The statistical analysis plan for the 0.9% Saline vs. Plasma-Lyte 148® for Intensive care fluid Therapy (SPLIT) study

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Introduction

Although 0.9% saline is the most commonly used intravenous (IV) fluid in the world, recent data raise the possibility that, compared to buffered crystalloid fluids like Plasma-Lyte 148®, the administration of 0.9% saline might increase the risk of developing acute kidney injury (AKI). The 0.9% Saline vs. Plasma-Lyte 148® for Intensive care fluid Therapy (SPLIT) study is a component of a bi-national, multidisciplinary, collaborative and coordinated research programme investigating the comparative effectiveness of 0.9 % saline versus Plasma-Lyte 148 ® as IV fluid therapy. A manuscript providing an overview of the statistical analysis plan (SAP) for all of the studies that make up this programme was submitted for publication on the 19th of September 2014. This document provides additional details in relation to the SPLIT study SAP and supersedes all previous documents. This SAP was prepared prior to the completion of SPLIT study recruitment and was published online on the 26th of September 2014. All SPLIT study analyses will be conducted according to this pre-specified SAP in order to reduce the risk of analysis bias arising from knowledge of the study results emerging during the analyses.

Methods

Overview

The 0.9% Saline vs. Plasma-Lyte 148® for Intensive care fluid Therapy (The SPLIT study) is a prospective, multicentre, randomised, double-blind, cluster, double crossover feasibility study conducted over 28 weeks in four New Zealand ICUs which is being coordinated by the Medical Research Institute of New Zealand. The SPLIT study will compare 0.9% saline to Plasma-Lyte 148 ® as the default IV crystalloid fluid therapy. Two ICUs will initially use blinded 0.9% saline as the routine IV fluid while the other two will use blinded Plasma-Lyte 148®. Every seven weeks, the ICUs will swap their routine fluid. Patients who remain in the ICU through one or more crossover periods will continue to receive the fluid to which they were originally assigned.

Patients will be followed until hospital discharge with censoring applied at death or at day 90 (2160 hours) from the time of SPLIT study enrolment with the exception that all patients who require renal replacement therapy will be followed up for 3 months to establish whether or not they have end-stage renal failure according RIFLE criteria(1). The primary outcome is the proportion of patients with either acute kidney injury (AKI) or renal failure according to the risk, injury, failure, loss, end-stage (RIFLE) criteria definitions based on serum creatinine levels(1).

Study data will be collected at each site by trained research coordinators using a web-based case report form. The study website includes features for automatic checking of the internal consistency of data and requires manual verification of values which are outside specified expected ranges. A range of website reporting functions will allow for remote monitoring of study data by monitoring staff at the co-ordinating centre. In addition, 100% source data verification of study eligibility criteria and serum creatinine values will be performed by a study monitor from the Medical Research Institute of New Zealand.

This trial was prospectively registered (ACTRN12613001370796). The study protocol has been published previously(2).

Aims

The overarching aim of this study is to provide preliminary data on the comparative effectiveness of 0.9% saline vs. Plasma-Lyte 148® as the routine IV fluid therapy in ICU patients.

The primary outcome will be the proportion of patients with either AKI or renal failure according to the risk, injury, failure, loss, end-stage (RIFLE) criteria definitions as based on serum creatinine levels.(1) For the purposes of the RIFLE criteria,(1) the baseline creatinine level will be the lowest serum creatinine in the hospital laboratory records for the six months prior to the current ICU admission. The peak creatinine will be defined as the highest serum creatinine during ICU admission.

Secondary outcomes will be the delta creatinine (difference between the serum creatinine measured immediately prior to study enrolment and peak creatinine in ICU), the cumulative incidence of acute AKI by category based on the RIFLE classification,(1) the cumulative incidence of acute AKI by KDIGO criteria,(3) the need for RRT during ICU and after hospital discharge, the proportion of patients requiring mechanical ventilation and duration of mechanical ventilation, the proportion of patients who require ICU readmission during their hospital admission, ICU

and hospital length of stay, and ICU and in-hospital mortality.

The total volumes of study fluids, open label Plasma-Lyte 148®, open label 0.9% saline, 5% dextrose, paediatric maintenance fluids, other crystalloids, 4% albumin, 20% albumin, gelofusine, voluven / volulyte, other colloids, packed red blood cells, fresh frozen plasma, platelets, and cryoprecipate administered daily between day zero and day three (inclusive) as well as the total volumes of study fluid, open label Plasma-Lyte 148®, and open label 0.9% saline administered up until day 90 from the time of SPLIT enrolment will be reported.

The study will provide data including recruitment rates, and estimates of effect sizes that will be used to inform sample size calculations and aid in the design of future trials. Data will also be used for statistical modelling purposes in order to determine the number of clusters required and the overall sample size for a larger scale cluster double crossover study of ICU fluid therapy.

Participants & pre-specified subgroups

All patients who require crystalloid fluid therapy will be eligible for study inclusion except for those who are receiving or expected to require renal replacement therapy within six hours of ICU admission, those who are usually on dialysis for end stage renal failure, those who are admitted to the ICU solely for consideration of organ donation or for palliative care, and those who have been enrolled in the study previously.

The following groups of patients are pre-defined as subgroups of interest:
1. Patient with sepsis (APACHE III admission diagnostic codes 501, 502, 503, 504)
2. Patients with trauma (APACHE III admission diagnostic codes 601, 602, 603, 604, 605)
3. Patients with traumatic brain injury (APACHE III admission diagnostic code 601)
4. Patients with an APACHE-II score of ≥25 (the APACHE-II score will be calculated using physiological data for the 24 hours immediately prior to the first receipt of study fluid)
5. Patients admitted to the ICU following cardiac surgery (APACHE III admission diagnostic codes 1206, 1207, 1208, 1209, 1212)

Definitions of key outcome variables

Acute kidney injury and renal failure

Acute kidney injury (AKI) will be defined according to the risk, injury, failure, loss, end-stage (RIFLE) criteria definitions using serum creatinine criteria. Serum creatinine levels will be censored at patient death or day 90. In addition to AKI based on RIFLE criteria, the cumulative incidence of patients with AKI and renal failure defined according to KDIGO criteria and the delta creatinine will be reported.(4) For the RIFLE criteria and KDIGO criteria, the baseline creatinine will be defined as the lowest serum creatinine in the hospital laboratory records for the six months prior to the current ICU admission. The delta creatinine is defined as the difference between the serum creatinine measured most recently before study enrolment and the peak serum creatinine measured after study enrolment during the index ICU admission. The need for RRT in ICU will be assessed daily and, for patients who receive RRT in ICU, the indication(s) for commencing RRT will be reported. Pre-specified indications for RRT will be as follows: (i) clinically significant oliguria, (ii) serum potassium >6.5mmol/L, (iii) arterial or venous pH<7.2, (iv) serum urea >25mmol/L, (v) serum serum creatinine >300µmol/L, (vi) organ oedema, (vii) other renal failure-related indication, (viii) other non renal failure-related indication.

Mortality

In-hospital mortality is defined as all-cause mortality during the index hospital admission. Causes of death will be categorised as cerebral, cardiac, septic, bleeding, and other. Categorisation of deaths will be based on a detailed cause of death provided to the coordinating centre by each site investigator and will be adjudicated by two study investigators independently (PY and DM) with disagreements resolved by discussion with other members of the management committee where required.

Analysis principles and handling of missing data

All analyses will be by intention-to-treat. Allocation concealment will be maintained until all analyses are completed. In the primary analysis, no assumptions will be made for missing values and, where baseline or peak serum creatinine levels are not available, we will perform a complete case analysis. If missing data are found to exceed 5%, we will undertake sensitivity analyses to account for extreme scenarios for missing values. For patients with no serum creatinine data at all, we will consider the extreme scenarios that either all patients with missing data have AKI / failure or no patients with missing data have AKI / failure. For patients with missing baseline serum creatinine data, we

will consider the extreme scenarios that either the baseline serum creatinine value equals the peak measured value in ICU or that the baseline value is normal based on the Modification of Diet in Renal Disease formula, as recommended by the Acute Dialysis Quality Initiative working group (assuming an average GFR of 75mL/min/1.73m2).(5) If the peak serum creatinine value is missing, we will consider the extreme scenarios that either the peak measured serum creatinine is equal to the baseline measured serum creatinine or that all patients with a missing peak serum creatinine levels have AKI / failure.

Justification of sample size

No large-scale randomised interventional trial has compared the use of 0.9% saline to a buffered crystalloid solution. As such, the principal reasons for conducting this study will be to determine feasibility and inform future sample size calculations. Because of the cluster crossover design, the study is set to run for a specific period of time and has no fixed recruitment number. Although, based on retrospective data from participating ICUs, we expect that the number of participants will be between 2300 and 2500.

Description of analyses

All continuous variables will be assessed for normality and log-transformed where appropriate. Baseline comparisons between groups will be determined using chi-square tests for equal proportion (or Fishers exact tests for small numbers), student t-tests for normally distributed variables and Wilcoxon ranks sum tests otherwise.

Binomial outcomes will be analysed using logistic or poisson regression models with results reported as Odds Ratios (95%CI) or Relative Risks (95%CI). Survival time and time free of RRT from randomisation to day 90 will be analysed using the log-rank test. The distribution of causes of death among patients who died will be compared using a Chi-square test. Continuous outcomes will be analysed using mixed linear modelling with results reported as differences (95%CI) or ratios (95%CI) as appropriate. Outcomes will be analysed at an individual patient level using hierarchical longitudinal analysis techniques accounting for attending hospital and fluid sequence with patients nested within sites and sites crossing over, not patients. Study site will be treated as a fixed effect and results will be reported both overall and at an individual site level. Heterogeneity across sites will be determined by fitting interactions between treatment and site. Subgroup analyses will be performed on the pre-specified subgroups of interest irrespective of whether there is evidence of a treatment effect. Heterogeneity between subgroups will be determined by fitting an interaction between treatment and subgroup.

Unadjusted analyses will be performed for all outcome variables and additional analyses will be performed incorporating adjustment for the following pre-specified baseline variables: Presence or absence of trauma, APACHE-III admission diagnosis, age, ICU admission source, and APACHE-II score. Delta creatinine will also be adjusted for the baseline serum creatinine level.

All analyses will be performed using SAS version 9.3 (SAS Institute Inc., Cary, USA) and a two-sided p-value of 0.05 will be considered to be statistically significant. As the principal aim of this study is to provide preliminary data and determine feasibility, no adjustment for multiple comparisons will be made.

Presentation of results

Trial Profile

The flow of patients through the study will be presented in a Consolidated Standards of Reporting Trials (CONSORT) diagram(6) (Figure 1).

Characteristics of patients and baseline comparisons

Baseline characteristics will be presented by treatment group (Table 1). Discrete variables will be presented as numbers. Percentages will be calculated using available data. Where values are missing the denominator will be stated. Continuous variables will be summarised using standard measures of central tendency and dispersion, i.e. mean and standard deviation (SD), or median and interquartile range [IQR]. Admission diagnosis will be presented as shown in Table 2.

Presentation of outcome data

The main outcomes will be reported as shown in Table 3. Forest plots for the relative risk of developing AKI or failure overall, for designated subgroups, and for individual study sites will be reported. The probability of remaining RRT-free to day 90 for patients who receiving Plasma-Lyte® 148 or 0.9% saline will be reported using

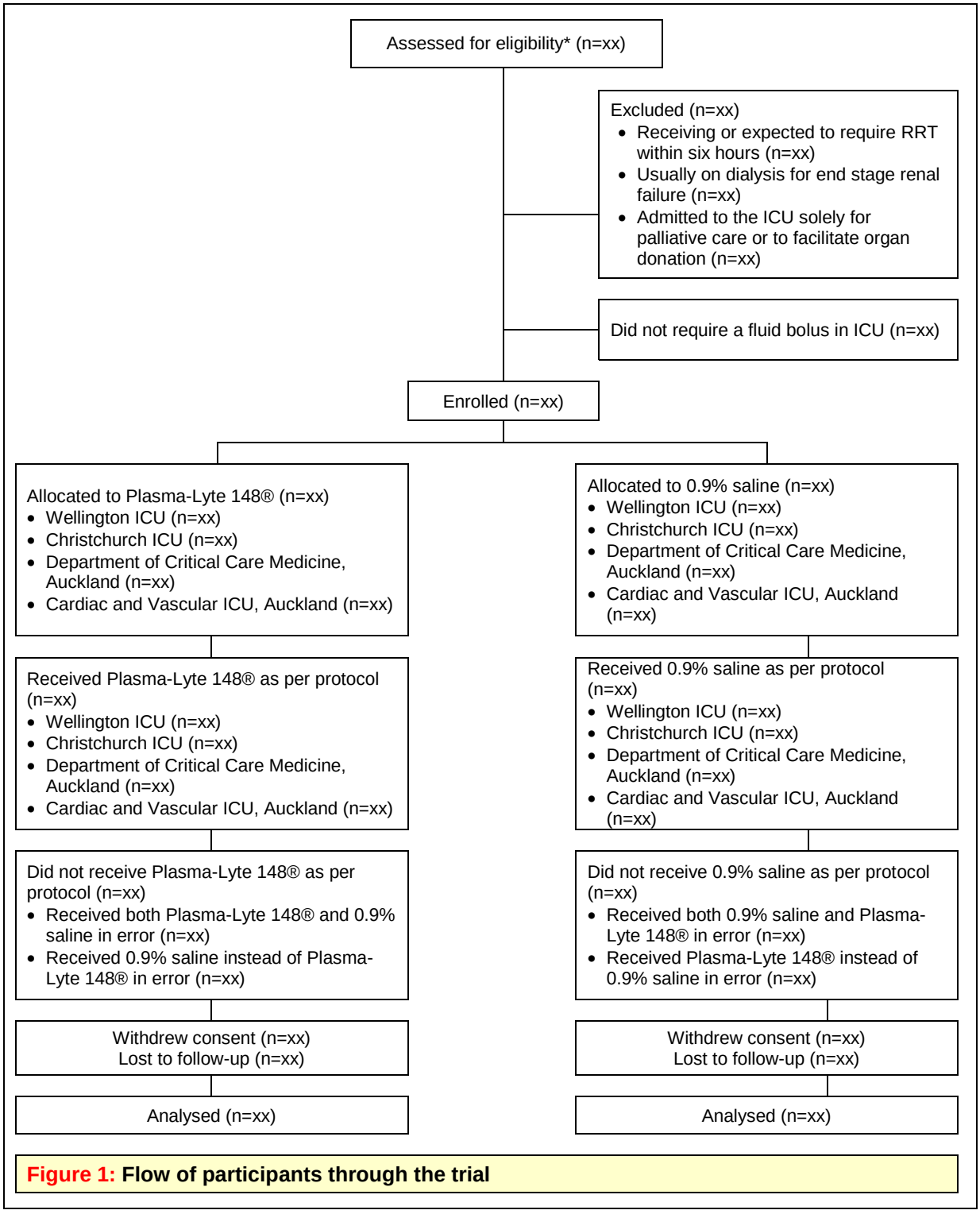

Figure 1: Flow of participants through the trial

* All patients admitted to one of the study ICUs during the 28 weeks of recruitment were screened for study enrolment except for three patients who decided not to participate in the study prior to ICU admission.

Kaplan-Meier estimates. The probability of survival and the risk of in hospital death at day 90 will be reported in a similar fashion. Causes of death will be reported. The pre- randomisation and peak daily serum creatinine levels up until day seven between groups will be presented graphically along with a comparison of means of individual daily averages for seven days including day zero. The type and amount of IV fluid administered from day zero to day three (including study fluids) will be presented in a table along with the total volume of each study fluid and open label 0.9% saline and Plasma-Lyte 148® administered up until day 90.

Table 1: Characteristics of the Patients at Baseline.*

Characteristic	Plasma-Lyte 148 (N=xxxx)	0.9% saline (N=xxxx)
Age (years)	xx.x ± xx.x	xx.x ± xx.x
Male sex – no. / total no. (%)	xx/xx (xx.x)	xx/xx (xx.x)
Weight	xx.x ± xx.x	xx.x ± xx.x
Ethnicity – no. / total no. (%)		
New Zealand European	xx/xx (xx.x)	xx/xx (xx.x)
Maori	xx/xx (xx.x)	xx/xx (xx.x)
Pacific Islander	xx/xx (xx.x)	xx/xx (xx.x)
Other	xx/xx (xx.x)	xx/xx (xx.x)
Comorbidities – no. / total no. (%)		
Chronic respiratory disease	xx/xx (xx.x)	xx/xx (xx.x)
Chronic CVS disease	xx/xx (xx.x)	xx/xx (xx.x)
Leukaemia / myeloma	xx/xx (xx.x)	xx/xx (xx.x)
Immunosuppression by disease	xx/xx (xx.x)	xx/xx (xx.x)
Immunosuppression by therapy	xx/xx (xx.x)	xx/xx (xx.x)
Hepatic failure	xx/xx (xx.x)	xx/xx (xx.x)
Cirrhosis	xx/xx (xx.x)	xx/xx (xx.x)
Lymphoma	xx/xx (xx.x)	xx/xx (xx.x)
AIDS	xx/xx (xx.x)	xx/xx (xx.x)
Metastatic cancer	xx/xx (xx.x)	xx/xx (xx.x)
Source of admission to ICU – no. / total no. (%)		
Emergency department	xx/xx (xx.x)	xx/xx (xx.x)
Hospital floor	xx/xx (xx.x)	xx/xx (xx.x)
Another ICU	xx/xx (xx.x)	xx/xx (xx.x)
Another hospital (excluding from another ICU)	xx/xx (xx.x)	xx/xx (xx.x)
Operating room	xx/xx (xx.x)	xx/xx (xx.x)
After emergency surgery	xx/xx (xx.x)	xx/xx (xx.x)
After elective surgery	xx/xx (xx.x)	xx/xx (xx.x)
Diagnosis on admission – no. / total no. (%)		
Surgical cases	xx/xx (xx.x)	xx/xx (xx.x)
Non surgical cases	xx/xx (xx.x)	xx/xx (xx.x)
APACHE II† score	xx.x ± xx.x	xx.x ± xx.x
Mechanical ventilation – no. / total no. (%)	xx/xx (xx.x)	xx/xx (xx.x)
Time from ICU admission to randomisation – hr	xx.x ± xx.x	xx.x ± xx.x
Serum creatinine (µmol/L)		
Baseline (pre-illness)	xx.x ± xx.x	xx.x ± xx.x
Most recent	xx.x ± xx.x	xx.x ± xx.x
Crystalloids received in the 24 hr before randomisation – ml		
Plasma-Lyte 148 ®	xxxx.x [xxxx.x-xxxx.x]	xxxx.x [xxxx.x-xxxx.x]
0.9% saline	xxxx.x [xxxx.x-xxxx.x]	xxxx.x [xxxx.x-xxxx.x]
5% dextrose	xxxx.x [xxxx.x-xxxx.x]	xxxx.x [xxxx.x-xxxx.x]
Paediatric maintenance fluids†	xxxx.x [xxxx.x-xxxx.x]	xxxx.x [xxxx.x-xxxx.x]
Other crystalloids	xxxx.x [xxxx.x-xxxx.x]	xxxx.x [xxxx.x-xxxx.x]
Colloids received in the 24 hr before randomisation – ml		
4% albumin	xxxx.x [xxxx.x-xxxx.x]	xxxx.x [xxxx.x-xxxx.x]
20% albumin	xxxx.x [xxxx.x-xxxx.x]	xxxx.x [xxxx.x-xxxx.x]
Gelofusine	xxxx.x [xxxx.x-xxxx.x]	xxxx.x [xxxx.x-xxxx.x]
Voluven or Volulyte	xxxx.x [xxxx.x-xxxx.x]	xxxx.x [xxxx.x-xxxx.x]
Other colloids	xxxx.x [xxxx.x-xxxx.x]	xxxx.x [xxxx.x-xxxx.x]
Blood products received in the 24 hr before randomisation – ml		
Packed red cells	xxxx.x [xxxx.x-xxxx.x]	xxxx.x [xxxx.x-xxxx.x]
Fresh frozen plasma	xxxx.x [xxxx.x-xxxx.x]	xxxx.x [xxxx.x-xxxx.x]
Platelets	xxxx.x [xxxx.x-xxxx.x]	xxxx.x [xxxx.x-xxxx.x]
Cryoprecipitate	xxxx.x [xxxx.x-xxxx.x]	xxxx.x [xxxx.x-xxxx.x]
Subgroups – no. / total no. (%)		
Sepsis	xx/xx (xx.x)	xx/xx (xx.x)
Trauma	xx/xx (xx.x)	xx/xx (xx.x)
Traumatic brain injury	xx/xx (xx.x)	xx/xx (xx.x)
Cardiac surgery	xx/xx (xx.x)	xx/xx (xx.x)
APACHE II score ≥25	xx/xx (xx.x)	xx/xx (xx.x)

* plus-minus values are mean ±SD. Values followed by ranges in square brackets are median [IQR].
† 'paediatric maintenance fluids' are 10% dextrose + 72mmol/L NaCl in 500ml + 20mmol/L KCl (for children <6 months), 5% dextrose + 72 mmol/L NaCl + 20mmol/L KCl (for children 6 months to 5 years), 2.5% dextrose + 36 mmol/L NaCl + 10-20mmol/L (for children >5 years to 16 years)
† Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating an increased risk of death.

Table 2: Admission diagnoses of the study patients*.

Diagnosis	Plasma-Lyte 148 (N=xxxx)	0.9% saline (N=xxxx)
Operative admission diagnoses – no. / total no. (%)		
Cardiovascular	xx/xx (xx.x)	xx/xx (xx.x)
Gastrointestinal	xx/xx (xx.x)	xx/xx (xx.x)
Gynaecological	xx/xx (xx.x)	xx/xx (xx.x)
Neurological	xx/xx (xx.x)	xx/xx (xx.x)
Musculoskeletal / skin	xx/xx (xx.x)	xx/xx (xx.x)
Renal	xx/xx (xx.x)	xx/xx (xx.x)
Respiratory	xx/xx (xx.x)	xx/xx (xx.x)
Trauma	xx/xx (xx.x)	xx/xx (xx.x)
Other postoperative	xx/xx (xx.x)	xx/xx (xx.x)
Non-operative admission diagnoses – no. / total no. (%)		
Cardiovascular	xx/xx (xx.x)	xx/xx (xx.x)
Gastrointestinal	xx/xx (xx.x)	xx/xx (xx.x)
Haematological	xx/xx (xx.x)	xx/xx (xx.x)
Metabolic	xx/xx (xx.x)	xx/xx (xx.x)
Neurological	xx/xx (xx.x)	xx/xx (xx.x)
Renal	xx/xx (xx.x)	xx/xx (xx.x)
Respiratory	xx/xx (xx.x)	xx/xx (xx.x)
Sepsis	xx/xx (xx.x)	xx/xx (xx.x)
Trauma	xx/xx (xx.x)	xx/xx (xx.x)
Other medical diseases	xx/xx (xx.x)	xx/xx (xx.x)

* Admission diagnoses are based on the Acute Physiology and Chronic Health Evaluation (APACHE) III admission diagnostic codes.

Interim analysis and Data Safety Monitoring Board (DSMB)

An independent DSMB has been appointed for the study. The members of the DSMB are Prof Anders Perner, Prof Thomas Morgan, and Prof Andrew Forbes. There are no planned interim analyses for this study and given the current widespread use of the IV fluids being tested in routine practice, it is not anticipated that the DSMB will make recommendations to stop the trials early on the basis of reported adverse events. However, the DSMB retain the right to access all trial data and may recommend to the trial management committee that a trial is ceased.

Consent

The SPLIT study compares the effectiveness of two established treatments which are both commonly administered to patients in usual clinical practice.(7) Given the low risk nature of the research, we will use a process of 'opt-out consent' which involves the provision of information to patients and their next of kin and the opportunity to opt-out of the use of their data if they wish. This approach has been approved by the New Zealand and Health and Disability Ethics Committee (reference 12-NTB-57).

Proposed list of Tables and Figures

Main manuscript

- Table 1: Characteristics of the patients at baseline (as shown in Table 1 above)
- Table 2: Outcomes (as shown in Table 3 below)
- Figure 1: Assessment, randomisation, and follow-up of the patients (as shown in Figure 1 above)
- Figure 2a: Kaplan-Meier estimate of the probability of remaining RRT-free to day 90 (as described in the section on presentation of outcome data)
- Figure 2b: Subgroup analyses presented as Forest plots (as described in the section on presentation of outcome data)
- Figure 3: Serum creatinine levels through to day 7 (as described in the section on presentation of outcome data)

Supplementary material

- Table S1: Admission diagnoses of the study patients (as shown in Table 3 above)
- Table S2: Study and non-study fluids administered (as described in the section on the presentation of outcome data)
- Table S3: Cause-specific in hospital mortality within the 90-day follow-up period
- Figure S1a: Kaplan-Meier estimate of the probability of survival to day 90 (as described in the section on presentation of outcome data)
- Figure S1b: Subgroup analyses of the relative risk of death presented as Forest plots (as described in the section on presentation of outcome data)

Table 3: Outcomes.*

Variable	Plasma-Lyte 148	0.9% saline	Relative Risk (95% CI)	P value
Outcome				
Primary outcome of acute kidney injury or failure† – no./ total no. (%)	xx/xx (xx.x)	xx/xx (xx.x)	x.xx (x.xx to x.xx)	x.xx
Secondary outcomes – no./ total no. (%)				
Renal outcomes				
RIFLE				
RIFLE-R	xx/xx (xx.x)	xx/xx (xx.x)	x.xx (x.xx to x.xx)	x.xx
RIFLE-I	xx/xx (xx.x)	xx/xx (xx.x)	x.xx (x.xx to x.xx)	x.xx
RIFLE-F	xx/xx (xx.x)	xx/xx (xx.x)	x.xx (x.xx to x.xx)	x.xx
RIFLE-L	xx/xx (xx.x)	xx/xx (xx.x)	x.xx (x.xx to x.xx)	x.xx
RIFLE-E	xx/xx (xx.x)	xx/xx (xx.x)	x.xx (x.xx to x.xx)	x.xx
KDIGO				
Stage 1	xx/xx (xx.x)	xx/xx (xx.x)	x.xx (x.xx to x.xx)	x.xx
Stage 2	xx/xx (xx.x)	xx/xx (xx.x)	x.xx (x.xx to x.xx)	x.xx
Stage 3	xx/xx (xx.x)	xx/xx (xx.x)	x.xx (x.xx to x.xx)	x.xx
Renal replacement therapy use				
ICU use	xx/xx (xx.x)			
Indications				
Oliguria				
Hyperkalaemia with serum potassium >6.5mmol/L	xx/xx (xx.x)	xx/xx (xx.x)	x.xx (x.xx to x.xx)	x.xx
Acidaemia with pH <7.20	xx/xx (xx.x)	xx/xx (xx.x)	x.xx (x.xx to x.xx)	x.xx
Serum urea >25mmol/L	xx/xx (xx.x)	xx/xx (xx.x)	x.xx (x.xx to x.xx)	x.xx
Serum creatinine >300µmol/L	xx/xx (xx.x)	xx/xx (xx.x)	x.xx (x.xx to x.xx)	x.xx
Organ oedema	xx/xx (xx.x)	xx/xx (xx.x)	x.xx (x.xx to x.xx)	x.xx
Other renal failure related indication	xx/xx (xx.x)	xx/xx (xx.x)	x.xx (x.xx to x.xx)	x.xx
Other non renal failure related indication	xx/xx (xx.x)	xx/xx (xx.x)	x.xx (x.xx to x.xx)	x.xx
Ongoing use after hospital discharge	xx/xx (xx.x)	xx/xx (xx.x)	x.xx (x.xx to x.xx)	x.xx
			Mean difference (95% CI)	
Delta creatinine‡ (µmol/L)	xx.x ± xx.x	xx.x ± xx.x	x.xx (x.x to x.x)	x.xx
			Ratio of geometric means (95% CI)	
Service utilisation				
Days in ICU	xx.x [xx.x-xx.x]	xx.x [xx.x-xx.x]	x.xx (x.xx to x.xx)	x.xx
Days in hospital	xx.x [xx.x-xx.x]	xx.x [xx.x-xx.x]	x.xx (x.xx to x.xx)	x.xx
Days of mechanical ventilation (among patients requiring mechanical ventilation)	xx.x [xx.x-xx.x]	xx.x [xx.x-xx.x]	x.xx (x.xx to x.xx)	x.xx
			Relative Risk (95% CI)	
Use of mechanical ventilation – no./ total no. (%)	xx/xx (xx.x)	xx/xx (xx.x)	x.xx (x.xx to x.xx)	x.xx
ICU readmission required during index hospital admission – no./ total no. (%)	xx/xx (xx.x)	xx/xx (xx.x)	x.xx (x.xx to x.xx)	x.xx
Mortality				
Death in ICU	xx/xx (xx.x)	xx/xx (xx.x)	x.xx (x.xx to x.xx)	x.xx
Death in hospital	xx/xx (xx.x)	xx/xx (xx.x)	x.xx (x.xx to x.xx)	x.xx

* plus-minus values are mean ±SE. Values followed by square brackets are geometric mean [95% CI]
† based on serum creatinine levels in accordance with RIFLE criteria
‡ Difference between the most recent pre-randomisation serum creatinine level and the peak serum creatinine level measured during the ICU stay (censored at day 90)

Funding

This study is investigator-initiated and study analyses will be conducted independently of the funding organisations. This study is primarily funded by a grant from the Health Research Council of New Zealand. In addition, Baxter Pty Ltd has provided a grant to support this study and is providing study fluid.

Competing interests

Rinaldo Bellomo, Seton Henderson, Shay McGuinness, and Paul Young report receiving honoraria (<USD$5000) from Baxter Healthcare Pty Ltd for consulting activities. The Medical Research Institute of New Zealand received a research grants from Baxter to support this study and Baxter Healthcare Pty Ltd provided study fluids

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