



Plasma-Lyte148[®] versUs Saline

PLUS Study

A multi-centre, blinded, randomised, controlled trial to determine whether fluid resuscitation and therapy with a “balanced” crystalloid solution (Plasma-Lyte 148[®]) compared with 0.9% sodium chloride (saline) decreases 90-day mortality in critically ill patients requiring fluid resuscitation

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1. Protocol Synopsis

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|-----------------------------|---|
| Title | A multi-centre, blinded, randomised, controlled trial (RCT) to determine whether fluid resuscitation and therapy with a “balanced” crystalloid solution (Plasma-Lyte 148®) decreases 90-day mortality in critically ill patients requiring fluid resuscitation when compared to the same treatment with 0.9% sodium chloride (saline) |
| Short Title | Plasma-Lyte 148® versus Saline (PLUS) Study |
| Design | Prospective, multi-centre, parallel group, concealed, blinded, randomised, controlled trial |
| Outcomes | <p><u>Primary</u> Death from all causes within 90 days after randomisation</p> <p><u>Secondary</u></p> <ul style="list-style-type: none"> • Mean and peak serum creatinine concentration during the first seven days • Maximum post-randomisation increase in serum creatinine in ICU during the index hospital admission • Proportion of patients newly treated with renal replacement therapy up to 90 days after randomisation • Proportion of patients treated with and duration of treatment with vasoactive drugs • Duration of Mechanical Ventilation in ICU • Length of stay and all-cause mortality at ICU discharge • Length of stay and all-cause mortality at 28 days • Length of stay and all-cause mortality at hospital discharge • Quality of life assessed at six months after randomisation • Health services use during the six months after randomisation • Subgroup analyses: Outcomes will also be examined in four subgroups defined by the following baseline characteristics; patients with or without kidney injury (defined by threshold creatinine concentration), with or without sepsis (defined using 2016 SOFA-based criteria), admitted to the ICU directly after surgery or not, low versus high severity of illness (defined by APACHE II score <25 or ≥25) |
| Intervention | Plasma-Lyte 148® or 0.9% saline for all resuscitation episodes and compatible crystalloid therapy whilst in ICU, from the first episode of fluid resuscitation (randomisation) for up to 90 days |
| Sample Size | 8,800 patients |
| Eligibility Criteria | <p><u>Inclusion Criteria</u></p> <ul style="list-style-type: none"> • The patient will receive fluid resuscitation defined as a bolus of fluid prescribed to be administered over one hour or less to increase or maintain intravascular volume that is in addition to maintenance fluids, or specific fluids used to replace non-physiological fluid losses • The patient is expected to be in the ICU the day after tomorrow • The patient is not expected to be well enough to be eating tomorrow • An arterial or central venous catheter is in situ, or placement is imminent as part of routine management • Both Plasma-Lyte 148® and 0.9% saline are considered equally appropriate for the patient • The requirement for fluid resuscitation is supported by at least one of seven pre-specified clinical signs: heart rate > 90 beats per minute; systolic blood pressure < 100 mmHg or mean arterial pressure < 75 mmHg; central venous pressure < 10 mmHg; pulmonary artery wedge pressure < 12 mmHg; capillary refill time > 1 second; OR urine output < 0.5 ml/kg for at least one hour <p><u>Exclusion criteria</u></p> <ul style="list-style-type: none"> • Age less than 18 years • Patients who have previously received fluid resuscitation (as defined above) <u>prescribed in the ICU</u> during this current ICU admission • Patients transferred directly from another ICU who have received fluid resuscitation (as defined above) during that ICU admission • Contraindication to either study fluid e.g. previous allergic reaction to Plasma-Lyte 148® • Patients admitted to the ICU with specific fluid requirements: the treatment of burns; following liver transplantation surgery; for correction of specific electrolyte abnormalities • Patients with traumatic brain injury or those considered at risk of developing cerebral oedema • Patients in whom death is deemed imminent and inevitable • Patients with an underlying disease process with a life expectancy of <90 days • Patients in whom it is unlikely the primary outcome can be ascertained • Known or suspected pregnancy • Patients who have previously been enrolled in PLUS |

2. Glossary of Abbreviations and Terms

| | |
|--------------------|--|
| ADR | Adverse Drug Reaction |
| AKI | Acute Kidney Injury |
| ANZICS | Australian and New Zealand Intensive Care Society |
| ANZICS CORE | Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation |
| APACHE | Acute Physiology and Chronic Health Evaluation |
| APD | Adult Patient Database |
| CHEST | Crystalloid vs. Hydroxyethyl Starch Trial |
| CRF | Case Report Form |
| DSMC | Independent Data and Safety Monitoring Committee |
| eCRF | electronic Case Report Form |
| EQ-5D-5L | A descriptive system of health-related quality of life states consisting of five dimensions, developed by the European Quality of Life Group (EuroQoL) |
| GCP | Good Clinical Practice - guidelines developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| HREC | Human Research Ethics Committee |
| ICU | Intensive Care Unit |
| IV | Intravenous |
| NEAF | National Ethics Application Form |
| NICE-SUGAR | Normoglycemia in Intensive Care Evaluation - Survival Using Glucose Algorithm Regulation Study |
| NHMRC | Australian National Health and Medical Research Council |
| QOL | Quality of Life |
| RCT | Randomised Controlled Trial |
| RGO | Research Governance Officer |
| RRT | Renal Replacement Therapy |
| SADR | Serious Adverse Drug Reaction |
| SAFE | Saline versus Albumin Fluid Evaluation |
| SDM | Substitute Decision Maker |
| SOP | Standard Operating Procedures |
| SPLIT | Saline vs. Plasma-Lyte 148® for ICU Fluid Therapy Study |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |

3. Administrative information

3.1 Chief Investigator

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3.3 Management Committee

- Professor Simon Finfer (CHAIR), Professorial Fellow - Critical Care & Trauma Division | The George Institute for Global Health, NSW
- Professor John Myburgh, Director - Critical Care & Trauma Division | The George Institute for Global Health, NSW
- Professor Rinaldo Bellomo, Staff Specialist - Intensive Care Unit | The Austin Hospital, VIC
- Dr Paul Young, Staff Specialist - Intensive Care Medicine | Wellington Regional Hospital, NZ
- Associate Professor David Gattas, Staff Specialist - Intensive Care Unit | Royal Prince Alfred Hospital, NSW
- Dr Manoj Saxena, Staff Specialist - Intensive Care Unit | St George Hospital, NSW
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- Ms Naomi Hammond, Research Fellow - Critical Care & Trauma Division | The George Institute for Global Health, NSW
- Ms Sharon Micallef, Project Manager (PLUS) - Critical Care & Trauma Division | The George Institute for Global Health, NSW
- Dr Parisa Glass, Deputy Director - Critical Care & Trauma Division | The George Institute for Global Health, NSW
- Ms Diane Mackle, Study Coordinator for NZ (PLUS) - Medical Research Institute of New Zealand

Terms of reference for study committees and conflict of interest statements are specified in the Management Committee Charter.

3.4 Funding

The study is funded by a Project Grant from the Australian National Health and Medical Research Council (NHMRC) - Project Grant ID 177267

The study is supported by Baxter Healthcare Corporation and its subsidiary Baxter Healthcare Pty Ltd.

3.5 Role of Funding Bodies

The study will be designed and conducted, and the results analysed, presented and published by the investigators independent of the funding agencies and commercial partners.

3.6 Trial Identification/Registration

World Health Organisation (WHO) Universal Trial Number (UTN): U1111-1178-8334

ClinicalTrials.gov Registry Identifier: NCT02721654

4. Introduction

4.1 Background

Fluid for resuscitation of critically ill patients

Fluid resuscitation is a fundamental component of the management of acutely and critically ill patients and the choice of fluid is a longstanding issue of debate.^{1, 2} Two pivotal trials, the Saline versus Albumin Fluid Evaluation (SAFE) study³ and the Crystalloid vs. Hydroxyethyl Starch Trial (CHEST),⁴ remain the two largest Randomised Controlled Trials (RCTs) ever conducted in Intensive Care Medicine. These trials have influenced clinical practice and medical regulatory authorities^{5, 6} worldwide.

The SAFE study compared 4% albumin (the dominant natural colloid in the world) to 0.9% saline in 6,997 critically ill adults and found that while overall albumin and saline produced similar outcomes,³ 0.9% saline use was associated with significantly decreased mortality in patients with traumatic brain injury.⁷ CHEST compared 6% hydroxyethyl starch (the dominant artificial colloid in the world) to 0.9% saline in 7,000 critically ill adult patients and found that hydroxyethyl starch was associated with an increase in the incidence of acute kidney injury (AKI) requiring treatment with renal replacement therapy (RRT).⁴

Heavily influenced by these two RCTs, subsequent high-quality meta-analyses recommend that the use of colloids for fluid resuscitation confers no benefit to patients over crystalloids and are associated with net harm.^{8, 9} Consequently, the use of crystalloids has increased and 0.9% saline has been the most commonly used crystalloid solution worldwide.¹⁰ However, the safety and efficacy of using any crystalloid over another has not been tested in a high-quality, large-scale RCT. In the absence of such a trial, the use of 0.9% saline is increasingly being challenged by emerging evidence that suggests its high chloride content may have clinically important adverse effects and that resuscitation with so-called “balanced” or “buffered” crystalloids may offer patients better outcomes.

Concerns about 0.9% saline and high chloride fluids

“Normal” or 0.9% saline has a markedly non-physiological chloride content of 150 mmol/L compared to approximately 100 mmol/L in plasma. When administered rapidly and in appreciable amounts, 0.9% saline induces a hyperchloraemic acidosis that may persist for hours or days in critically ill patients.¹¹

Until recently, these metabolic perturbations were considered by clinicians to be relatively benign. Recent experimental data from animal models of sepsis have demonstrated that excessive chloride administration through the administration of 0.9% saline results in an increase in histological injury to kidneys, a greater release of biomarkers of kidney injury and increased mortality compared with crystalloid solutions with a more physiologic chloride content, such as the prototype Hartmann’s or Plasma-Lyte[®] solutions.¹²

Human studies also suggest that 0.9% saline may have harmful effects. In a blinded, cross-over, randomised controlled study in healthy human volunteers, the administration of two litres of 0.9% saline significantly decreased renal cortical blood flow compared to Plasma-Lyte 148[®].¹³

In a widely cited sequential observational study in an Australian ICU, the average per patient use of 0.9% saline was reduced from 3200 mL to 60 mL resulting in a reduction in the mean chloride administered from 694 to 496 mmol per patient, while administration of balanced crystalloids increased from 550 mL to 3400 mL per patient.¹⁴ The intervention was initially applied for 6 months and extended to a further 12 months, at which time a significant reduction in the incidence of Acute Kidney Injury (AKI) and need for Renal Replacement Therapy (RRT) was observed.¹⁵ (Figure 1) Furthermore, the observed hospital mortality reduced from 14.9% to 12.7%, a relative risk reduction of 14.7% ($p=0.08$).

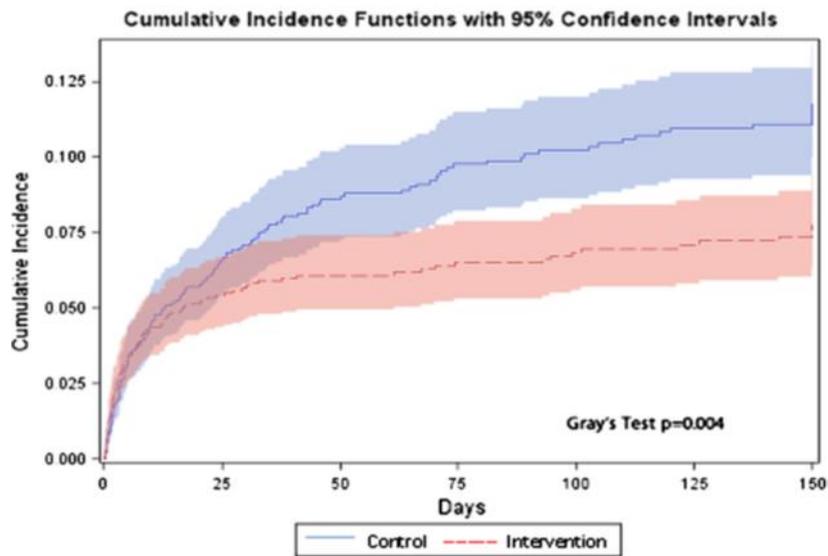


Figure 1: Cumulative incidence of renal replacement therapy during restriction of intravenous chloride intake

In a series of retrospective observational studies from a large US hospital claims database, outcomes of post-operative patients having open abdominal surgery who received either 0.9% saline or exclusively Plasma-Lyte A[®] or Plasma-Lyte148[®] were compared.¹⁶ Using multivariable logistic regression and propensity score matching the investigators observed that the use of Plasma-Lyte[®] was associated with a significant reduction in major post-operative complications compared to 0.9% saline. The same investigators analysed similar data in critically ill adults with sepsis and reported that treatment with Plasma-Lyte[®] was associated with a reduction in hospital mortality from 22.9% to 19.6%.¹⁷ In a third study, the investigators found that increases in serum chloride concentration were associated with increased hospital mortality in patients with the systemic inflammatory response syndrome. After adjusting for illness severity and crystalloid fluid volume, reduced chloride administration was associated with decreased hospital mortality.¹⁸

A meta-analysis of high vs. low-chloride content intravenous fluid resuscitation in perioperative and critical care patients reported that 0.9% saline was associated with a 60% increase in the relative risk of developing AKI, an approximate 300% increase in relative risk for metabolic acidosis, an increased risk of receiving blood transfusion and an increased duration of mechanical ventilation.¹⁹

As most of the emerging evidence suggesting a potential benefit associated with the use of balanced crystalloid solutions over 0.9% saline comes from experimental and observational studies, the generalisability and applicability of these results to clinical practice remains uncertain due to the

limitations of internal validity, particularly confounding and ascertainment bias inherent in observational studies.²⁰

Has practice changed in response to recent evidence?

There is little evidence of a substantive global change in clinical practice in response to the emerging evidence mentioned above. For example, in a recent randomised controlled study of two resuscitation strategies in 1341 emergency room patients with sepsis in the USA, close to 100% of enrolled patients were resuscitated with 0.9% saline.²¹

In Australia, overall sales of 1L bags of 0.9% saline by Baxter Healthcare Pty Ltd (the major supplier of intravenous crystalloids in Australia) totalled over 6.1 million units in 2013 compared with slightly more than 207,000 units of Plasma-Lyte 148®. (Baxter personal communication)

Our group has monitored patterns of fluid resuscitation in Australian and New Zealand ICUs by collecting prospective data through the ANZICS Clinical Trials Group Point Prevalence Program.²² Between 2007 and 2013, the proportion of patients receiving crystalloid increased significantly from 28.9% in 2007 to 50.5% in 2013 ($p=0.01$). Of these, the proportion of patients receiving balanced salt solutions has increased steadily. (Figure 2) This change in practice was primarily due to a significant decrease in the use of colloids.

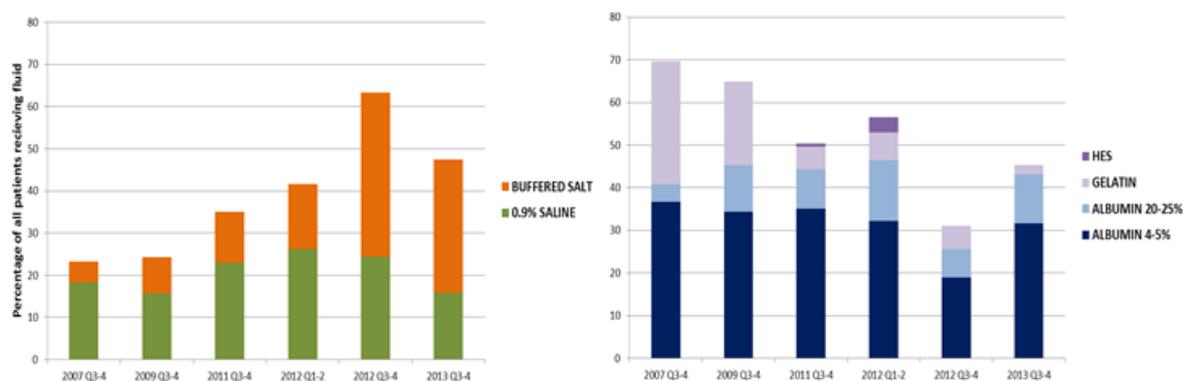


Figure 2. Patterns of crystalloid (left panel) and colloid (right panel) use in Australian and New Zealand ICUs from 2007 to 2013.

Which balanced crystalloid solution?

In Australia, there are two licenced proprietary balanced crystalloid solutions: Hartmann's solution and Plasma-Lyte 148®. In a randomised blind comparison between these two solutions in complex post-operative patients, Hartmann's solution was associated with higher serum chloride concentrations than Plasma-Lyte 148® ($p=0.03$).²³ Hartmann's solution contains lactate and was associated with increased blood lactate concentration compared to Plasma-Lyte 148® in both critically ill patients and after complex major surgery ($p=0.01$). While iatrogenic hyperlactataemia may not be harmful, it may create diagnostic confusion in critically ill patients where hyperlactataemia is regularly used as marker of physiological instability or as a resuscitation endpoint.²⁴

The most recent data comes from a cluster randomised pilot trial conducted in four New Zealand ICUs - the Saline vs. Plasma-Lyte 148® for ICU Fluid Therapy (SPLIT) Study.²⁵ In this trial, there was no significant difference in the primary outcome of acute kidney injury or failure (defined using the creatinine criteria of the RIFLE score²⁶) between Plasma-Lyte 148® and 0.9% saline (9.6 vs. 9.2%, $p=0.77$). Although the trial had insufficient power to examine effects on risk of death, the relative risk of in-hospital death was 12.8% lower in patients assigned Plasma-Lyte® (7.5% vs. 8.6%; RR 0.87; 95%CI 0.66 to 1.55; $p=0.36$).

The above considerations suggest that Plasma-Lyte 148® would be the logical comparator to 0.9% saline from a biochemical and clinical perspective.

4.2 Rationale

Rationale for a large-scale high-quality trial comparing Plasma-Lyte 148® with 0.9% saline for fluid resuscitation

Worldwide, 0.9% saline is administered to millions of patients and has traditionally been the most widely used resuscitation fluid.¹⁰ The emerging evidence outlined above suggests that balanced crystalloid solutions may be associated with decreased mortality and risk of AKI, although substantial clinician uncertainty remains.

The additional cost of Plasma-Lyte 148® over 0.9% saline is approximately \$2 per litre. To place this in an Australian context, an admission to the ICU costs approximately \$4000/day, RRT in the ICU approximately \$300/day, and the average course of RRT treatment in ICU approximately \$1500.²⁷ That balanced crystalloids are used in one third of patients requiring fluid resuscitation in Australian ICUs demonstrates an increasing acceptance of balanced crystalloids, although 0.9% saline remains the fluid most commonly used, a pattern that is more prevalent worldwide.

Given the limitations of current evidence, there is now a scientific, ethical and health economic imperative to provide an accurate and reliable estimate of the comparative risks versus benefit of Plasma-Lyte 148® versus 0.9% saline. This can only be obtained from a high-quality, large-scale randomised trial as along the lines of the SAFE study and CHEST previously conducted by our group.

5. Study Objectives

5.1 Aim

To conduct a multi-centre, blinded, randomised, controlled trial (RCT) to determine whether fluid resuscitation and therapy with a “balanced” crystalloid solution (Plasma-Lyte 148®) decreases 90-day mortality in critically ill patients requiring fluid resuscitation when compared with the same treatment using 0.9% sodium chloride (saline).

5.2 Hypothesis

The PLUS study will test the hypothesis that in a heterogeneous population of critically ill adults random assignment to Plasma-Lyte 148® for intravascular volume resuscitation and crystalloid fluid therapy in the Intensive Care Unit (ICU) results in different 90-day all-cause mortality when compared with random assignment to 0.9% sodium chloride (saline) for the same treatment.

6. Study Design

This study is a prospective, multi-centre, parallel group, concealed, blinded, randomised, controlled trial.

The primary endpoint will be death from all causes at 90 days after randomisation.

8,800 patients will be enrolled at approximately 40-50 study sites in Australia and New Zealand. Participants will be randomly assigned to receive either Plasma-Lyte 148® or 0.9% saline for all resuscitation episodes and for all compatible crystalloid therapy while in ICU for up to 90 days after the first episode of fluid resuscitation (randomisation). Other crystalloid fluids may be used as carrier fluids for the infusion of any drug for which either Plasma-Lyte 148® or 0.9% saline is considered incompatible.

7. Study Outcome

7.1 Primary Outcome

Death from all causes 90 days after randomisation

7.2 Secondary Outcomes

- Mean and peak serum creatinine concentration during the first seven days
- Maximum post-randomisation increase in serum creatinine in ICU during the index hospital admission
- Proportion of patients newly treated with renal replacement therapy up to 90 days after randomisation
- Proportion of patients treated with and duration of treatment with vasoactive drugs
- Duration of Mechanical Ventilation in ICU
- Length of stay and all-cause mortality at ICU discharge
- Length of stay and all-cause mortality at 28 days
- Length of stay and all-cause mortality at hospital discharge
- Quality of life assessed at six months after randomisation
- Health services use during the six months after randomisation
- Subgroup analyses: Outcomes will also be examined in four subgroups defined by the following baseline characteristics; patients with or without kidney injury (defined by threshold creatinine concentration), with or without sepsis (defined using 2016 SOFA-based criteria), admitted to the ICU directly after surgery or not, low versus high severity of illness (defined by APACHE II score <25 or ≥25)

7.3 Economic Evaluation

A cost-effectiveness analysis will be conducted at 6-months following randomisation comparing costs and quality-adjusted life years gained between treatment arms.

8. Study Participants

8.1 Study Setting

This study will be conducted in approximately 40-50 Intensive Care Units in Australia and New Zealand.

8.2 Inclusion Criteria

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

8.3 Exclusion Criteria

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

9. Study Interventions

9.1 Randomisation

Permuted block randomisation with variable block sizes, stratified by site will be conducted via a password-protected, secure website.

Following successful randomisation, each patient will be assigned a unique 'patient study number' and be assigned to receive either Plasma-Lyte 148® or 0.9% saline (blinded study treatment).

9.2 Study Treatment

Following randomisation, each study participant will receive either Plasma-Lyte 148® or 0.9% saline alone for all resuscitation episodes and for all compatible intravenous crystalloid therapy while in ICU (for up to 90 days). Other crystalloid fluids may be used as carrier fluids for the infusion of any drug for which either Plasma-Lyte 148® or 0.9% saline is considered incompatible.

Both study fluids are manufactured by Baxter Healthcare Pty Ltd (Old Toongabbie, NSW) and will be labelled, packed and distributed by the company directly to the study sites in periodic shipments. Study fluid will be coded and labelled in compliance with applicable regulations, and in a manner that protects the blinding.

The study treatments will be supplied in identical 1000 mL bags. Both fluids are colourless, clear solutions and macroscopically indistinguishable.

All clinician's involved in the prescription of blinded study treatment must read Product Information for both Plasma-Lyte 148® and 0.9% saline which provide detailed information about the composition, indications, side effects, suggested dosage and contraindications of the study treatments. Study fluids must be stored below 30 degrees Celsius.

Study participants, treating clinicians, study investigators and data collectors will be 'blind' to study treatment allocation.

Management of fluid storage and allocation will be determined on a site by site basis and designed to maximise protocol adherence and avoid both wastage and unintended use of non-study fluids.

9.3 Study Fluid Regimen

Patients will receive the study fluid to which they have been assigned for all episodes of fluid resuscitation and for all compatible intravenous crystalloid therapy thereafter in the ICU until 90 days following randomisation. Any patient who is discharged from the ICU but re-admitted within 90 days of randomisation will receive the blinded study fluid to which they had previously been assigned. Any patient in the ICU after day 90 will receive unblinded crystalloid fluid at the discretion of the treating clinicians.

The volume of study fluid being administered will be titrated against clinical endpoints determined by the treating clinicians and reviewed as clinically appropriate during the period of resuscitation and ICU treatment.

Patients treated with drug infusions diluted in crystalloid fluids will receive drug infusions in small volumes of crystalloid administered using syringe drivers or other volumetric infusion systems according to the protocol of each ICU.

9.4 Concomitant treatment during trial period

Aside from the study treatment, patient management will be otherwise unaffected and the treating clinicians will be free to provide whatever medical care is deemed best and necessary for the patient.

Where specific crystalloid solutions become clinically indicated the appropriate crystalloid fluid will be allowed by the protocol as directed by the attending clinicians. All study and non-study fluids administered will be recorded.

There will be no attempt to control which intravenous fluids are used prior to a patient's admission to the ICU (such as that which may be given in the emergency department or operating theatre) or intravenous fluids given after discharge from the ICU, regardless of whether or not this is within the 90 day study period.

9.5 Precautions and Adverse Reactions

Plasma-Lyte 148® and 0.9% saline are registered products with both the Australian Therapeutic Goods Administration and Medsafe (New Zealand). The treating clinician must be aware of the precautions and potential adverse reactions for Plasma-Lyte 148® and 0.9% saline detailed in Product Information. The study exclusion criteria ensure that patients likely to experience adverse effects of Plasma-Lyte 148® and 0.9% saline are excluded. Patients will be monitored for the known side effects of intravenous therapy with Plasma-Lyte 148® and 0.9% saline.

9.6 Withdrawal of Study Treatment

Following randomisation, every effort should be made to ensure patients continue to receive study treatment as described in the protocol.

Study treatment may be stopped in the following circumstances:

- Request to withdraw by the patient or their substitute decision maker/person responsible: The patient or their substitute decision maker/person responsible may request the study treatment be stopped if they decide to do so, at any time, without needing to give a reason. Consent to continue follow up and in particular to determine vital status at 90 days will be sought
- Definite indication, or a contraindication, to either study treatment becomes apparent: The patient will remain in the study and the follow-up schedule will continue unchanged, however no further study treatment will be delivered while the contra-indication remains

- Adverse or serious adverse reaction to study treatment: The patient will remain in the study and the follow-up schedule will continue unchanged, however no further study treatment will be delivered

9.7 Unblinding

Study participants, treating clinicians, study investigators and data collectors will be blinded to study treatment allocation.

The unblinding of a participant's allocated study treatment will only be performed when knowledge of the treatment allocation is necessary for the continued safe management of the participant. The treating clinician or investigator should contact the coordinating centre if they consider there is a need for unblinding and the request will be adjudicated in a timely fashion by the study Chief Investigator or a nominated delegate.

In any case of unblinding, the follow-up schedule of data collection will be maintained.

10. Data Collection

Study participants will be followed-up for 6 months post-randomisation, or to death, whichever is the earlier.

10.1 Screening

Patients will be screened and evaluated to assess eligibility for the study. A screening log will be kept to monitor recruitment and report the size of the patient population from which eligible patients have been recruited.

10.2 Randomisation

The patient's demographics will be entered into a web based randomisation system. Each eligibility criterion will be answered with a Yes / No response and only patients meeting all criteria will proceed to randomisation.

10.3 Baseline

Patient demographics, admission diagnosis and clinical information will be collected to assess baseline balance between each treatment group. Clinical information will allow calculation of the Acute Physiology and Chronic Health Evaluation (APACHE) II²⁸ score - a numerical score to classify illness severity in intensive care patients - calculated using 12 routinely collected physiological parameters (e.g. temperature, blood pressure).

10.4 During ICU Stay

Daily clinical information and laboratory data will be recorded whilst the patient is in ICU for up to 90 days post randomisation to document response to treatment and to monitor safety.

10.5 Follow up at Day 90 and 6 months

Follow-up for the primary outcome will be until death or 90 days post randomisation, whichever is the earliest. At day 90, vital status, length of stay in the ICU, length of stay in hospital, date and cause of death (if appropriate) will be recorded. Follow up at 6 months will assess vital status, quality of life (QOL) and functional capacity using the EQ-5D-5L quality of life questionnaire²⁹.

On completion of 6 month follow-up, where possible, record linkage to routinely collected health data will be performed on all patients enrolled in PLUS. Encrypted patient identifiers (name, address, date of birth) will be sent offsite to state and national data linkage units who will perform linkage of study participants to the various datasets (excluding the Medicare Benefits Schedule and Pharmaceutical Benefits Schedule [Medicare Australia]). This will enable assessment of longer term outcomes and for cost-effectiveness analyses to be conducted.

10.6 Data Collection Method

While in the hospital, study participants will have relevant study data extracted from their medical record. If they are discharged from the hospital, they (or a nominated carer) will be contacted by telephone at 90 days post-randomisation for information on vital status and at 6 months to assess quality of life and functional capacity.

The Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation (ANZICS CORE) Adult Patient Database (APD) number will be collected at Day 90. Data routinely collected and available in the ANZICS CORE APD may be used to cross check data entered in the PLUS database.

10.7 Case Report Forms

Data will be collected using a secure online electronic Case Report Form (eCRF) designed and managed by The George Institute for Global Health and a commercial provider.

10.8 Record retention

All paper study records, including consent documentation, paper CRFs (if used) and electronic records will be kept for 15 years following the completion of the study.

10.9 Schedule of Assessments

| Task | Screening | Randomisation | Baseline | Day 1 to 14 ¹ | Day 15 to 90 ¹ | Day 90 follow-up | 6 month follow-up |
|---|-----------|---------------|----------|--------------------------|---------------------------|------------------|-------------------|
| Assess ability to gain consent & follow-up | X | | | | | | |
| Assess eligibility to enter study | X | | | | | | |
| Demographics & eligibility checklist | | X | | | | | |
| Administer study treatment | | | | X | X | | |
| ICU admission date, source, primary diagnosis | | | X | | | | |
| Sub group categories at baseline ² | | | X | | | | |
| APACHE II score [28] | | | X | | | | |
| SOFA Scores | | | X | X | X | | |
| Laboratory Data | | | X | X | X | | |
| Vital signs | | | X | X | | | |
| Mechanical Ventilation | | | X | X | X | | |
| Renal Replacement Therapy | | | X | X ³ | X ³ | X | |
| Study fluid input | | | | X | X | | |
| Other fluid input | | | | X | | | |
| Urine output | | | | X | | | |
| Other fluid output | | | | X | | | |
| Reconciliation of study treatment | | | | X | X | | |
| Temporary or permanent withdrawal of study treatment | | | | X | X | | |
| Consent | | | X | | | | |
| Vital status (cause of death at Day 90 if applicable) | | | | | | X | X |
| Discharge date from ICU, from hospital | | | | | | X | |
| Quality of Life assessment (EQ-5D-5L) | | | | | | | X |
| Linkage to health services data (economic evaluation) | | | | | | | X |
| Adverse reactions | | | | | X | | |
| Protocol deviations | | | | | X | | |

¹ Whilst in ICU only

² With or without kidney injury / with or without sepsis / post-op ICU admission / low versus high severity of illness

³ Duration of Renal Replacement Therapy for patients with new renal injury collected up to 90 days

11.Data Management

Data management will be provided by The George Institute for Global Health. The principle means of data collection and data processing will be electronic via a password protected website. All computerised forms will be electronically signed by the authorised study staff and all changes made following the electronic signing will have an electronic audit trail with a signature and date.

A comprehensive guide to data collection with definitions and rationale will be provided together with a paper version of the case report forms. Paper documents will be stored in secure locked cabinets with access limited to authorised persons.

A comprehensive guide to accessing the data entry forms on the website and entering all follow-up data is also provided in the Data Completion Manual and Operations Manual. All of these documents are also available in PDF format for printing from the study website as required to assist the research co-ordinator to ensure high-quality data collection and data entry.

12. Safety Monitoring and Reporting

It is recognised that the patient population in the ICU will experience a number of aberrations in laboratory values, signs and symptoms due to the severity of the underlying disease and the impact of standard treatments in the ICU. These will not necessarily constitute adverse events or serious adverse events unless they are considered to be related to study treatment or in the principal investigator's clinical judgement are not recognised events consistent with the patient's underlying disease and expected clinical course.

In this study, reporting of adverse events will be restricted to events that are considered to be related to study treatment (possibly, probably or definitely). Investigators are advised to refer to the product information for details of adverse reactions associated with Plasma-Lyte 148® and 0.9% saline. Events collected as study outcomes will not be reported as adverse events.

12.1 Adverse Drug Reactions (ADR)

In respect of marketed medicinal products, a well-accepted definition of an adverse drug reaction is:

A response to a drug which is noxious and unintended and which occurs in doses normally used in humans for prophylaxis, diagnosis or therapy of disease or for modification of physiological function.³⁰

Any adverse reaction thought to be study treatment related will be reported to the coordinating centre within 7 days of discovery. The site principal investigator will be responsible for determining the causal relationship as either possible, probable or definitely study treatment related. Notification will be by fax, scanned document sent by email or by completing an ADR form on the web based data management system.

All adverse reactions will be reviewed by the coordinating centre staff and recorded in a safety database and will be reported to the independent data and safety monitoring committee (DSMC) on a regular basis.

12.2 Serious Adverse Drug Reactions (SADRs)

Serious adverse events are defined as any untoward medical occurrence that meets one of more of the following criteria:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that jeopardises the study patient and requires intervention to prevent one of the other outcomes listed in the definition above

The classification of 'serious adverse event' is not related to the assessment of the severity of the adverse event. An event that is mild in severity may be classified as a serious adverse event based on the above criteria. Given that critically ill patients are likely to meet any of the above listed criteria in the course of their ICU admission, only serious events that are thought to be related to study treatment will be reported.

Serious adverse drug reactions should be reported to the coordinating centre within 24 hours of participating site study staff becoming aware of the occurrence. A member of the coordinating centre will be available 24 hours a day for out of 'business hours' reporting.

12.3 Suspected Unexpected Serious Adverse Reactions (SUSARs)

A SUSAR is an SADR which is considered *unexpected*. An SADR whose nature, severity, specificity, or outcome is not consistent with the term or description used in the product information, should be considered unexpected. These will also be reported to the coordinating centre within 24 hours of participating site study staff becoming aware of the occurrence.

12.4 Reporting SADR and SUSARs

The minimum information to report will include:

- Patient initials and study number
- Nature of the event
- Commencement and cessation of the event
- Outcome of the event
- The principal or co-investigator's opinion of the relationship between study drug and the event (possibly, probably or definitely related)
- Whether treatment was required for the event and what treatment was administered

The coordinating centre staff will be responsible for following-up all SADRs and SUSARs to ensure all details are available. The coordinating centre is also responsible for alerting other participating sites to the reported SADR or SUSAR and reporting to the regulatory authorities within required time frames.

It is the responsibility of each principal investigator to inform the local or lead HREC of all SADR and SUSAR events which occur at their hospital, in accordance with local requirements. Copies of any reporting and correspondence to and from the local HREC or RGO should also be sent to the coordinating centre.

12.5 Unblinding for an SADR or SUSAR

To unblind the treatment allocation for a SADR or SUSAR, the principal investigator or treating clinician must make a decision about the need to unblind the study treatment for that patient. Wherever possible, it is preferable to maintain blinding. However, if knowledge of the study treatment type is required to treat the adverse reaction quickly and correctly, then unblinding may be required.

12.6 Independent Data and Safety Monitoring Committee

A Data Safety and Monitoring Committee (DSMC), independent from the coordinating centre and investigators, will perform an ongoing review of predefined safety parameters, study outcomes and overall study conduct. The DSMC will be comprised of experts in clinical trials, fluid therapy, statistics and intensive care medicine.

The DSMC will review all unblinded adverse reactions at predetermined intervals during the study or as deemed appropriate by the DSMC (see section 13.3). The primary responsibility of the DSMC is to review interim analyses of outcome data and to recommend to the Study Management Committee whether the study needs to be changed, unblinded or terminated based on these analyses. Full details of the DSMC procedures and processes are documented in the DSMC charter.

12.7 Study Termination and Completion

The study may be terminated at any time at the request of the Study Management Committee, or a regulatory authority, with proper and timely notification of all parties concerned. The local or lead HREC will be informed promptly and the coordinating centre or the investigator will supply reason(s) for the termination or suspension, as specified by the applicable regulatory requirements. Otherwise, the study is considered completed upon completion of all patient treatments and evaluations.

13. Statistical Methods

13.1 Power Calculation and Sample Size

The planned sample size is 8,800 patients. The largest dataset available indicates the possibility of a 3.2% absolute decrease in mortality with balanced fluids compared with 0.9% saline in critically ill patients. The population to be included in the PLUS study is based on the population recruited to the landmark Normoglycemia in Intensive Care Evaluation Study-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study.³¹ The control group in this study included over 90% of patients who were mechanically ventilated at randomisation and who had a day 90 mortality rate of 24.9%. Allowing for a 2% secular reduction of interval mortality from 2008 to 2015 we expect a mortality of 23% in patients assigned to 0.9% saline resuscitation (control). Data from a subgroup of patients from the SPLIT trial with similar inclusion criteria to the PLUS study confirms a relative risk reduction of 12.5% that is consistent across subgroups. Thus the study has been designed to have 90% power to detect a 2.9% reduction in 90 day mortality in the study population; this is less than the reduction in mortality reported in database studies.

Based on these data-derived assumptions, a study of 8596 patients would provide 90% power to detect a 2.9% absolute decrease in mortality with the use of Plasma-Lyte 148®, representing a 12.5% relative risk reduction. However, allowing for approximately 2% loss to follow up at 90 days for such a large pragmatic trial, we plan to include an additional 172 patients.

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

13.2 Statistical Analysis Plan

The main analyses will be conducted on an intention-to-treat basis using standard statistical methods for categorical and continuous data. The primary analysis of 90-day mortality will be performed using a chi-square test. Analyses will also be conducted in pre-defined subgroup pairs defined by baseline characteristics: patients with or without kidney injury (defined by threshold creatinine concentration), with or without sepsis (defined using 2016 SOFA-based criteria), or admitted to the ICU directly after surgery or not, low versus high severity of illness (defined by APACHE II score <25 or ≥25). A detailed statistical analysis plan will be prepared and published before the first interim analysis.

We will conduct a cost-effectiveness analysis comparing costs and quality-adjusted life-years gained between treatment arms based on data collected to 6-months following randomisation. Depending on the primary outcome of the trial, further analyses may include a longer term cohort study and a modelled economic evaluation. All economic analyses will adopt a health care payer perspective in order to capture relevant costs and consequences of treatment assignment to the health system. Methodology will reflect the pragmatic approach adopted in the CHEST cost-effectiveness analysis.³² The PLUS cost-effectiveness analysis will be informed by a separate Statistical Analysis Plan.

13.3 Interim Analyses

In order to address safety concerns, at least one formal interim analysis will be conducted when 2933 patients (one third of planned recruitment) have completed 90 day follow-up. The purpose of this interim analysis is to test for the difference in mortality between the two study fluids to check for potential safety issues as well as assess for efficacy.

To maintain the overall type-I error rate (i.e., α), we will select conservative stopping rules such as Haybittle-Peto. This method uses a critical value of 3 standard-deviations for the interim stages, so that the critical value at the final analysis is close to one without interim monitoring. Further details including the timing and content of interim reviews are described in the Data Safety and Monitoring Committee charter.

14. Quality Control and Quality Assurance

14.1 Responsibilities of the Investigator

The investigator agrees to perform the clinical trial in accordance with this clinical trial protocol, ICH guidelines for Good Clinical Practice³³ and all applicable regulatory requirements. The investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the co-ordinating centre.

The investigator agrees to provide reliable data and all information requested by the clinical trial protocol in an accurate and legible manner according to the instructions provided. The investigator agrees to allow representatives of the co-ordinating centre to have direct access to source documents.

14.2 Responsibilities of the Coordinating Centre

The co-ordinating centre is responsible for taking all reasonable steps to ensure the proper conduct of the clinical trial protocol.

14.2.1 Site Initiation

Prior to initiation of the study at each participating site, the co-ordinating centre will be responsible for providing adequate training to the Principal Investigator and study personnel. The training will cover all aspects of the study protocol and procedures and will include practical training on the use of the web-based randomisation system, electronic case report forms (eCRF) website and study materials. The Site 'initiation visit' will be conducted by teleconference, video conference or face to face meeting at the participating site. Written and electronic materials will be supplied for study staff and for the education of clinical ICU staff at each participating site.

14.2.2 Monitoring during the study

A study monitor from the coordinating centre will visit each participating study site on several occasions during the recruitment phase, in accordance with the Monitoring Plan. This will ensure that the study is conducted according to the protocol, good clinical practice (GCP) guidelines and relevant regional regulatory requirements. The main duty of the study monitor is to help the investigator and the co-ordinating centre maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the trial.

The investigator and study personnel will assist the monitoring staff by providing all appropriate documentation, and being available to discuss the study. These monitoring visits will include but will not be limited to review of the following aspects:

- Adherence to the protocol including consistency with inclusion and exclusion criteria
- The completeness and accuracy of the case report forms (CRFs) and source documentation
- Patient recruitment
- Adverse Event documentation and reporting
- Study treatment allocation
- Patient compliance with the study treatment regimen
- Study treatment accountability

- Compliance with regulations

The coordinating centre team will conduct regular remote monitoring on the web-based database by applying validation and consistency rules and with regular data cleaning to ensure the integrity of the study data.

14.2.3 Site Close out

At completion of the trial, a final monitoring and close out visit will be conducted by the study monitor in accordance with the Monitoring Plan. Secure facilities for the storage of study data for 15 years will also be confirmed at this visit.

14.3 Source Document Requirements

According to the ICH guidelines for Good Clinical Practice³³, the monitoring team will check source documents to confirm the existence of the participant and the integrity of the study data. Source documents include the original documents related to the trial, to medical treatment and to the history of the participant. Adequate and accurate source documents allow the investigator and the site monitor to verify the reliability and authenticity of data recorded on the eCRFs and ultimately to validate that the clinical study was carried out in accordance with the protocol.

14.4 Management of Protocol Deviations

A protocol deviation is an unanticipated or unintentional departure from the expected conduct of an approved study that is not consistent with the current research protocol or consent document. A protocol deviation may be an omission, addition or change in any procedure described in the protocol.

The investigator should not implement any deviation from or changes to the protocol without agreement by the study management committee and documented approval from the HREC of the amendment, except where necessary to eliminate an immediate hazard(s) to trial participants. In the event of an emergency intended to eliminate an apparent immediate hazard to participants the Investigator may implement or omit any medical procedure as deemed appropriate.

Substantive deviations from the protocol must be documented and promptly reported to the study management committee and the HREC (if applicable). The report should summarise the event and action taken.

14.5 Study Treatment Accountability

14.5.1 Study treatment inspection and accountability

The investigator or delegate at each participating site will be responsible for receiving, inspecting and documenting the study fluid prior to placement in ICU/hospital storage. The investigator or delegate will inventory and acknowledge receipt of all shipments of study treatment. Documentation of study fluid distribution, receipt, use and disposal will be kept to enable comprehensive tracking and reconciliation of all study treatments, used or unused.

Study fluids must be kept in a secure area with restricted access. The study fluids must be stored and handled in accordance with the manufacturer's instructions. The investigator or delegate will also keep accurate records of the quantities of the investigational products dispensed, used and returned by each participant.

14.5.2 Disposal of Study Treatment

All used, partially used and unused study fluid bags should be returned to the site Research Coordinator once the infusion or the need for infusion has finished. The research co-ordinator will cross check the study fluid volume that is identified on the hospital charts against the study fluid volume that has been used from the study bags.

For safety reasons, institutional regulation and storage capacity at sites, the destruction of dispensed (used and unused) study fluid bags may be performed by investigational site staff according to local guidelines before a monitoring visit. Documentation of destruction with a complete and accurate account of study fluid destroyed must be available for verification by the study monitor and filed in the investigator site file.

The study monitor will periodically check the supplies of study fluids and study treatment accountability records held by the investigator to verify accountability of all study treatment used.

At the conclusion of the study, all unused study fluid (which has not been allocated to a patient) will be destroyed unless other arrangements have been approved by the coordinating centre. Final destruction of unallocated study treatment boxes must only occur following written authorisation from the coordinating centre. The coordinating centre will verify that a final report of study treatment accountability is prepared and maintained in the investigator study file.

Further instructions on study treatment accountability, handling and storage will be provided in the operations manual.

14.6 Direct Access to Data and Documents

The study may be audited by government regulatory authorities, local HRECs or qualified representatives of The George Institute for Global Health as permitted by regulations. Therefore, access to medical records, other source documents such as ICU charts and other study related files must be made available at all study sites for monitoring and audit purposes during the course of the study and after its completion.

Participants will not be identified by name, and confidentiality of information in medical records will be preserved. The confidentiality of the participant will be maintained unless disclosure is required by regulations.

15. Ethical Considerations

15.1 Ethical Principles

The study will be conducted in accordance with ethical principles consistent with the Declaration of Helsinki³⁴ and all relevant national and local guidelines on the ethical conduct of research.^{35, 36, 37}

15.2 Human Research Ethics Committee

The protocol for this project will be reviewed by the Human Research Ethics Committee (HREC) at each participating site. In jurisdictions where single ethical review of multicentre trials is in place, one principal investigator (known as the coordinating investigator) will take responsibility for applying to a lead HREC on behalf of investigators covered by that committee. Each site principal investigator will then be responsible for applying for local research governance approval at their site.

Documentation of the approval of the protocol and the consent documents will be provided to the coordinating centre before the study may begin at any site. The coordinating centre will assist with this process by preparing a standard application form (in Australia, the National Ethics Application Form [NEAF]; in New Zealand, the National Application Form) and template consent documents. The content and format of the standard information statements and consent forms will be adapted if necessary to comply with local HREC guidelines and requirements.

During the trial, any amendment or modification to the study protocol should be notified to the HREC by the Principal Investigator and approved by the HREC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the HREC should be informed as soon as possible thereafter.

Each Principal Investigator will be responsible for informing the HREC of any event likely to affect the safety of patients or the continued conduct of the clinical trial.

The Principal Investigator will produce progress reports, adverse event reports, and any other required documentation to the HREC in accordance with their guidelines. Copies of all HREC and research governance officer correspondence will be provided to the coordinating centre together with a copy of the approved consent documents. Copies of the same documents will also be kept with the study investigator files.

15.3 Informed Consent Procedures

This study involves the random assignment of Plasma-Lyte 148® or 0.9% saline for fluid resuscitation in Intensive Care patients. Plasma-Lyte 148® and 0.9% saline are both commonly used in clinical practice for a variety of conditions and are not experimental products. All study related assessments are part of standard care of ICU patients requiring fluid resuscitation, with the exception of follow up of patient status following discharge from hospital and the conduct of a quality of life questionnaire.

The Australian NHMRC National Statement on the Ethical Conduct in Human Research³⁵, the New Zealand Code of Health and Disability Consumers' Rights and New Zealand Guidelines on Ethics in

Health Research^{36, 37} acknowledge that research involving patients who are heavily dependent on medical care, such as the patients in this study, is necessary to assess and improve the efficacy and safety of interventions used in their treatment.

The principal investigators, or their nominated delegate at each site, will obtain written informed consent from any conscious and comprehending patient, prior to their enrolment in the study. Obtaining written and informed consent directly from patients in the ICU prior to enrolment in a clinical trial is frequently not possible as the patient is often unconscious, sedated, intubated and too ill to understand information relating to clinical trial participation. Additionally, fluid resuscitation is usually a matter of clinical urgency and a treatment that must be carried out without delay to avoid adverse consequences for the patient that include the onset or worsening of organ dysfunction and at the extreme, may contribute to an increased risk of death.

15.3.1 Australian Context

Under these circumstances, the approach to obtaining consent in this study in Australia will be based on that developed from the guidelines of the Australian NHMRC National Statement (Chapter 4.4: People highly dependent on medical care who may be unable to give consent) and also from the ANZICS Clinical Trials Group Ethics Handbook for Researchers (2005)³⁸ and will follow the following hierarchy:

a) Consent from patient PRIOR to randomisation

Where it is possible for a conscious and comprehending patient to give informed consent to take part in this study before project related activities are undertaken, the study will be explained verbally to that patient by the principal investigator or their nominated delegate. Intensive care physicians are highly experienced at caring for critically ill patients and also evaluating the competence of their patients to understand their illness and consent for therapeutic interventions. If the patient is deemed competent and consents to participate, they will be given a copy of the signed and dated consent form and the participant information sheet and any other documentation discussed through the consent process. Given the urgent nature of fluid resuscitation this consent process is likely to be possible only in elective surgical patients who are known to be coming to the ICU for their post-operative care, or a stable patient in the ICU who subsequently becomes unstable and requires fluid resuscitation.

b) Consent from 'substitute decision maker' PRIOR to randomisation

If a potential participant lacks the capacity to give consent due to their medical condition, whenever possible, consent will be obtained from a legally recognised 'substitute decision maker' (SDM). The procedure for obtaining consent from the SDM must be approved by the local HREC prior to use. Given the urgency of fluid resuscitation, it will likely be rare that prior consent from a substitute decision maker can be obtained in a timely manner.

c) Inclusion without prior consent with option to continue or withdraw

This trial is studying approved crystalloid fluids in an accepted patient population. Any potential benefit of the fluids may only be realised if administered in a timely fashion. Where it is not possible or practicable for the patient or the SDM to provide consent prior to randomisation (the overwhelming majority of cases), subject to approval by the relevant HREC and all applicable laws

the patient will be enrolled into the study without prior consent and as soon as possible and appropriate, the patient or SDM will be informed of the patient's participation in the study. At this stage, the patient or SDM will be given the option to consent to continuing in the study or to withdraw from the study. If they request withdrawal of study treatment, permission to use study-related data and permission to collect and use outcome data will be sought.

d) Deceased patients

For patients enrolled in the study under the process explained in 15.3c above, where the patient dies before consent has been obtained, permission to use study related information will be sought from the relevant HREC.

e) Where informed consent cannot be obtained from the patient or SDM

In circumstances where a patient never regains competency following enrolment into the trial under the process explained in 15.3c above and there are no SDMs available, an approach will be made to the relevant HREC to request that de-identified study data may be retained and used.

All interaction between research staff and potential or actual participants and their relatives will take into consideration the stress or emotional factors associated with critical illness and ensure that the dependency of potential participants and their relatives on medical personnel providing treatment does not compromise the freedom of a decision to participate.

15.3.2 New Zealand Context

In New Zealand, the approach used will be consistent with section 7.4 of the Health and Disability Code which outlines the framework for providing treatment to patients who are unable to consent for themselves.

The specific approach will be:

1. To consider whether study treatment and study participation is in the best interest of each individual patient and,
2. As soon as it is practical and reasonable, to seek the advice of persons interested in the patient's welfare to establish that study participation is consistent with the patient's wishes.

All participants who recover sufficiently will be given the opportunity to provide informed consent for ongoing study participation and for the use of data collected for the study

15.4 Confidentiality and Privacy

All patient data pertaining to the study will be stored in a computer database maintaining confidentiality in accordance with local legislation regarding privacy and use of health data. When archiving or processing data pertaining to the investigator and/or to the patients, the coordinating centre will take all appropriate measures to safeguard and prevent access to this data by any unauthorised third party.

The investigator will maintain the confidentiality of all study documentation, and take measures to prevent accidental or premature destruction of these documents. The investigator will retain the study documents for at least fifteen (15) years after the completion or discontinuation of the study. The investigator must notify the study management committee prior to destroying any study documents following study completion or discontinuation. If the investigator's situation is such that archiving can no longer be ensured by him/her, the investigator will inform the study management committee and the relevant records will be transferred to a mutually agreed designee.

If any investigator retires, relocates, or otherwise withdraws from conducting the study, the responsibility for maintaining records may be transferred to the coordinating centre, or other investigator. The coordinating centre must be notified of and agree to the change. All associated documentation must also be updated.

16. Publication Policy

The study will be conducted in the name of the 'PLUS Study Investigators'. Central project coordination and data management will be provided by The George Institute for Global Health, Sydney.

Authorship of publications arising from the study will be consistent with current ANZICS Clinical Trials Group policies with full credit assigned to all collaborating investigators, research coordinators and institutions. Responsibility for the content of manuscripts will rest with the writing committee, and where listed the chair of the writing committee will be listed first with subsequent members listed alphabetically.

Funding bodies will be acknowledged in all publications.

17. Proposed Project Timeline

| Date | Project Milestone |
|--------------------------|--|
| February 2016 | Draft study protocol finalised |
| February - December 2016 | Ethics application and subsequent regulatory requirements Site feasibility and site selection |
| February 2017 | Investigator Start-up Meetings (Australia and New Zealand) |
| May - July 2017 | Site initiation and induction. Commence recruitment |
| June 2017 – June 2020 | Patient recruitment period |
| July – December 2020 | Database lock, data analysis and initial results |

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19. Appendices

- 19.1 Product Information for Plasma-Lyte 148®
- 19.2 Product Information for Sodium Chloride (0.9%)
- 19.3 EQ-5D-5L Questionnaire (English Version for Australia)
- 19.4 EQ-5D-5L Questionnaire (English Version for New Zealand)

Product Information

Plasma-Lyte 148 (approx. pH 7.4) IV Infusion

Name of the medicine

Plasma-Lyte 148 (approx. pH 7.4) IV Infusion

Description

Plasma-Lyte 148 (approx. pH 7.4) IV Infusion is a sterile, clear, nonpyrogenic isotonic solution in a single dose container for intravenous administration.

Each 1000mL of Plasma-Lyte 148 (approx. pH 7.4) IV Infusion contains:

| | |
|------------------------|-----------------|
| Sodium Chloride | 5.26 g |
| Sodium Gluconate | 5.02 g |
| Sodium Acetate | 3.68 g |
| Potassium Chloride | 370 mg |
| Magnesium Chloride | 300 mg |
| Sodium Hydroxide | pH adjustment |
| Water for Injections | q.s. to 1000 mL |
| pH range | 6.5 to 8.0 |
| Approximate Osmolality | 271 mOsm/kg |
| Approximate Kilojoules | 66 kJ |

Plasma-Lyte 148 (approx. pH 7.4) IV Infusion when administered intravenously is a source of water, electrolytes, and calories. It contains no antimicrobial agents. The osmolality is 271 mOsm/kg. An injection with an osmolality within the range of 250 to 350 mOsm/kg is considered to be isotonic. Administration of substantially hypertonic solutions may cause vein damage.

Each 1000mL of Plasma-Lyte 148 (approx. pH 7.4) IV Infusion has an ionic concentration of:

| | |
|-----------|----------|
| Sodium | 140 mmol |
| Potassium | 5 mmol |
| Magnesium | 1.5 mmol |
| Chloride | 98 mmol |
| Acetate | 27 mmol |
| Gluconate | 23 mmol |

Pharmacology

Plasma-Lyte 148 (approx. pH 7.4) IV Infusion is a source of water and electrolytes. It is capable of inducing diuresis depending on the clinical condition of the patient.

Plasma-Lyte 148 (approx. pH 7.4) IV Infusion produces a metabolic alkalinising effect. Acetate and gluconate ions are metabolised ultimately to carbon dioxide and water, which requires the consumption of hydrogen cations.

Indications

Plasma-Lyte 148 (approx. pH 7.4) IV Infusion is indicated as a source of water and electrolytes or as an alkalinising agent.

Contraindications

Plasma-Lyte 148 (approx. pH 7.4) IV infusion is contraindicated in patients with a known hypersensitivity to the product.

Precautions

Plasma-Lyte 148 (approx. pH 7.4) IV Infusion is not indicated for

- the treatment of hypochloremic hypokalaemic alkalosis and should be used with caution, in patients with hypochloremic hypokalaemic alkalosis.
- the primary treatment of severe metabolic acidosis.
- hypomagnesaemia.

Although Plasma-Lyte 148 (approx. pH 7.4) IV Infusion has a potassium concentration similar to the concentration in plasma, it is insufficient to produce a useful effect in case of severe potassium deficiency; therefore, it should not be used for correction of severe potassium deficiency.

Plasma-Lyte 148 (approx. pH 7.4) IV Infusion should be used with great care, if at all, in patients with congestive heart failure, severe renal insufficiency, and in clinical states in which there exists oedema with sodium retention.

Plasma-Lyte 148 (approx. pH 7.4) IV Infusion should be administered with particular caution, if at all to patients with conditions that may cause sodium retention, fluid overload and oedema.

Plasma-Lyte 148 (approx. pH 7.4) IV Infusion should be used with caution if at all, in patients with hyperkalaemia or conditions predisposing to hyperkalaemia (such as severe renal impairment or adrenocortical insufficiency, acute dehydration or extensive tissue injury or burns) and in patients with cardiac disease and in conditions where potassium retention is present.

Plasma-Lyte 148 (approx. pH 7.4) IV Infusion should be used with great care in patients with metabolic or respiratory alkalosis. The administration of acetate or gluconate ions should be done with great care in those conditions in which there is an increased level or an impaired utilisation of these ions, such as severe hepatic insufficiency.

Depending on the volume and rate of infusion, intravenous administration of Plasma-Lyte 148 (approx. pH 7.4) IV Infusion can cause fluid and/or solute overloading resulting in dilution of serum electrolyte concentrations, overhydration /hypervolemia, congested states, including pulmonary congestion and oedema, and clinically relevant electrolyte disturbances and acid-base imbalance. The risk of dilutional states is inversely proportional to the electrolyte concentrations of the infusion. The risk of solute overload causing congested states with peripheral and pulmonary oedema is directly proportional to the electrolyte concentrations of the infusion.

In patients with diminished renal function, administration of Plasma-Lyte 148 (approx. pH 7.4) IV Infusion may result in sodium and/or potassium or magnesium retention.

Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance, electrolyte concentrations, and acid base balance during prolonged parenteral therapy or whenever the condition of the patient warrants such evaluation.

Plasma-Lyte 148 (approx. pH 7.4) IV Infusion should be used with particular caution, if at all, in patients with alkalosis or at risk for alkalosis. Excess administration may result in metabolic alkalosis.

Hypersensitivity/infusion reactions, including anaphylactoid reactions, have been reported with Plasma-Lyte 148 (approx. pH 7.4) IV Infusion. The infusion must be stopped immediately if any signs or symptoms of a suspected hypersensitivity reaction develop. Appropriate therapeutic countermeasures must be instituted as clinically indicated.

Solutions containing magnesium should be used with caution, if at all, in patients with:

- Hypermagnesaemia or conditions predisposing to hypermagnesaemia including, but not limited to, severe renal impairment or magnesium therapy such as eclampsia.
- Myasthenia gravis.

Plasma-Lyte 148 (approx. pH 7.4) IV Infusion should be administered with particular caution, if at all, to hypervolemia or overhydrated patients.

Plasma-Lyte 148 (approx. pH 7.4) IV Infusion should be administered with particular caution, if at all, to patients with conditions that may cause sodium retention, fluid overload and edema, such as patients with primary hyperaldosteronism, secondary hyperaldosteronism (associated with, for example, hypertension, congestive heart failure, renal artery stenosis, or nephrosclerosis), or preeclampsia.

Plasma-Lyte 148 (approx. pH 7.4) IV Infusion contains no calcium and an increase in plasma pH due to its alkalinising effect may lower the concentration of ionised (not protein-bound) calcium. Plasma-Lyte 148 (approx. pH 7.4) IV Infusion should be administered with particular caution, if at all, to patients with hypocalcaemia.

Do not connect flexible plastic containers in series in order to avoid air embolism due to possible residual air contained in the primary container. Pressurising intravenous solutions contained in flexible plastic containers to increase flow rates can result in air embolism if the residual air in the container is not fully evacuated prior to administration.

Use of a vented intravenous administration set with the vent in the open position could result in air embolism. Vented intravenous administration sets with the vent in the open position should not be used with flexible plastic containers.

Use in Pregnancy (No Category)

There are no adequate data from the use of Plasma-Lyte 148 (approx. pH 7.4) IV Infusion in pregnant women. The potential risks and benefits for each specific patient should be carefully considered before using Plasma-Lyte 148 (approx. pH 7.4) IV Infusion in pregnant women.

Use in Lactation

There are no adequate data from the use of Plasma-Lyte 148 (approx. pH 7.4) IV Infusion in lactating women. The potential risks and benefits for each specific patient should be carefully considered before using Plasma-Lyte 148 (approx. pH 7.4) IV Infusion in lactating women.

Paediatric Use

Safety and effectiveness of Plasma-Lyte 148 (approx. pH 7.4) IV Infusion in paediatric patients have not been established by adequate or well controlled trials, however, the use of electrolyte solutions in the paediatric population is referenced in the medical literature. The precautions and adverse reactions identified in this document should be observed in the paediatric population.

Use in the elderly

Clinical studies of Plasma-Lyte 148 (approx. pH 7.4) IV Infusion did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or medicine therapy.

When selecting the type of infusion solution and the volume/rate of infusion for an elderly patient, consider that elderly patients are generally more likely to have cardiac, renal, hepatic and other diseases or concomitant drug therapy.

Carcinogenicity

Studies with Plasma-Lyte 148 (approx. pH 7.4) IV Infusion have not been performed to evaluate carcinogenic potential.

Genotoxicity

Studies with Plasma-Lyte 148 (approx. pH 7.4) IV Infusion have not been performed to evaluate mutagenic potential.

Effects on fertility

Studies with Plasma-Lyte 148 (approx. pH 7.4) IV Infusion have not been performed to evaluate effect on fertility.

Effect on laboratory tests

There have been reports of false-positive test results using the Bio Rad Laboratories Platelia *Aspergillus* EIA test in patients receiving Baxter gluconate containing Plasma-Lyte solutions. These patients were subsequently found to be free of *Aspergillus* infection. Therefore, positive test results for this test in patients receiving Baxter gluconate containing Plasma-Lyte solutions should be interpreted cautiously by other diagnostic methods.

General

The Viaflex plastic container is fabricated from a specially formulated polyvinyl chloride (PL 146 Plastic) The amount of water that can permeate from inside the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the plastic container can leach out certain chemical components from the plastic in very small amounts, however, biological testing was supportive of the safety of the plastic container materials.

Interactions with other medicines

Caution must be exercised in the administration of Plasma-Lyte 148 (approx. pH 7.4) IV Infusion to patients treated with drugs that may increase the risk of sodium and fluid retention such as corticosteroids or corticotropin.

Caution is advised when administering Plasma-Lyte 148 (approx. pH 7.4) IV Infusion to patients treated with drugs for which renal elimination is pH dependent. Due to its alkalinising effect (formation of bicarbonate), Plasma-Lyte 148 (approx. pH 7.4) IV Infusion may interfere with the elimination of such drugs:

- renal clearance of acidic drugs such as salicylates, barbiturates and lithium may be increased
- renal clearance of alkaline drugs such as sympathomimetics (e.g. ephedrine, pseudoephedrine), quinidine or dextroamphetamine (dexamphetamine) sulfate may be decreased.

Because of its potassium content, Plasma-Lyte 148 (approx. pH 7.4) IV Infusion should be administered with caution in patients treated with agents or products that can cause hyperkalaemia or increase the risk of hyperkalaemia, such as potassium sparing diuretics (amiloride, spironolactone, triamterene) with ACE inhibitors, angiotensin II receptor antagonists or the immunosuppressants tacrolimus and cyclosporine.

Adverse effects

Reactions that may occur because of the solution or the technique of administration include febrile response or infection at the site of infusion. Other reactions that may occur include:

Circulatory effects: Extravasation
Hypervolemia
Venous thrombosis
Phlebitis extending from the site of injection

If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic countermeasures, and save the remainder of the fluid for examination if deemed necessary.

The following adverse reactions have been reported in the post-marketing experience with unspecified Plasma-Lyte products and Plasma-Lyte products without Glucose, listed by MedDRA System Organ Class (SOC), then by Preferred Term in order of severity, where feasible:

Immune System Disorders:

Hypersensitivity/infusion reactions including anaphylactoid reaction and the following manifestations: tachycardia, palpitations, chest pain, chest discomfort, dyspnoea, respiratory rate increased, flushing, hyperaemia, asthenia, feeling abnormal, piloerection, oedema peripheral and pyrexia.

General Disorders and Administration Site Conditions:

Infusion site reactions e.g. infusion site pain and burning sensation.

Other adverse reactions reported with Plasma-Lyte products with Glucose are:

- other manifestations of hypersensitivity/infusion reactions including hypotension, wheezing, urticaria, cold sweat and chills
- hyperkalaemia

Dosage and administration

Dosage

As directed by the physician. Dosage is dependent on age, weight and clinical condition of the patient as well as laboratory determinations. Dosage, rate, and duration of administration are to be individualised and depend upon the indication for use, the patient's age, weight, clinical condition, and concomitant treatment, and on the patient's clinical and laboratory response to treatment.

Each Viaflex container is for single patient use only.

Parenteral medicine products should be inspected visually for particulate matter and discolouration prior to the administration whenever solution and container permit.

All injections in Viaflex plastic containers are intended for intravenous administration using sterile equipment.

Additives may be incompatible. Complete information is not available. As with all parenteral solutions, compatibility of the additives with the solution must be assessed before addition. Before adding a substance or medication, verify that it is soluble and/or stable in water and that the pH range of Plasma-Lyte 148 (approx. pH 7.4) IV Infusion is appropriate. After addition, check for possible colour change and/or the appearance of precipitates, insoluble complexes or crystals. The instructions for use of the medication to be added and other relevant literature must be consulted.

Those additives known to be incompatible should not be used. Consult with a pharmacist, if available. If, in the informed judgement of the physician, it is deemed advisable to introduce additives, use aseptic technique. Mix thoroughly when additives have been introduced. Do not store solutions containing additives.

Directions for use

Warning: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Do not administer unless solution is clear and seal is intact.

To open

Tear overwrap down side at slit and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilisation process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually. Check for minute leaks by squeezing the inner bag firmly. If leaks are found, discard solution, as sterility may be impaired. If supplemental medication is desired, follow the directions below.

Preparation for Administration

1. Suspend container from eyelet support.
2. Remove plastic protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

To Add Medication

Warning: Additives may be incompatible

To add medication before solution administration

1. Prepare medication site.
2. Using a syringe with a 0.63 to 0.80 mm needle, puncture resealable medication port and inject.
3. Mix solution and medication thoroughly. For high density medication such as potassium chloride, squeeze ports while ports are upright and mix thoroughly.

To add medication during solution administration

1. Close clamp on the set.
2. Prepare medication site.
3. Using a syringe with a 0.63 to 0.80 mm needle, puncture resealable medication port and inject.
4. Remove container from IV pole and turn to an upright position.
5. Evacuate both ports by squeezing them while container is in the upright position.
6. Mix solution and medication thoroughly.
7. Return container to in use position and continue administration.

After opening the container, the contents should be used immediately and should not be stored for a subsequent infusion. Do not reconnect any partially used containers.

Overdosage

If overdosage is suspected (through the monitoring of electrolytes, especially sodium and potassium), administration of the medicine should be discontinued and the patient observed closely.

Excessive administration of Plasma-Lyte 148 (approx. pH 7.4) IV Infusion may lead to metabolic alkalosis. Metabolic alkalosis may be accompanied by hypokalaemia as well as a decrease in ionised serum calcium and magnesium. See PRECAUTIONS.

An excessive volume of Plasma-Lyte 148 (approx. pH 7.4) IV Infusion may lead to fluid and sodium overload with a risk of oedema (peripheral and/or pulmonary) particularly when renal sodium excretion is impaired. See PRECAUTIONS.

Excessive administration of potassium may lead to the development of hyperkalaemia, especially in patients with severe renal impairment. See PRECAUTIONS.

Excessive administration of magnesium may lead to hypermagnesaemia. See PRECAUTIONS.

When assessing an overdose, any additives in the solution must be also be considered. The effect of overdose may require immediate medical attention and treatment.

Presentation and storage conditions

Plasma-Lyte 148 (approx. pH 7.4) IV Infusion in Viaflex plastic containers is available as shown below:

| Code | Size (mL) | AUST R |
|---------|-----------|--------|
| AHB2543 | 500 | 231424 |
| AHB2544 | 1000 | 231425 |

Storage condition

Store product below 30°C.
Do not freeze.

Name and address of the sponsor

Baxter Healthcare Pty Ltd
1 Baxter Drive
Old Toongabbie, NSW 2146.

Poison schedule of the medicine

Unscheduled

**Date of first inclusion in the Australian Register of Therapeutic Goods
(the ARTG)**

11 December 2014

Viaflex and Plasma-Lyte are trademarks of Baxter International Inc

PRODUCT INFORMATION

SODIUM CHLORIDE (0.45%, 0.9%, 3%) INTRAVENOUS INFUSION BP

Name of the medicine

The active ingredient is sodium chloride formulated in Water for Injections. The chemical name is sodium chloride with molecular formula NaCl. It occurs as a colourless or white crystal and is freely soluble in water.

Chemical Structure: NaCl

MW :58.44

CAS: 7647-14-5

Description

The Sodium Chloride Intravenous Infusion preparations are sterile, non-pyrogenic solutions of sodium chloride in Water for Injections. The concentration of sodium chloride in each preparation is shown in Table 1 (see *Presentation and storage conditions*). The preparations do not contain an antimicrobial agent or added buffer. However, during the sterilisation step a small amount of hydrochloric acid may leach out resulting in a slightly acidic solution with a pH of 4.0 – 7.0. Sodium Chloride 0.9% solutions are isotonic as indicated by their osmolarity shown in Table 1. Sodium chloride 3% (AHB1354, 1026 mOsmol/L) is hypertonic and sodium chloride 0.45% (AHB1313, 154 mOsmol/L) is hypotonic, as shown by their osmolarities.

Pharmacology

Mechanism of Action:

Sodium is the major cation of extracellular fluid and functions principally in the control of water distribution, fluid and electrolyte balance and osmotic pressure of body fluids. Chloride, the major extracellular anion, closely follows the physiological disposition of sodium cation in maintenance of acid-base balance, isotonicity and electrodynamic characteristic of the cells.

Thus, Sodium Chloride Intravenous Infusion has a value as a source of water and electrolytes.

Pharmacokinetics

As Sodium Chloride Intravenous Infusion is administered to the systemic circulation by intravenous infusion, the bioavailability (absorption) of the active components is complete (100 per cent).

Indications

Sodium Chloride (0.9%) Intravenous Infusion is indicated for extracellular fluid replacement and in the management of metabolic alkalosis in the presence of fluid loss, and for restoring or maintaining the concentration of sodium and chloride ions.

Hypertonic Sodium Chloride (3%) Intravenous Infusion is used in the management of severe sodium chloride depletion when electrolyte restoration is required.

Hypotonic Sodium Chloride (0.45%) Intravenous Infusion is mainly used as a hydrating agent solution.

Contraindications

The use of Sodium Chloride Intravenous Infusion requires careful evaluation of risks and benefits by the attending physician. It must not be used in the following conditions unless the physician has determined that potential benefits outweigh risks:

- congestive heart failure
- severe impairment of renal function,
- clinical states in which there exists oedema with sodium retention (see *Precautions*).

Sodium Chloride 3% Intravenous Infusion is contraindicated for electrolyte replacement in the presence of increased, normal, or only slightly decreased serum electrolyte concentrations.

Precautions

Warning

Care should be exercised regarding possible incompatibility outcomes resulting from the interaction between the plastic container (Viaflex[®] plastic bag fabricated from a specially formulated polyvinyl chloride, PL 146 Plastic) or active ingredients and the added therapeutic substances (see also *Dosage and Administration*). Small amounts of the components, eg. di-2-ethylhexyl phthalate (DEHP) up to 5 ppm, may leach out during its shelf life. During the sterilisation step a small amount of hydrochloric acid may leach out resulting in a slightly acidic solution (see *Description*). The safety of the Viaflex plastic bag containers has been shown in tests with animals according to the USP biological tests for plastic container, as well as by tissue culture toxicity studies.

In a dilute condition, osmolarity/L is approximately the same as osmolality/kg. As shown in Table 1, Sodium Chloride (3%) Intravenous Infusion is hypertonic as indicated by its osmolarity, 1026 mOsmol/L. The administration of substantially hypertonic solution may lead to a wide variety of complications. This includes crenation (cell shrinkage) of red blood cells and general cellular dehydration. Thus it should be administered through a large central vein, for rapid dilution of the hypertonic solution (see *Dosage and Administration*).

In contrast, the Sodium Chloride (0.45%) is hypotonic (154 mOsmol/L). It may be infused with caution by peripheral vein administration, but may lead to cell swelling or oedema.

Hypersensitivity/infusion reactions, including hypotension, pyrexia, tremor, chills, urticaria, rash, and pruritus, have been reported with Sodium Chloride 0.9%.

Stop the infusion immediately if signs or symptoms of hypersensitivity/infusion reactions develop. Appropriate therapeutic countermeasures must be instituted as clinically indicated.

Hyponatraemia

The infusion of solutions with sodium (0.45 or <0.9%) may result in hyponatraemia, which may warrant close clinical monitoring. Hyponatraemia can lead to headache, nausea, seizures, lethargy, coma, cerebral edema and death.

The risk for hyponatraemia is increased in children, elderly patients, women, postoperatively, persons with psychogenic polydipsia, patients treated with medications that increase the risk of hyponatraemia (such as certain antiepileptic and psychotropic medications).

The risk for developing hyponatraemic encephalopathy is increased in paediatric patients (≤ 16 years of age), women (in particular pre-menopausal women), patients with hypoxemia and in patients with underlying central nervous system disease

General

Clinical evaluation and appropriate laboratory determinations are essential to monitor renal function, changes in fluid balance, electrolyte concentration and acid-base balance.

Sodium Chloride Intravenous Infusion may cause fluid and/or solute overload. The risk of dilutional states is inversely proportional to the electrolyte concentrations of the injections. The risk of solute overload causing congested states with peripheral and pulmonary oedema is directly proportional to the electrolyte concentration administered.

Clinical evaluation and periodic laboratory determinations may be necessary to monitor changes in fluid balance, electrolyte concentrations, and acid-base balance during prolonged parenteral therapy or whenever the condition of the patient or the rate of administration warrants such evaluation.

Thus, caution should be exercised in patients with hypertension, heart failure, cerebral oedema, renal disease, pulmonary or peripheral oedema, pre-eclampsia, liver cirrhosis, conditions associated with sodium retention, and in geriatric patients, and infants.

Sodium Chloride Intravenous Infusion should be used with caution in patients receiving corticosteroids or corticotropin, because of potential sodium and fluid retention.

Sodium Chloride Intravenous Infusion should be used with particular caution, if at all, in patients with or at risk for Hypernatraemia, Hyperchloraemia, Hypervolemia and conditions that may cause sodium retention, fluid overload and edema (central and peripheral).

Its use may result in electrolyte abnormalities, including hypokalaemia or hyperkalaemia (see *Adverse Reactions* and *Overdosage*).

Rapid correction of hyponatraemia or hypernatraemia is potentially dangerous.

Carcinogenicity/mutagenicity

Studies with sodium chloride have not been performed to evaluate carcinogenic or mutagenic potential.

Use in pregnancy (Category A)

There are no adequate and well-controlled studies of Sodium Chloride Intravenous Infusion in animals or in pregnant women. However, Sodium Chloride Intravenous Infusion contains no components known to have adverse effects on the foetus at physiological concentrations. Physicians should carefully consider the potential risks and benefits for each specific patient before administering Sodium Chloride.

Use in lactation

Following intravenous administration, a fraction of sodium and chloride ions is expected to be excreted into human milk. However, at physiological concentrations, neither of these ions is known to have adverse effects on a breastfeeding baby.

Physicians should carefully consider the potential risks and benefits for each specific patient before administering Sodium Chloride.

Paediatric use

Plasma electrolyte concentrations should be closely monitored in the paediatric population because of their impaired ability to regulate fluids and electrolytes.

Use in elderly

Geriatric patients are generally more likely to have cardiac, renal, hepatic, and other diseases or concomitant drug therapy and should be taken into consideration for selecting the type of infusion solution and the volume/rate of infusion.

The infusion of hypotonic fluids together with the non-osmotic secretion of anti-diuretic hormone may result in hyponatraemia. Hyponatraemia can lead to headache, nausea, seizures, lethargy, coma, cerebral edema and death; therefore, acute symptomatic hyponatraemic encephalopathy is considered a medical emergency.

Effects on Ability to Drive and Use Machines

There is no information on the effects of [Sodium Chloride 0.9%] on the ability to operate automobile or other heavy machinery.

Interactions with other medicines

Sodium Chloride Intravenous Infusion should not be administered simultaneously with blood products through the same administration set, because of the possibility of pseudo-agglutination or haemolysis.

If Sodium Chloride (0.45% or 0.9%) Intravenous Infusion is used as a vehicle for a drug delivery, a thorough review of the Product Information document(s) of such drug(s) should be made to ensure that no incompatibility might occur. Salting out, i.e., a precipitation of organic base drug may occur in the presence of salt.

Caution is advised in patients treated with lithium. Renal sodium and lithium clearance may be increased during administration of Sodium Chloride resulting in decreased lithium levels.

Adverse Effects

Adverse effects, which may occur because of the solution or the technique of administration, include febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection, extravasation and hypervolaemia.

If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic countermeasures and save the remainder of the fluid for examination if deemed necessary.

Inappropriate use of Sodium Chloride Intravenous Infusion may cause fluid or solute overload resulting in electrolyte abnormalities, overhydration, congestive conditions, including central, peripheral or pulmonary oedema, electrolyte imbalances and acid-base imbalance.

Post-marketing Adverse Reactions

The following adverse reactions have been reported in the post-marketing experience, listed by MedDRA System Organ Class (SOC), then, where feasible, by Preferred Term in order of severity.

- **IMMUNE SYSTEM DISORDERS:**
Hypersensitivity/infusion reactions, including hypotension, pyrexia, tremor, chills, urticaria, rash, pruritus.
- **GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS:**
Infusion site reactions, such as infusion site erythema, injection site streaking, burning sensation, infusion site urticaria.

Other Adverse Reactions / Class Reactions

Use appropriate section of your label to incorporate the following class like reactions.

The following adverse reactions have not been reported with this product but may occur:

- Hyponatraemia
- Hyperchloraemic metabolic acidosis
- Hyponatremia, which may be symptomatic

Dosage and Administration

General directive

Sodium Chloride (0.45%, 0.9% % 3%) is for intravenous infusion.

To be used as directed by the doctor.

Dosage, rate, and duration of administration are to be individualised and depend upon the indication for use, the patient's age, weight, clinical condition, and concomitant treatment, and on the patient's clinical and laboratory response to treatment.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. The solution should be clear and free from particles. Do not administer unless solution is clear and seal is intact. Additives may be incompatible. Suitability of potential additives has not been demonstrated. Complete information is not available. Those additives known to be incompatible should not be used. Before adding a substance or medication, verify that it is soluble and/or stable in water and that the pH range of Sodium Chloride solution is appropriate. The instructions for use of the medication to be added and other relevant literature must be consulted. Consult with a pharmacist, if available.

If in the informed judgment of the doctor, it is deemed advisable to introduce additives, use aseptic technique. Mix thoroughly when additives have been introduced. After addition, check for a possible colour change and/or the appearance of precipitates, insoluble complexes or crystals. Do not store solutions containing additives. The stability of this product when mixed with additive has not been demonstrated.

See Precautions, Interactions with other medicines.

When other electrolytes or medicines are added to this solution, the dosage and the infusion rate will also be dictated by the dose regimen of the additions.

The product should be used for one patient on one occasion only. Any unused portion should be discarded.

Hypertonic solutions are preferably administered via a large central vein. If hypertonic solutions are administered peripherally, a large arm vein should be used and, if possible, the injection site should be altered daily. IV infusion of 3% Sodium Chloride solution should not exceed 100 mL/hr and serum electrolyte concentrations should be determined to assess the need for further administration.

Direction for use of Viaflex plastic container

Warning: Do not use flexible plastic containers in series connections. Such use could result in embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is completed.

Pressurising intravenous solutions contained in flexible plastic containers to increase flow rates can result in air embolism if the residual air in the container is not fully evacuated prior to administration.

Use of a vented intravenous administration set with the vent in the open position could result in air embolism. Vented intravenous administration sets with the vent in the open position should not be used with flexible plastic containers.

To open: Tear overwrap down side at slit and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilisation process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually. Check for minute leaks by squeezing inner bag firmly. If leaks are found, discard the product as sterility may be impaired. If supplemental medication is desired, follow directions below.

Preparation for Administration: Sodium Chloride Intravenous Infusion is a sterile preparation. Thus, aseptic technique must be applied throughout the administration.

- (1) Suspend container from eyelet support.
- (2) Remove plastic protector from outlet port at the bottom of container.
- (3) Attach administration set.

To Add Medication:

Warning. Additives may be incompatible (See *Precautions, Interactions with other drugs*)

To add medication before solution administration: Supplemental medication may be added with needle through the medication injection port. To proceed, swab medication site (port) with alcohol swab. Using syringe with 0.63 to 0.80 mm needle, puncture resealable medication port and inject. Mix solution and medication thoroughly. For high density medication such as potassium chloride, squeeze ports while ports are upright and mix thoroughly.

To add medication during solution administration: Close clamp on the set. Prepare medication port. Using syringe with 0.63 to 0.80 mm needle, puncture resealable medication port and inject. Remove container from IV pole and/or turn to upright position. Evaluate both ports by squeezing them while container is in the upright position. Mix solution and medication thoroughly. Return container to in use position and continue administration.

Overdosage

Infusion of excess Sodium Chloride Intravenous preparations may cause

- fluid overload
- sodium overload (which can lead to central and/or peripheral edema).
- hypernatraemia, (0.9% or 3% Sodium Chloride Intravenous Infusions)
- hyponatraemia (0.9% or 0.45% Sodium Chloride Intravenous Infusions)
- other electrolyte abnormalities.

No specific antidotes to this preparation are known.

Should overdose occur, prompt and careful clinical assessment is essential. Treat the symptoms and institute appropriate supportive measures as required.

Symptoms of hypernatraemia

Hypernatraemia may cause nausea, vomiting, diarrhoea and cramps, reduced salivation and lacrimation, increased thirst, hypotension, and tachycardia.

CNS effects include headache, dizziness, restlessness, weakness, muscle twitching or rigidity, respiratory paralysis, seizures, coma, and death.

Treatment of hypernatraemia:

Treatment usually requires free water replacement. Plasma sodium concentrations should be corrected slowly. If hypernatraemia is severe, I.V. hypotonic or isotonic saline or 5 percent glucose may be used to restore normal plasma sodium concentrations at a rate of no more than 10 to 12 mmol/L daily (0.5 mmol/L per hour). If plasma sodium levels are greater than 200 mmol/L or if the patient has renal impairment or is moribund, dialysis may be needed. Diazepam or other appropriate treatment may be required to treat convulsions.

Symptoms of hyponatraemia:

Symptoms may include headache, confusion, nausea, vomiting, somnolence, weakness, cerebral oedema, seizures, coma, respiratory arrest and death.

Treatment of hyponatraemia:

Acute hyponatraemia requires immediate assessment.

Symptomatic hyponatraemia associated with plasma sodium concentrations below 120 mmol/L may require the administration of i.v. isotonic or hypertonic sodium chloride.

A loop diuretic may be required if there is fluid overload.

The aim is to render the patient asymptomatic, usually by restoring plasma sodium concentration to between 120 mmol/L and 130 mmol/L, at a rate of 10 to 12 mmol/L in each 24 hour period.

Careful monitoring of plasma sodium concentrations and total body water is essential.

As in hypernatraemia, rapid correction of hyponatraemia is potentially dangerous.

If neurological deterioration occurs, further investigation by MRI imaging of brain, including brain stem, is indicated.

Presentation and storage conditions

Sodium Chloride Intravenous Infusion is supplied in Viaflex plastic bags as shown below.

Table 1 : Sodium Chloride (0.45%, 0.9%, 3%) Intravenous Infusion preparations

| Code No. | Name of the active components [concentrations (% , mmol/1000 mL)] | Osmolarity ^α (mOsmol/L) | ARTG / AUSTR | Pack Size* |
|----------|--|---------------------------------------|-----------------|-------------|
| AHB1306 | Sodium Chloride (0.9%, 154) | 308 [300] | 19477 | 50 mL |
| AHB1307 | Sodium Chloride (0.9%, 154) | 308 [300] | 48515 | 100 mL |
| AHB1322 | Sodium Chloride (0.9%, 154) | 308 [300] | 48517 | 250 mL |
| AHB1323 | Sodium Chloride (0.9%, 154) | 308 [300] | 48519 | 500 mL |
| AHB1324 | Sodium Chloride (0.9%, 154) | 308 [300] | 48520 | 1000 mL |
| AHB1363 | Sodium Chloride (0.9%, 154) | 308 (300) | 19477 | 50 ml x 2 |
| AHB1364 | Sodium Chloride (0.9%, 154) | 308 (300) | 48515 | 100 mL x 2 |
| AHB1313 | Sodium Chloride (0.45%, 77) | 154 [150] | 19472 | 500 mL x 18 |
| AHB1354 | Sodium Chloride (3%, 513) | 1026 [1000] | 19500 | 1000 mL |

Note: Osmolarities^α are calculated figures, whilst those in the [bracket] are approximate Osmolalities (mOsmol/kg); AHB1354 product is *hypertonic* as indicated by the osmolarity of 1026 mOsmol/L, whilst AHB1313 is *hypotonic*.

*Not all packs are marketed.

Storage: Store below 30°C. Do not freeze.

Name and address of the sponsor

Baxter Healthcare Pty Limited
ABN: 43 000 392 781
1 Baxter Drive
Toongabbie NSW 2146
Australia

Poison schedule of the medicine

Unscheduled.

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG)

Aust R 19472 30 Sep 1991
Aust R 19477 30 Sep 1991
Aust R 19500 30 Sep 1991
Aust R 48515 21 Apr 1994
Aust R 48517 21 Apr 1994
Aust R 48519 21 Apr 1994
Aust R 48520 21 Apr 1994

Date of most recent amendment

22 October 2013



Health Questionnaire

English version for Australia

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems with walking around
- I have slight problems with walking around
- I have moderate problems with walking around
- I have severe problems with walking around
- I am unable to walk around

PERSONAL CARE

- I have no problems with washing or dressing myself
- I have slight problems with washing or dressing myself
- I have moderate problems with washing or dressing myself
- I have severe problems with washing or dressing myself
- I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

PAIN / DISCOMFORT

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

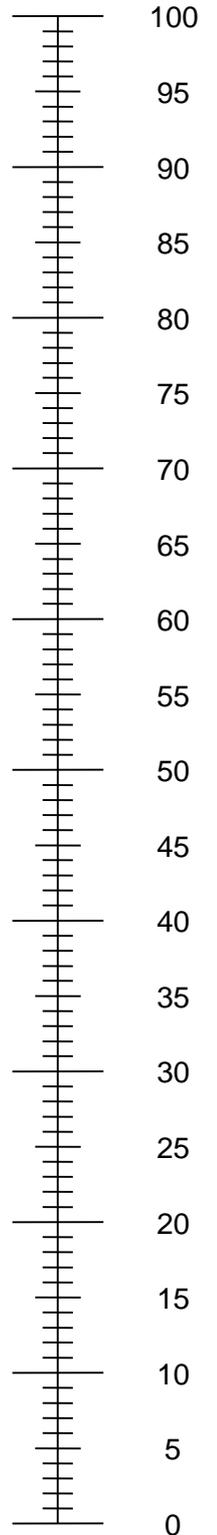
ANXIETY / DEPRESSION

- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health
you can imagine



The worst health
you can imagine



Health Questionnaire

English version for New Zealand

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

SELF-CARE

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

PAIN / DISCOMFORT

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

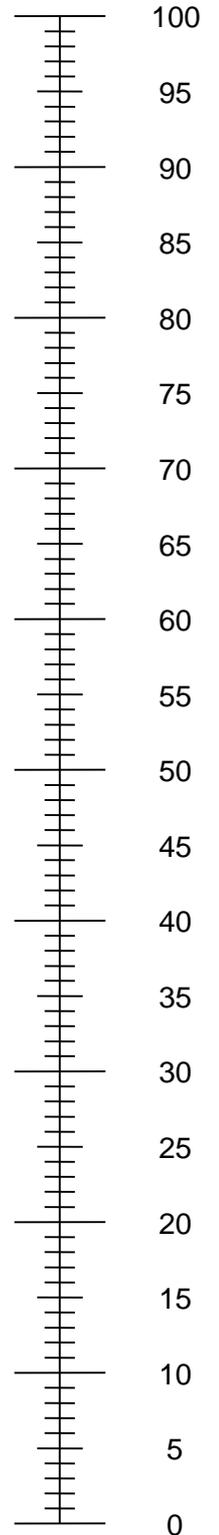
ANXIETY / DEPRESSION

- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health
you can imagine



The worst health
you can imagine