Overview of the study protocols and statistical analysis plan for the Saline versus Plasma-Lyte 148 for Intravenous Fluid Therapy (SPLIT) research program

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ABSTRACT

Background: 0.9% saline is the most commonly used intravenous (IV) fluid in the world but recent data raise the possibility that, compared with buffered crystalloid fluids such as Plasma-Lyte 148, the administration of 0.9% saline might increase the risk of developing acute kidney injury.

Objective: To provide an overview of the study protocols and statistical analysis plan for the six studies making up the (0.9% Saline v Plasma-Lyte 148 for Intravenous Fluid Therapy (SPLIT) research program.

Methods: The SPLIT study consists of six integrated clinical trials, including a double-blind, cluster, randomised, double-crossover study in intensive care unit patients, incorporating two nested studies within it; an open-label, before-and-after study in emergency department (ED) patients; a single-centre, double-blind, crossover trial in major surgical patients; and a randomised, double-blind study in ICU patients. All studies focus on biochemical and renal outcomes but will also provide preliminary data on patient-centred outcomes including inhospital mortality and requirements for dialysis.

Results and conclusion: The SPLIT study program will provide preliminary data on the comparative effectiveness of using 0.9% saline v Plasma-Lyte 148 for IV fluid therapy in ED, surgical and ICU patients.

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Although 0.9% saline is the most commonly used intravenous (IV) fluid in the world, recent data raise the possibility that, because of its high chloride content,[1] IV administration of 0.9% saline might increase the risk of a patient developing acute kidney injury (AKI) compared with administration of buffered crystalloid fluids such as Plasma-Lyte 148.[2] The 0.9% Saline v Plasma-Lyte 148 for IV Fluid Therapy (SPLIT) research program is a binational, multidisciplinary, collaborative and coordinated approach to investigate the comparative effectiveness of 0.9% saline v Plasma-Lyte 148 as IV fluid therapy.

Our statistical analysis plan (SAP) outlines the principles and methods of analysing and reporting of the SPLIT research program results. This plan was prepared before the completion of recruitment in any of the studies making up the program. The use of a prespecified SAP aims to reduce the risk of analysis bias arising from knowledge of the study results emerging during the conduct of the study analyses.[3]

Methods

Overview

The SPLIT research program involves six studies with different designs to facilitate successful investigation in each setting. We chose to study a broad spectrum of critically ill patients to increase the external validity of our findings. Unlike the recent high-profile IV fluid therapy studies, Crystalloid versus Hydroxyethyl Starch Trial (CHEST) and Scandinavian Starch for Severe Sepsis/Septic Shock (6S),[4] the SPLIT program will include cardiac surgical patients,[5] emergency department (ED) patients, and non-intensive care unit patients having major surgery. Data will be collected by trained personnel in each study centre.

Study A

Our SPLIT study is a prospective, multicentre, randomised, double-blind, cluster, double-crossover feasibility study conducted over 28 weeks in four New Zealand ICUs comparing 0.9% saline with Plasma-Lyte 148 as the routine IV crystalloid fluid therapy. Two ICUs will initially use blinded 0.9% saline as the routine IV fluid, and the other two will use blinded Plasma-Lyte 148. Every 7 weeks, the ICUs will change to the other fluid (Table 1a). The primary outcome is the proportion of patients with acute kidney injury (AKI) or renal failure according to the risk, injury, failure, loss, end-stage (RIFLE) criteria definitions based on serum creatinine levels.[6] Our trial was prospectively registered (ACTRN12613001370796). The study protocol has been published[7] and an expanded SAP is available (http://wellingtonicu.com/Data/Trials/SPLITSAP.pdf). One hundred per cent 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 (MRINZ).

Table 1a. Overview of design for Studies A, B and C

Study and centre	Fluid used 1st 7 weeks	2nd 7 weeks	3rd 7 weeks	4th 7 weeks
Study A*				
Centre 1	A	B	A	B
Centre 2	B	A	B	A
Centre 3	A	B	A	B
Centre 4	B	A	B	A
Studies B† and C‡	A	B	A	B

* 0.9% saline v Plasma-Lyte 148 for intensive care fluid therapy.
† 0.9% saline v Plasma-Lyte 148 for postoperative fluid therapy in adults undergoing cardiac surgery. ‡ 0.9 % saline v Plasma-Lyte 148 as primary fluid therapy in mechanically ventilated patients receiving nasogastric enteral nutrition.

Table 1b. Overview of design for Study D

Study	Fluid used 1st 3 weeks	Next 6 weeks	Next 3 weeks	Next 3 weeks	Next 6 weeks	Next 3 weeks
Study D*	Wash in fluid A	Study: fluid A	Wash out fluid A	Wash in fluid B	Study: fluid B	Wash out fluid B

* 0.9% saline v Plasma-Lyte 148 fluid intervention trial in major surgery patients.

Study B

Study B is a single-centre nested study within Study A, comparing the effect of 0.9% saline v Plasma-Lyte 148 on blood loss and blood product requirements in adults admitted to the ICU after cardiac surgery. The primary outcome is the volume of fluid loss from chest drains between ICU admission and 12 hours later. This trial was prospectively registered (ACTRN12614000289617).

Study C

Study C is a single-centre nested study within Study A comparing the effect of 0.9% saline v Plasma-Lyte 148 on gastrointestinal (GI) dysfunction in patients expected to be mechanically ventilated for >48 hours and receiving enteral nutrition via the nasogastric route. The primary outcome is the proportion of patients with GI intolerance (high gastric residual volumes, vomiting and diarrhoea).[8] This trial was prospectively registered (ACTRN12614000269639).

Study D

The SPLIT-Major Surgery study is a single-centre, blinded trial investigating 0.9% saline v Plasma-Lyte 148 as fluid therapy in adult patients undergoing major surgery (Table 1b). Adult patients admitted to the Austin Hospital undergoing major surgery requiring IV fluid therapy will be eligible for study inclusion. Major surgery is defined as surgery requiring at least an overnight hospital stay postoperatively. Patients will be randomly assigned, in one of two 6-week blocks, to use blinded 0.9% saline or Plasma-Lyte 148 solution. There will be a 3-week wash-in and a 3-week wash-out period between each fluid intervention. The purpose of the wash-in period is to check logistics and protocol adherence before starting data collection. The purpose of the wash-out period is to ensure that patients continue to receive study fluid in the ICU and on the wards for up to 3 weeks after their operation. The primary outcome measure will be AKI or renal failure based on creatinine levels, assessed in accordance with RIFLE criteria during the index hospital admission. The study will establish the pilot feasibility, safety and preliminary efficacy evidence base for the design of a large interventional trial to inform clinicians managing major surgery patients if 0.9% saline or Plasma-Lyte 148 is the preferred crystalloid fluid. This trial was prospectively registered (ACTRN12613001042730).

Study E

Study E is a multicentre, randomised, double-blind study of 0.9% saline v Plasma-Lyte 148 as the primary crystalloid fluid in adult ICU patients. In contrast to Study A, this study is a conventional individual patient, randomised trial and, compared with Study A, it will provide a greater level of detail about the biochemical and physiological effects of the study fluids. The primary outcome measure will be the worst (most negative) base excess as measured during the first 4 days after ICU admission. This trial has not yet begun and is yet to be registered.

Study F

The routine use of 0.9% Saline v Plasma-Lyte 148 for Intravenous fluid Therapy in ED patients (SPLIT-ED) study is a single-centre, open-label, before-and-after audit comparing the routine use of 0.9% saline v Plasma-Lyte 148 as the primary fluid therapy for adult ED patients. This study will compare one group of patients treated with Plasma-Lyte 148 over a 12-week period with another group of patients treated with 0.9% saline over the same 12-week period 1 year previously. The primary outcome measure is the delta creatinine (the difference between admission and peak creatinine in the first 7 days in hospital). This trial has not yet begun and is yet to be registered.

Aims

Our overall aim is to assess the comparative effectiveness of 0.9% saline v Plasma-Lyte 148 in ICU, major surgical and ED patients. The objectives are to estimate the effect of 0.9%

Table 2. Study populations and eligibility criteria

Study	Participants	Centres	Patient inclusion criteria	Patient exclusion criteria
A*	2300	4	• In ICU and needing CFT	• Receiving or expected to need RRT within 6 hours of ICU admission • Usually on dialysis for end-stage renal failure • Admitted to ICU solely for consideration of organ donation or palliative care • Previously enrolled in this study
B†	260	1	• ⩾ 18 years • admitted to ICU after cardiac surgery • enrolled in Study A at Wellington Hospital	• As for Study A
C‡	70	1	• ⩾ 18 years • enrolled in Study A at Wellington Hospital • expected to be on MV for ⩾ 48 hours at time of enrolment • receiving enteral nutrition via NG route	• As for Study A
D§	1000	1	• ⩾ 18 years • undergoing major surgery (needing ⩾ 1 night stay in hospital postoperatively)	• Raised intracranial pressure • Liver transplantation • Renal transplantation
E¶	60	3	• ⩾ 18 years • admitted to ICU and needing CFT	• Transferred from another hospital to a study ICU in order to receive RRT for acute kidney injury • Admitted to ICU for consideration of organ donation • Admitted to ICU after cardiac surgery
F**	6000	1	• ⩾ 18 years • presenting to ED and then admitted to hospital with serum creatinine measured in the ED	• On RRT for end-stage renal failure

ICU = intensive care unit. CFT = crystalloid fluid therapy. RRT = renal replacement therapy. MV = mechanical ventilation. NG = nasogastric. ED = emergency department. * 0.9% saline v Plasma-Lyte 148 for intensive care fluid therapy. † 0.9% saline v Plasma-Lyte 148 for postoperative fluid therapy in adults undergoing cardiac surgery. ‡ 0.9% saline v Plasma-Lyte 148 as primary fluid therapy in MV patients receiving enteral nutrition. § 0.9% saline v Plasma-Lyte 148 fluid intervention trial in major surgery patients. ¶ Pilot, randomised, blinded, multicentre, feasibility, safety and biochemical and physiological efficacy study of 0.9% saline v Plasma-Lyte 148 in intensive therapy. ** Routine use of 0.9% saline v routine use of Plasma-Lyte 148 for fluid intervention therapy in ED patients.

saline v Plasma-Lyte 148 on the following outcomes (when an outcome represents the primary outcome for a particular study, that study is italicised):

- the proportion of patients developing AKI or renal failure based on serum creatinine levels in accordance with RIFLE criteria (*Study A*, *Study D*, Study E, Study F)
- the change in serum creatinine levels (Study A, Study D, Study E, *Study F*)
- the proportion of patients requiring renal replacement therapy (Study A, Study D, Study E, Study F)
- inhospital mortality, time to death, and cause of death (all studies)
- the ICU and hospital lengths of stay (all studies)
- chest drain losses in between ICU admission and 12 hours later in patients admitted after cardiac surgery (*Study B*)
- the proportion of adult cardiac surgical patients who require blood products (packed red blood cells, fresh frozen plasma, platelets and cryoprecipitate) (Study B)
- the proportion of adult cardiac surgical patients who develop major postoperative complications of death, myocardial infarction, renal failure requiring dialysis, or a new focal neurological deficit (Study B)
- the lowest daily haemoglobin level while in ICU and the daily fluid balance while in ICU (Study B)
- the proportion of patients with GI dysfunction (defined as high gastric residual volume, vomiting or diarrhoea[8]) (*Study C*)
- daily serum chloride levels and base excess (Study D)
- the difference in acid/base base excess between baseline and the worst (most negative) base excess levels measured postoperatively (Study D)
- the worst (most negative) base excess measured in the first 4 days in ICU (*Study E*).

All studies will provide data including protocol violation rates, eligibility and recruitment rates, and effect sizes that will be used to inform sample size calculations and aid in the design of future trials. Furthermore, data from Study A will

Table 3. RIFLE criteria and KDIGO definitions, based on serum creatinine levels

Classification of KD	Criteria
Risk	1.5–1.9 times increase in Cr*
Injury	2–2.9 times increase in Cr*
Failure	⩾ 3 times increase in Cr,* or increase in serum Cr to ⩾ 350 μmol/L with a rise of ⩾ 44 μmol/L, during ICU admission
Loss	Persistent loss of kidney function for 4 weeks
End-stage KD	Dialysis-dependent for > 3 months
KDIGO Stage 1	1.5–1.9 times increase in Cr,* or ⩾ 26.5 μmol/L increase in serum Cr
KDIGO Stage 2	2–2.9 times increase in Cr*
KDIGO Stage 3	⩾ 3 times increase in Cr,* or increase in serum Cr to ⩾ 353.6 μmol/L, or start of RRT

RIFLE = risk of kidney dysfunction, injury to the kidney, failure of kidney function, loss of kidney function and end-stage kidney disease. KDIGO = Kidney Disease: Improving Global Outcomes. KD = kidney disease. Cr = creatinine. ICU = intensive care unit. RRT = renal replacement therapy.
* During ICU admission, from baseline Cr level.

Table 4. Covariates to be included in adjusted analyses

Study	Covariates
A	Presence or absence of trauma, APACHE III admission diagnosis, age, ICU admission source, APACHE-II score. Δ Cr to be adjusted for baseline serum Cr
B	Preoperative clopidogrel or aspirin within 5 days of surgery (yes/no), operative status (elective, urgent, emergency), prior cardiac surgery (yes/no), EuroSCORE, age, sex
C	Diagnostic group (medical, surgical, trauma), APACHE II score, age, body mass index, sex
D	Type and duration of surgery, age, body mass index, sex
E	Medical v surgical, APACHE III admission diagnosis, age, ICU admission source, APACHE II score, baseline serum Cr
F	ED triage category, diagnostic group (medical, surgical, trauma), age, sex, ethnicity

APACHE = Acute Physiology and Chronic Health Evaluation. ICU = intensive care unit. Cr = creatinine. EuroSCORE = European System for Cardiac Operative Risk Evaluation. ED = emergency department.

be used for statistical modelling to determine the number of clusters required and the overall sample size for a larger-scale, double-cluster, crossover study of ICU fluid therapy.

Study populations and treatments

Table 2 shows the expected number of participants, number of study centres, and inclusion and exclusion criteria for each study. All eligible patients in Studies A to E will receive blinded study fluid with the rate, duration, and frequency of administration determined by the treating clinician. The allocation of study treatments for Studies A to D will be determined ahead of time by the study statistician and concealment of allocation will be maintained until all analyses are complete.

Studies A to C will run for 28 weeks. Patients will receive blinded study fluid appropriate for each 7-week study block (Table 1a). Patients who remain in the ICU through one or more crossover periods will continue to use the fluid to which they were originally assigned.

Study D will be conducted over 24 weeks. Study fluid will be used in the operating room, the ICU and the wards whenever crystalloid fluid therapy is required. The 24-week study period will allow for two treatment periods of 6 weeks each with a 3-week wash-in and a 3-week wash-out period for each treatment period (Table 1b).

Study E will run for 6 months. Eligible patients will be individually randomised to blinded 0.9% saline or Plasma-Lyte 148. Permuted block randomisation will be performed using a computer-based randomisation program and opaque sealed envelopes.

Study F will be conducted in two 12-week periods occurring at the same time of the year to minimise seasonal effects.[2] Data for the control period will be retrospectively taken for a 12-week period exactly 1 year before the start date of the intervention period. During the control period, 0.9% saline was the preferred primary crystalloid fluid therapy in the Wellington Hospital ED. Before the start of the 12-week open-label intervention period, there will be a 4-week period of staff education and logistic arrangements for fluid switching from 0.9% saline to Plasma-Lyte 148 as the routine crystalloid fluid for the ED. During the 12-week intervention period, patients in the ED will receive Plasma-Lyte 148 as the preferred primary crystalloid fluid. All patients presenting to the ED during the designated period of study will be screened for eligibility using computer databases. Details of the volume and type of fluid actually received by each patient will not be collected. However, a random sample of 100 patients in each treatment period who received IV fluid in the ED and were admitted to hospital will be reviewed to assess the volume and type of fluid administered.

Subgroups

The following groups of patients are predefined as subgroups of interest:

- cardiac surgical patients, patients with sepsis, trauma patients, patients with traumatic brain injury and patients with an Acute Physiology and Chronic Health Evaluation II score of ⩾ 25 (Study A)
- patients having elective cardiac surgery, patients on anticoagulation medication at the time of cardiac surgery and patients having valvular heart surgery (Study B)

Table 5. Baseline patient characteristics

Characteristic	Fluid used		Study					
	0.9% Saline	Plasma-Lyte 148	A	B	C	D	E	F
Mean age, years (SD)	xx (SD)	xx (SD)	✓	✓	✓	✓	✓	✓
Sex (male), *n* (%)	*n* (%)	*n* (%)	✓	✓	✓	✓	✓	✓
Mean weight, kg, or body mass index (SD)	xx (SD)	xx (SD)	✓	✓	✓	✓		
Ethnicity, *n* (%)								
New Zealand, European	*n* (%)	*n* (%)	✓	✓	✓		✓	✓
Australian, European	*n* (%)	*n* (%)	✓	✓	✓		✓	✓
Maori	*n* (%)	*n* (%)	✓	✓	✓		✓	✓
Pacific Islander	*n* (%)	*n* (%)	✓	✓	✓		✓	✓
Aboriginal or Torres Strait Islander	*n* (%)	*n* (%)	✓	✓	✓		✓	✓
Other	*n* (%)	*n* (%)	✓	✓	✓		✓	✓
Comorbid conditions, *n* (%)								
Chronic respiratory disease	*n* (%)	*n* (%)	✓		✓	✓		
Chronic cardiovascular disease	*n* (%)	*n* (%)	✓		✓	✓		
Leukaemia or myeloma	*n* (%)	*n* (%)	✓		✓	✓		
Immunosuppression from disease	*n* (%)	*n* (%)	✓		✓	✓		
Immunosuppression from therapy	*n* (%)	*n* (%)	✓		✓	✓		
Hepatic failure	*n* (%)	*n* (%)	✓		✓	✓		
Cirrhosis	*n* (%)	*n* (%)	✓		✓	✓		
Lymphoma	*n* (%)	*n* (%)	✓		✓	✓		
AIDS	*n* (%)	*n* (%)	✓		✓	✓		
Metastatic cancer	*n* (%)	*n* (%)	✓		✓	✓		
Diabetes	*n* (%)	*n* (%)		✓		✓		
Hypercholesterolaemia	*n* (%)	*n* (%)		✓				
Hypertension	*n* (%)	*n* (%)		✓		✓		
Peripheral vascular disease	*n* (%)	*n* (%)		✓		✓		
Cerebrovascular disease	*n* (%)	*n* (%)		✓		✓		
Smoking history	*n* (%)	*n* (%)		✓		✓		
Family history of ischaemic heart disease	*n* (%)	*n* (%)		✓		✓		
Admission data								
Emergency admission	*n* (%)	*n* (%)	✓	✓		✓	✓	
ICU admission from ED	*n* (%)	*n* (%)	✓			✓	✓	
ICU admission from hospital ward	*n* (%)	*n* (%)	✓			✓	✓	
ICU admission from operating theatre	*n* (%)	*n* (%)	✓			✓	✓	
ICU admission from other hospital	*n* (%)	*n* (%)	✓				✓	
ICU admission from other hospital ICU	*n* (%)	*n* (%)	✓				✓	
ED triage category 1	*n* (%)	*n* (%)						✓
ED triage category 2	*n* (%)	*n* (%)						✓
ED triage category 3	*n* (%)	*n* (%)						✓

ICU = intensive care unit. ED = emergency department.

- patients undergoing abdominal surgery, vascular surgery, thoracic surgery, emergency surgery and other surgeries (Study D).

Definitions of key outcome variables

AKI and renal failure

Study A, Study D, Study E and Study F define AKI and renal failure according to the RIFLE criteria definitions based on serum creatinine levels (Table 3). Creatinine levels will be censored at patient death or Day 90.[6] Study A and Study F will also have the cumulative incidence of AKI and renal failure defined according to Kidney Disease: Improving Global Outcomes criteria (Table 3).[9] In Study D, the baseline creatinine will be defined as the most recent serum creatinine in the hospital record for up to 6 months before the current surgical admission. In Study A and Study E, the baseline creatinine will be defined as the lowest creatinine

Table 5. Baseline patient characteristics (continued)

	Fluid used		Study					
Characteristic	0.9% Saline	Plasma-Lyte 148	A	B	C	D	E	F
Operative details								
Coronary artery bypass	*n* (%)	*n* (%)		✓		✓		
Valve	*n* (%)	*n* (%)		✓		✓		
Other cardiac	*n* (%)	*n* (%)		✓		✓		
Elective	*n* (%)	*n* (%)		✓		✓		
Urgent	*n* (%)	*n* (%)		✓		✓		
Emergency	*n* (%)	*n* (%)		✓				
Salvage	*n* (%)	*n* (%)		✓				
Cardiopulmonary bypass used	*n* (%)	*n* (%)		✓				
Mean cumulative cross-clamp time, minutes (SD)	xx (SD)	xx (SD)		✓				
Mean cumulative cardiopulmonary bypass time, minutes (SD)	xx (SD)	xx (SD)		✓				
Mean physiological and laboratory values (SD)								
Baseline pre-illness creatinine, μmol/L	xx (SD)	xx (SD)	✓			✓	✓	
Most recent creatinine, μmol/L	xx (SD)	xx (SD)	✓			✓	✓	✓
Baseline pH	xx (SD)	xx (SD)				✓	✓	
Baseline base excess	xx (SD)	xx (SD)					✓	
Baseline chloride levels	xx (SD)	xx (SD)				✓	✓	
Baseline haemoglobin, g/L	xx (SD)	xx (SD)		✓			✓	
ICU admission haemoglobin, g/L	xx (SD)	xx (SD)		✓				
APACHE II score	xx (SD)	xx (SD)	✓	✓	✓			
APACHE III score	xx (SD)	xx (SD)				✓	✓	
EuroSCORE II	xx (SD)	xx (SD)		✓				
Physiological support								
Mechanical ventilation at baseline, *n* (%)	*n* (%)	*n* (%)	✓					
Median total volume and type of crystalloid fluid received in previous 24 hours (IQR)	xx (xx–xx)	xx (xx–xx)	✓	✓	✓		✓	
Median total volume and type of colloid fluid received in previous 24 hours (IQR)	xx (xx–xx)	xx (xx–xx)	✓	✓	✓		✓	
Median total volume and type of blood products received in previous 24 hours (IQR)	xx (xx–xx)	xx (xx–xx)	✓	✓	✓		✓	

ICU = intensive care unit. APACHE = Acute Physiology and Chronic Health Evaluation. EuroSCORE = European System for Cardiac Operative Risk Evaluation. IQR = interquartile range.

in the hospital laboratory records for the 6 months before the current ICU admission. For Study F, in patients who had more than one admission during the audit period, the baseline creatinine will be defined as that measured on hospital discharge from the most recent admission.[10]

The delta creatinine is defined as the difference between:

- serum creatinine measured immediately before study enrolment and the peak serum creatinine measured during the index ICU admission (Study A and Study E)
- serum creatinine at baseline and highest serum creatinine measured during in the first 3 days after surgery (Study D)
- serum creatinine at baseline and the peak serum creatinine measured during the first 7 days of hospital admission (Study F).

Mortality

All studies will define inhospital mortality as all-cause mortality during the index hospital admission.

Analysis principles and handling of missing data

All analyses will be by intention-to-treat. For the blinded studies, allocation concealment will be maintained until all analyses are completed. In the primary analysis for Studies A to E, no assumptions will be made for missing values and, where baseline or peak creatinine levels are not available, we will perform a complete case analysis. For Study F, in patients for whom the serum creatinine level is not remeasured after the initial measurement in the ED, the delta creatinine will be defined as zero.

For Study A, 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 creatinine data, we will consider the extreme scenarios that either all patients with missing data have AKI or renal failure, or no patients with missing data have AKI or renal failure. For patients with missing baseline creatinine data, we will consider the extreme scenarios that either the baseline creatinine value equals the peak measured value in the 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 glomerular filtration rate of 75 mL/min/1.73 m^2).[11] If the peak creatinine value is missing, we will consider the extreme scenarios that either the peak measured creatinine is equal to the baseline measured creatinine or that all patients with a missing peak creatinine levels have AKI or renal failure. For Studies B to E, we will undertake multiple imputation for missing baseline and peak creatinine values as sensitivity analyses when values are missing for more than 5% of the study participants.

All analyses will be performed using SAS version 9.3 (SAS Institute) and a two-sided *P* of 0.05 will be considered to be statistically significant. Unadjusted analyses will be performed for all outcome variables and additional analyses will be performed incorporating adjustment for prespecified baseline variables (Table 4).

Justification of sample size

No large-scale interventional trial has compared the use of 0.9% saline with a buffered crystalloid solution. As such, the principal reasons for conducting this program of studies will be to determine feasibility and inform future sample size calculations. All studies are set to run for a specific period and have no fixed recruitment number. The expected number of participants has been determined by using hospital databases to estimate the number of participants meeting the eligibility criteria for each study.

Description of analyses

All continuous variables will be assessed for normality and log-transformed where appropriate. Baseline comparisons between groups will be determined using χ^2 tests for equal proportion (or the Fisher exact test for small numbers), student *t* tests for normally distributed variables and Wilcoxon rank-sum tests otherwise.

Binomial outcomes will be analysed using logistic or Poisson regression models with results reported as odds ratios with 95% confidence intervals or relative risks with 95% CIs. Continuous outcomes will be analysed using mixed linear modelling with results reported as differences with 95% CIs or ratios with 95% CIs, as appropriate. When studies have a crossover design (Studies A to D), outcomes will be analysed at an individual patient level, using hierarchical longitudinal analysis techniques accounting for the attending hospital and fluid sequence, with patients nested within sites and sites crossing over, not patients. When studies involve more than one site, the site will be treated as a fixed effect and results will be reported overall and at an individual site level. Heterogeneity across sites will be determined by fitting interactions between treatment and site.

Additional analyses will be performed adjusting for a predefined list of covariates (Table 4). Furthermore, should clinically and statistically significant differences be found to exist between treatment arms at baseline, additional covariate-adjusted sensitivity analysis will be performed to ensure any observed effects could not be attributed to baseline imbalances.

Subgroup analyses will be performed on the prespecified subgroups of interest (listed above), irrespective of whether there is evidence of a treatment effect. Heterogeneity between subgroups will be determined by fitting an interaction between treatment and subgroup.

Presentation of results

Trial profile

We will present the flow of patients through each study in modified Consolidated Standards of Reporting Trials diagrams.[12]

Characteristics of patients and baseline comparisons

We will present baseline characteristics by treatment group (Table 5). 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, including durations, will be summarised using standard measures of central tendency and dispersion, ie, mean and SD, or median and interquartile range (IQR). Admission diagnosis will be presented as shown in Table 6. When practicable, all outcomes will be reported as forest plots with 95% CI. Outcome data and secondary outcome variables for each study are shown in the Appendix (online at cicm.org.au/journal.php).

Interim analysis and data safety monitoring board

An independent data safety monitoring board (DSMB) will be appointed for each study. There are no planned interim analyses for these studies, and given the current widespread use of the IV fluids being tested in routine practice, it is not anticipated that the DSMBs will make recommendations to stop the trials early on the basis of reported adverse events. However, in each trial, the DSMB will retain the right to access all trial data and may recommend to the trial management committee that a trial is ceased.

Consent

The SPLIT research program compares the effectiveness of two established treatments which are both commonly administered to patients in clinical practice.[13] 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 for Study A (12/NTB/57), Study B (14/NTB/12) and Study C (14/NTB/10) by the New Zealand and Health and Disability Ethics Committee. Study D has been approved by the Austin Health Human Research Ethics Committee (HREC/13/Austin161). Study E has not yet been submitted for ethics review. Study F has been approved as an audit of practice change by the Capital and Coast District Health Board and therefore does not require ethics approval in New Zealand.

Funding

All studies are investigator initiated and study analyses will be conducted independently of the funding organisations. Study A is primarily funded by a grant from the Health Research Council of New Zealand. The cost of Study B, Study C and Study F have been underwritten by the MRINZ. A funding application has been made to the Australian and New Zealand College of Anaesthetists for Study D. Study E will be funded by the Austin Hospital Intensive Care Trust Fund.

Competing interests

Rinaldo Bellomo, Seton Henderson, Shay McGuinness, Laurence Weinberg and Paul Young have received honoraria of < US$5000 from Baxter Healthcare for consulting activities. The MRINZ and Australian and New Zealand Intensive Care Research Centre received research grants from Baxter Healthcare for these studies and Baxter Healthcare will provide study fluids.

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Appendix 1. Outcome data and secondary outcome variables

Variable	0.9% Saline	Plasma-Lyte 148	Point estimate (95% CI)	*P*
STUDY A				
Primary outcome				
Proportion of patients with either AKI or failure based on creatinine levels* in accordance with RIFLE criteria	n (%)	n (%)	RR (95% CI)	*P*
Secondary outcomes				
Delta creatinine†, mean (SD)	xx (SD)	xx (SD)	Difference in means (95% CI)	*P*
Cumulative incidence of AKI by RIFLE category				
• Risk	*n* (%)	*n* (%)	RR (95% CI)	*P*
• Injury	*n* (%)	*n* (%)	RR (95% CI)	*P*
• Failure	*n* (%)	*n* (%)	RR (95% CI)	*P*
• Loss	*n* (%)	*n* (%)	RR (95% CI)	*P*
• End stage renal failure	*n* (%)	*n* (%)	RR (95% CI)	*P*
Cumulative incidence of AKI by KDIGO category				
• Stage 1	*n* (%)	*n* (%)	RR (95% CI)	*P*
• Stage 2	*n* (%)	*n* (%)	RR (95% CI)	*P*
• Stage 3	*n* (%)	*n* (%)	RR (95% CI)	*P*
Proportion of patients requiring RRT	*n* (%)	*n* (%)	RR (95% CI)	*P*
Proportion of patients requiring RRT after hospital discharge (among those patients who required RRT in the ICU)	*n* (%)	*n* (%)	RR (95% CI)	*P*
Proportion of patients requiring mechanical ventilation	*n* (%)	*n* (%)	RR (95% CI)	*P*
Duration of mechanical ventilation, geometric mean (95% CI)	xx (95%CI)	xx (95%CI)	Ratio of geometric means (95% CI)	*P*
Length of ICU admission from the time of SPLIT enrolment, geometric mean (95% CI)	xx (95%CI)	xx (95%CI)	Ratio of geometric means (95% CI)	*P*
Length of hospital admission from the time of SPLIT enrolment, geometric mean (95% CI)	xx (95%CI)	xx (95%CI)	Ratio of geometric means (95% CI)	*P*
STUDY B				
Primary outcome				
Chest tube output from time of arrival to ICU until 12 hours post operatively geometric mean (95% CI)	xx (95%CI)	xx (95%CI)	Ratio of geometric means (95% CI)	*P*
Secondary outcomes				
Total volume of fluid in chest tube from arrival to ICU to 24 hours if still in ICU, geometric mean (95% CI)	xx (95%CI)	xx (95%CI)	Ratio of geometric means (95% CI)	*P*
Proportion of patients returning to theatre for bleeding	*n* (%)	*n* (%)	RR (95% CI)	*P*
Proportions of patients requiring blood products	*n* (%)	*n* (%)	RR (95% CI)	*P*

Composite outcome of proportion of patients developing a major post-operative complication • Myocardial infarction • Renal failure requiring dialysis • New focal neurological deficit • Death during hospital admission (all causes)	*n* (%)	*n* (%)	RR (95% CI)	*P*
Duration of mechanical ventilation, geometric mean (95% CI)	xx (95%CI)	xx (95%CI)	Ratio of geometric means (95% CI)	*P*
Time until free from inotropes, geometric mean (95% CI)	xx (95%CI)	xx (95%CI)	Ratio of geometric means (95% CI)	*P*
Fluid balance recorded in ICU on chart day 0,1,2,3, mean (SD)	xx (SD)	xx (SD)	Difference in means (95% CI)	*P*
Difference between preoperative weight and ICU discharge weight, mean (SD)	xx (SD)	xx (SD)	Difference in means (95% CI)	*P*
Lowest haemoglobin on ICU chart day 0,1,2,3, mean (SD)	xx (SD)	xx (SD)	Difference in means (95% CI)	*P*
Length of ICU admission from the time of SPLIT enrolment, geometric mean (95% CI)	xx (95%CI)	xx (95%CI)	Ratio of geometric means (95% CI)	*P*
Length of hospital admission from the time SPLIT of enrolment, geometric mean (95% CI)	xx (95%CI)	xx (95%CI)	Ratio of geometric means (95% CI)	*P*
STUDY C **Primary outcome**				
Composite outcome of proportion of patients with GI complications (plus each component of the composite end point reported separately): • High gastric residual volume (> 500 mL on NG aspiration) • Patients with vomiting (enteral formulae ejected for through the mouth irrespective of amount) • Patients with diarrhoea (three or more loose/liquid motions per day)	*n* (%)	*n* (%)	RR (95% CI)	*P*
Number of events of high gastric residual volume, geometric mean (95% CI)	xx (95%CI)	xx (95%CI)	Ratio of geometric means (95% CI)	*P*
Number of events of vomiting, geometric mean (95% CI)	xx (95%CI)	xx (95%CI)	Ratio of geometric means (95% CI)	*P*
Number of days of diarrhoea, geometric mean (95% CI)	xx (95%CI)	xx (95%CI)	Ratio of geometric means (95% CI)	*P*
Secondary outcomes				
Diet volume ratio (volume received/ volume prescribed) at 48 hours)	(%)	(%)	RR (95% CI)	*P*
Duration of NG enteral feeding, geometric mean (95% CI)	xx (95%CI)	xx (95%CI)	Ratio of geometric means (95% CI)	*P*
Cause of NG enteral feeding being ceased				
• Commencement of oral diet	*n* (%)	*n* (%)	RR (95% CI)	*P*
• Enteral feeding related complication	*n* (%)	*n* (%)	RR (95% CI)	*P*
• Other complication	*n* (%)	*n* (%)	RR (95% CI)	*P*

• ICU discharge	*n* (%)	*n* (%)	RR (95% CI)	*P*
• ICU death	*n* (%)	*n* (%)	RR (95% CI)	*P*
Length of ICU admission from the time of SPLIT enrolment, geometric mean (95% CI)	xx (95%CI)	xx (95%CI)	Ratio of geometric means (95% CI)	*P*
Length of hospital admission from the time SPLIT of enrolment, geometric mean (95% CI)	xx (95%CI)	xx (95%CI)	Ratio of geometric means (95% CI)	*P*
STUDY D				
Primary outcome				
Proportion of patients with either AKI or failure based on creatinine levels* in accordance with RIFLE criteria	*n* (%)	*n* (%)	RR (95% CI)	*P*
Secondary outcomes				
Increase between baseline and peak creatinine in the first 3 days after surgery, mean (SD)	xx (SD)	xx (SD)	Difference in means (95% CI)	*P*
Cumulative incidence of AKI by RIFLE category in the first 3 days after surgery				
• Risk	*n* (%)	*n* (%)	RR (95% CI)	*P*
• Injury	*n* (%)	*n* (%)	RR (95% CI)	*P*
• Failure	*n* (%)	*n* (%)	RR (95% CI)	*P*
• Loss	*n* (%)	*n* (%)	RR (95% CI)	*P*
• End stage renal failure	*n* (%)	*n* (%)	RR (95% CI)	*P*
Increase between baseline and peak chloride levels in the first 3 days after surgery, mean (SD)	xx (SD)	xx (SD)	Difference in means (95% CI)	*P*
Development of metabolic acidosis (defined as a base deficit > 2 mEq/L or a bicarbonate level <20 mmol/L) in the first 3 days after surgery	*n* (%)	*n* (%)	RR (95% CI)	*P*
Development of acidaemia defined as a pH <7.3 in the first 3 days after surgery	*n* (%)	*n* (%)	RR (95% CI)	*P*
Proportion of patients requiring RRT	*n* (%)	*n* (%)	RR (95% CI)	*P*
Proportion of patients developing a postoperative complication (defined by Clavien–Dindo classification) and the Classification of Hospital Acquired Diagnoses (CHADx). The CHADx classification groups over 4500 ICD- 10-AM codes into a manageable hierarchy of 17 classes and 145 sub-classes to characterise hospital acquired complications)	*n* (%)	*n* (%)	RR (95% CI)	*P*
Proportion of patients requiring ICU admission	*n* (%)	*n* (%)	RR (95% CI)	*P*
Inhospital mortality	*n* (%)	*n* (%)	RR (95% CI)	*P*
Length of ICU admission, geometric mean (95% CI)	xx (95%CI)	xx (95%CI)	Ratio of geometric means (95% CI)	*P*

Length of hospital admission, geometric mean (95% CI)	xx (95%CI)	xx (95%CI)	Ratio of geometric means (95% CI)	*P*
STUDY E **Primary outcome**				
The base excess by arterial blood gases during the first 4 days after ICU admission, mean (SD)	xx (SD)	xx (SD)	Difference in means (95% CI)	*P*
Secondary outcomes				
Delta creatinine†, mean (SD)	xx (SD)	xx (SD)	Difference in means (95% CI)	*P*
Proportion of patients with either AKI or failure based on creatinine levels* in accordance with RIFLE criteria	*n* (%)	*n* (%)	RR (95% CI)	*P*
Cumulative incidence of AKI by RIFLE category in the first 3 days after surgery				
• Risk	*n* (%)	*n* (%)	RR (95% CI)	*P*
• Injury	*n* (%)	*n* (%)	RR (95% CI)	*P*
• Failure	*n* (%)	*n* (%)	RR (95% CI)	*P*
• Loss	*n* (%)	*n* (%)	RR (95% CI)	*P*
• End stage renal failure	*n* (%)	*n* (%)	RR (95% CI)	*P*
Proportion of patients requiring RRT	*n* (%)	*n* (%)	RR (95% CI)	*P*
Proportion of patients requiring RRT after hospital discharge (among those patients who required RRT in the ICU)	*n* (%)	*n* (%)	RR (95% CI)	*P*
Inhospital mortality	*n* (%)	*n* (%)	RR (95% CI)	*P*
Length of ICU admission, geometric mean (95% CI)	xx (95%CI)	xx (95%CI)	Ratio of geometric means (95% CI)	*P*
Length of hospital admission, geometric mean (95% CI)	xx (95%CI)	xx (95%CI)	Ratio of geometric means (95% CI)	*P*
STUDY F **Primary outcome**				
The difference between admission and peak creatinine, mean (SD)	xx (SD)	xx (SD)	Difference in means (95% CI)	*P*
Secondary outcomes				
Proportion of patients with either AKI or failure based on creatinine levels* in accordance with RIFLE criteria	*n* (%)	*n* (%)	RR (95% CI)	*P*
Proportion of patients with either AKI or failure based on creatinine levels* in accordance with KDIGO criteria	*n* (%)	*n* (%)	RR (95% CI)	*P*
Cumulative incidence of AKI by RIFLE category				

• Risk	*n* (%)	*n* (%)	RR (95% CI)	*P*
• Injury	*n* (%)	*n* (%)	RR (95% CI)	*P*
• Failure	*n* (%)	*n* (%)	RR (95% CI)	*P*
• Loss	*n* (%)	*n* (%)	RR (95% CI)	*P*
• End stage renal failure	*n* (%)	*n* (%)	RR (95% CI)	*P*
Cumulative incidence of AKI by KDIGO category				
• Stage 1	*n* (%)	*n* (%)	RR (95% CI)	*P*
• Stage 2	*n* (%)	*n* (%)	RR (95% CI)	*P*
• Stage 3	*n* (%)	*n* (%)	RR (95% CI)	*P*
Composite outcome of the proportion of patients: requiring renal replacement therapy, inhospital death and need for ICU admission	*n* (%)	*n* (%)	RR (95% CI)	*P*
Proportion of patients requiring RRT	*n* (%)	*n* (%)	RR (95% CI)	*P*
Proportion of patients with an inhospital death	*n* (%)	*n* (%)	RR (95% CI)	*P*
Proportion of patients requiring ICU admission	*n* (%)	*n* (%)	RR (95% CI)	*P*
Length of ICU admission, geometric mean (95% CI)	xx (95%CI)	xx (95%CI)	Ratio of geometric means (95% CI)	*P*
Length of hospital admission, geometric mean (95% CI)	xx (95%CI)	xx (95%CI)	Ratio of geometric means (95% CI)	*P*

AKI = acute kidney injury. RR = relative risk. GI = gastrointestinal. ICU = intensive care unit. KDIGO = kidney disease: improving global outcomes. NG= nasogastric. SPLIT = 0.9% saline v Plasma-Lyte 148 for intensive care unit fluid therapy. RIFLE = risk, injury, failure, loss, end stage renal failure. RRT = renal replacement therapy. * Highest value measured during the patient's stay in the ICU (censored at day 90). † Difference between the pre-enrolment creatinine and the peak creatinine measured during the ICU stay (censored at day 90).