ward, another hospital (excluding other ICU), other ICU) - Comorbidities (APACHE II variables) - APACHE II score - SOFA score (52) - Creatinine on admission to the ICU - Serum chlorine and other laboratory tests, if available - Dose of vasopressors (mcg/Kg/min) administered at randomization - Inotropic dose (mcg/Kg/min) administered at randomization - Mode of ventilation support at the time of randomization	

Version Comparison – BASICS – Versions 1.2.2 to 1.4.1

PREVIOUS CONTENT **Version 1.2.2** **Version Date: June, 2016**	ALTERED CONTENT **Version 1.4.1** **Version Date: August, 2016**	**Justification**
randomization - Date of birth - Gender - Weight (checked with balance) - Height - Origin of the patient (operating room [elective and emergency surgery], emergency room, ward, another hospital (excluding another ICU), other ICU) - Comorbidities (APACHE II variables) - APACHE II score - SOFA score (51) - Creatinine on admission to the ICU - Serum chlorine and other laboratory tests, if available	Daily data from Day 1 to Day 3 and on Day 7 - Quantity and speed of infusion of administered study fluids - Total fluid volume infused during the day - Fluid balance - Diuresis - Serum creatinine - Serum chlorine, if available, only in centers that routinely collect the serum chlorine level - Use of red blood cell concentrate - SOFA score, broken down by component (52) Data on ICU Discharge - Date of discharge from the ICU (or death) - Vital status at discharge from the ICU	

Version Comparison – BASICS – Versions 1.2.2 to 1.4.1

PREVIOUS CONTENT	ALTERED CONTENT	Justification
Version 1.2.2	**Version 1.4.1**	
Version Date: June, 2016	**Version Date: August, 2016**	
- Dose of vasopressors (mcg/Kg/min) administered at randomization - Inotropic dose (mcg/Kg/min) administered at randomization - Mode of ventilation support at the time of randomization Daily data from Day 1 to Day 5 - Quantity, type and speed of infusion of fluids administered. - Fluid balance - Diuresis - Only on Day 1: Serum chlorine, if available, only in centers that routinely collect the serum chlorine level - Acute renal failure requiring renal replacement therapy - Use of red blood cell concentrate	Hospital discharge - Date of hospital discharge (or death) - Vital status at hospital discharge - Reasons (based on Table 6) to initiate renal replacement therapy - Number of days on mechanical ventilation during hospital stay 90-day data: - Vital state in 90 days - Use of renal replacement therapy (dialysis) in the period *The 90-day data will be collected by a single telephone exchange that will contact the patient, his legal representative or family member.* Data in six months: Short quality of life assessment, through EQ-5D-5L questionnaire (in 10% of the total patient sample)	

Version Comparison – BASICS – Versions 1.2.2 to 1.4.1

PREVIOUS CONTENT **Version 1.2.2** **Version Date: June, 2016**	ALTERED CONTENT **Version 1.4.1** **Version Date: August, 2016**	Justification
Day 3 specific data • SOFA score, broken down by component (51) • Serum creatinine Day 5 specific data • Serum creatinine • Serum chlorine, if available, only in centers that routinely collect serum chlorine level Data at ICU discharge - Date of discharge from the ICU (or death) - Vital status at discharge from the ICU Hospital discharge - Date of hospital discharge (or death) - Vital status at hospital discharge - Reasons (based on Table 6) to		

Version Comparison – BASICS – Versions 1.2.2 to 1.4.1

PREVIOUS CONTENT **Version 1.2.2** **Version Date: June, 2016**	ALTERED CONTENT **Version 1.4.1** **Version Date: August, 2016**	Justification
initiate renal replacement therapy - Number of days on mechanical ventilation during hospital stay 90-day data: - Vital state in 90 days - Use of renal replacement therapy (dialysis) in the period The 90-day data will be collected by a single telephone exchange that will contact the patient, his legal representative or family member.		
Page 24 Randomization Section		
The randomization list will be generated electronically using appropriate software. Randomization will be carried out in blocks (blocks of 4 patients) stratified by center and will be factorial for the two interventions performed. The confidentiality of the randomization list will be maintained through a centralized, automated, internet-based randomization system, available 24 hours	The randomization list will be generated electronically using appropriate software. Randomization will be carried out in blocks (blocks of 12 patients) stratified by center and will be factorial for the two interventions performed. The confidentiality of the randomization list will be maintained through a centralized, automated, internet-based randomization system, available 24 hours a day, developed	Previously was predicted blocks of four patients. Now we define that randomization will be carried out in blocks (blocks of 12 patients) stratified by center and will be factorial for the two interventions performed, infusion speed (fast versus slow) and fluid (A-F).

Version Comparison – BASICS – Versions 1.2.2 to 1.4.1

PREVIOUS CONTENT **Version 1.2.2** **Version Date: June, 2016**	ALTERED CONTENT **Version 1.4.1** **Version Date: August, 2016**	**Justification**
a day, developed by a team of programmers and researchers from the Research Institute of Hospital do Coração (IP-HCor). The group to which the patient will be allocated will only be released after registration of the information in the electronic system, which prevents the investigator and the assistant team from predicting which of the treatment groups the patient will be allocated to. To include the patient in the study, the researcher simply has to access the IP-HCor website (https://servicos.hcor.com.br/iep/estudoclinico) and fill out a simple clinical form.	by a team of programmers and researchers from the Research Institute of Hospital do Coração (IP-HCor). The group to which the patient will be allocated will only be released after registration of the information in the electronic system, which prevents the investigator and the assistant team from predicting which of the treatment groups the patient will be allocated to. To include the patient in the study, the researcher simply has to access the IP-HCor website (https://servicos.hcor.com.br/iep/estudoclinico) and fill out a simple clinical form.	

Version Comparison – BASICS – Versions 1.4.1 to 1.5

PREVIOUS CONTENT	ALTERED CONTENT	Justification
Version 1.4.1	**Version 1.5**	
Version Date: August, 2016	**Version Date: September, 2016**	
Cover Page		
Study Registry: - ClinicalTrials.gov: To be registered - REBEC: To be registered	**Study Registry:** ClinicalTrials.gov: NCT02875873	Update on study registry
Page 18 Interventions		
Eligible patients who require volume replacement therapy will receive the study fluid, Plasma-Lyte® or 0.9% saline at infusion speeds of 999 ml/h or 333 ml/h, according to randomization, in quantity and frequency of administration determined by the attending physician (Figure 1). In the case of infusion of maintenance serum, the study drug should be used at the speed typically applied for this purpose (40-120 ml/h, depending on the service). When possible, medications and solutions whose active ingredient is also compatible with 0.9% saline or Plasma-Lyte® (for example, sedative drugs, vasopressors and antibiotics) will be infused according to the study group (Figure 1). Guidelines will be proposed to investigators to indicate fluid infusion (Chart 3). The type of therapy (type of fluid	Eligible patients who require volume replacement therapy will receive the study fluid, Plasma-Lyte® or 0.9% saline at infusion speeds of 999 ml/h or 333 ml/h, according to randomization, in quantity and frequency of administration determined by the attending physician (Figure 1). In the case of infusion of maintenance serum, the study drug should be used at the speed typically applied for this purpose (40-120 ml/h, depending on the service). When possible, medications and solutions whose active ingredient is also compatible with 0.9% saline or Plasma-Lyte® (for example, sedative drugs, vasopressors and antibiotics) will be infused according to the study group (Figure 1). Guidelines will be proposed to investigators to indicate fluid infusion (Chart 3). A list of drugs compatible with Plasma-Lyte® is given in Appendix 1. Appendix 2 suggests medications that can be	Inclusion of a phrase mentioning the list of compatible drugs with study fluids.

Version Comparison – BASICS – Versions 1.4.1 to 1.5

PREVIOUS CONTENT **Version 1.4.1** **Version Date: August, 2016**	ALTERED CONTENT **Version 1.5** **Version Date: September, 2016**	Justification
and speed) to which the patient is allocated will be used in all episodes of fluid resuscitation during his stay in the ICU. As much as possible, volume replacement therapy with crystalloid solution during investigations and procedures performed outside the ICU will be with the designated study fluid. However, clinicians should be aware of special situations in which Plasma-Lyte® or 0.9% saline solution is contraindicated, in which the study fluid should not be used (Chart 4). In addition, regarding the use of study fluids, a list of medications compatible with both solutions will be provided to the sites so that their dilution is carried out according to the randomization group. In situations of imminent risk (Chart 5), the patient will be able to receive fluids at rapid flow (999 ml/h) regardless of the speed group to which he is randomized.	safely diluted in both Plasma-Lyte® and saline solution, and these medications should be diluted in the study fluid whenever possible. The type of therapy (type of fluid and speed) to which the patient is allocated will be used in all episodes of fluid resuscitation during his stay in the ICU. As much as possible, volume replacement therapy with crystalloid solution during investigations and procedures performed outside the ICU will be with the designated study fluid. However, clinicians should be aware of special situations in which Plasma-Lyte® or 0.9% saline solution is contraindicated, in which the study fluid should not be used (Chart 4). In addition, regarding the use of study fluids, a list of medications compatible with both solutions will be provided to the sites so that their dilution is carried out according to the randomization group. In situations of imminent risk (Chart 5), the patient will be able to receive fluids at rapid flow (999 ml/h) regardless of the speed group to which he is randomized.	
Page 38 Appendix 1 – New item		

Version Comparison – BASICS – Versions 1.4.1 to 1.5

<table>
<tr><th>PREVIOUS CONTENT</th><th>ALTERED CONTENT</th><th rowspan="3">Justification</th></tr>
<tr><th>Version 1.4.1</th><th>Version 1.5</th></tr>
<tr><th>Version Date: August, 2016</th><th>Version Date: September, 2016</th></tr>
<tr><td></td><td>
Appendix 1 - List of compatibility with Plasma-Lyte®:

This list of compatibility of Plasma-Lyte® is a literal translation of the document obtained by the investigators of the Study PLUS (ANZICS) that evaluated the compatibility of Plasma-Lyte® with a series of drugs for routine use at the intensive care unit.

The solution:

Plasma-Lyte® 148 pH 7.4 is a crytalloid solution composed of various electrolytes, including buffers; consult the composition below[1]:

<table>
<tr><th>Component</th><th>Na^+ mEq/L</th><th>K^+ mEq/L</th><th>Cl^- mEq/L</th><th>Mg^{2+} mEq/L</th><th>$C_2H_3CO_2$ Acetate mEq/L</th><th>$C_6H_{12}O_7$ Gluconate mEq/L</th></tr>
<tr><td>mEq/L</td><td>140</td><td>5</td><td>98</td><td>3</td><td>27</td><td>23</td></tr>
</table>
</td><td>Inclusion of Appendix 1 with a list of drugs that can be dilutes in Plasma-Lyte®</td></tr>
</table>

Version Comparison – BASICS – Versions 1.4.1 to 1.5

PREVIOUS CONTENT	ALTERED CONTENT	Justification
Version 1.4.1	**Version 1.5**	
Version Date: August, 2016	**Version Date: September, 2016**	
	<table><tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>**mmol/l**</td><td>140</td><td>5</td><td>98</td><td>1.5</td><td>27</td><td>23</td></tr></table> Plasma-Lyte® 148 pH 7.4 is indicated as source of water and electrolytes or as alkalizing agent[1]. During the administration of Plasma-Lyte® 148 pH 7.4, it may be necessary to administer different drugs through Y infusion. Baxter ordered a study aiming to evaluate the physical compatibility of Plasma-Lyte 148 pH 7.4, with range of drugs commonly used in the surgical block/center and in intensive cares. The study was conducted by an independent agency in facilities audited by the Food and Drug Administration (FDA), a North American food and drug control department, and by the Therapeutic Goods Administration (TGA), an Australian regulatory agency, in order to comply with the global quality standards. **The study:** Plasma-Lyte® 148 pH 7.4 was tested with 87 drugs in terms of physical compatibility	

Version Comparison – BASICS – Versions 1.4.1 to 1.5

PREVIOUS CONTENT	ALTERED CONTENT	Justification
Version 1.4.1	**Version 1.5**	
Version Date: August, 2016	**Version Date: September, 2016**	
	(appearance and turbidity) immediately after being mixed and also 1 and 4 hours after mixing. Plasma-Lyte® 148 pH 7.4 was mixed in a 1: 1 ratio with each tested drug to stimulate Y_2 administration. Compatibility was determined by: 1. Visual examinations performed in the laboratory with normal diffused fluorescent light. 2. Turbidity measured with high intensity unidirectional light using a portable turbidimeter model 2100P (Hach). **Definition of compatibility** Previous studies by Lawrence Trissel et al. indicated that incompatibility can be defined by the visible particulate material, opacity or change in turbidity in relation to control solutions[3]. An increase in turbidity of 0.5 nephelometric turbidity units (NTU) or more in relation to baseline values was previously identified as an incompatibility criterion[4].	

Version Comparison – BASICS – Versions 1.4.1 to 1.5

PREVIOUS CONTENT	ALTERED CONTENT	Justification
Version 1.4.1	**Version 1.5**	
Version Date: August, 2016	**Version Date: September, 2016**	
	Results: The study results indicate that the following drugs are compatible, based on visual observation and on turbidity. **Drug Manufacturer Concentration** **Tested Acyclovir** Hospira 25 mg/ml **Tranexamic acid** Pfizer 100 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 **Caspofungin** MSD 70 mg/100 ml **Cefazolin** Hospira 2000 mg/50 ml **Cefoxitin** Hospira 20 mg/ml **Ceftazidime** Hospira 100 mg/ml **Cyclophosphamide** Baxter 8 mg/ml **Ciprofloxacin** Bayer 2 mg/ml **Clindamycin** Pfizer 900 mg/50 ml **Clonidine** Boehringer Ingelheim 20 mcg/ml **Calcium Chloride** Baxter 40 mg/ml	

Version Comparison – BASICS – Versions 1.4.1 to 1.5

PREVIOUS CONTENT	ALTERED CONTENT	Justification
Version 1.4.1	**Version 1.5**	
Version Date: August, 2016	**Version Date: September, 2016**	
	Potassium Chloride Baxter 0.5 mmol/ml **Lidocaine Hydrochloride** Pfizer 8 mg/ml **Cloxacillin** Teva 100 mg/ml **Dexamethasone** Aspen 4 mg/ml **Digoxin** Aspen 0.25 mg/ml **Potassium dihydrogen** phosphate Baxter 0.5 mmol/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 **Furosemide** Sandoz 10 mg/ml **Gentamicin** Pfizer 10 mg/ml **Glycopyrrolate** Aspen 0.2 mg/ml **Calcium Gluconate** Baxter 40 mg/ml **Granisetron** Hospira 0.05 mg/ml	

Version Comparison – BASICS – Versions 1.4.1 to 1.5

PREVIOUS CONTENT	ALTERED CONTENT	Justification
Version 1.4.1	**Version 1.5**	
Version Date: August, 2016	**Version Date: September, 2016**	
	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 **NovoRapid Insulin** Novo Nordisk 1 unit/ml **Isoprenaline** Hospira 1 mg/100 ml **Labetalol** Sandoz Canada 5 mg/ml **Lincomycin** Pfizer 2 mg/ml **Meropenem** Hospira 40 mg/ml **Metaraminol** 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 **Moxifloxacin** Bayer 1.6 mg/ml **Naloxone** Hospira 0.4 mg/ml **Neostigmine** AstraZeneca 0.5 mg/ml **Sodium Nitroprusside** Hospira 0.6 mg/ml **Noradrenaline** Hospira 16 mg/100 ml **Oxytocin** Aspen 1 unit/ml	

Version Comparison – BASICS – Versions 1.4.1 to 1.5

PREVIOUS CONTENT	ALTERED CONTENT	Justification
Version 1.4.1	**Version 1.5**	
Version Date: August, 2016	**Version Date: September, 2016**	
	Ondansetron GSK 1 mg/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 **Protamine** Sanofi 10 mg/ml **Ketamine** Hospira 2 mg/ml **Rocuronium** Hospira 10 mg/ml **Salbutamol** GSK 0.05 mg/ml **Syntometrine** Novartis 1 ml/4 ml **Sugammadex** MSD 25 mg/ml **Magnesium Sulfate** Baxter 0.4 mmol/ml **Morphine Sulfate** Hospira 1 mg/ml **Suxamethonium** AstraZeneca 2 mg/ml **Thiopentone** Link 50 mg/ml **Tramadol** Sandoz 50 mg/ml **Trimethoprim/Sulfamethoxazole** Hospira 1 mg/25 ml **Glyceryl Trinitrate** Hospira 30 mg/50 ml **Vancomycin** Hospira 20 mg/ml **Verapamil** Abbott 2.5 mg/ml **Voriconazole Pfizer** 5 mg/ml	

Version Comparison – BASICS – Versions 1.4.1 to 1.5

<table>
<tr><th>PREVIOUS CONTENT</th><th>ALTERED CONTENT</th><th rowspan="3">Justification</th></tr>
<tr><th>Version 1.4.1</th><th>Version 1.5</th></tr>
<tr><th>Version Date: August, 2016</th><th>Version Date: September, 2016</th></tr>
<tr><td></td><td>It was observed visually that the following drugs were clear and colorless fluids, but turbidity increased by more than 0.5 NTU in relation to the moment immediately after mixing (baseline value).

<table>
<tr><th>Drug</th><th>Manufacturer</th><th>Tested Concentration</th><th>Observation</th></tr>
<tr><td>Pantoprazole</td><td>Sandoz</td><td>800 mcg/ml</td><td>0.68 NTU immediately after mixing, 0.86 NTU after 1 hour and 1.50 NTU after 4 hours</td></tr>
<tr><td>Phenytoin</td><td>Hospira</td><td>50 mg/ml</td><td>0.18 NTU immediately after mixing, 0.19 NTU after 1 hour and 0.72 NTU after 4 hours</td></tr>
</table>
</td><td></td></tr>
</table>

Version Comparison – BASICS – Versions 1.4.1 to 1.5

<table>
<tr><th>PREVIOUS CONTENT</th><th>ALTERED CONTENT</th><th rowspan="3">Justification</th></tr>
<tr><th>Version 1.4.1</th><th>Version 1.5</th></tr>
<tr><th>Version Date: August, 2016</th><th>Version Date: September, 2016</th></tr>
<tr><td></td><td>It was observed visually that the following drugs underwent changes when mixed, but there was a change by less than 0.5 NTU in turbidity in relation to the moment immediately after mixing (baseline value).

<table>
<tr><th>Drug</th><th>Manufacturer</th><th>Tested Concentration</th><th>Observation</th></tr>
<tr><td>Amiodarone</td><td>Sanofi</td><td>9 mg/ml</td><td>Foam on the top part of the clear and colorless fluid immediately after mixing and 1 hour afterwards. Less foam after 4 hours.</td></tr>
<tr><td>Cyclosporine</td><td>Sandoz</td><td>2.5 mg/ml</td><td>Clear and colorless fluid, formation of bubbles inside the solution with the addition of physiological</td></tr>
</table>
</td><td></td></tr>
</table>

Version Comparison – BASICS – Versions 1.4.1 to 1.5

PREVIOUS CONTENT	ALTERED CONTENT	Justification
Version 1.4.1	**Version 1.5**	
Version Date: August, 2016	**Version Date: September, 2016**	

			serum. The bubbles continued after 1 and 4 hours.

Changes were observed in visual appearance of the following drugs immediately after mixing and an increase in turbidity by more than 0.5 NTU in relation to the moment immediately after mixing (baseline value).

Drug	Manufacturer	Tested Concentration	Observation
Mofetil Mycophenolate	Roche	6 mg/ml	White and turbid fluid immediately, 1 hour and 4 hours after mixing. 640 NTU immediately after mixing, > 1000 NTU after 1 hour and 809 NTU after 4

Version Comparison – BASICS – Versions 1.4.1 to 1.5

PREVIOUS CONTENT Version 1.4.1 Version Date: August, 2016	ALTERED CONTENT Version 1.5 Version Date: September, 2016	Justification
	hours. **Propofol** Sandoz 10 mg/ml Milky fluid immediately, 1 hour and 4 hours after mixing. Number of NTU above the normal range immediately, 1 hour and 4 hours after mixing. **References** [1]Plasma-Lyte 148 SPC, ANZ [2] Allen LV, Levinson RS, Phisutsinthop D. Compatibility of various admixtures with secondary additives at Y- injection sites of intravenous administration sets. Am J Hosp Pharm. 1977; 34:939-943 [3]Trissel LA, Gilbert DL, Martinex JF. Concentration dependency of vancomycin hydrochloride compatibility with beta-lactam antibiotics during simulated Y-site administration. Hosp Pharmacy. 1998;	

Version Comparison – BASICS – Versions 1.4.1 to 1.5

<table>
<tr><th>PREVIOUS CONTENT</th><th>ALTERED CONTENT</th><th rowspan="3">Justification</th></tr>
<tr><td>Version 1.4.1</td><td>Version 1.5</td></tr>
<tr><td>Version Date: August, 2016</td><td>Version Date: September, 2016</td></tr>
<tr><td></td><td>33:1515-1522).

[4]Trissel LA, Martinex JF. Compatibility of pipercillin sodium plus Tazobactam with selected drugs during simulated Y-site injection. Am J Hosp Pharm. 1994; 51:672-678</td><td></td></tr>
<tr><td colspan="3">Page 44 Appendix 2 – New item</td></tr>
<tr><td></td><td>Appendix 2 - Simplified list of drugs compatible with Plasma-Lyte® and Saline Solution and which can be diluted in the study fluid, together with its maximum concentration
<table><tr><th>Sedative and Analgesic Drugs</th><th>Antibiotic and Antimicrobial Drugs</th></tr><tr><td>Midazolam 1 mg/ml</td><td>Vancomycin 20 mg/ml</td></tr><tr><td>Fentanyl 10 mcg/ml</td><td>Piperacillin/ Tazobactam 4500 mg/50 ml</td></tr></table></td><td>Inclusion of Appendix 2 with a list of drugs that can be dilutes in Plasma-Lyte® and saline and their maximum concentration</td></tr>
</table>

Version Comparison – BASICS – Versions 1.4.1 to 1.5

PREVIOUS CONTENT	ALTERED CONTENT	Justification
Version 1.4.1	**Version 1.5**	
Version Date: August, 2016	**Version Date: September, 2016**	

Ketamine 2 mg/ml	Meropenem 40 mg/ml
Thiopentone 50 mg/ml	Imipenem 5 mg/ml
Morphine Sulfate 1 mg/ml	Amikacin 40 mg/ml
Vasopressors and Vasodilators	Gentamicin 10 mg/ml
Norepinephrine 16 mg/100 ml	Cefazolin 2000 mg/50 ml
Dobutamine 5 mg/ml	Ceftazidime 100 mg/ml
Dopamine 3.2 mg/ml	Ciprofloxacin 2 mg/ml
Epinephrine 12 mg/100 ml	Moxifloxacin 1.6 mg/ml
Nitroprusside 0.6 mg/ml **Sodium**	Trimethoprim/ Sulfamethoxazole 1 mg/25 ml

Version Comparison – BASICS – Versions 1.4.1 to 1.5

PREVIOUS CONTENT	ALTERED CONTENT	Justification
Version 1.4.1	**Version 1.5**	
Version Date: August, 2016	**Version Date: September, 2016**	

Milrinone 300 mcg/ml	Fluconazole 200 mg/100 ml
Esmolol 10 mg/ml	Voriconazole 5 mg/ml
Clonidine 20 mcg/ml	Clindamycin 900 mg/50 ml
Symptomatic Corticosteroids	**and others**
Dexamethasone 4 mg/ml	Ondansetron 1 mg/ml
Hydrocortisone 100 mg/2 ml	Metoclopramide 5 mg/ml
Anticoagulants	Esomeprazole 0.4 mg/ml
Heparin 1000 units/ml	Tramadol 50 mg/ml

For the BaSICS study, we recommend not to dilute anticonvulsants (except

Version Comparison – BASICS – Versions 1.4.1 to 1.5

PREVIOUS CONTENT	ALTERED CONTENT	Justification
Version 1.4.1	**Version 1.5**	
Version Date: August, 2016	**Version Date: September, 2016**	
	sedatives), antiarrhythmic or immunosuppressant drugs in the study fluid	

Version Comparison – BASICS – Versions 1.5 to 2.0

PREVIOUS CONTENT	ALTERED CONTENT	Justification
Version 1.5	**Version 2.0**	
Version Date: September, 2016	**Version Date: January, 2018**	
Cover Page		
Principal investigator's contact: Alexandre Cavalcanti Biasi	**Principal investigator's contact:** Alexandre Biasi Cavalcanti	Correction on PI's full name
Page 2 - Version History Section		
There was no previous content	**Version History** **Version 1.2. - Initial** **Version 1.4.1** This version presents the following changes: • Unification of endpoints for the two interventions to be tested • Change of the date of definition of secondary endpoints from days 3 and 5 to 3 and 7 • Change of days of collection of information • Clarification of the definitions of	Inclusion of Version History

Version Comparison – BASICS – Versions 1.5 to 2.0

PREVIOUS CONTENT	ALTERED CONTENT	Justification
Version 1.5	**Version 2.0**	
Version Date: September, 2016	**Version Date: January, 2018**	
	acute kidney injury • Recalculation of the study's power • Adjustment in the guidelines for use of the study fluid • Inclusion of quality of life analysis in 180 days in a sub-sample of 1,100 patients • Change in the number of individuals by randomization block **<u>Version 1.5</u>** This version does <u>not</u> bring any change in inclusion and exclusion criteria, endpoints or definitions of the study. The only proposed changes are: 1. Addition of the registration number in ClinicalTrials.gov 2. Addition of an appendix with the list of drugs that can be diluted in Plasma-Lyte® for aid of the sites.	

Version Comparison – BASICS – Versions 1.5 to 2.0

PREVIOUS CONTENT **Version 1.5** **Version Date: September, 2016**	ALTERED CONTENT **Version 2.0** **Version Date: January, 2018**	Justification
	<u>Version 2.0</u> This version presents as changes the exclusion of the exclusion criterion referring to hyperkalemia and some text adjustments and team updates.	
Page 3 - Organization Section		
Organization Coordinating Site: Instituto de Pesquisa do Hospital do Coração (IEP-HCor) *Work team at the coordinating site:* - Fernando G Zampieri – interventionist physician. Instituto de Pesquisa HCor, São Paulo, SP. Member of BRICNet – Rede Brasileira de Pesquisa em Medicina Intensiva (Brazilian Network for Research in Intensive Medicine). - Letícia Kawano Dourado – interventionist physician and pulmonologist. Instituto de	**Organization** Coordinating Site: Instituto de Pesquisa do Hospital do Coração (IP-HCor) *Work team at the coordinating site:* - Fernando G Zampieri – interventionist physician. Instituto de Pesquisa HCor, São Paulo, SP. Member of BRICNet – Rede Brasileira de Pesquisa em Medicina Intensiva (Brazilian Network for Research in Intensive Medicine). - Letícia Kawano Dourado – interventionist physician and pulmonologist. Instituto de Pesquisa	Update on team members from coordinating site

Version Comparison – BASICS – Versions 1.5 to 2.0

PREVIOUS CONTENT	ALTERED CONTENT	Justification
Version 1.5	**Version 2.0**	
Version Date: September, 2016	**Version Date: January, 2018**	
Pesquisa HCor, São Paulo, SP. - Juliana Borges Oliveira – nurse. Instituto de Pesquisa HCor, São Paulo, SP. Specialist in site management. - Perla Carvalho Romanus – Instituto de Pesquisa HCor, São Paulo, SP. Specialist in data management. - Beatriz Gonzales Pacheco da Silva – biomedical technician, Instituto de Pesquisa HCor, São Paulo, SP. Regulatory Assistant. - Lucas Petri Damiani – statistician. Instituto de Pesquisa HCor, São Paulo, SP. Planning and statistical analyses. - Alexandre Biasi Cavalcanti - interventionist physician. Instituto de Pesquisa HCor, São Paulo, SP. Member of BRICNet – Rede Brasileira de Pesquisa em Medicina Intensiva (Brazilian Network for Research in Intensive Medicine). Overall study coordination	HCor, São Paulo, SP. - Juliana Borges Oliveira – nurse. Instituto de Pesquisa HCor, São Paulo, SP. Specialist in site management. - Lucas Martins de Lima – System Analyst. Instituto de Pesquisa HCor, São Paulo, SP. Research Technician – Data Management. - Beatriz Gonzales Pacheco da Silva – pharmacist, Instituto de Pesquisa HCor, São Paulo, SP. Regulatory Assistant. - Lucas Petri Damiani – statistician. Instituto de Pesquisa HCor, São Paulo, SP. Planning and statistical analyses. - Alexandre Biasi Cavalcanti - interventionist physician. Instituto de Pesquisa HCor, São Paulo, SP. Member of BRICNet – Rede Brasileira de Pesquisa em Medicina Intensiva (Brazilian Network for Research in Intensive Medicine). Overall study coordination	

Version Comparison – BASICS – Versions 1.5 to 2.0

PREVIOUS CONTENT	ALTERED CONTENT	Justification
Version 1.5	**Version 2.0**	
Version Date: September, 2016	**Version Date: January, 2018**	
Page 6 - Synopsis Section - Item on Exclusion Criteria		
Exclusion criteria 1. Age < 18 years 2. Kidney failure under renal replacement therapy or with expectation of requiring renal replacement therapy in the next six hours 3. Severe hyponatremia (serum Na ≤ 120 mmol/L) 4. Severe hypernatremia (serum Na ≥ 160 mmol/L) 5. Hyperkalemia (serum K ≥ 5.5 mmol/L) 6. Death considered imminent and inevitable within 24 hours 7. Patients with suspected or	Exclusion criteria 1. Age < 18 years 2. Kidney failure under renal replacement therapy or with expectation of requiring renal replacement therapy in the next six hours 3. Severe hyponatremia (serum Na ≤ 120 mmol/L) 4. Severe hypernatremia (serum Na ≥ 160 mmol/L) 5. Death considered imminent and inevitable within 24 hours 6. Patients with suspected or confirmed brain death 7. Patients under exclusive palliative cares 8. Patient previously included in the BaSICS study	Adjustment in this section according to exclusion criteria update

Version Comparison – BASICS – Versions 1.5 to 2.0

PREVIOUS CONTENT	ALTERED CONTENT	Justification
Version 1.5	**Version 2.0**	
Version Date: September, 2016	**Version Date: January, 2018**	
confirmed brain death 8. Patients under exclusive palliative cares 9. Patient previously included in the BaSICS study		
Page 20 - Methods - Outline		
The BaSICS study (*Balanced Solution in Intensive Care Study*) is a randomized, pragmatic, multicenter, 2x2 factorial, data recording-based and patient- and healthcare staff-blinded study. The study will compare two resuscitation therapies with fluids in a factorial manner in critically ill patients admitted to Intensive Care Units (ICUs). The study is expected to recruit about 11,000 patients in at least 70 Brazilian ICUs for 16 months. Eligible patients must be randomized to receive 0.9% saline or balanced solution (Plasma-Lyte®) and factorially for infusion speeds of 999 ml/h or 333 ml/h and will be evaluated during 90 days after randomization .	The BaSICS study (*Balanced Solution in Intensive Care Study*) is a randomized, pragmatic, multicenter, 2x2 factorial, data recording-based and patient- and healthcare staff-blinded study. The study will compare two resuscitation therapies with fluids in a factorial manner in critically ill patients admitted to Intensive Care Units (ICUs). The study is expected to recruit about 11,000 patients in at least 70 Brazilian ICUs for 36 months. Eligible patients must be randomized to receive 0.9% saline or balanced solution (Plasma-Lyte®) and factorially for infusion speeds of 999 ml/h or 333 ml/h and will be evaluated during 90 days after randomization .	Update on the amount of time to complete this trial from 16 to 36 months

Version Comparison – BASICS – Versions 1.5 to 2.0

PREVIOUS CONTENT	ALTERED CONTENT	Justification
Version 1.5	**Version 2.0**	
Version Date: September, 2016	**Version Date: January, 2018**	
The protocol for this study follows the recommendations of the *SPIRIT 2013 Statement.*	The protocol for this study follows the recommendations of the *SPIRIT 2013 Statement.*	
Page 20 - Methods - Study Sites		
The participation of at least 70 Brazilian ICUs will be necessary, including at least 16 patients per month for 16 months to recruit this sample size.	The participation of at least 70 Brazilian ICUs will be necessary, including at least 16 patients per month for 36 months to recruit this sample size.	Update on the amount of time to complete this trial from 16 to 36 months
Page 21 – Methods – Eligibility		
Exclusion Criteria The following exclusion criteria will be applied: 1. Age < 18 years 2. Kidney failure under renal replacement therapy or with expectation of requiring renal replacement therapy in the next six hours 3. Severe hyponatremia (serum Na ≤ 120 mmol/L) 4. Severe hypernatremia (serum Na ≥	*Exclusion Criteria* The following exclusion criteria will be applied: 1. Age < 18 years 2. Kidney failure under renal replacement therapy or with expectation of requiring renal replacement therapy in the next six hours 3. Severe hyponatremia (serum Na ≤ 120 mmol/L) 4. Severe hypernatremia (serum Na ≥ 160	There was an initial fear that balanced solutions could cause more hiperkalemia because of the potassium. However, recent papers suggest that balanced solutions are safe even in this situation. Therefore, exclusion criterion does not seem to make sense anymore and would exclude an important population. We did not have any adverse event related to potassium, which can sustain our decision. References O'Malley CM1, Frumento RJ, Hardy MA, Benvenisty AI, Brentjens TE, Mercer JS,

Version Comparison – BASICS – Versions 1.5 to 2.0

PREVIOUS CONTENT **Version 1.5** **Version Date: September, 2016**	ALTERED CONTENT **Version 2.0** **Version Date: January, 2018**	Justification
160 mmol/L) 5. Hyperkalemia (serum K ≥ 5.5 mmol/L) 6. Death considered imminent and inevitable within 24 hours 7. Patients with suspected or confirmed brain death 8. Patients under exclusive palliative cares 9. Patient previously included in the BaSICS study	mmol/L) 6. Death considered imminent and inevitable within 24 hours 7. Patients with suspected or confirmed brain death 8. Patients under exclusive palliative cares 9. Patient previously included in the BaSICS study	Bennett-Guerrero E. **A randomized, double-blind comparison of lactated Ringer's solution and 0.9% NaCl during renal transplantation.** Anesth Analg. 2005 May;100(5):1518-24, table of contents. Anamika Adwaney David W Randall Mark J Blunden John R Prowle Christopher J Kirwan. **Perioperative Plasma-Lyte use reduces the incidence of renal replacement therapy and hyperkalaemia following renal transplantation when compared with 0.9% saline: a retrospective cohort study**. Clinical Kidney Journal, Volume 10, Issue 6, 1 December 2017, Pages 838–844
Page 24 – Methods - Interventions		
Chart 4. <u>Situations in which study fluids should not be administered:</u> Severe hyperchloremia (Cl ≥ 120 mmol/L) Severe hypernatremia (Na ≥ 160 mmol/L) Severe hyponatremia (Na ≤ 120 mmol/L)	Chart 4. <u>Situations in which study fluids should not be administered:</u> Severe hyperchloremia (Cl ≥ 120 mmol/L) Severe hypernatremia (Na ≥ 160 mmol/L) Severe hyponatremia (Na ≤ 120 mmol/L)	Adjustment in this section according to exclusion criteria update

Version Comparison – BASICS – Versions 1.5 to 2.0

PREVIOUS CONTENT **Version 1.5** **Version Date: September, 2016**	ALTERED CONTENT **Version 2.0** **Version Date: January, 2018**	**Justification**
Hyperkalemia (K ≥ 5.5 mmol/L)		
Page 28 – Methods – Randomization		
The randomization list will be generated electronically using appropriate software. Randomization will be carried out in blocks (blocks of 12 patients) stratified by center and will be factorial for the two interventions performed. The confidentiality of the randomization list will be maintained through a centralized, automated, internet-based randomization system, available 24 hours a day, developed by a team of programmers and researchers from the Research Institute of Hospital do Coração (IP-HCor). The group to which the patient will be allocated will only be released after registration of the information in the electronic system, which prevents the	The randomization list will be generated electronically using appropriate software. Randomization will be carried out in blocks (blocks of 12 patients) stratified by center and will be factorial for the two interventions performed. The confidentiality of the randomization list will be maintained through a centralized, automated, internet-based randomization system, available 24 hours a day, developed by a team of programmers and researchers from the Research Institute of Hospital do Coração (IP-HCor). The group to which the patient will be allocated will only be released after registration of the information in the electronic system, which prevents the investigator and the assistant team from	Update on the electronic system which is current being used in this trial

Version Comparison – BASICS – Versions 1.5 to 2.0

PREVIOUS CONTENT **Version 1.5** **Version Date: September, 2016**	ALTERED CONTENT **Version 2.0** **Version Date: January, 2018**	**Justification**
investigator and the assistant team from predicting which of the treatment groups the patient will be allocated to. To include the patient in the study, the researcher simply has to access the IP-HCor website (https://servicos.hcor.com.br/iep/estudoclinico) and fill out a simple clinical form.	predicting which of the treatment groups the patient will be allocated to. To include the patient in the study, the researcher simply has to access the study website (https:// http://basics.hcor.novatela.com.br/Entrar/Login) and fill out a simple clinical form.	
Page 33 - Ethics and Dissemination - Consent		
Written consent will be requested from all eligible patients or their legal/family representative when the patient's clinical conditions such as cognitive impairments or communication limitations (e.g. patient on mechanical ventilation) do not allow for direct obtaining (mechanical ventilation, sedation). Regarding the process of obtaining the consent form for this study, we consider that: 1) the study intervention, volume expansion with crystalloid for seriously ill patients, is administered on an emergency basis in almost all cases,	Written consent will be requested from all eligible patients or their legal/family representative when the patient's clinical conditions such as cognitive impairments or communication limitations (e.g. patient on mechanical ventilation) do not allow for direct obtaining (mechanical ventilation) , sedation). Regarding the process of obtaining the consent form for this study, we consider that: 1) the study intervention, volume expansion with crystalloid for seriously ill patients, is administered on an emergency basis in almost all cases, with no possibility of delays. 2) in most Brazilian ICUs, family	Text adjustment informing that our national resolution allows the waiver of the consent in special cases.

Version Comparison – BASICS – Versions 1.5 to 2.0

PREVIOUS CONTENT **Version 1.5** **Version Date: September, 2016**	ALTERED CONTENT **Version 2.0** **Version Date: January, 2018**	**Justification**
with no possibility of delays. 2) in most Brazilian ICUs, family members remain in the unit for limited periods of time (1 to 2 times a day), therefore, they are not immediately available for the consent process. 3) Plasma-Lyte® and 0.9% saline solution are routinely used in clinical practice with exactly the same indications and without robust evidence of differences in clinical effect. 4) the fluid prescription standard worldwide is very variable and reflects regional preferences because there is no good clinical evidence (e.g. 60% of expansions with crystalloids in Brazil are carried out with 0.9% saline solution and the remainder with balanced solutions, while more than half of the time balanced solutions are used in other countries). 5) there is no consensus on the speed of infusion that should be used in critically ill patients or data that justify or refute any of the chosen speeds 6) the national resolution 466 of 2012, in section III, subsection 2, item “g”, provides obtaining the consent form *a posteriori* in special cases. In view of the above, we reinforce that the process of obtaining	members remain in the unit for limited periods of time (1 to 2 times a day), therefore, they are not immediately available for the consent process. 3) Plasma-Lyte® and 0.9% saline solution are routinely used in clinical practice with exactly the same indications and without robust evidence of differences in clinical effect. 4) the fluid prescription standard worldwide is very variable and reflects regional preferences because there is no good clinical evidence (e.g. 60% of expansions with crystalloids in Brazil are carried out with 0.9% saline solution and the remainder with balanced solutions, while more than half of the time balanced solutions are used in other countries). 5) there is no consensus on the speed of infusion that should be used in critically ill patients or data that justify or refute any of the chosen speeds 6) the national resolution 466 of 2012, in section III, subsection 2, item “g”, provides "*to obtain the free and clarified consent of the research patient and/or his legal representative, even in cases of researches that, for its nature, may imply justifiably, in consent a posteriori;*” In view of the above, we	

Version Comparison – BASICS – Versions 1.5 to 2.0

PREVIOUS CONTENT **Version 1.5** **Version Date: September, 2016**	ALTERED CONTENT **Version 2.0** **Version Date: January, 2018**	**Justification**
consent will be carried out in all cases, without exception. Investigators in the BaSICS study are committed to obtaining the consent form before the patient's inclusion in the study, whenever possible. However, we understand that in several cases it is fully justified and it will only be possible to obtain consent *a posteriori*. If the patient is unable to consent to his participation, the term will be obtained as quickly as possible, either through his family member / legal representative or the patient himself, when able to consent. The consent request and the pertinent study information provided to the legal representative must be conducted by the principal investigator, co-investigator or the study coordinator. The patient's legal representative and the research professional assigned to obtain the consent must date and sign two copies of the informed consent form, one copy of which must be delivered to the patient's legal representative and one copy must be filed with the other study documents. It will be clearly exposed to the patients'	reinforce that the process of obtaining consent will be carried out in all cases, without exception. Investigators in the BaSICS study are committed to obtaining the consent form before the patient's inclusion in the study, whenever possible. However, we understand that in several cases it is fully justified and it will only be possible to obtain consent *a posteriori*. If the patient is unable to consent to his participation, the term will be obtained as quickly as possible, either through his family member / legal representative or the patient himself, when able to consent. The consent request and the pertinent study information provided to the legal representative must be conducted by the principal investigator, co-investigator or the study coordinator. The patient's legal representative and the research professional assigned to obtain the consent must date and sign two copies of the informed consent form, one copy of which must be delivered to the patient's legal representative and one copy must be filed with the other study	

Version Comparison – BASICS – Versions 1.5 to 2.0

PREVIOUS CONTENT **Version 1.5** **Version Date: September, 2016**	ALTERED CONTENT **Version 2.0** **Version Date: January, 2018**	Justification
legal representatives that their participation is voluntary and may withdraw from the study at any time without any implication in the quality and conduct of the subsequent medical treatment. The ICF proposed by the study must be evaluated by each research center and, if there is a need for changes, these must be approved by the Study Coordinating Center before submission to LEC.	documents. It will be clearly exposed to the patients' legal representatives that their participation is voluntary and may withdraw from the study at any time without any implication in the quality and conduct of the subsequent medical treatment. The ICF proposed by the study must be evaluated by each research center and, if there is a need for changes, these must be approved by the Study Coordinating Center before submission to LEC.	
Page 33 - Ethics and Dissemination - Confidentiality		
No patient identification data will be sent to the Study Coordinating Center. The electronic data collection form will identify the patient and the investigating center by the corresponding number. The data obtained from the medical record must be kept confidential by the research centers, in cabinets with restricted access and the guarantee of anonymity of all data in provisional and definitive reports will be ensured.	Only the data necessary to perform the follow-up after 90 days of discharge will be made available to the Study Coordinating Center, such as name and phone number, the rest of the information is confidential and will be kept confidential by the participating center. The electronic data collection form will identify the patient and the investigating center by the corresponding number. The data obtained from the medical record must be kept confidential by the research centers, in cabinets with restricted access and the guarantee of anonymity of all data in provisional and definitive reports will be	Text adjustment informing that the coordinating site will be able to access sensible information from patients recruited to this trial in order to perform the 90 days follow up

Version Comparison – BASICS – Versions 1.5 to 2.0

PREVIOUS CONTENT	ALTERED CONTENT	Justification
Version 1.5	**Version 2.0**	**Justification**
Version Date: September, 2016	**Version Date: January, 2018**	
	ensured.	

Version Comparison – BASICS – Versions 2.0 to 3.0

PREVIOUS CONTENT	ALTERED CONTENT	Justification
Version 2.0	**Version 3.0**	
Version Date: January, 2018	**Version Date: March, 2020**	
Cover Page		
Version: 2.0 – January 24, 2018 **Funding**: PROADI – Programa de Apoio ao Desenvolvimento Institucional do SUS (SUS Institutional Development Support Program) **Study Registry:** - ClinicalTrials.gov: NCT02875873 **Principal investigator's contact**: Alexandre Biasi Cavalcanti; Instituto de Pesquisa HCor-Hospital do Coração, São Paulo, SP **E-mail**: abiasi@hcor.com.br	**Coordinating Site** Instituto de Pesquisa HCor Rua Abílio Soares, 250 – 12º andar Paraíso – São Paulo/SP - Brasil **Steering Committee** Alexandre B Cavalcanti, MD, PhD Fernando G Zampieri, MD Nilton Brandao, MD, PhD Flávia R Machado, MD, PhD Rodrigo S Biondi, MD Flávio G Rezende de Freitas, MD, PhD John A. Kellum, MD **Funding** PROADI-SUS – Programa de Apoio ao Desenvolvimento Institucional do	Update on cover page presentation.

Version Comparison – BASICS – Versions 2.0 to 3.0

PREVIOUS CONTENT	ALTERED CONTENT	Justification
Version 2.0	**Version 3.0**	
Version Date: January, 2018	**Version Date: March, 2020**	
Secondary Sponsor: Baxter Hospitalar	SUS Baxter Hospitalar **Version** 3.0 de March 2020 **Study Registry** NCT02875873	
Page 2 – Version History		

Version Comparison – BASICS – Versions 2.0 to 3.0

PREVIOUS CONTENT	ALTERED CONTENT	Justification
Version 2.0	**Version 3.0**	
Version Date: January, 2018	**Version Date: March, 2020**	
Version History **Version 1.2. - Initial** **Version 1.4.1** This version presents the following changes: • Unification of endpoints for the two interventions to be tested • Change of the date of definition of secondary endpoints from days 3 and 5 to 3 and 7 • Change of days of collection of information • Clarification of the definitions of acute kidney injury • Recalculation of the study's power	**Version History** **Version 1.2.2 - Initial** **Version 1.4.1** This version presents the following changes: • Unification of endpoints for the two interventions to be tested • Change of the date of definition of secondary endpoints from days 3 and 5 to 3 and 7 • Change of days of collection of information • Clarification of the definitions of acute kidney injury • Recalculation of the study's power • Adjustment in the guidelines for use of the study fluid • Inclusion of quality of life analysis in 180 days in a sub-sample of 1,100 patients • Change in the number of individuals by randomization block	

Version Comparison – BASICS – Versions 2.0 to 3.0

PREVIOUS CONTENT	ALTERED CONTENT	Justification
Version 2.0	**Version 3.0**	
Version Date: January, 2018	**Version Date: March, 2020**	
• Adjustment in the guidelines for use of the study fluid • Inclusion of quality of life analysis in 180 days in a sub-sample of 1,100 patients • Change in the number of individuals by randomization block **Version 1.5** This version does NOT bring any change in inclusion and exclusion criteria, endpoints or definitions of the study. The only proposed changes are: 1. Addition of the registration number in ClinicalTrials.gov 2. Addition of an appendix with the list of drugs that can be diluted in Plasma-Lyte® for aid of the sites.	**Version 1.5** This version does NOT bring any change in inclusion and exclusion criteria, endpoints or definitions of the study. The only proposed changes are: 1. Addition of the registration number in ClinicalTrials.gov 2. Addition of an appendix with the list of drugs that can be diluted in Plasma-Lyte® for aid of the sites. **Version 2.0** This version presents as changes the exclusion of the exclusion criterion referring to hyperkalemia and some text adjustments and team updates. **Version 3.0** This version presents as changes the alteration of quality of life assessment through EQ-5D-3L questionnaire in six months and some text adjustments and team updates.	

Version Comparison – BASICS – Versions 2.0 to 3.0

PREVIOUS CONTENT **Version 2.0** **Version Date: January, 2018**	ALTERED CONTENT **Version 3.0** **Version Date: March, 2020**	Justification
Version 2.0 This version presents as changes the exclusion of the exclusion criterion referring to hyperkalemia and some text adjustments and team updates.		
Page 3 - Organization		
Organization Coordinating Site: Instituto de Pesquisa do Hospital do Coração (IP-HCor) Work team at the coordinating site: ⦚ Fernando G Zampieri – interventionist physician. Instituto de Pesquisa HCor, São Paulo, SP. Member of BRICNet – Rede Brasileira de Pesquisa em Medicina Intensiva (Brazilian Network for Research in Intensive Medicine). ⦚ Letícia Kawano Dourado – Intensivist physician and pulmonologist. Instituto de Pesquisa HCor, São Paulo, SP. ⦚ Juliana Borges Oliveira – nurse. Instituto de Pesquisa HCor, São Paulo, SP. Specialist in site management.	**Coordinating Site:** Instituto de Pesquisa do Hospital do Coração (IP-HCor) Alexandre Biasi Cavalcanti *Principal Investigator* P.: 55 11 30536611 Ext 8201 abiasi@hcor.com.br Fernando Godinho Zampieri *Principal Investigator* P.: 55 11 3053-6611 Ext 8239 Fgzampieri@gmail.com Rafael Marques Soares Rodrigo Magalhães Gurgel *Site Management*	Update on Organization presentation and update on members of coordinating site and steering committee

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⦚ Lucas Martins de Lima – System Analyst. Instituto de Pesquisa HCor, São Paulo, SP. Research Technician – Data Management. ⦚ Beatriz Gonzales Pacheco da Silva – pharmacist, Instituto de Pesquisa HCor, São Paulo, SP. Regulatory Assistant. ⦚ Lucas Petri Damiani – statistician. Instituto de Pesquisa HCor, São Paulo, SP. Planning and statistical analyses. ⦚ Alexandre Biasi Cavalcanti - Intensivist physician. Instituto de Pesquisa HCor, São Paulo, SP. Member of BRICNet – Rede Brasileira de Pesquisa em Medicina Intensiva (Brazilian Network for Research in Intensive Medicine). Overall study coordination Steering Committee: ⦚ Alexandre Biasi Cavalcanti – intensivist physician. Instituto de Pesquisa HCor, São Paulo, SP. Member of BRICNet – Rede Brasileira de Pesquisa em Medicina Intensiva (Brazilian Network for Research in Intensive Medicine). ⦚ Luciano Azevedo – intensivist physician. Hospital Sírio-Libanês & Hospital São Paulo, UNIFESP, São Paulo, SP.	*Site Management* P.: 55 11 3053-6611 Ext 8211 rmsoares@hcor.com.br Tamiris Miranda Abait *Site Management* P.: 55 11 3053-6611 Ext 8204 tabait@hcor.com.br Lucas Martins de Lima *Data Management* P.: 55 11 3053-6611 Ext 8208 lmlima@hcor.com.br **Department Coordinators:** Ligia Nasi Laranjeira *Ethics and Regulatory* P.: 55 11 3053-6611 Ext 8228 rgurgel@hcor.com.br Beatriz Gonzales Pacheco da Silva *Ethics and Regulatory* P.: 55 +55 11 3053-6611 Ext 8236 bpacheco@hcor.com.br Nanci Valeis *Ethics and Regulatory*	

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Member of BRICNet – Rede Brasileira de Pesquisa em Medicina Intensiva (Brazilian Network for Research in Intensive Medicine). ⦚ Thiago Domingos Correa – intensivist physician. Hospital Israelita Albert Einstein, São Paulo, SP. Member of BRICNet – Rede Brasileira de Pesquisa em Medicina Intensiva (Brazilian Network for Research in Intensive Medicine). ⦚ Fernando G Zampieri – interventionist physician. Hospital Alemão Oswaldo Cruz. Member of BRICNet – Rede Brasileira de Pesquisa em Medicina Intensiva (Brazilian Network for Research in Intensive Medicine). ⦚ Flávia Ribeiro Machado – intensivist physician. UTI Anestesiologia do Hospital São Paulo, UNIFESP, São Paulo, SP. Member of BRICNet – Rede Brasileira de Pesquisa em Medicina Intensiva (Brazilian Network for Research in Intensive Medicine). ⦚ Murillo Assunção – intensivist physician. Hospital Israelita Albert Einstein, São Paulo, SP. Member of BRICNet – Rede Brasileira de Pesquisa em Medicina	Manager Lucas Damiani Denise Paisani *Statistics* *Site Management* Eliana Santucci *Data Management* **Steering Committee:** • Alexandre Biasi Cavalcanti – Study Chair. Instituto de Pesquisa HCor, São Paulo, SP. Member of BRICNet – Rede Brasileira de Pesquisa em Medicina Intensiva (Brazilian Network for Research in Intensive Medicine). • Fernando G Zampieri – Principal Investigator. Instituto de Pesquisa HCor, São Paulo, SP. Member of BRICNet – Rede Brasileira de Pesquisa em Medicina Intensiva (Brazilian Network for Research in Intensive Medicine).	

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Intensiva (Brazilian Network for Research in Intensive Medicine). } Suzana Margareth Ajeje Lobo – intensivist physician. Hospital de Base de São José do Rio Preto and professor of the School of Medicine of São José do Rio Preto. Member of BRICNet – Rede Brasileira de Pesquisa em Medicina Intensiva (Brazilian Network for Research in Intensive Medicine). } Otávio Berwanger – epidemiologist physician. Instituto de Pesquisa HCor, São Paulo, SP. } Nilton Brandão – intensivist physician. Professor of the School of Medicine of Universidade Federal das Ciências da Saúde de Porto Alegre } John A Kellum - research physician. Intensive Care Unit of the University of Pittsburgh, Pittsburgh, United States. } Derek C Angus - intensivist physician. Director of Intensive Care Department of the University of Pittsburgh, Pittsburgh, United States.	• Flávia Ribeiro Machado – intensivist physician. Anestesiology ICU do Hospital São Paulo, UNIFESP, São Paulo, SP. Member of BRICNet – Rede Brasileira de Pesquisa em Medicina Intensiva (Brazilian Network for Research in Intensive Medicine). • Nilton Brandão – intensivist physician. Professor of the School of Medicine of Universidade Federal das Ciências da Saúde de Porto Alegre • Rodrigo Santos Biondi – intensivist physician. Instituto de Cardiologia do Distrito Federal, Brasilia, DF. • Flávio Geraldo Rezende Freitas – intensivist physician. Hospital SEPACO e Hospital São Paulo, UNIFESP, São Paulo, SP • John A Kellum – research physician. Intensive Care Unit of the University of Pittsburgh, Pittsburgh, United States.	

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Page 6 – Synopsis – Subgroups defined *a priori*		
Subgroups defined *a priori* - Patients with sepsis. - Patients with baseline acute kidney injury (KIDGO Stage 1) - Surgical patients - Patients with cranioencephalic trauma - APACHE II ≥ 25 or < 25 points - Patients that received > 1000 ml of sodium chloride in 24 hours prior to randomization versus ≤ 1000 ml - Patients who have received > 6,000 ml of fluids during the first 3 days. This analysis will be considered merely exploratory, once these subgroups cannot be defined initially (at the moment of randomization).	Subgroups defined *a priori* - Patients with sepsis. - Patients with baseline acute kidney injury (KDIGO Stage 1) - Surgical patients - Patients with cranioencephalic trauma - APACHE II ≥ 25 or < 25 points - Patients that received > 1000 ml of sodium chloride in 24 hours prior to randomization versus ≤ 1000 ml - Patients who have received > 6,000 ml of fluids during the first 3 days. This analysis will be considered merely exploratory, once these subgroups cannot be defined initially (at the moment of randomization).	Correction of typo in the word KDIGO

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Page 20 – Methods - Eligibility		
Exclusion Criteria The following exclusion criteria will be applied: 1. Age < 18 years 2. Kidney failure under renal replacement therapy or with expectation of requiring renal replacement therapy in the next six hours 3. Severe hyponatremia (serum Na ≤ 120 mmol/L) 4. Severe hypernatremia (serum Na ≥ 160 mmol/L) 6. Death considered imminent and inevitable within 24 hours 7. Patients with suspected or confirmed brain death 8. Patients under exclusive palliative cares	*Exclusion Criteria* The following exclusion criteria will be applied: 1. Age < 18 years 2. Kidney failure under renal replacement therapy or with expectation of requiring renal replacement therapy in the next six hours 3. Severe hyponatremia (serum Na ≤ 120 mmol/L) 4. Severe hypernatremia (serum Na ≥ 160 mmol/L) 5. Death considered imminent and inevitable within 24 hours 6. Patients with suspected or confirmed brain death 7. Patients under exclusive palliative cares 8. Patient previously included in the BaSICS	Correction in the number of the list

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9. Patient previously included in the BaSICS study	study	
Page 25 - Endpoints		
Secondary endpoints: - Kidney failure requiring renal replacement therapy in 90 days - - Kidney injury KDIGO ≥ 2 (51) on days 3 and 7 after randomization. For the diagnosis of kidney injury we will consider serum creatinine and diuresis: Serum creatinine ≥ 2.0 times the reference values or diuresis below 0.5 ml/kg/h for over 12h. The reference creatinine will be the lowest between randomization creatinine and previous creatinine (the oldest available in the last six months and prior to current admission). If there is no previous creatinine available, we will estimate its value using the MDMR equation: Creatinine = (75/[186x(age-0.203) x F x N]-0.887	Secondary endpoints: - Kidney failure requiring renal replacement therapy in 90 days - - Kidney injury KDIGO > 2 (51) on days 3 and 7 after randomization. For the diagnosis of kidney injury we will consider serum creatinine and diuresis: Serum creatinine ≥ 2.0 times the reference values or diuresis below 0.5 ml/kg/h on daily average. In case diuresis value isn't available, creatinine value will be used. The reference creatinine will be the lowest between randomization creatinine and previous creatinine (the oldest available in the last six months and prior to current admission). If there is no previous creatinine available, we will estimate its value using the MDMR equation: Creatinine = (75/[186x($age^{-0.203}$)	Adjustment on KDIGO score for kidney injury from KDIGO ≥ 2 to KDIGO > 2 and use of creatinine value

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Where F= 0,742 (female patients) and N = 1,21 for black patients - If, at the time of randomization, the patient already has KDIGO 2 criteria, it will not be counted as part of the sample to assess this outcome. - - New respiratory, hepatic, cardiac, neurological and coagulation dysfunction (using SOFA score) on days 3 and 7 (52). - - Mechanical ventilation-free days during the first 28 days after randomization. Tertiary endpoints (exploratory): - - Death by any cause at the ICU and hospital - - Length of stay at the ICU - - Duration of hospitalization	x F x N]$^{-0.887}$ Where F= 0,742 (female patients) and N = 1,21 for black patients - If, at the time of randomization, the patient already has KDIGO 2 criteria, it will not be counted as part of the sample to assess this outcome. - - New respiratory, hepatic, cardiac, neurological and coagulation dysfunction (using SOFA score) on days 3 and 7 (52). - - Mechanical ventilation-free days during the first 28 days after randomization. Tertiary endpoints (exploratory): - - Death by any cause at the ICU and hospital - - Length of stay at the ICU - - Duration of hospitalization	
Page 25 - Endpoints		
Other exploratory endpoints:	**Other exploratory endpoints:**	Alteration from EuroQol 5D-5L to 5D-3L

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- Comparison of serum chlorine values between the four possible study groups over time. - Quality of life assessment through EQ-5D-5L questionnaire in six months, to be conducted in sample of approximately 10% of the patients, obtained randomly	- Comparison of serum chlorine values between the four possible study groups over time. - Quality of life assessment through EQ-5D-3L questionnaire in six months, to be conducted in sample of approximately 10% of the patients, obtained randomly	Questionnaire alteration was made after Steering Committee's evaluation and identification that EQ5D5L version did not have a Portuguese validation and there were no data from other publications with its use, therefore, this questionnaire was changed for the EQ5D3L version.
Page 32 Statistical Analysis		

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Statistical analysis Detailed statistical analysis plan will be drawn up before the inclusion of patients begins. The fundamental characteristics of the statistical analysis plan are described below. All analyses will follow the intent to treat principle. We will evaluate the effect of Plasma-Lyte® compared to 0.9% sodium chloride and the effect of the two infusion rates on the primary outcome using a hazard ratio with a 95% confidence interval and comparison of Kaplan-Meier curves (using the log rank test). For binary secondary endpoints we will perform the comparison using relative risks, 95% confidence intervals and chi-square tests. For continuous outcomes with normal distribution, we will present the medical difference, 95% confidence interval and P value calculated by t test. For continuous endpoints with asymmetric distribution, we will perform the Wilcoxon test. We will analyze the effect of the fluids under study on primary outcomes	**Statistical analysis** Detailed statistical analysis plan will be drawn up before the inclusion of patients begins. The fundamental characteristics of the statistical analysis plan are described below. All analyses will follow the intent to treat principle. We will evaluate the effect of Plasma-Lyte® compared to 0.9% sodium chloride and the effect of the two infusion rates on the primary outcome using a *hazard ratio* with a 95% confidence interval and comparison of Kaplan-Meier curves (using the log rank test). For binary secondary endpoints we will perform the comparison using relative risks, 95% confidence intervals and chi-square tests. For continuous outcomes with normal distribution, we will present the medical difference, 95% confidence interval and P value calculated by *t* test. For continuous endpoints with asymmetric distribution, we will perform the Wilcoxon test. We will analyze the effect of the fluids under study on primary outcomes according	Correction of typo in the word KDIGO

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according to the following subgroups: - Sepsis patients (50). - Patients with baseline acute kidney injury (KIDGO Stage 1) - Surgical patients - Patients with cranioencephalic trauma - APACHE II > 25 or < 25 points - Patients that received > 1000 ml of sodium chloride in 24 hours prior to randomization versus ≤ 1000 ml - We will also evaluate the effect of Plasma-Lyte® versus sodium chloride in patients who have received> 6,000ml of fluids during the first 3 days. This analysis will be considered merely exploratory, once these subgroups cannot be defined initially (at the moment of randomization).	to the following subgroups: - Sepsis patients (50). - Patients with baseline acute kidney injury (KDIGO Stage 1) - Surgical patients - Patients with cranioencephalic trauma - APACHE II ≥ 25 or < 25 points - Patients that received > 1000 ml of sodium chloride in 24 hours prior to randomization versus ≤ 1000 ml - We will also evaluate the effect of Plasma-Lyte® versus sodium chloride in patients who have received> 6,000ml of fluids during the first 3 days. This analysis will be considered merely exploratory, once these subgroups cannot be defined initially (at the moment of randomization).	