Supplementary Appendix:
Study Protocol and Statistical Analysis Plan

Trial: Isotonic Solutions and Major Adverse Renal Events Trial (SMART)

Manuscript: Balanced Crystalloids versus Saline for Critically Ill Adults
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This Supplementary Appendix contains the following items:

1) Original Study Protocol [dated 5/13/15]
2) Final Study Protocol [dated 6/15/17]
3) Summary of changes to Study Protocol
4) Original Statistical Analysis Plan [dated 12/9/16]
5) Final Statistical Analysis Plan [published 3/16/17]
6) Summary of changes to Statistical Analysis Plan

Isotonic Solutions and Major Adverse Renal Events Trial (SMART)

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1.0 Study Summary

Title: Isotonic Solutions and Major Adverse Renal Events Trial (SMART)

Study Aims:

- Primary: To compare the effect of 0.9% saline versus physiologically-balanced isotonic fluids on the development of major adverse kidney events by 30 days ($MAKE_{30}$) in patients admitted to the intensive care unit
- Secondary: To evaluate the effect of the same intervention in the same population on laboratory outcomes of change in creatinine and incidence of metabolic acidosis and alkalosis; urinary and serum markers of acute kidney injury; and clinical outcomes of in-hospital mortality, ICU-free days, and receipt of renal replacement therapy

Study Hypotheses:

- Primary: Use of physiologically-balanced isotonic fluids in ICU patients will decrease the development of $MAKE_{30}$
- Secondary: Use of physiologically-balanced isotonic fluids in ICU patients will decrease creatinine rise and metabolic acidosis, decrease receipt of renal replacement therapy, increase ICU-free days, and decrease mortality

Inclusion Criteria:

1. Admitted to an adult intensive care unit (ICU) at Vanderbilt University Medical Center

Exclusion Criteria:

1. Age < 18 years

Study Population: All adult patients admitted to an adult ICU at VUMC

Consent: Given the current use of all isotonic solutions studied in routine clinical practice, the lack of established risk or benefit with any solution, the impracticability of obtaining informed consent prior to receipt of intravenous fluid in every critically ill patient admitted to VUMC, and randomization at the level of the intensive care unit and not by each individual patient, a waiver of informed consent will be requested.

Randomization: Each ICU will be initially randomized to a fluid group (0.9% Saline versus physiologically-balanced isotonic fluid) and will then crossover between fluid groups every month during the one year study period.

Study Interventions:

- **0.9% Saline Arm:** Patients in an ICU randomized to 0.9% Saline on whom a provider orders isotonic fluid will receive the ordered volume of 0.9% Sodium Chloride.

- **Physiologically-Balanced Isotonic Fluid Arm:** Patients in an ICU randomized to physiologically-balanced isotonic fluid on whom a provider orders isotonic fluid will receive the ordered volume of Plasma-Lyte© A or Lactated Ringer's unless a pre-specified contraindication is present (see below).

Primary Endpoint:

- Development of major adverse kidney event by hospital discharge or day 30 ($MAKE_{30}$). A major adverse kidney event is defined as at least one of the following: mortality, need for new renal replacement therapy, or persistent renal dysfunction at the time of hospital discharge (defined as ≥ 200% of creatinine from baseline).

Secondary Endpoints:

1. In-Hospital Mortality
2. 60 day Mortality
3. In-ICU Mortality
4. ICU-free days to day 28
5. Vasopressor-free days to day 28
6. Incidence of new RRT in the first 28 days
7. Duration of new RRT in the first 28 days
8. Peak creatinine in the first 28 days
9. Change from baseline to peak creatinine in the first 28 days
10. Incidence of metabolic acidosis and alkalosis
11. Urinary biomarkers of pre-renal and intra-renal acute renal failure
12. Serum biomarkers of intravascular volume overload and acute renal failure

2.0 Background

The administration of intravenous fluids is ubiquitous in the care of the critically ill[1]. Commonly available isotonic crystalloid solutions contain a broad spectrum electrolyte compositions including a range chloride concentrations[2]. Recent studies have associated solutions with supraphysiologoic chloride content with hyperchloremia[3,4], metabolic acidosis and renal vasoconstriction[5,6], acute kidney injury and renal replacement therapy[7], and increased mortality[8,9] but no large, randomized-controlled trials have been conducted. In order to determine the impact of physiologically-balanced isotonic solutions compared to 0.9% sodium chloride on clinical outcomes in critically ill patients, a randomized controlled trial is needed[10].

2.1 Electrolyte Composition of Commonly Used Crystalloids

The administration of crystalloids occurs commonly in the intensive care unit as a means of resuscitation, maintenance of intravascular volume, and as a carrier for intravenous medications. The most commonly available isotonic intravenous fluid solutions are 0.9% Saline, Lactated Ringer's, and Plasma-Lyte© which vary widely with respect to their electrolyte content (Table 2A). Particular attention has been paid to the supra-physiologic chloride content of 0.9% Saline.

Table 2A.

Concentration (mmol/L)				
	Plasma	0.9% NaCl	Lactated Ringer's	Plasma-Lyte©
Sodium	140	154	130	140
Potassium	5	0	4	5
Chloride	100	154	109	98
Calcium	2.2	0	1.5	0
Magnesium	1	0	0	1.5
Bicarbonate	24	0	0	0
Lactate	1	0	28	0
Acetate	0	0	0	27
Gluconate	0	0	0	23

2.2 Hyperchloremic metabolic acidosis

Multiple prior studies have demonstrated a relationship between the receipt of chloride-rich fluid and the development of metabolic acidosis[11–14]. This relationship is

hypothesized to be explained by the Stewart physicochemical approach[15] in which the hydrogen ion concentration in the plasma is determined by the independent variables of partial pressure of carbon dioxide, weak acids (primarily protein), and the balance of sodium, potassium, magnesium, calcium, chloride, and lactate ions known as the strong ion difference. In this understanding, increasing concentrations of chloride relative to sodium decrease the strong ion difference and increase the hydrogen ion concentration contributing to metabolic acidosis.

2.3 Chloride and Sepsis Resuscitation

Early administration of intravenous fluid is a cornerstone of current sepsis management[16]. The high prevalence of fluids with supraphysiologic chloride concentrations has led to study of these solutions in animal models of sepsis resuscitation. Administration of high-chloride saline solutions in animal models of sepsis have suggested that increased fluid chloride content contributes to the development of acidosis[17], inflammatory mediator release[18], hypotention[19], and mortality[20]. A recent retrospective, propensity-matched analysis of chloride content in fluids used for early resuscitation of patients with septic shock showed an association between higher chloride content and increased mortality[8] as did a meta-analysis of randomized controlled trials of intravenous fluid choice in sepsis[9]. There are currently no controlled studies comparing isotonic fluids with difference chloride contents during sepsis resuscitation in humans.

2.4 Chloride and Renal Function

Animal studies have suggested a role for chloride in regulating renal blood flow. A study of denervated dog kidneys infused with chloride-solutions showed vasoconstriction only in the renal vessels associated with decreased glomerular filtration[5]. Proposed mechanisms for chloride-mediated vasoconstriction include tubuloglomerular feedback in which chloride detection in the distal tubule triggers mesangial contraction and decreased filtration, thromboxane-mediated vasoconstriction, and chloride-mediated potentiation of angiotensin II response in the renal vasculature.

Studies on human volunteers have shown decreased renal blood flow[6], increased time to micturition, and decreased diuresis and natiuresis in patients treated with fluids with higher chloride content[21,22]. Studies of patients undergoing surgery have linked higher chloride solutions to decreased urine output[23] and increased urinary markers of kidney injury[24]. A randomized controlled trial of lactated Ringer's versus 0.9% saline in patients undergoing renal transplantation was stopped early for a higher incidence of hyperkalemia and metabolic acidosis in the 0.9% saline group[25].

Recently, a prospective, open-label, before-after study of over 1400 patients in a single intensive care unit transitioning from use of higher to lower chloride solutions demonstrated an association between higher chloride fluid and the development of acute kidney injury and use of renal replacement therapy[7]. Observational studies are examining the relationship between chloride content and mortality in ICU patients (NCT02083198) and randomized trials are comparing the incidence of acute kidney injury with chloride-rich versus chloride-poor fluids during cardiac surgery (NCT02020538) but to date no randomized study examining the impact of chloride content on renal outcomes or mortality in critically ill patients has been conducted.

3.0 Rationale and Specific Aims

In order to determine the impact of physiologically-balanced isotonic fluid versus 0.9% saline on clinical outcomes of critically ill patients, a randomized controlled trial is needed.

- Primary Aim: To compare the effect of 0.9% saline versus physiologically-balanced isotonic fluids on the development of major adverse kidney events by 30 days ($MAKE_{30}$) in intensive care unit patients

- Secondary Aim: To evaluate the effect of the same intervention in the same population on laboratory outcomes of change in creatinine and incidence of metabolic acidosis and alkalosis; and clinical outcomes including in-hospital mortality, ICU-free days, and receipt of renal replacement therapy

To complete these aims, we will enroll patients from participating ICUs at Vanderbilt University Medical Center for the study period of one year in a cluster-randomized controlled trial of 0.9% saline versus physiologically-balanced isotonic fluid (Lactated Ringer's or Plasma-Lyte©).

4.0 Previous Human Studies

Increasing recognition of the potential differences in "isotonic" intravenous fluids has led to several prior studies examining chloride concentration in IV fluid in humans. As detailed above, prior studies have examined the role of fluid chloride content in healthy human volunteers, patients undergoing surgery, patients with septic shock, and critically ill patients generally. There are ongoing observational studies in ICU patients and a randomized controlled trial in cardiac surgery of higher versus lower chloride fluid. The above studies provide the rationale for a large, prospective randomized controlled trial of fluids with higher versus lower chloride content in the critically ill.

5.0 Study Description

This is a single-center, multiple-ICU, cluster-randomized, controlled, multiple crossover study to evaluate the impact of physiologically-balanced isotonic fluids versus 0.9% saline on the development of acute kidney injury. The participating ICUs will be randomized to utilization of 0.9% sodium chloride or physiologically-balance isotonic fluid (Lactated Ringers or Plasma-Lyte© A). Every patient admitted to an ICU at Vanderbilt Medical Center during the study period who meets no exclusion criteria will be enrolled and will receive the assigned study fluid if isotonic fluid is ordered by the treating provider and none of the prespecified contraindications are present. All other decisions regarding fluid administration including indication, timing, rate, volume, and endpoint will remain at the discretion of the treating provider. The study will not impact the use of oral fluids or non-isotonic IV fluids. Every month each ICU will undergo a cross-over in assigned fluid group such that each ICU will experience each fluid group assignment for equal time periods during the study.

For logistical purposes, the study will be conducted as two, independent, parallel, randomized, multiple-crossover trials – one for patients enrolled from the medical ICU (SMART-MED) and one for patients enrolled from the other ICUs (SMART-SURG). Success of the ongoing pilot study (SALT) in the MICU of establishing the infrastructure needed to deliver the study intervention will allow enrollment in SMART-MED to begin immediately in the MICU and run continuously for a one-year study duration. The initiation of enrollment in the other ICUs (SMART-SURG) will be dependent on successfully transferring the infrastructure for delivery of the assigned intervention to these ICUs and is anticipated to be delayed 6 months from the start of the SMART-MED trial. The two, parallel trials (SMART-MED and SMART-SURG) will be 'harmonized' with identical design, intervention, and data collection to allow for analysis of all patients concurrently in accordance with a pre-specified data-analysis plan. In the event that logistical difficulties prevent the safe and effective conduct of the study in the ICUs in which it has not yet been pilot tested (SMART-SURG), the patients enrolled in SMART-MED will be analyzed independently, adhering to a pre-specified data analysis plan.

6.0 Inclusion and Exclusion Criteria

6.1 Inclusion Criteria: Admitted to an adult intensive care unit (ICU) at Vanderbilt University Medical Center

6.2 Exclusion Criteria: Age<18 years old

7.0 Enrollment/Randomization

7.1 Study Sites: Patients for this study will be enrolled upon admission to the participating intensive care unit (ICU) or adjacent ICU-"step down" units at Vanderbilt University Medical Center. Participating ICUs within Vanderbilt University Hospital will include:

SMART-MED: Medical ICU (8T3)
SMART-SURG: Surgical ICU (9T3), Cardiovascular ICU (5N), Trauma ICU (10N), Neurological and Neurosurgical ICU (6T3).

7.2 Study Population: All patients admitted to an ICU at Vanderbilt Medical Center during the study period will be enrolled unless meeting exclusion criteria. Patients will be enrolled prior to receiving their first administration of isotonic IV fluid in the ICU. Based on the admission rates to the participating ICUs in recent years, at least 3,000 patients will be admitted to the MICU (SMART-MED) and 5,000 patients to the surgical ICUs (SMART-SURG) for a total of at least 8,000 patients admitted to all study ICUs (SMART) during the one year study period.

7.3 Enrollment: All patients will be enrolled in this cluster-randomized controlled, multiple crossover trial at the time of admission to the participating ICU prior to the administration of any isotonic IV fluid in the ICU.

7.4 Consent:

"Normal Saline" (0.9% sodium chloride), Lactated Ringer's, and Plasma-Lyte© are all non-prescription isotonic intravenous fluids currently used in the routine care of patients admitted to the ICUs at Vanderbilt University Medical Center. Currently, choice of isotonic fluid is based on provider preference as there are no large randomized trials, evidence-based guidelines, or expert recommendations to support the choice of one isotonic crystalloid over another. In current practice, isotonic fluids are frequently used as carriers for medications mixed by the pharmacy without any input of the treating team into the choice of isotonic fluid being administered. Additionally, recent national shortages of 0.9% saline and lactated ringers have dictated which isotonic fluids are administered to critically ill patients at Vanderbilt. Furthermore, we have discussed this randomization with the ICU directors of the participating ICUs who agree that equipoise exists on choice of isotonic intravenous fluid for their specific ICU patients and have agreed to allow their ICUs to be randomized and participate in the study.

Because all of the isotonic fluids examined in this study are currently in routine use in the study ICUs and there is no known difference in risk or benefit among them, a waiver of informed consent will be requested.

In addition to the minimal risk posed by the study, obtaining informed consent prior to participation would not be feasible or practicable. Patients frequently receive

fluid immediately after ICU admission and time delays in obtaining informed consent from the patient or surrogate prior to fluid administration might compromise patient safety. In addition, trying to consent every critical care admission at the time of their admission is not practicable. Furthermore, the randomization is at the level of the ICU, meaning the "default" isotonic fluid for that ICU would be whatever they are randomized to, so obtaining a different isotonic iv fluid at a patient specific level would require considerable work on the clinical team. The focus of the study on the choice of isotonic fluid by ICU on a hospital-wide basis also precludes individual patient consent. With all ICUs at Vanderbilt randomized to a treatment arm, a patient who refused participation would have to be moved to an ICU at another institution, which might compromise patient safety.

7.5 Randomization:

Participating ICUs will be randomized to an initial fluid group (0.9% Saline or physiologically-balanced isotonic fluid) using an *a priori* determined randomization scheme derived from a software program. Following the initial assignment, each ICU will crossover between fluid groups every month during the study period. Individual patients will not be randomized for the purposes of this study. Patients that are transferred between two participating ICUs will be treated according to the assignment for the unit in which they currently are cared for but will be analyzed by their original group assignment for the primary analysis.

The effect of differing sodium, chloride, and potassium contents of Plasma-Lyte©, Lactated Ringer's, and 0.9% Sodium Chloride on patients' metabolic laboratory studies over the course of the ICU stay would make blinding of the treating providers and nursing staff impossible. Therefore, clinical personnel will not be blinded to the study intervention. However, all on-study and outcome data will be collected by study staff blinded to study group assignment.

8.0 Study Procedures

8.1 Treatment Arms

Patients in an ICU randomized to 0.9% Saline will receive 0.9% sodium chloride whenever isotonic intravenous fluid administration is ordered by the treating provider. Patients in an ICU randomized to physiologically-balanced isotonic fluid will receive Plasma-Lyte© A or Lactated Ringer's whenever isotonic intravenous fluid administration is ordered by the treating provider. The total volume, rate, initiation, cessation, and addition of electrolytes and glucose to the isotonic fluid assigned will be at the discretion of the ordering provider. Adherence with the administration of assigned fluid

in the study ICUs will be ensured by dual interventions at the level of pharmacy IV fluid supply and physician order entry.

Pharmacy Supply:

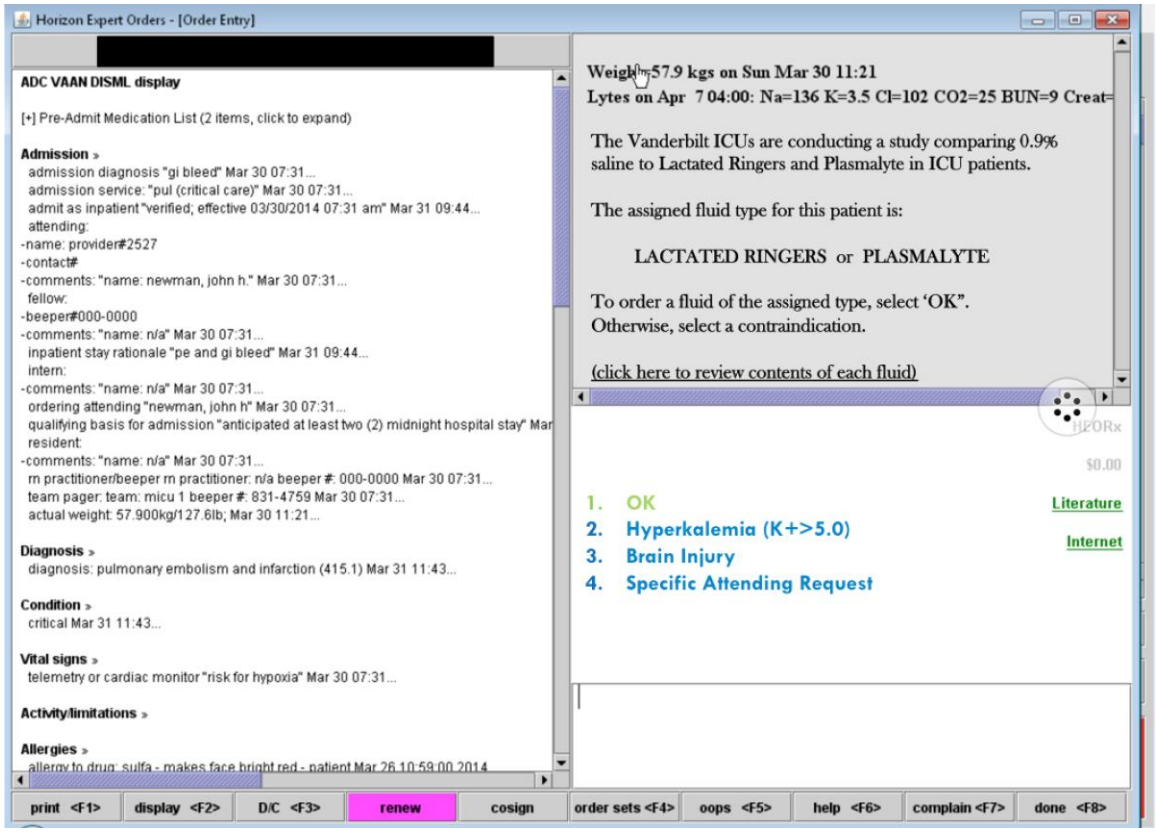
For the duration of the study, each study ICU will be routinely stocked only with the isotonic fluid assigned for that block. Upon request, the alternative isotonic fluid will be available from the inpatient pharmacy.

Order Entry:

For the duration of the study, when a provider begins an order for the administration of any isotonic fluid in the electronic order entry system an "Isotonic Fluid Wizard" (Figure 8A) will: 1) Inform the provider of the study, 2) Solicit the presence of contraindications to the assigned study fluid, and 3) If contraindications are not present, guide the provider to order the assigned study fluid. The manner in which fluid orders can be customized with regard to total volume, rate, electrolyte and dextrose content will not be affected by the advisor.

There are no established contraindications to the choice of 0.9% saline once the decision has been made to administer isotonic fluid. **Because of the marginally higher potassium content of Plasma-Lyte© and Lactated Ringer's, patients being treated for hyperkalemia will be allowed to receive 0.9% saline regardless of study group. Because of the concern for the use of relatively hypotonic solutions in patients with elevated intracranial pressure, these patients will also be allowed to receive 0.9% saline regardless of study group**. While there may be patients in whom treating providers prefer not to administer Ca2+ or lactate (as in Lactated Ringer's) or magnesium (as in Plasma-Lyte©), because an alternative physiologically-balanced solution would be available without these electrolytes, 0.9% saline would not be allowed for these indications in those assigned to the physiologically-balanced isotonic fluid group. Instead, the provider would have the option of choosing the other physiologically balanced solution (i.e. choose Plasma-Lyte© if worried about administering Ca2+ or lactate and choose Lactated Ringer's if worried about administering magnesium or acetate). Exception would be made only for the specific request of an identified attending provider.

Figure 8A



8.2 Duration of Treatment

All patients admitted to study ICUs during the study period will be treated with the study fluid assigned to that ICU until they are physically discharged from the ICU. Enrolled patients who remain in the ICU through a crossover between fluid groups will be treated with the assigned study ICU fluid which will change on the crossover date.

8.3 Safety Monitoring

This study will take place in the environment of the intensive care unit in which each participant will have access to invasive or noninvasive monitoring, a bed-side nurse with high-acuity nurse-to-patient staffing ratio, and a high level of laboratory monitoring as a part of routine ICU care. Additionally, study personnel will readily available to answer questions at any time during the study course.

Furthermore, after the six months, an interim analysis will be undertaken to ensure that one of the isotonic fluid groups does not have significantly fewer incidences of $MAKE_{30}$ (see section 12. Statistical Analysis for details).

8.4 Data Collection

Data collected will be divided into Data at Enrollment, Daily Study Data for days 1-30, Data at Termination, and Study Fluid Usage Data. Data at Enrollment, Study Day Data, and Data at Termination will be abstracted directly from the electronic medical record and entered into the secure online database REDcap. Study Fluid Usage and Compliance Data will be obtained from the Pharmacy and Hospital Billing Records and will be entered into the secure online database REDcap.

8.4.1 Data at Enrollment

1. Study Enrollment Data:
    a. Medical Record Number
    b. Date and Time of ICU Admission ("Time Zero")
    c. Study ICU at enrollment

2. Demographic Data:
    a. Age
    b. Gender
    c. Race
    d. Ethnicity
    e. Height (cms)
    f. Body Weight (kg)
    g. Date and time of Hospital Admission

3. Baseline Assessments:
    The following information will be recorded during the 12 hours prior to and 24 hours following ICU admission ("Time Zero"). If more than one value is available for this 36-hour period, the value closest to the time of ICU admission ("Time Zero") will be recorded.

    Respiratory Variables:
    a. Presence of Invasive Mechanical Ventilation

    Hemodynamic Variables
    a. Heart Rate (beats / min)
    b. Systolic Blood Pressure (mmHg)
    c. Mean Arterial Pressure (mmHg)
    d. Central Venous Pressure (mmHg)
    e. Vasopressor Use Y/N (receipt of norepinephrine, epinephrine, dopamine, phenylephrine, or vasopressin)
    f. Ionotrope Use Y/N (receipt of dobutamine or milrinone)

Renal and Metabolic Variables

a. Sodium
b. Potassium
c. Chloride
d. Bicarbonate
e. BUN
f. Creatinine
g. Hemoglobin
h. Total Protein
i. Albumin
j. Prothrombin Time
k. Lactate
l. Receipt of Renal Replacement Therapy

8.4.2 Daily Study Data

Daily Assessments

Data for each of the following variables will be recorded on Study Day 1 (the day following ICU admission) through day 30, death, or hospital discharge. Values will represent either (1) the value closest to 0800 on that date (FIRST), (2) the most extreme value encountered on that date (HIGHEST or LOWEST), or (3) any value present on that date (ANY).

1. Respiratory Variables:
    a. ANY Mechanical Ventilation

2. Hemodynamic Variables
    a. FIRST Heart Rate (beats/min)
    b. FIRST Mean Arterial Pressure (mmHg)
    c. ANY Vasopressor Use (receipt of norepinephrine, epinephrine, dopamine, phenylephrine, or vasopressin)

3. Metabolic Variables
    a. FIRST Sodium, HIGHEST Sodium, LOWEST Sodium
    b. FIRST Potassium, HIGHEST Potassium, LOWEST Potassium
    c. FIRST Chloride, HIGHEST Chloride, LOWEST Chloride
    d. FIRST Bicarbonate, HIGHEST Bicarbonate, LOWEST Bicarbonate
    e. FIRST BUN, HIGHEST BUN, LOWEST BUN
    f. FIRST Creatinine, HIGHEST Creatinine, LOWEST Creatinine

4. Renal Variables (from 7AM to 7AM)
    a. ANY Renal Replacement Therapy

Fluid Administration
1. (Administrative) – For each ICU during each month of the study we will collect the pharmacy total for cases of normal saline, lactated ringers, and Plasma-lyte©.
2. (Patient-level) – The isotonic fluid wizard built into the electronic order entry system will export for every isotonic fluid order placed:
    a. Medical Record Number
    b. Date and time of order placement
    c. Fluid Type
    d. Fluid Volume
    e. Selection of "OK" versus Specific Contraindication

8.4.3 Data at Termination
Data for each of the following variables will reflect data available at the time of death or discharge from the hospital.

1. Died before hospital discharge (Y/N); (if Y) Date and Time of death
2. Discharge from ICU (Y/N); (if Y) Date and Time of First Discharge from the ICU; Date and Time of Final Discharge from ICU during hospitalization
3. Transferred to another study ICU during the study period (Y/N); date, time, and new ICU of each ICU transfer during hospitalization
4. Discharge from Hospital (Y/N); (if Y) Date and Time of Discharge from Hospital
5. ICD-9 code, O/E ratios, and 60 day mortality from hospital records

8.5 Outcome Measures

Primary Endpoint: Development of Major Adverse Kidney Events by hospital discharge or day 30. The primary endpoint will be considered present if at least one of the following occur:
    a. A patient dies prior to the earlier of hospital discharge or day 30
    b. A patient receives new renal replacement therapy between enrollment and day 30
    c. A patient has persistent renal dysfunction at the earlier of hospital discharge or day 30 (persistent renal dysfunction is defined as ≥ 200% of creatinine from baseline)

Secondary Endpoints:

1. In-Hospital Mortality
2. 60 day Mortality
3. In-ICU Mortality
4. ICU-free days to day 28
5. Vasopressor-free days to day 28
6. Ventilator-free days to day 28
7. Incidence of new RRT in the first 28 days
8. Duration of new RRT in the first 28 days
9. Dialysis-free survival to day 28
10. Peak creatinine in the first 28 days
11. Change from baseline to peak creatinine in the first 28 days
12. Peak serum chloride
13. Change in serum chloride by generalized estimating equations
14. Change in serum bicarbonate by generalized estimating equations
15. Urinary biomarkers of pre-renal and intra-renal etiologies of acute kidney injury

ICU-free days to 28 days after enrollment will be defined as the number of days alive and not admitted to an intensive care unit service after the patient's final discharge from the intensive care unit before 28 days. If the patient is admitted to an intensive care unit service at day 28 or dies prior to day 28, ICU-free days will be 0.

Ventilator-free days to day 28 will be defined as the number of days alive and with unassisted breathing to day 28 after enrollment, assuming a patient survives for at least two consecutive calendar days after initiating unassisted breathing and remains free of assisted breathing. If a patient returns to assisted breathing and subsequently achieves unassisted breathing prior to day 28, VFD will be counted from the end of the last period of assisted breathing to day 28. If the patient is receiving assisted ventilation at day 28 or dies prior to day 28, VFD will be 0.

Biomarkers/Specimens:

In order to try to elucidate a potential mechanism of how 0.9% NaCl may cause renal failure and/or worse outcomes, biomarker analysis of biospecimens will be undertaken. From a select group of up to 1000 patients, urine and blood/plasma that is leftover and to be discarded from the laboratory after all ordered labs are performed will be collected. Leftover specimens from the laboratory will be used to prevent direct interaction between any patients and the study team. Specifically, urine will be collected from up to 750 (375 in each group) patients who develop acute renal failure while in the ICU. In addition, a random sampling of leftover urine specimens from up to 250 ICU patients will also be stored to ensure specimens are available from patients without kidney injury also. Similarly, a random sampling of leftover plasma from up to

500 patients will also be retrieved from the clinical laboratory prior to them discarding the specimens. This leftover plasma will also be stored. All specimens will be stored frozen at -80^{0}C in a locked freezer owned by the principal investigator in a locked freezer room until analysis. Collection and analysis of biospecimens will be dependent on receipt of funding.

9.0 Risks and Benefits:

For patients in whom the treating provider has ordered the administration of isotonic intravenous fluid, there are currently no established risks or benefits to the selection of 0.9% saline versus physiologically-balanced isotonic fluids. Whether the differences in content of chloride, potassium, calcium, magnesium, and bases have clinical implications is unknown. At this time there is no reason to believe that participation in this study would expose patients to greater medical risks or benefits than those experienced by critically ill patients receiving routine care. All of the isotonic intravenous fluids are used in routine care in all the Vanderbilt adult ICUs. The greater benefit of the study would be to society in the form of improved understanding of the relatively effects of these commonly used fluid solutions.

A potential risk to patients participating in this study involves the collection of personal health information. In order to limit the associated risks, the minimum amount of health information necessary for study conduct will be collected. After collection, the data will be stored in a secure online database (REDcap) and will be de-identified to protect participant privacy. In addition, any biospecimens collected will be stored in a secure, locked freezer in a locked room of specimen freezers.

10.0 Adverse Events:

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant administered an intervention that does not necessarily have to have a causal relationship with this treatment. An adverse event therefore can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an intervention, whether or not the incident is considered to be related to the intervention.

A serious adverse event (SAE) is defined as any untoward medical occurrence that meets any of the following criteria:

a. Results in death

b. Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event and NOT an event that hypothetically might have caused death if it would have been more severe)
c. Requires inpatient hospitalization
d. Prolongs an existing hospitalization
e. Results in persistent or significant disability or incapacity
f. Results in a congenital anomaly or birth defect
g. Important medical event that requires an intervention to prevent any of a-f above.

The Principal Investigator will be responsible for overseeing the safety of this trial on a daily basis. He will be available at any time for questions from the bedside nurses, who will also be monitoring the patients continuously for adverse events and serious adverse events which will be recorded and reported to the IRB. Adverse events will be recorded in a case report form in the study record and serious adverse events will be recorded in a case report form and reported to the IRB within 10 business days.

In addition, a clinical investigator experienced in monitoring and conducting clinical trials in critically ill patients will serve as the Data Safety Monitor (DSM) and will be available to oversee the study. In addition to assisting the PI with monitoring the trial for safety, the DSM will also perform the single interim analysis. If the data meet the stopping rules for efficacy at the interim analysis, the DSM will communicate a recommendation to stop the trial at that time. In addition, the DSM will also be available to review serious adverse events in a timely manner. They will be asked to be available for rapid access by the investigators in the case of the need to evaluate serious adverse events or any other major unanticipated or safety related issues. Furthermore, in cases of serious adverse events, the DSM will have the ability to pause the trial to investigate possible safety issues and/or suggest changes to the design of the study to abrogate any safety issues.

11.0 Study Withdrawal/Discontinuation

Patients can be withdrawn from study participation in the following circumstances:

- The investigator decides that the patient should be withdrawn for safety considerations.
- There is a significant protocol violation in the judgment of the PI.

The reason and date of every withdrawal will be recorded in the patient study records. Follow-up will be performed for all patients who discontinue due to an adverse event or any other safety parameter. Follow-up will also be performed for all patients who end participation in the protocol for another reason, but who also have an adverse event or

other safety parameter that could have led to discontinuation. Follow-up will be conducted until the condition has resolved, until diagnosis of the adverse event or safety parameter is deemed chronic and stable, or as long as clinically appropriate. This follow-up will be documented in the patient study record as well. Any biospecimens collected on patients who have been withdrawn will be identified from the freezer and discarded.

12.0 Statistical Considerations

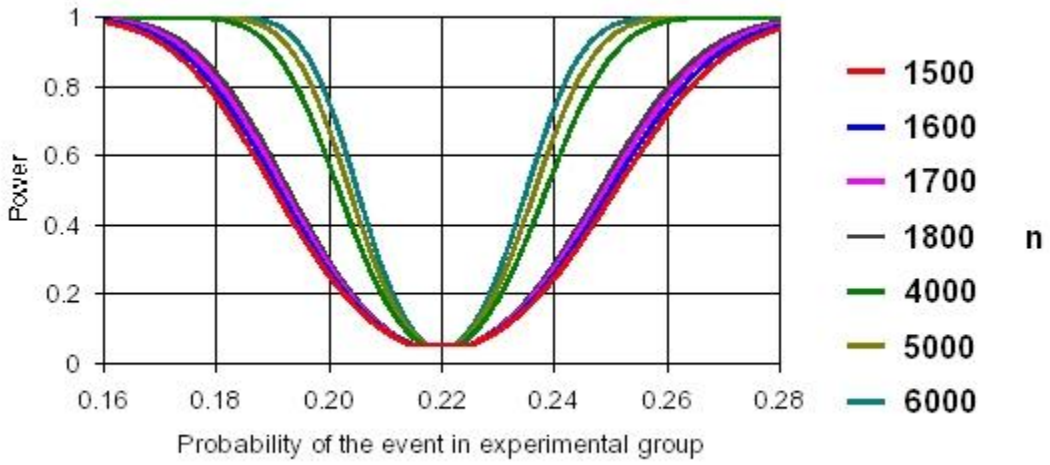
Although the artificial induction of a hyperchloremic and acidemic state by infusion of chloride-rich intravenous fluids can be potentially injurious to all organ systems, kidney injury has been the most commonly described organ injury associated with the use of unbalanced fluids (7). Major Adverse Kidney Events ($MAKE_{30}$) is a composite outcome defined or more of the following: death, new use of renal replacement therapy, or persistence of renal dysfunction at hospital discharge or at 30 days (defined as an increase in serum creatinine ≥ 200% from baseline) (26,27). This composite outcome focused on renal injury has been proposed as an meaningful endpoint for clinical trials as all of these outcomes are patient-centered, are well suited for an intervention that begins early in a patient's hospital course, and these outcomes have established criterion validity in their known association with other poor outcomes in patients with kidney disease such as cardiovascular disease and poor quality of life (27).

Sample Size

In clinical practice, the use of balanced intravenous fluids instead of chloride-rich fluids is an intervention with no increased cost and both types of fluids are equally available to the practitioner. Therefore any difference between treatment groups is clinically meaningful in regards to the $MAKE_{30}$ primary endpoint. In previous studies using the $MAKE_{30}$ composite endpoint in critically ill patients (26), the development of this endpoint occurred at a rate of 22%.

SMART-MED is anticipated to enroll between 3,000 and 3,600 patients over the one year study period. Barring logistical difficulties, SMART-SURG is anticipated to enroll between 5,000 and 6,500 patients over the one year study period. Enrollment of 8,000 patients in the SMART study overall would allow detection of a difference of 2.6% in the incidence of the primary endpoint with 80% power using a type I error of 0.05. Enrollment of 3,000 patients in the SMART-MED study alone would allow detection of a difference of 4.2% in the primary endpoint with 80% power using a type I error rate of 0.05 (Figure 12A). We will use the Fisher's exact test to compare the rates of the $MAKE_{30}$ composite outcome between treatment groups.

Figure 12A. Power by incidence of MAKE30 in the intervention arm and number enrolled in each arm.



Data Analysis Plan

All data from patients enrolled in the study will be analyzed in an intention-to-treat fashion. If both SMART-MED and SMART-SURG are able to be completed, they will be analyzed together with baseline characteristics, on-study variables, and outcomes presented for the overall population (SMART) by randomized study arm. If SMART-SURG is unable to be conducted to due logistical issues, the SMART-MEDCICAL trial will be analyzed independently with no change to the data analysis plan except exclusion of the subgroup analysis by ICU.

Demographics and Baseline Characteristics

Demographics and baseline characteristics will include age, gender, race, primary diagnosis thought to be causing critical illness, secondary active medical problems, amount and type of intravenous fluid given prior to enrollment, presence of and stage of AKI, comorbidities, baseline vital signs and laboratories, baseline APACHE II and SOFA scores. Descriptive statistics, including mean and standard deviation, median, interquartile ranges, minimum and maximum, and the number and percent of subjects in specified categories will be used to summarize the demographic and baseline variables for the three study arms separately. These will be compared between groups using Wilcoxon rank-sum tests for continuous variables and Chi-square test (or Fisher's exact Test) for categorical variables. All statistical analyses will be done using the statistical software R, IBM SPSS, or Stata.

Primary Endpoint:

Development of $MAKE_{30}$, defined by one or more of the following:

1. All-cause in-hospital death after enrollment
2. New need for in-hospital renal replacement therapy after enrollment, truncated at 30 days
3. An increase in the baseline creatinine by ≥ 200% at hospital discharge, truncated at 30 days

Baseline creatinine will be defined as the creatinine measured closest to hospital admission in the 6 months prior to hospitalization. If a pre-hospital creatinine measurement is not available, we will calculate the patient's estimated creatinine using the Modification of Diet in Renal Disease (MDRD) formula (28,29).

Secondary Clinical Endpoints

1. All-cause in-hospital death after enrollment
2. New need for in-hospital renal replacement therapy after enrollment, truncated at 30 days
3. An increase in the baseline creatinine by ≥ 200% at hospital discharge, truncated at 30 days
4. 60 day mortality
5. ICU-free days, defined as 28 – the number of midnights admitted to an ICU, in-hospital death = 0
6. Vasopressor-free days, defined as 28 – the number of midnights a patient is receiving continuous infusion of an intravenous vasopressor, in-hospital death = 0
7. Ventilator-free days, defined as 28 – the number of midnights a patient is receiving invasive mechanical ventilation, in-hospital death = 0
8. Duration of renal replacement therapy
9. Peak serum creatinine in the first 28 days
10. Electronic Acute Physiology Score daily during the trial period

Secondary Biochemical Efficacy Endpoints

1. Serum chloride
2. Serum bicarbonate
3. Serum sodium

Interim Analysis

Enrollment will occur over an expected one year period in which all Vanderbilt ICUs are randomly assigned to one month blocks of alternating balanced fluids only or

0.9% saline only. Blocks will be only one month in length to minimize the effect of seasonal variability.

Thirty days after the conclusion of the sixth month of the study, the DSMB will review one interim analysis to determine if further study is warranted. The stopping boundary for efficacy will be met if (1) the difference in the incidence of the primary outcome (MAKE30) between groups is greater than or equal to 2.6% with a p value less than 0.001 AND (2) the p value is less than 0.001 for either death or new renal replacement therapy. As even small differences between groups would be clinically meaningful and given the importance to determine with as much certainty as possible whether balanced fluids are superior to chloride-rich fluids, there will not be a futility stopping boundary.

Prespecified Subgroup Analyses

We aim to enroll a very heterogeneous group of critically ill patients in order to collect the most amount of data to answer the question of whether chloride-rich intravenous fluids may be detrimental to patients admitted to an ICU. However we expect that there may be a differential effect of balanced fluids on patients based upon a number of baseline characteristic differences that warrant subgroup analysis and possibly analysis for an effect modification. The primary analysis of the composite $MAKE_{30}$ outcome will occur in all patients enrolled in the trial; however as secondary analyses, the following subgroups will be analyzed separately in regards to the $MAKE_{30}$ and secondary clinical outcomes:

1. Patients with any amount of AKI on enrollment
2. Patients who received any amount of non-assigned intravenous fluids either prior to or after enrollment (for example, patients who receive 0.9% saline in the ER prior to ICU admission where they are then assigned to the balanced fluids group)
3. Subgroup analysis by ICU location (medical, trauma, surgical, cardiovascular, neuro)**
4. Patients never requiring renal replacement therapy during the trial period
5. Patients never requiring vasoactive infusions for hypotension
6. Diabetic ketoacidosis present on ICU admission
7. Head trauma
8. Patients that remain in the ICU during a scheduled change in fluid assignment
9. Sepsis (including sepsis, severe sepsis, and septic shock) present on ICU admission

**ICU subgroups applies only if SMART-SURG completed

Randomization

This is a single-center, multiple-ICU, cluster-randomized controlled trial to evaluate the impact of physiologically balanced isotonic fluids compared with 0.9% saline on the development of major adverse kidney events at 30 days. Each ICU will be initially randomized to a fluid group (0.9% Saline versus physiologically-balanced isotonic fluid) and will then crossover 11 times between groups during the one year study period (Figure 12B). This cluster randomized design will accomplish the following: 1) Fluids are randomly assigned in one month blocks regardless of season and ICU volume, 2) The one month block length will minimize any possible interaction between fluid type and seasonal variation in ICU diagnoses and, 3) Prevents any amount of selection bias by the individual practitioner. The block assignments will be randomly generated for each ICU, however the ICU staff, treating teams, and study staff will not be blinded to the randomization scheme and study group assignments once it is created. This has the theoretical potential of introducing both a selection bias and observer bias into this study; however we are protected against given that all ICU patients with fluid orders are automatically enrolled in the study and the $MAKE_{30}$ outcome is very objective and not subject to observer interpretation.

Figure 12B: Block-randomized, cross-over design

6/1/15 ← → **5/30/15**

	N/year	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th
MICU	2,300	NS	LR/PLA	NS	LR/PLA	NS	LR/PLA	NS	LR/PLA	NS	LR/PLA	NS	LR/PLA
SICU	2126	B	A	B	A	B	A	A	B	A	B	A	B
CVICU	1892	A	B	A	B	A	B	B	A	B	A	B	A
Trauma	1693	B	A	B	A	B	A	A	B	A	B	A	B
Neuro	1212	B	A	B	A	B	A	A	B	A	B	A	B

*A and B will be randomly assigned prior to beginning enrollment
SMART-MEDICAL is MICU
SMART-SURGICAL is SICU, CVICU, Trauma, Neuro

Statistical Considerations

Continuous variables will be described as median and 95% confidence intervals (bootstrapped) and number and percentage for categorical variables. All between group comparisons with continuous variables will be performed using Wilcoxon Rank-sum tests and Fisher's exact test for categorical variables. In regards to repeatedly measured variables, changes between groups will be compared using generalized estimating equations (GEE). Kaplan-Meier curves and log-rank tests will be used to analyze time-to-event comparisons between groups. Prespecified subgroups as outlined above will be compared in regards to the type of fluids received and the $MAKE_{30}$ primary outcome using logistic regression models. If the point estimates of the odds ratios based on the subgroup analyzed fall on opposite sides of an odds ratio of 1, a test for interaction using logistic regression will also be performed for that particular subgroup analysis

using as independent variables the type of fluid received, the subgroup, and an interaction term between the type of fluid and subgroup with the $MAKE_{30}$ outcomes as the dependent variable.

13.0 Privacy/Confidentiality Issues

At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identifies will be collected and when such data is requisite. As quickly as feasible, all data collected will be uploaded into a password-protected computerized database maintained within REDCap, a secure, web-based application for building and managing online databases. All patients will be assigned a unique study number for use in the computerized database. As soon as possible (probably at time of publication), all identifiers will be destroyed in the database.

14.0 Follow-up and Record Retention

The study will commence at enrollment and study intervention will last until ICU discharge. Patient clinical outcomes will be collected up until 60 days after enrollment. Identified data in the secure database REDCap will be stored for an indefinite period of time to allow for subsequent data analysis and future reference. However, all patients will be assigned a unique study number for use in the computerized database. As soon as possible (probably at time of publication), all identifiers will be destroyed in the database.

15.0 References

1. Finfer S, Liu B, Taylor C, Bellomo R, Billot L, Cook D, Du B, McArthur C, Myburgh J, SAFE TRIPS Investigators. Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. *Crit Care Lond Engl*. 2010;14(5):R185. doi:10.1186/cc9293.
2. Yunos NM, Bellomo R, Story D, Kellum J. Bench-to-bedside review: Chloride in critical illness. *Crit Care Lond Engl*. 2010;14(4):226. doi:10.1186/cc9052.
3. Yunos NM, Kim IB, Bellomo R, Bailey M, Ho L, Story D, Gutteridge GA, Hart GK. The biochemical effects of restricting chloride-rich fluids in intensive care. *Crit Care Med*. 2011;39(11):2419-2424. doi:10.1097/CCM.0b013e31822571e5.
4. Smith RJ, Reid DA, Delaney EF, Santamaria JD. Fluid therapy using a balanced crystalloid solution and acid-base stability after cardiac surgery. *Crit Care Resusc J Australas Acad Crit Care Med*. 2010;12(4):235-241.
5. Wilcox CS. Regulation of renal blood flow by plasma chloride. *J Clin Invest*. 1983;71(3):726-735.
6. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg*. 2012;256(1):18-24. doi:10.1097/SLA.0b013e318256be72.
7. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA J Am Med Assoc*. 2012;308(15):1566-1572. doi:10.1001/jama.2012.13356.
8. Raghunathan K, Shaw A, Nathanson B, Stürmer T, Brookhart A, Stefan MS, Setoguchi S, Beadles C, Lindenauer PK. Association Between the Choice of IV Crystalloid and In-Hospital Mortality Among Critically Ill Adults With Sepsis. *Crit Care Med*. 2014. doi:10.1097/CCM.0000000000000305.
9. Rochwerg B, Alhazzani W, Sindi A, Heels-Ansdell D, Thabane L, Fox-Robichaud A, Mbuagbaw L, Szczeklik W, Alshamsi F, Altayyar S, Ip W-C, Li G, Wang M, Wludarczyk A, Zhou Q, Guyatt GH, Cook DJ, Jaeschke R, Annane D. Fluid Resuscitation in Sepsis: A Systematic Review and Network Meta-analysis. *Ann Intern Med*. 2014. doi:10.7326/M14-0178.
10. Dellinger RP. Crystalloids for Fluid Resuscitation in Sepsis: Where Is the Balance? *Ann Intern Med*. 2014. doi:10.7326/M14-1565.
11. Scheingraber S, Rehm M, Sehmisch C, Finsterer U. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. *Anesthesiology*. 1999;90(5):1265-1270.
12. Waters JH, Miller LR, Clack S, Kim JV. Cause of metabolic acidosis in prolonged surgery. *Crit Care Med*. 1999;27(10):2142-2146.

13. Waters JH, Gottlieb A, Schoenwald P, Popovich MJ, Sprung J, Nelson DR. Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. *Anesth Analg*. 2001;93(4):817-822.
14. Young JB, Utter GH, Schermer CR, Galante JM, Phan HH, Yang Y, Anderson BA, Scherer LA. Saline versus Plasma-Lyte A in initial resuscitation of trauma patients: a randomized trial. *Ann Surg*. 2014;259(2):255-262. doi:10.1097/SLA.0b013e318295feba.
15. Stewart PA. Modern quantitative acid-base chemistry. *Can J Physiol Pharmacol*. 1983;61(12):1444-1461.
16. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent J-L, Moreno R, Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013;41(2):580-637. doi:10.1097/CCM.0b013e31827e83af.
17. Kellum JA, Bellomo R, Kramer DJ, Pinsky MR. Etiology of metabolic acidosis during saline resuscitation in endotoxemia. *Shock Augusta Ga*. 1998;9(5):364-368.
18. Kellum JA, Song M, Li J. Lactic and hydrochloric acids induce different patterns of inflammatory response in LPS-stimulated RAW 264.7 cells. *Am J Physiol Regul Integr Comp Physiol*. 2004;286(4):R686-692. doi:10.1152/ajpregu.00564.2003.
19. Kellum JA, Song M, Venkataraman R. Effects of hyperchloremic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis. *Chest*. 2004;125(1):243-248.
20. Kellum JA. Fluid resuscitation and hyperchloremic acidosis in experimental sepsis: improved short-term survival and acid-base balance with Hextend compared with saline. *Crit Care Med*. 2002;30(2):300-305.
21. Williams EL, Hildebrand KL, McCormick SA, Bedel MJ. The effect of intravenous lactated Ringer's solution versus 0.9% sodium chloride solution on serum osmolality in human volunteers. *Anesth Analg*. 1999;88(5):999-1003.
22. Reid F, Lobo DN, Williams RN, Rowlands BJ, Allison SP. (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study. *Clin Sci Lond Engl 1979*. 2003;104(1):17-24. doi:10.1042/.
23. Wilkes NJ, Woolf R, Mutch M, Mallett SV, Peachey T, Stephens R, Mythen MG. The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. *Anesth Analg*. 2001;93(4):811-816.
24. Boldt J, Suttner S, Brosch C, Lehmann A, Röhm K, Mengistu A. The influence of a balanced volume replacement concept on inflammation, endothelial activation, and kidney integrity in elderly cardiac surgery patients. *Intensive Care Med*. 2009;35(3):462-470. doi:10.1007/s00134-008-1287-1.

25. O'Malley CMN, Frumento RJ, Hardy MA, Benvenisty AI, Brentjens TE, Mercer JS, Bennett-Guerrero E. A randomized, double-blind comparison of lactated Ringer's solution and 0.9% NaCl during renal transplantation. *Anesth Analg*. 2005;100(5):1518-1524, table of contents. doi:10.1213/01.ANE.0000150939.28904.81.
26. Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, Bihorac A, Birkhahn R, Cely CM, Chawla LS, Davison DL, Feldkamp T, Forni LG, Gong MN, Gunnerson KJ, Haase M, Hackett J, Honore PM, Hoste EA, Joannes-Boyau O, Joannidis M, Kim P, Koyner JL, Laskowitz DT, Lissauer ME, Marx G, McCullough PA, Mullaney S, Ostermann M, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care.* 2013;17:R25.
27. Palevsky PM, Molitoris BA, Okusa MD, Levin A, Waikar SS, Wald R, Chertow GM, Murray PT, Parikh CR, Shaw AD, Go AS, Faubel SG, Kellum JA, Chinchilli VM, Liu KD, Cheung AK, Weisbord SD, Chawla LS, Kaufman JS, Devarajan P, Toto RM, Hsu C-Y, Greene T, Mehta RL, Stokes JB, Thompson AM, Thompson BT, Westenfelder CS, Tumlin JA, et al. Design of clinical trials in acute kidney injury: report from an NIDDK workshop on trial methodology. *Clin J Am Soc Nephrol.* 2012. pp. 844–850.
28. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F, Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med.* 2006;145:247–254.
29. Závada J, Hoste E, Cartin-Ceba R, Calzavacca P, Gajic O, Clermont G, Bellomo R, Kellum JA, AKI6 investigators. A comparison of three methods to estimate baseline creatinine for RIFLE classification. *Nephrol Dial Transplant.* 2010;25:3911–3918.

Isotonic Solutions and Major Adverse Renal Events Trial (SMART) Study Protocol

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Study Schema

1.0 Study Summary

Title: Isotonic Solutions and Major Adverse Renal Events Trial (SMART)

Study Aims:

- Primary: To compare the effect of saline versus balanced crystalloids on the development of major adverse kidney events within 30 days (MAKE30) in patients admitted to the intensive care unit
- Secondary: To evaluate the effects of the same intervention in the same population on secondary outcomes.

Study Hypotheses:

- Primary: Use of balanced crystalloids for intravenous fluid administration among ICU patients will decrease the development of MAKE30 compared with use of saline
- Secondary: Use of balanced crystalloid for intravenous fluid administration among ICU patients will decrease the incidence of in-hospital mortality, decrease the incidence of acute kidney injury, decrease the incidence of new RRT, and decrease the incidence of persistent renal dysfunction.

Inclusion Criteria:

1. Admitted to an adult intensive care unit (ICU) at Vanderbilt University Medical Center

Exclusion Criteria:

1. Age < 18 years

Study Population: All adult patients admitted to an adult ICU at VUMC

Consent: Given the current use of all isotonic solutions studied in routine clinical practice, the lack of established risk or benefit with any solution, the impracticability of obtaining informed consent prior to receipt of intravenous fluid in every critically ill patient admitted to VUMC, and randomization at the level of the intensive care unit, a waiver of informed consent will be requested.

Randomization: Each ICU will be initially randomized to a fluid group (saline vs balanced crystalloids) and will then crossover between fluid groups every month during the study period.

Study Interventions:

- **Saline Group:** Patients in an ICU randomized to saline for whom a provider orders isotonic crystalloid will receive the ordered volume of 0.9% sodium chloride.

- **Balanced Crystalloid Group:** Patients in an ICU randomized to balanced crystalloids for whom a provider orders isotonic crystalloid will receive the ordered volume of Plasma-Lyte A® or lactated Ringer's unless a pre-specified contraindication is present (see below).

Primary Endpoint:

- Development of major adverse kidney events by hospital discharge or day 30 (MAKE30). A major adverse kidney event is defined as at least one of the following: mortality, need for new renal replacement therapy, or persistent renal dysfunction at the time of hospital discharge (defined as final serum creatinine ≥ 200% of baseline).

Secondary Endpoints:

1. In-hospital mortality before ICU discharge, before 30 days, and before 60 days
2. ICU-free days to day 28
3. Ventilator-free days to day 28
4. Vasopressor-free days to day 28
5. Renal replacement therapy-free days to day 28
6. Incidence of new RRT
7. Duration of new RRT
8. Incidence of persistent renal dysfunction
9. Incidence of Stage II or greater AKI by KDIGO creatinine criteria
10. Highest serum creatinine value
11. Change from baseline to highest serum creatinine value
12. Final serum creatinine value before hospital discharge or 30 days
13. Serum values for sodium, potassium, chloride, bicarbonate, blood urea nitrogen, and creatinine from enrollment through hospital discharge or 30 days
14. *Urinary biomarkers of pre-renal and intra-renal acute renal failure*
15. *Serum biomarkers of intravascular volume overload and acute renal failure*

2.0 Background

The administration of intravenous fluids is ubiquitous in the care of the critically ill[1]. Commonly available isotonic crystalloid solutions contain a broad spectrum electrolyte compositions including a range chloride concentrations[2]. Recent studies have associated solutions with supraphysiologoic chloride content with hyperchloremia[3,4], metabolic acidosis and renal vasoconstriction[5,6], acute kidney injury and renal replacement therapy[7], and increased mortality[8,9] but no large, randomized-controlled trials have been conducted. In order to determine the impact of balanced crystalloids compared to saline on clinical outcomes in critically ill patients, a randomized controlled trial is needed[10].

2.1 Composition of Commonly Used Crystalloids

The administration of crystalloids occurs commonly in the intensive care unit as a means of resuscitation, maintenance of intravascular volume, and as a carrier for intravenous medications. The most commonly available intravenous fluid solutions are 0.9% sodium chloride, lactated Ringer's, and Plasma-Lyte A® which vary widely with respect to their electrolyte content (Table 2A). Particular attention has been paid to the chloride content of 0.9% sodium chloride.

Table 2A.

	Concentration (mmol/L)			
	Plasma	0.9% NaCl	Lactated Ringer's	Plasma-Lyte A®
Sodium	140	154	130	140
Potassium	5	0	4	5
Chloride	100	154	109	98
Calcium	2.2	0	1.5	0
Magnesium	1	0	0	1.5
Bicarbonate	24	0	0	0
Lactate	1	0	28	0
Acetate	0	0	0	27
Gluconate	0	0	0	23

2.2 Hyperchloremic metabolic acidosis

Multiple prior studies have demonstrated a relationship between the receipt of chloride-rich fluid and the development of metabolic acidosis[11–14]. This relationship is

hypothesized to be explained by the Stewart physicochemical approach[15] in which the hydrogen ion concentration in the plasma is determined by the independent variables of partial pressure of carbon dioxide, weak acids (primarily protein), and the balance of sodium, potassium, magnesium, calcium, chloride, and lactate ions known as the strong ion difference. In this understanding, increasing concentrations of chloride relative to sodium decrease the strong ion difference and increase the hydrogen ion concentration contributing to metabolic acidosis.

2.3 Chloride and Sepsis Resuscitation

Early administration of intravenous fluid is a cornerstone of current sepsis management[16]. The high prevalence of fluids with supraphysiologic chloride concentrations has led to study of these solutions in animal models of sepsis resuscitation. Administration of high-chloride saline solutions in animal models of sepsis have suggested that increased fluid chloride content contributes to the development of acidosis[17], inflammatory mediator release[18], hypotention[19], and mortality[20]. A recent retrospective, propensity-matched analysis of chloride content in fluids used for early resuscitation of patients with septic shock showed an association between higher chloride content and increased mortality[8] as did a meta-analysis of randomized controlled trials of intravenous fluid choice in sepsis[9].

2.4 Chloride and Renal Function

Animal studies have suggested a role for chloride in regulating renal blood flow. A study of denervated dog kidneys infused with chloride-solutions showed vasoconstriction only in the renal vessels associated with decreased glomerular filtration[5]. Proposed mechanisms for chloride-mediated vasoconstriction include tubuloglomerular feedback in which chloride detection in the distal tubule triggers mesangial contraction and decreased filtration, thromboxane-mediated vasoconstriction, and chloride-mediated potentiation of angiotensin II response in the renal vasculature.

Studies on human volunteers have shown decreased renal blood flow[6], increased time to micturition, and decreased diuresis and natiuresis in patients treated with fluids with higher chloride content[21,22]. Studies of patients undergoing surgery have linked higher chloride solutions to decreased urine output[23] and increased urinary markers of kidney injury[24]. A randomized controlled trial of lactated Ringer's versus saline in patients undergoing renal transplantation was stopped early for a higher incidence of hyperkalemia and metabolic acidosis in the saline group[25].

Recently, a prospective, open-label, before-after study of over 1400 patients in a single intensive care unit transitioning from use of higher to lower chloride solutions

demonstrated an association between higher chloride fluid and the development of acute kidney injury and use of renal replacement therapy[7].

3.0 Rationale and Specific Aims

In order to determine the impact of isotonic crystalloid composition on clinical outcomes of critically ill adults, a randomized controlled trial is needed.

- Primary Aim: To compare the effect of balanced crystalloids versus saline on the development of major adverse kidney events by 30 days (MAKE30) among intensive care unit patients

- Secondary Aim: To evaluate the effect of the same intervention in the same population on secondary outcomes.

To complete these aims, we will enroll patients from participating ICUs at Vanderbilt University Medical Center in a cluster-randomized, multiple-crossover trial of balanced crystalloid (lactated Ringer's or Plasma-Lyte A®) versus saline.

4.0 Previous Human Studies

Increasing recognition of the potential differences in "isotonic" intravenous fluids has led to several prior studies examining chloride concentration in IV fluid in humans. As detailed above, prior studies have examined the role of fluid chloride content in healthy human volunteers, patients undergoing surgery, patients with septic shock, and critically ill patients generally. The above studies provide the rationale for a large, prospective randomized controlled trial of isotonic crystalloids with higher versus lower chloride content in the critically ill.

5.0 Study Description

This is a single-center, cluster-randomized, multiple-crossover trial comparing balanced crystalloids to saline with regard to death, new RRT, or persistent renal dysfunction. The participating ICUs will be randomized to utilization of 0.9% sodium chloride or balanced crystalloids (lactated Ringers or Plasma-Lyte A®). Every patient admitted to an ICU at Vanderbilt Medical Center during the study period who meets no exclusion criteria will be enrolled and will receive the assigned study fluid if isotonic crystalloid is ordered by the treating provider and none of the pre-specified contraindications are present. All other decisions regarding fluid administration

including indication, timing, rate, volume, and endpoint will remain at the discretion of the treating provider. The study will not impact the use of oral fluids or other IV fluids. Every month each ICU will undergo a cross-over in assigned fluid group such that each ICU will experience each fluid group assignment for equal time periods during the study.

For logistical purposes, the study will be registered as two, independent, parallel, randomized, multiple-crossover trials – one for patients enrolled from the medical ICU (SMART-MED) and one for patients enrolled from the other ICUs (SMART-SURG). Success of the pilot study (SALT) in the MICU of establishing the infrastructure needed to deliver the study intervention will allow enrollment in SMART-MED to begin immediately in the MICU. The initiation of enrollment in the other ICUs (SMART-SURG) will be dependent on successfully transferring the infrastructure for delivery of the assigned intervention to these ICUs and is anticipated to be delayed 6 months from the start of the SMART-MED trial. SMART-MED and SMART-SURG will have an identical design, intervention, and data collection to allow for analysis of all patients concurrently in accordance with a single, pre-specified data-analysis plan.

6.0 Inclusion and Exclusion Criteria

6.1 Inclusion Criteria: Admitted to an adult intensive care unit (ICU) at Vanderbilt University Medical Center

6.2 Exclusion Criteria: Age<18 years old

7.0 Enrollment/Randomization

7.1 Study Sites: Patients for this study will be enrolled upon admission to the participating intensive care unit (ICU) at Vanderbilt University Medical Center. Participating ICUs within Vanderbilt University Hospital will include:

SMART-MED: Medical ICU (8T3)
SMART-SURG: Surgical ICU (9T3), Cardiovascular ICU (5N), Trauma ICU (10N), Neurological and Neurosurgical ICU (6T3).

7.2 Study Population: All patients admitted to an ICU at Vanderbilt Medical Center during the study period will be enrolled unless meeting exclusion criteria. Patients will be enrolled prior to receiving their first administration of IV fluid in the ICU.

7.3 Enrollment: All adult patients will be enrolled in this cluster-randomized, multiple-crossover trial at the time of admission to the participating ICU prior to the administration of any IV fluid in the ICU.

7.4 Consent:

Saline, lactated ringers, and Plasma-Lyte A® are all intravenous crystalloids currently used in the routine care of patients admitted to the ICUs at Vanderbilt University Medical Center. Currently, no high quality data suggest that choice of crystalloid affects clinical outcomes among critically ill adults. During the SMART trial, each time a study crystalloid is ordered, the study will confirm that the treating clinician does not feel that any study crystalloid is required for the safe treatment of that specific patient at that specific point in time. The trial is felt to pose minimal risk because (1) exposure to the study crystalloids occurs only for patients whose treating clinician has already decided to administer an IV crystalloid, (2) all of the crystalloid solutions examined are already used in routine practice in the study environment, (3) no definitive prior data suggest clinical outcomes are better with one crystalloid relative to the others, and (4) the study confirms with every crystalloid order that the treating clinician does not feel any one crystalloid type is required for safe treatment of the patient. Given the minimal risk, the focus of the study on crystalloid use at an ICU level, and the impracticability of consenting each patient admitted to each ICU prior to the first administration of crystalloid, a waiver of informed consent was requested.

7.5 Randomization:

Each month of the study, each ICU will be assigned to either saline or balanced crystalloids. So that each ICU will experience an equal number of months assigned to saline and balanced crystalloids while minimizing monthly imbalances in the hospital's overall use of each crystalloid, we will generate two sequences of study group assignment ([1] saline during odd-numbered months and balanced crystalloid during even-numbered months; [2] balanced crystalloid during odd-numbered months and saline during even-numbered months). We will plan for three ICUs to be assigned to one sequence and the remaining two ICUs to the opposite sequence. To facilitate the early administration of the assigned crystalloid in the ED and operating room prior to the patient's physical arrival in the ICU, a single computer-generated, simple randomization will be performed in which the three ICUs that admit the majority of patients from the ED (medical ICU, trauma ICU, and surgical ICU) are randomized 'en bloc' to one sequence of crystalloid group assignments and the two ICUs that admit the majority of patients from the operating room (neurological ICU and cardiac ICU) are randomized 'en bloc' to the opposite sequence of crystalloid group assignments. Individual patients will not be randomized for the purposes of this study. Patients that

are transferred between two participating ICUs will be treated according to the assignment for the unit in which they currently are cared for but will be analyzed by their original group assignment for the primary analysis.

The effect of differing sodium, chloride, and potassium contents of Plasma-Lyte A®, lactated Ringer's, and 0.9% sodium chloride on patients' metabolic laboratory studies over the course of the ICU stay would make blinding of the treating providers and nursing staff impossible. Therefore, clinical personnel will not be blinded to the study intervention. However, all on-study and outcome data will be collected by study staff blinded to study group assignment.

8.0 Study Procedures

8.1 Treatment Arms

Patients in an ICU randomized to saline will receive 0.9% sodium chloride whenever isotonic intravenous crystalloid administration is ordered by the treating provider. Patients in an ICU randomized to balanced crystalloid will receive Plasma-Lyte A® or lactated Ringer's whenever isotonic intravenous fluid administration is ordered by the treating provider. The total volume, rate, initiation, cessation, and addition of electrolytes and glucose to the isotonic fluid assigned will be at the discretion of the ordering provider. Adherence with the administration of assigned fluid in the study ICUs will be ensured by dual interventions at the level of pharmacy IV fluid supply and physician order entry.

Pharmacy Supply:

For the duration of the study, each study ICU will be routinely stocked primarily with the isotonic crystalloid assigned for that month. Upon request, the alternative isotonic crystalloid will be available from the pharmacy.

Order Entry:

For the duration of the study, when a provider begins an order for the administration of any isotonic crystalloid in the electronic order entry system an "Isotonic Fluid Wizard" will: 1) Inform the provider of the study, 2) Solicit the presence of contraindications to the assigned study fluid, and 3) If contraindications are not present, guide the provider to order the assigned study fluid. The manner in which fluid orders can be customized with regard to total volume, rate, electrolyte and dextrose content will not be affected by the advisor.

There are no established contraindications to the choice of 0.9% saline once the decision has been made to administer an isotonic crystalloid. **Because of the marginally higher potassium content of Plasma-Lyte A® and lactated Ringer's, patients being**

treated for hyperkalemia will be allowed to receive saline regardless of study group. Because of the concern for the use of relatively hypotonic solutions in patients with elevated intracranial pressure, these patients will also be allowed to receive saline regardless of study group. While there may be patients in whom treating providers prefer not to administer Ca2+ or lactate (as in lactated Ringer's) or magnesium (as in Plasma-Lyte A®), because an alternative balanced solution would be available without these electrolytes, saline would not be allowed for these indications in those assigned to the balanced crystalloid group. Instead, the provider would have the option of choosing the other balanced crystalloid (i.e. choose Plasma-Lyte A® if worried about administering Ca2+ or lactate and choose lactated Ringer's if worried about administering magnesium or acetate).

The non-assigned crystalloid will also be made available via the pharmacy if a formal statement is submitted that the attending physician feels the non-assigned crystalloid is required for the safe treatment of a specific patient.

8.2 Duration of Treatment

All patients admitted to study ICUs during the study period will be treated with the study fluid assigned to that ICU until they are physically discharged from the ICU. Enrolled patients who remain in the ICU through a crossover between fluid groups will be treated with the assigned study ICU fluid which will change on the crossover date.

8.3 Safety Monitoring

This study will take place in the environment of the intensive care unit in which each participant will have access to invasive or noninvasive monitoring, a bed-side nurse with high-acuity nurse-to-patient staffing ratio, and a high level of laboratory monitoring as a part of routine ICU care. Additionally, study personnel will readily available to answer questions at any time during the study course.

Furthermore, interim analyses will be undertaken to ensure that one of the isotonic fluid groups does not have a significantly lower incidence of MAKE30 (see section 12. Statistical Analysis for details).

8.4 Data Collection

8.4.1 Data at Enrollment

1. Study Enrollment Data:
    a. Encounter Number ("Study ID")
    b. Medical Record Number
    c. Date and Time of ICU Admission ("Time Zero")
    d. Study ICU at enrollment (Medical/Cardiac/Neuro/Trauma/Surgical)

2. Demographic Data:
    a. Age (years)
    b. Gender (male/female)
    c. Race (White/Black/Asian/Alaskan/PacificIsland/Other)
    d. Ethnicity (Hispanic, Non-hispanic)
    e. Height (cm)
    f. Weight (kg)
    g. Date and time of Hospital Admission
    h. Source of admission to ICU (ED/OR/outside hospital transfer/hospital ward/outpatient/another ICU within the hospital)
    i. Admitting service
    j. ICD-9 and ICD-10 diagnoses

3. Comorbidities:
    a. Exlihauser comorbidities
    b. CKD stage III or greater by CKD-EPI criteria
    c. Prior receipt of renal replacement therapy
    d. Predicted risk of in-hospital mortality by University HealthSystem Consortium expected in-hospital mortality

4. Invasive Support:
   The following information will be recorded during the 12 hours prior to and 24 hours following ICU admission ("Time Zero"). If more than one value is available for this 36-hour period, the value closest to the time of ICU admission ("Time Zero") will be recorded.
    a. Receipt of Mechanical Ventilation (Y/N)
    b. Receipt of vasopressors (Y/N) (norepinephrine, epinephrine, dopamine, phenylephrine, or vasopressin)

5. Renal function
    a. All serum creatinine values from the clinical laboratory system between 12 months prior to hospitalization and 30 days after ICU admission
    b. Stage II or greater acute kidney injury by KDIGO creatinine criteria

6. Serum laboratory values
    a. All serum values for sodium, potassium, chloride, bicarbonate, and blood urea nitrogen between 12 months prior to hospitalization and 30 days after ICU admission

8.4.2 Daily Study Data

Daily Assessments

Data for each of the following variables will be recorded from ICU admission through 30 days after ICU admission, death, or hospital discharge.

1. Invasive Support:
    a. Receipt of mechanical ventilation
    b. Receipt of vasopressors

2. Serum Laboratory variables
    a. Sodium
    b. Potassium
    c. Chloride
    d. Bicarbonate
    e. Blood urea nitrogen
    f. Creatinine

3. Renal Variables
    a. Receipt of RRT
    b. Indications for RRT among patients receiving new RRT
        i. Oliguria
        ii. Hyperkalemia with serum potassium > 6.5 mEq/L
        iii. Acidemia with pH < 7.20
        iv. Blood urea nitrogen > 70 mg/dL
        v. Serum creatinine > 3.39 mg/dL
        vi. Organ edema
        vii. Other renal failure–related indication
        viii. Other non–renal failure–related indication
    c. Plan to continue RRT after discharge

Fluid Administration

1. For each intravenous fluid or blood product order between 24 hours prior to ICU admission and 30 days after ICU admission, the data, time, composition, volume, rate, location, and ordering provider will be collected. Intravenous fluids and blood products for which data will be collected will include:
    a. 0.9% sodium chloride
    b. lactated Ringer's
    c. Plasma-Lyte A®
    d. 0.45% sodium chloride
    e. 0.225% sodium chloride
    f. dextrose in water
    g. 20% and 5% albumin

h. Packed red blood cells
i. Platelets
j. Fresh frozen plasma
k. Semisynthetic colloids

8.4.3 Data at Termination

1. Date and time of:
    a. Death
    b. ICU transfer
    c. Final ICU discharge
    d. Hospital discharge
    e. Cessation of mechanical ventilation
    f. Cessation of vasopressors
    g. Cessation of renal replacement therapy

8.5 Outcome Measures

Primary Endpoint: Major Adverse Kidney Events within 30 days. The primary endpoint will be considered present if at least one of the following occur:

a. A patient dies prior to the earlier of hospital discharge or day 30
b. A patient receives new renal replacement therapy between enrollment and hospital discharge or day 30
c. A patient has persistent renal dysfunction at the earlier of hospital discharge or day 30 (persistent renal dysfunction is defined as a final inpatient serum creatinine ≥ 200% of baseline)

Secondary Endpoints:

1. In-hospital mortality before ICU discharge, before 30 days, and before 60 days
2. ICU-free days to day 28
3. Ventilator-free days to day 28
4. Vasopressor-free days to day 28
5. Renal replacement therapy-free days to day 28
6. Incidence of new RRT
7. Duration of new RRT
8. Incidence of persistent renal dysfunction
9. Incidence of Stage II or greater AKI by KDIGO creatinine criteria
10. Highest serum creatinine value
11. Change from baseline to highest serum creatinine value
12. Final serum creatinine value before hospital discharge or 30 days

13. Serum values for sodium, potassium, chloride, bicarbonate, blood urea nitrogen, and creatinine from enrollment through hospital discharge or 30 days
14. *Urinary biomarkers of pre-renal and intra-renal acute renal failure*
15. *Serum biomarkers of intravascular volume overload and acute renal failure*

Biomarkers/Specimens:

In order to try to elucidate a potential mechanism of how saline may cause renal failure and/or worse outcomes, analysis of biospecimens will be undertaken. From a select group of patients, urine and plasma that is leftover and to be discarded from the clinical laboratory after all ordered labs are performed will be collected by study personnel. All specimens will be stored frozen at -80^{0}C in a locked freezer in a locked freezer room until analysis. Collection and analysis of biospecimens will be dependent on receipt of funding.

9.0 Risks and Benefits:

For patients for whom the treating provider has ordered the administration of isotonic intravenous crystalloid, there are currently no established risks or benefits to the selection of saline versus balanced crystalloids. Whether the differences in composition have clinical implications is unknown. At this time there is no reason to believe that participation in this study would expose patients to greater medical risks or benefits than those experienced by critically ill patients receiving usual care. All of the intravenous isotonic crystalloids are used in routine care in all the Vanderbilt adult ICUs. The greater benefit of the study would be to society in the form of improved understanding of the relative effects of these commonly used intravenous solutions.

A potential risk to patients participating in this study involves the collection of personal health information. In order to limit the associated risks, the minimum amount of health information necessary for study conduct will be collected. After collection, the data will be stored in a secure online database and will be de-identified to protect participant privacy. In addition, any biospecimens collected will be stored in a secure, locked freezer in a locked room of specimen freezers.

10.0 Adverse Events:

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant administered an intervention that does not necessarily have to have a causal relationship with this treatment. An adverse event therefore can be any unfavorable and unintended sign, symptom, or disease temporally associated with the

use of an intervention, whether or not the incident is considered to be related to the intervention.

A serious adverse event (SAE) is defined as any untoward medical occurrence that meets any of the following criteria:

a. Results in death
b. Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event and NOT an event that hypothetically might have caused death if it would have been more severe)
c. Requires inpatient hospitalization
d. Prolongs an existing hospitalization
e. Results in persistent or significant disability or incapacity
f. Results in a congenital anomaly or birth defect
g. Important medical event that requires an intervention to prevent any of a-f above.

The Principal Investigator will be responsible for overseeing the safety of this trial on a daily basis. He will be available at any time for questions from the bedside nurses, who will also be monitoring the patients continuously for adverse events and serious adverse events. Serious and unexpected adverse events associated with study interventions will be recorded in a case report form in the study record and reported to the IRB within 10 business days. As critically ill adults receiving intravenous crystalloid administration are known to be at risk for numerous adverse outcomes including Major Adverse Kidney Events, death, new RRT, persistent renal dysfunction, acute kidney injury, receipt of mechanical ventilation, receipt of vasopressors, hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypochloremia, hyperchloremia, acidosis, and alkalosis, these events will be systematically recorded as study outcomes. These study outcomes will not be individually reported to the IRB as adverse events, unless the investigators or clinical team believe the event was related to the study intervention.

In addition, a Data and Safety Monitoring Board (DSMB) will be appointed to oversee the conduct of the trial. The DSMB will be comprised of two academic intensivists outside the study institution experienced in the conduct of clinical trials in critical illness. The DSMB will be available to review serious adverse events related to the study intervention in a timely manner. They will be asked to be available for rapid access by the investigators in the case of the need to evaluate serious adverse events or any other major unanticipated or safety related issues. Furthermore, in cases of serious adverse events related to the study intervention, the DSMB will have the ability to pause the trial to investigate possible safety issues and/or suggest changes to the design of the study to abrogate any safety issues.

11.0 Study Withdrawal/Discontinuation

Patients can be withdrawn from study participation in the following circumstances:

- The investigator decides that the patient should be withdrawn for safety considerations.
- There is a significant protocol violation in the judgment of the PI.

The reason and date of every withdrawal will be recorded in the study records. Follow-up will be performed for all patients who discontinue due to an adverse event or any other safety parameter. Follow-up will also be performed for all patients who end participation in the protocol for another reason, but who also have an adverse event or other safety parameter that could have led to discontinuation. Follow-up will be conducted until the condition has resolved, until diagnosis of the adverse event or safety parameter is deemed chronic and stable, or as long as clinically appropriate. This follow-up will be documented in the patient study record as well.

12.0 Statistical Considerations

Although the artificial induction of a hyperchloremic and acidemic state by infusion of chloride-rich intravenous fluids can be potentially injurious to all organ systems, kidney injury has been the primary focus of prior research comparing saline to balanced crystalloids(7). Major Adverse Kidney Events (MAKE30) is a composite outcome defined by one or more of the following: death, new use of renal replacement therapy, or persistence of renal dysfunction at hospital discharge or at 30 days (defined as a final serum creatinine ≥ 200% the baseline value) (26,27). This composite outcome focused on renal injury has been proposed as an meaningful endpoint for clinical trials as all of these outcomes are patient-centered, are well suited for an intervention that begins early in a patient's hospital course, and these outcomes have established criterion validity in their known association with other poor outcomes in patients with kidney disease such as cardiovascular disease and poor quality of life (27).

Final Sample Size Justification

(Protocol Amendment 5/10/16; Published with Statistical Analysis Plan 3/16/17)

As a cluster-randomized, multiple-crossover trial, SMART will enroll for a fixed duration to account for seasonal effects and ensure an equal number of study periods in which each study unit is assigned to each study arm. The final planned study duration is 82 unit-months over a calendar period of two years. The total number of patients enrolled will depend on the rate of admissions to study ICUs during the fixed time period of the trial.

Based on data from the study ICUs in the year prior to the trial, we anticipated that the final planned study duration of 82 unit-months would result in enrollment of around 14,000 patients with an overall rate of MAKE30 around 15%. Enrollment of 14,000 patients would provide 90% power at an alpha level of 0.05 to detect an absolute difference between the saline and balanced crystalloid groups in MAKE30 of 1.9%, a relative risk reduction of 12%. This relative risk reduction is similar to the relative risk reduction reported in prior research comparing balanced crystalloid to saline among critically ill adults.

Final Anticipated Sample Size

(Protocol Amendment 3/29/17)

As a cluster-randomized, multiple-crossover trial, SMART will enroll for a fixed duration, 82 unit-months over a calendar period of two years, and the total number of patients enrolled will depend on the rates of admissions to study ICUs during the fixed time period of the trial. The number of patients admitted to each of the participating ICUs has increased over the duration of the trial and we now anticipate at least 15,000 and no more than 16,500 patients will be enrolled during the planned study period.

Final Data Analysis Plan

(Published with Statistical Analysis Plan 3/16/17)

All analyses will be performed using R version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria). All analyses will be conducted at the level of the individual patient during an individual hospitalization in an intention-to-treat fashion unless otherwise specified. Continuous variables will be reported as mean ± standard deviation, mean and 95% confidence interval, or median and interquartile range; categorical variables as frequencies and proportions. Between-group comparisons will be made with the Mann-Whitney rank sum test for continuous variables, chi-square test for categorical variables, generalized estimating equations for repeatedly measured variables, and generalized linear mixed-effects models for analyses of the primary and secondary outcomes. A two-sided P value < 0.05 will be considered to be statistically significant. As a large, pragmatic trial enrolling every adult admitted to the five participating intensive care units, the SMART study population will contain a wide spectrum of (1) exposure to the study intervention, (2) baseline risk of the primary outcome, and (3) physiologically-distinct patient subgroups. The primary and secondary analyses evaluate the effect of the intervention overall and across the spectrum of exposure to crystalloid, baseline risk of MAKE30, and patient subgroups.

Primary Analysis

To account for the cluster-level-allocation, cluster-level-crossover structure of the trial, the primary analysis will be an intention-to-treat comparison of the primary outcome of MAKE30 between the saline and balanced crystalloid groups using a

generalized linear mixed-effects model including fixed effects (group assignment, age, gender, race, source of admission, mechanical ventilation, vasopressor receipt, diagnosis of sepsis, and diagnosis of traumatic brain injury) and random effects (intensive care unit).

Main Secondary Analysis

Anticipating (1) a wide range in the total volume of crystalloid received by study participants and (2) the potential for greater difference in outcomes between study groups among those patients who receive larger volumes of crystalloid, the main secondary analysis will compare the proportion of patients experiencing MAKE30 in the saline and balanced crystalloid groups, accounting for patients' overall volume of isotonic crystalloid received. For this analysis, we will construct a logistic regression model with MAKE30 as the outcome and independent variables of study group, total isotonic crystalloid received between enrollment and 30 days, and the interaction between the two (as a cross-product term). This will allow us to determine whether any volume of crystalloid receipt exists at which use of balanced crystalloids decreases the risk of MAKE30 compared with saline.

Given that total crystalloid receipt is a variable that emerges after enrollment, we will perform sensitivity analyses (1) using total crystalloid receipt in the 72 hours after enrollment (before incident acute kidney injury or death are likely to have affected isotonic crystalloid administration), (2) replacing the actual total crystalloid receipt with predicted total crystalloid receipt based on a multivariable linear regression model using patient and ICU characteristics available at the time of enrollment derived from crystalloid administration in the study ICUs in the year prior to the trial, and (3) comparing outcomes between study groups among a "modified intention-to-treat" population of patients who received at least 500 mL of any study crystalloid in the 72 hours after enrollment.

Additional Secondary Analyses

We will perform the following additional secondary analyses:

(1) *Comparison of secondary outcomes between study groups.*

(2) *Effect modification by severity of illness and pre-specified subgroups.* Using generalized linear mixed effects modeling, we will examine the interaction between crystalloid assignment and the following baseline variables with respect to the primary outcome of MAKE30 in the intention-to-treat population:

a. Source of admission to the ICU (Emergency department, Operating room, Transfer from another hospital, Hospital ward, Other)
b. Study ICU (Medical, Surgical, Cardiac, Neurological, Trauma). [Because cluster cannot be treated as a random effect for this subgroup, we will use logistic regression modeling]
c. Sepsis or septic shock (Yes, No)

d. Traumatic brain injury (Yes, No)
e. Receipt of mechanical ventilation (Yes, No)
f. Receipt of vasopressors (Yes, No)
g. Category of renal dysfunction at the time of enrollment (No renal dysfunction, Acute kidney injury, Chronic kidney disease, End-stage renal disease receiving RRT)
h. Risk of in-hospital mortality as predicted by baseline University HealthSystem Consortium expected in-hospital mortality (continuous variable ranging 0.0 to 1.0)

(3) *Sensitivity analysis excluding patients admitted in the week prior to a crossover ('washout').* We will repeat the primary analysis comparing MAKE30 between study groups in the intention to treat population excluding those admitted in the 7 days prior to a crossover in ICU crystalloid assignment (simulating a "washout" period). Prior data from the study ICUs suggests that less than 10% of patients remain in the ICU for longer than 7 days. Excluding those admitted within 7 days of a crossover in ICU crystalloid assignment will allow use of a baseline factor to exclude the majority of patients who would go on to experience a crossover in crystalloid assignment due to the study design.

(4) *Sensitivity analysis excluding patients who were transferred between ICUs or remained in the ICU through a crossover ('per protocol').* We will repeat the primary analysis comparing MAKE30 between study groups in the intention to treat population excluding those who remained in the intensive care unit through a crossover in crystalloid assignment or were transferred between study ICUs.

(5) *Sensitivity analysis including only each patient's first admission to a participating intensive care unit during the study period.* We will repeat the primary analysis comparing MAKE30 between study groups in the intention to treat population including only the first ICU admission in the study for each patient.

Corrections for multiple testing

All of the additional secondary analyses will be considered hypothesis-generating and no corrections for multiple comparisons will be performed.

Handling of Missing Data

Of the components of the MAKE30 primary outcome, data regarding in-hospital mortality and receipt of new renal replacement therapy are not anticipated to be missing for any patients. In contrast, the persistent renal dysfunction component of MAKE30 may suffer from missing data for serum creatinine value at baseline or between enrollment and hospital discharge. In a pilot study of 974 patients in the same hospital, 31 patients (3.2%) had no measured serum creatinine between enrollment and hospital discharge. Of these 31 patients, 6 (19.4%) died within hours of ICU admission

and qualified for the MAKE30 outcome via the in-hospital mortality criteria. The remaining 25 (80.6%) were low acuity ICU patients with a normal creatinine value measured in the 24 hours prior to ICU admission who were discharged from the hospital within 48 hours without another serum creatinine measurement. Of these, 24 had a subsequent outpatient serum creatinine value measured in the next 90 days, all of which were in the normal range. Thus, patients without a serum creatinine measurement between enrollment and hospital discharge, who do not experience in-hospital mortality or new RRT, will be classified as having not experienced the MAKE30 outcome.

With regard to missing data for baseline serum creatinine, in the same pilot study 595 of 974 patients (61.0%) had a measured serum creatinine value between 12 months and 24 hours prior to hospital admission. Of those without such a measurement, 259 of 379 (68.3%) had a value measured between 24 hours prior to hospital admission and study enrollment. Only 120 of 974 patients (12.3%) did not have an available serum creatinine value prior to enrollment. For the main analysis, patients without a measured serum creatinine value between 12 months prior to hospital admission and enrollment will have a baseline creatinine value estimated using a previously-described three-variable formula. Multiple alternative approaches to missing baseline creatinine data will be explored in sensitivity analyses including use of complete cases, multivariable single imputation, and use of the first creatinine after enrollment or the highest or lowest creatinine during the study.

Final Plan for Interim Analyses

(Protocol Amendment 5/10/16, Published with Statistical Analysis Plan 3/16/17)

With the final study duration of 82 unit-months over two calendar years, the DSMB will conduct two interim analyses. The first will occur 6 months after study initiation. The second will occur halfway between the first interim analysis and the end of the trial. Both interim analyses will use the same stopping criteria. The stopping boundary for efficacy will be met if (1) the unadjusted difference in the incidence of the primary outcome (MAKE30) between study groups is greater than or equal to 2.6% with a P value less than 0.001 AND (2) the P value is less than 0.001 for the difference between study groups in the incidence of either in-hospital mortality or receipt of new RRT. As even small differences between groups would be clinically meaningful, and given the importance of determining with as much certainty as possible whether balanced crystalloids are superior to saline, a futility stopping boundary will not be employed. Use of the conservative Haybittle-Peto boundary ($P < 0.001$) will allow the final analysis to be performed using an unchanged level of significance ($P = 0.05$).

13.0 Privacy/Confidentiality Issues

At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identifies will be collected and when such data is requisite. As quickly as feasible, all data collected will be uploaded into a password-protected computerized database maintained within a secure, web-based application for building and managing online databases. All patients will be assigned a unique study number for use in the computerized database. At the time of publication all identifiers will be removed.

14.0 Follow-up and Record Retention

The study will commence at enrollment and study intervention will last until ICU discharge. Patient clinical outcomes will be collected up until 60 days after enrollment. Identified data in the secure database will be stored for an indefinite period of time to allow for subsequent data analysis and future reference. However, all patients will be assigned a unique study number for use in the computerized database. At the time of publication, all identifiers will be removed.

15.0 References

1. Finfer S, Liu B, Taylor C, Bellomo R, Billot L, Cook D, Du B, McArthur C, Myburgh J, SAFE TRIPS Investigators. Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. *Crit Care Lond Engl*. 2010;14(5):R185. doi:10.1186/cc9293.
2. Yunos NM, Bellomo R, Story D, Kellum J. Bench-to-bedside review: Chloride in critical illness. *Crit Care Lond Engl*. 2010;14(4):226. doi:10.1186/cc9052.
3. Yunos NM, Kim IB, Bellomo R, Bailey M, Ho L, Story D, Gutteridge GA, Hart GK. The biochemical effects of restricting chloride-rich fluids in intensive care. *Crit Care Med*. 2011;39(11):2419-2424. doi:10.1097/CCM.0b013e31822571e5.
4. Smith RJ, Reid DA, Delaney EF, Santamaria JD. Fluid therapy using a balanced crystalloid solution and acid-base stability after cardiac surgery. *Crit Care Resusc J Australas Acad Crit Care Med*. 2010;12(4):235-241.
5. Wilcox CS. Regulation of renal blood flow by plasma chloride. *J Clin Invest*. 1983;71(3):726-735.
6. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg*. 2012;256(1):18-24. doi:10.1097/SLA.0b013e318256be72.
7. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA J Am Med Assoc*. 2012;308(15):1566-1572. doi:10.1001/jama.2012.13356.
8. Raghunathan K, Shaw A, Nathanson B, Stürmer T, Brookhart A, Stefan MS, Setoguchi S, Beadles C, Lindenauer PK. Association Between the Choice of IV Crystalloid and In-Hospital Mortality Among Critically Ill Adults With Sepsis. *Crit Care Med*. 2014. doi:10.1097/CCM.0000000000000305.
9. Rochwerg B, Alhazzani W, Sindi A, Heels-Ansdell D, Thabane L, Fox-Robichaud A, Mbuagbaw L, Szczeklik W, Alshamsi F, Altayyar S, Ip W-C, Li G, Wang M, Wludarczyk A, Zhou Q, Guyatt GH, Cook DJ, Jaeschke R, Annane D. Fluid Resuscitation in Sepsis: A Systematic Review and Network Meta-analysis. *Ann Intern Med*. 2014. doi:10.7326/M14-0178.
10. Dellinger RP. Crystalloids for Fluid Resuscitation in Sepsis: Where Is the Balance? *Ann Intern Med*. 2014. doi:10.7326/M14-1565.
11. Scheingraber S, Rehm M, Sehmisch C, Finsterer U. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. *Anesthesiology*. 1999;90(5):1265-1270.
12. Waters JH, Miller LR, Clack S, Kim JV. Cause of metabolic acidosis in prolonged surgery. *Crit Care Med*. 1999;27(10):2142-2146.

13. Waters JH, Gottlieb A, Schoenwald P, Popovich MJ, Sprung J, Nelson DR. Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. *Anesth Analg*. 2001;93(4):817-822.
14. Young JB, Utter GH, Schermer CR, Galante JM, Phan HH, Yang Y, Anderson BA, Scherer LA. Saline versus Plasma-Lyte A in initial resuscitation of trauma patients: a randomized trial. *Ann Surg*. 2014;259(2):255-262. doi:10.1097/SLA.0b013e318295feba.
15. Stewart PA. Modern quantitative acid-base chemistry. *Can J Physiol Pharmacol*. 1983;61(12):1444-1461.
16. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent J-L, Moreno R, Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013;41(2):580-637. doi:10.1097/CCM.0b013e31827e83af.
17. Kellum JA, Bellomo R, Kramer DJ, Pinsky MR. Etiology of metabolic acidosis during saline resuscitation in endotoxemia. *Shock Augusta Ga*. 1998;9(5):364-368.
18. Kellum JA, Song M, Li J. Lactic and hydrochloric acids induce different patterns of inflammatory response in LPS-stimulated RAW 264.7 cells. *Am J Physiol Regul Integr Comp Physiol*. 2004;286(4):R686-692. doi:10.1152/ajpregu.00564.2003.
19. Kellum JA, Song M, Venkataraman R. Effects of hyperchloremic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis. *Chest*. 2004;125(1):243-248.
20. Kellum JA. Fluid resuscitation and hyperchloremic acidosis in experimental sepsis: improved short-term survival and acid-base balance with Hextend compared with saline. *Crit Care Med*. 2002;30(2):300-305.
21. Williams EL, Hildebrand KL, McCormick SA, Bedel MJ. The effect of intravenous lactated Ringer's solution versus 0.9% sodium chloride solution on serum osmolality in human volunteers. *Anesth Analg*. 1999;88(5):999-1003.
22. Reid F, Lobo DN, Williams RN, Rowlands BJ, Allison SP. (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study. *Clin Sci Lond Engl 1979*. 2003;104(1):17-24. doi:10.1042/.
23. Wilkes NJ, Woolf R, Mutch M, Mallett SV, Peachey T, Stephens R, Mythen MG. The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. *Anesth Analg*. 2001;93(4):811-816.
24. Boldt J, Suttner S, Brosch C, Lehmann A, Röhm K, Mengistu A. The influence of a balanced volume replacement concept on inflammation, endothelial activation, and kidney integrity in elderly cardiac surgery patients. *Intensive Care Med*. 2009;35(3):462-470. doi:10.1007/s00134-008-1287-1.

25. O'Malley CMN, Frumento RJ, Hardy MA, Benvenisty AI, Brentjens TE, Mercer JS, Bennett-Guerrero E. A randomized, double-blind comparison of lactated Ringer's solution and 0.9% NaCl during renal transplantation. *Anesth Analg*. 2005;100(5):1518-1524, table of contents. doi:10.1213/01.ANE.0000150939.28904.81.
26. Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, Bihorac A, Birkhahn R, Cely CM, Chawla LS, Davison DL, Feldkamp T, Forni LG, Gong MN, Gunnerson KJ, Haase M, Hackett J, Honore PM, Hoste EA, Joannes-Boyau O, Joannidis M, Kim P, Koyner JL, Laskowitz DT, Lissauer ME, Marx G, McCullough PA, Mullaney S, Ostermann M, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care.* 2013;17:R25.
27. Palevsky PM, Molitoris BA, Okusa MD, Levin A, Waikar SS, Wald R, Chertow GM, Murray PT, Parikh CR, Shaw AD, Go AS, Faubel SG, Kellum JA, Chinchilli VM, Liu KD, Cheung AK, Weisbord SD, Chawla LS, Kaufman JS, Devarajan P, Toto RM, Hsu C-Y, Greene T, Mehta RL, Stokes JB, Thompson AM, Thompson BT, Westenfelder CS, Tumlin JA, et al. Design of clinical trials in acute kidney injury: report from an NIDDK workshop on trial methodology. *Clin J Am Soc Nephrol.* 2012. pp. 844–850.
28. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F, Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med.* 2006;145:247–254.
29. Závada J, Hoste E, Cartin-Ceba R, Calzavacca P, Gajic O, Clermont G, Bellomo R, Kellum JA, AKI6 investigators. A comparison of three methods to estimate baseline creatinine for RIFLE classification. *Nephrol Dial Transplant.* 2010;25:3911–3918.

Isotonic Solutions and Major Adverse Renal Events Trial (SMART)

Study Protocol Revision Sequence

8/21/2014 Study Protocol drafted for R01 Submission

5/13/2015 Institutional review board (IRB) review of original Study Protocol

6/1/2015 Beginning of enrollment

5/10/2016 **Amendment to Study Protocol**
(1) Study duration increased from 60 unit-months to 82 unit-months.
(2) Second interim analysis added due to increased study duration.

12/09/2016 Original Statistical Analysis Plan completed

3/16/2017 Final Statistical Analysis Plan published

3/29/2017 **Amendment to Study Protocol**
(3) Total enrollment covered by the IRB increased to accommodate higher than anticipated rate of admissions to the participating ICUs during the study period.

4/30/2017 Completion of enrollment

6/15/2017 **Amendment to Study Protocol**
(4) Final Statistical Analysis Plan (as published in *Trials*, PMID: 28302179) incorporated into the Final Study Protocol.

6/30/2017 Completion of 60-day follow-up

ISOTONIC SOLUTIONS AND MAJOR ADVERSE RENAL EVENTS TRIAL (SMART) STATISTICAL ANALYSIS PLAN

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INTRODUCTION

The administration of intravenous (IV) fluid is ubiquitous in the care of the critically ill[1]. Globally, 0.9% sodium chloride (saline) is the most common resuscitation fluid, but recent data have associated saline with hyperchloremia[2,3], metabolic acidosis and renal vasoconstriction[4,5], acute kidney injury and renal replacement therapy (RRT)[6], and increased mortality[7,8]. While several observational studies[7,9–11], a before-and-after trial[6], and meta-analyses[8,12] suggested increased rates of acute kidney injury, RRT receipt, and death with saline compared to balanced crystalloids, two recent randomized pilot trials found no difference between crystalloids in any patient outcome[13,14]. The number of patients enrolled in these pilot trials was insufficient to exclude small, but potentially clinically meaningful, differences in patient outcomes between saline and balanced crystalloids. Thus, the optimal choice of isotonic crystalloid for the treatment of critically ill adults remains unknown[15,16]. To determine the impact of balanced crystalloids compared with saline on clinical outcomes among critically ill adults, a large, prospective, controlled trial is needed[13,17].

The current trial aims to compare the effect of balanced crystalloids versus saline on the development of major adverse kidney events (the composite of death, new RRT, or persistent renal dysfunction) among intensive care unit (ICU) patients. Secondary aims are to evaluate the effect of balanced crystalloids versus saline on laboratory values (serum chloride, serum bicarbonate, serum creatinine), organ injury (acute kidney injury, receipt of RRT), and additional clinical outcomes (ventilator-free days, ICU-free days, in-hospital mortality). We hypothesize that use of balanced crystalloids among ICU patients will reduce the incidence of major adverse kidney events.

METHODS

Design

The Isotonic Solutions and Major Adverse Renal Events Trial (SMART) is a prospective, unblinded, pragmatic, cluster-level-allocation, cluster-level-crossover trial being conducted between June 1, 2015 and April 30, 2017 in five ICUs at Vanderbilt University Medical Center in Nashville, TN. SMART compares saline (0.9% sodium chloride) to balanced crystalloids (Lactated ringers and Plasma-Lyte A®) with regard to the primary outcome of Major Adverse Kidney Events within 30 days (MAKE30) – the composite of in-hospital death, receipt of new RRT, or persistent renal dysfunction (discharge creatinine ≥ 200% of baseline creatinine). Consistent with the concept of a pragmatic clinical trial[18,19], eligibility criteria are broad, the sample size is large, and study procedures are embedded into routine care and executed by clinical personnel. The trial was approved by the Vanderbilt University Medical Center Institutional Review Board (IRB) with waiver of informed consent (IRB#141349). The trial was registered with ClinicalTrials.gov prior to initiation of patient enrollment (NCT02444988; NCT02547779). An independent Data and Safety Monitoring Board (DSMB) is monitoring the progress and safety of the trial. The trial is investigator-initiated with funding provided by the Vanderbilt Institute for Clinical and Translational Research through a Clinical and Translational Science Award (CTSA) from the National Center for Advancing Translational Sciences (UL1 TR000445).

Study Sites and Period

SMART is being conducted in five academic ICUs at Vanderbilt University Medical Center: a 34-bed medical ICU, a 22-bed neurological and neurosurgical ICU, a 27-bed cardiovascular ICU, a 31-bed trauma ICU, and a 22-bed surgical ICU. Participating ICUs began enrollment sequentially over the first year of the study (Figure 1). Each ICU will enroll patients for at least 12 months and will enroll for an equal number of saline and balanced crystalloid months.

Population

All adults (age ≥ 18 years) admitted to a participating ICU at Vanderbilt University Medical Center during the study period are enrolled at the time of ICU admission. Enrolled patients who are discharged from the hospital are eligible again if they are admitted to a participating ICU again during the study period.

Consent

Saline, Lactated ringers, and Plasma-Lyte A® are all intravenous crystalloids currently used in the routine care of patients admitted to the ICUs at Vanderbilt University Medical Center. Currently, no high quality data suggest that choice of crystalloid affects clinical outcomes among critically ill adults. During the SMART trial, each time a study crystalloid is ordered, the study confirms that the treating clinician does not feel that any study crystalloid is required for the safe treatment of that specific patient at that specific point in time (see *Study Interventions*). The trial is felt to pose minimal risk because (1) exposure to the study crystalloids occurs only for patients whose treating clinician has already decided to administer an IV crystalloid, (2) all of the crystalloid solutions examined are already used in routine practice in the study environment, (3) no definitive prior data suggest clinical outcomes are better with one crystalloid relative to the others, and (4) the study confirms with every crystalloid order that the treating clinician does not feel any one crystalloid type is required for safe treatment of the patient. Given the minimal risk, the focus of the study on crystalloid use at an ICU level, and the impracticability of consenting each patient admitted to each ICU prior to the first administration of crystalloid, a waiver of informed consent was granted by the Vanderbilt institutional review board (IRB#141349).

Randomization and Allocation

Each month of the study, each ICU is assigned to either saline or balanced crystalloids. So that each ICU would experience an equal number of months assigned to saline and balanced crystalloids while minimizing monthly imbalances in the hospital's overall use of each crystalloid, we generated two sequences of study group assignment ([1] saline during odd-numbered months and balanced crystalloid during

even-numbered months; [2] balanced crystalloid during odd-numbered months and saline during even-numbered months) and planned for three ICUs to be assigned to one sequence and the remaining two ICUs to the opposite sequence. To facilitate the early administration of the assigned crystalloid in the ED and operating room prior to the patient's physical arrival in the ICU, a single computer-generated, simple randomization was performed in which the three ICUs that admit the majority of patients from the ED (medical ICU, trauma ICU, and surgical ICU) were randomized 'en bloc' to one sequence of crystalloid group assignments and the two ICUs that admit the majority of patients from the operating room (neurological ICU and cardiac ICU) were randomized 'en bloc' to the opposite sequence of crystalloid group assignments (Figures 1-2).

Concealment and Blinding

As available laboratory values overtly reflect the crystalloid being used and prior studies have shown high levels of provider awareness of crystalloid assignment despite attempts at blinding[13], patients, clinicians, and investigators are not blinded to crystalloid assignment. All study data, including the objective primary outcome, will be electronically extracted from the medical record in an automated manner unaffected by study group assignment.

Study Interventions

Study protocol determines only the choice of intravenous isotonic crystalloid: 0.9% sodium chloride (saline group) versus the treating clinician's preference of Lactated Ringer's solution or Plasma-Lyte A® (balanced crystalloid group). Composition of each crystalloid solution is displayed in Table E1. Lactated Ringer's and Plasma-Lyte A® are the balanced crystalloids commonly available in the United States[20]. Lactated Ringer's and Plasma-Lyte A® both offer a significantly lower chloride content than saline, but other minor differences in composition lead some clinicians to prefer one balanced crystalloid or the other for particular patients (e.g., some clinicians prefer Plasma-Lyte A® over Lactated Ringer's for patients receiving blood transfusion)[21]. Allowing clinicians to select either Lactated Ringer's or Plasma-Lyte A® when a balanced crystalloid is assigned is anticipated to improve compliance

with balanced crystalloid assignment and emulate how balanced crystalloids are used in practice while maintaining relevant comparator groups consisting of crystalloid with a higher chloride content (saline) versus crystalloids with a lower chloride content (Lactated Ringer's and Plasma-Lyte A®). Decisions regarding crystalloid rate, volume, and additive content are deferred to treating clinicians.

Delivery of the assigned crystalloid to patients occurs via interventions in pharmacy supply and clinician order entry. Each month, the dispensing cabinets within the ICUs are stocked with 1000-mL bags of the assigned crystalloid. Additionally, any order for intravenous crystalloid for a patient located in a study ICU triggers an advisor application within the electronic order entry system. The advisor application informs providers about the study, asks about relative contraindications to the assigned crystalloid, and (if relative contraindications are not present) guides providers to order the assigned crystalloid. Accepted relative contraindications for patients assigned to balanced crystalloid include (1) "hyperkalemia" and (2) "brain injury". The severity of "hyperkalemia" and "brain injury" at which saline will be used in favor of balanced crystalloids is determined by the treating clinician. The non-assigned crystalloid is also made available via the pharmacy if a formal statement is submitted that the attending physician feels the non-assigned crystalloid is required for the safe treatment of a specific patient.

Although the study focuses on crystalloid use in the ICU, crystalloid administration prior to ICU admission in the emergency department or operating room may introduce contamination and limit separation between study arms. Therefore, between January 1, 2016 and April 30, 2017, the Vanderbilt University Medical Center Emergency Department (ED) is coordinating their crystalloid use with the medical, surgical, and trauma ICUs such that patients admitted to those units from the ED begin receiving the assigned crystalloid during evaluation and management in the ED (NCT02614040). Clinical outcomes of patients treated with study crystalloids in the ED and hospitalized outside the ICU will be recorded and reported separately. Similarly, to the extent that is logistically feasible, for patients identified in the operating room as coming from or being admitted to one of the participating ICUs, the request is made that they receive the fluid assigned to the corresponding ICU during their operative

procedure. Fluid administered prior to enrollment by the emergency medical system and outside hospitals, and fluid administered after discharge from the ICU, is not controlled by the study.

Each day patients receive the crystalloid to which their ICU is currently assigned. The necessity that an intravenous crystalloid be clinically available at all times precluded the use of washout periods and patients who remain in the ICU through a crossover (i.e., from one calendar month to another) may potentially be exposed to both types of crystalloid. Although this introduces the potential for contamination of study groups, in a pilot trial at the same institution, the total volume of non-assigned crystalloid administered due to the lack of a washout period was less than 125 mL per patient[14]. As described in the *Statistical Analysis* section below, patients will be analyzed in the group to which they were assigned at the time of study enrollment in an intention-to-treat fashion (e.g., a patient admitted to an ICU during a month assigned to saline will be analyzed in the saline group even if that patient remains in the ICU after the ICU switches assignment to balanced crystalloids).

Data Collection

This pragmatic trial uses data collected via routine clinical care and electronically extracted from the electronic health record (EHR). All data are stored confidentially in an institutional patient data management system. Data collected include: pre-study renal function; demographic characteristics, admitting location and diagnosis, and severity of illness at enrollment; receipt of intravenous crystalloids, other fluids, and blood products; serum electrolyte and creatinine values; receipt of RRT, mechanical ventilation, and vasopressors; and vital status and serum creatinine at hospital discharge. Electronic extraction of these data from the EHR has been previously validated against the reference standard of two-physician manual chart review[22]. For all patients who receive new RRT, study personnel will perform manual chart review to confirm the absence of prior RRT and identify the indication for RRT.

Primary Outcome

The primary outcome will be the proportion of patients meeting one or more criteria for Major Adverse Kidney Events within the 30 days after enrollment (MAKE30): in-hospital mortality, receipt of new RRT, or persistent renal dysfunction defined as a final inpatient serum creatinine value ≥ 200% of baseline[22–24]. In-hospital mortality will be defined as death from any cause prior to hospital discharge censored at 30 days after ICU admission. Receipt of new RRT will be defined as receipt of any modality of RRT between ICU admission and the first of hospital discharge or 30 days, among patients not known to have received RRT prior to ICU admission. Persistent renal dysfunction will be defined as a final serum creatinine value before hospital discharge (censored at 30 days after enrollment) ≥ 200% of the baseline creatinine value. The value for baseline serum creatinine will be determined using a previously-described hierarchical approach[22]. The lowest serum creatinine between 12 months and 24 h prior to hospital admission will be used when available. If no such creatinine value is available, the lowest creatinine value between 24 h prior to hospital admission and the time of ICU admission will be used. If no creatinine value is available between 12 months prior to hospital admission and the time of ICU admission, a baseline creatinine value will be estimated using a previously-described formula [creatinine = 0.74 − 0.2 (if female) + 0.08 (if African American) + 0.003 × age (in years)][25]. Patients known to have received RRT prior to enrollment will be considered ineligible to meet criteria for new RRT or persistent renal dysfunction, but may qualify for MAKE30 by experiencing in-hospital mortality.

Secondary Outcomes

Secondary outcomes will include additional clinical outcomes, additional renal outcomes, and biochemical outcomes. Additional clinical outcomes will include in-hospital mortality before ICU discharge, before 30 days, and before 60 days; ICU-free days, ventilator-free days, vasopressor-free days, and RRT-free days, all through 28 days after enrollment. Additional renal outcomes will include new RRT receipt, persistent renal dysfunction, stage II or greater AKI by Kidney Disease Improving Global Outcomes (KDIGO) creatinine criteria[26], highest serum creatinine value, change from

baseline creatinine to highest creatinine, final serum creatinine value before hospital discharge, and duration of new RRT. Biochemical outcomes will include serum values for sodium, potassium, chloride, bicarbonate, blood urea nitrogen, and creatinine from enrollment through day 30.

Power Calculation

Based on data from the study ICUs in the year prior to the trial, we anticipate the planned study duration (Figure 1) will result in enrollment of around 14,000 patients with an overall rate of MAKE30 around 15%. Enrollment of 14,000 patients will provide 90% power at an alpha level of 0.05 to detect an absolute difference between the saline and balanced crystalloid groups in MAKE30 of 1.9%, a relative risk reduction of 12%, which is comparable to the 12% relative risk reduction for in-hospital mortality reported in a recent pilot trial[13] (additional details in the Appendix 3).

Data and Safety Monitoring Board and Interim Analysis

A Data and Safety Monitoring Board (DSMB) was appointed to oversee the conduct of the trial and review two interim analyses. The DSMB is comprised of two academic intensivists outside the study institution experienced in the conduct of clinical trials in critical illness. The first interim analysis occurred six months after study initiation, examining patients enrolled between June 1, 2015 and November 30, 2015. The second interim analysis occurred halfway between the first interim analysis and the end of the trial, examining patients enrolled between June 1, 2015 and July 31, 2016 (additional details in the Appendix 4). Both interim analyses used the same stopping criteria: "*The stopping boundary for efficacy will be met if (1) the unadjusted difference in the incidence of the primary outcome (MAKE30) between study groups is greater than or equal to 2.6% with a P value less than 0.001 AND (2) the P value is less than 0.001 for the difference between study groups in the incidence of either in-hospital mortality or receipt of new RRT. As even small differences between groups would be clinically meaningful, and given the importance of determining with as much certainty as possible whether balanced crystalloids are superior to saline, a futility stopping boundary will not be employed. Use of the conservative Haybittle-Peto boundary (P <*

0.001) will allow the final analysis to be performed using an unchanged level of significance (P = 0.05)." At the time of this submission, both interim analyses have been completed and the DSMB has recommended continuing the trial to completion.

In addition, the DSMB is available to evaluate adverse events or serious adverse events during the conduct of the trial. In cases of serious adverse events, the DSMB has the ability to pause the trial to investigate possible safety issues and suggest changes to the design of the study to abrogate any safety issues.

Statistical Analysis Principles

All analyses will be performed using R version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria). To maximize transparency and reproducibility, a complete version of the R code that will be used to analyze the final study data is available in Additional File 1. This ensures that (1) statistical reviewers or external investigators will be able to replicate the pre-specified analysis of the trial independently and (2) any changes or additions to the statistical analysis introduced by investigators or reviewers after completion of enrollment will be evident as differences between the pre-specified code and the analysis code included with the final publication.

All analyses will be conducted at the level of the individual patient during an individual hospitalization in an intention-to-treat fashion unless otherwise specified. Continuous variables will be reported as mean ± standard deviation, mean and 95% confidence interval, or median and interquartile range; categorical variables as frequencies and proportions. Between-group comparisons will be made with the Mann-Whitney rank sum test for continuous variables, chi-square test for categorical variables, generalized estimating equations for repeatedly measured variables, and generalized linear mixed-effects models for analyses of the primary and secondary outcomes. A two-sided P value < 0.05 will be considered to be statistically significant.

Analytic Rationale

As a large, pragmatic trial enrolling every adult admitted to the five participating intensive care units, the SMART study population will contain a wide spectrum of (1) exposure to the study intervention, (2) baseline risk of the primary outcome, and (3)

physiologically-distinct patient subgroups. The primary and secondary analyses evaluate the effect of the intervention overall and across the spectrum of exposure to crystalloid, baseline risk of MAKE30, and patient subgroups.

Primary Analysis

To account for the cluster-level-allocation, cluster-level-crossover structure of the trial, the primary analysis will be an intention-to-treat comparison of the primary outcome of MAKE30 between the saline and balanced crystalloid groups using a generalized linear mixed-effects model including fixed effects (group assignment, age, gender, race, source of admission, mechanical ventilation, vasopressor receipt, diagnosis of sepsis, and diagnosis of traumatic brain injury) and random effects (intensive care unit)[27,28].

In preparation for SMART, we electronically collected the same set of variables that would be used to analyze SMART from the records of all 11,582 patients admitted to the study ICUs between January 1, 2014 and December 31, 2014. With the data on MAKE30 from the 11,582 patients admitted in the year before the trial, using generalized linear mixed-effects modeling treating the five ICUs as clusters and the 12 months as periods, we calculated the intra-cluster correlation coefficient to be 0.142, the intra-period correlation coefficient to be 0.026, and the intra-cluster intra-period correlation coefficient to be <0.001.

Using the data from the 11,582 patients admitted in the year before the trial, we performed a series of simulated trials evaluating a variety of trial conditions and potential results including: (1) outcome differences between groups ranging from no difference to a 50% relative risk reduction, (2) heterogeneity of treatment effect by cluster, (3) change in the incidence of the outcome in the control group over the course of the trial, (4) varying levels of intra-cluster correlation, and (5) varying levels of intra-period correlation. In each case the generalized linear mixed-effect model appeared to adequately account for the correlation between participants. Analysis using generalized linear mixed-effects modeling and generalized estimating equations accounting for the same variables produced identical odds ratios and 95% confidence intervals for the difference between the simulated groups in the primary outcome.

Main Secondary Analysis

Anticipating (1) a wide range in the total volume of crystalloid received by study participants and (2) the potential for greater difference in outcomes between study groups among those patients who receive larger volumes of crystalloid, the main secondary analysis will compare the proportion of patients experiencing MAKE30 in the saline and balanced crystalloid groups, accounting for patients' overall volume of isotonic crystalloid received. For this analysis, we will construct a logistic regression model with MAKE30 as the outcome and independent variables of study group, total isotonic crystalloid received between enrollment and 30 days, and the interaction between the two (as a cross-product term). This will allow us to determine whether any volume of crystalloid receipt exists at which use of balanced crystalloids decreases the risk of MAKE30 compared with saline.

Given that total crystalloid receipt is a variable that emerges after enrollment, we will perform sensitivity analyses (1) using total crystalloid receipt in the 72 hours after enrollment (before incident acute kidney injury or death are likely to have affected isotonic crystalloid administration), (2) replacing the actual total crystalloid receipt with predicted total crystalloid receipt based on a multivariable linear regression model using patient and ICU characteristics available at the time of enrollment derived from crystalloid administration in the study ICUs in the year prior to the trial, and (3) comparing outcomes between study groups among a "modified intention-to-treat" population of patients who received at least 500 mL of any study crystalloid in the 72 hours after enrollment.

Additional Secondary Analyses

We will perform the following additional secondary analyses:

(1) *Comparison of secondary outcomes between study groups.*

(2) *Effect modification by severity of illness and pre-specified subgroups.* Using generalized linear mixed effects modeling, we will examine the interaction between crystalloid assignment and the following baseline variables with respect to the primary outcome of MAKE30 in the intention-to-treat population:

a. Source of admission to the ICU (Emergency department, Operating room, Transfer from another hospital, Hospital ward, Other)
b. Study ICU (Medical, Surgical, Cardiac, Neurological, Trauma). [Because cluster cannot be treated as a random effect for this subgroup, we will use logistic regression modeling]
c. Sepsis or septic shock (Yes, No)
d. Traumatic brain injury (Yes, No)
e. Receipt of mechanical ventilation (Yes, No)
f. Receipt of vasopressors (Yes, No)
g. Category of renal dysfunction at the time of enrollment (No renal dysfunction, Acute kidney injury, Chronic kidney disease, End-stage renal disease receiving RRT)
h. Risk of in-hospital mortality as predicted by baseline University HealthSystem Consortium expected in-hospital mortality (continuous variable ranging 0.0 to 1.0)

(3) Sensitivity analysis excluding patients admitted in the week prior to a crossover ('washout'). We will repeat the primary analysis comparing MAKE30 between study groups in the intention to treat population excluding those admitted in the 7 days prior to a crossover in ICU crystalloid assignment (simulating a "washout" period). Prior data from the study ICUs suggests that less than 10% of patients remain in the ICU for longer than 7 days[14]. Excluding those admitted within 7 days of a crossover in ICU crystalloid assignment will allow use of a baseline factor to exclude the majority of patients who would go on to experience a crossover in crystalloid assignment due to the study design.

(4) Sensitivity analysis excluding patients who were transferred between ICUs or remained in the ICU through a crossover ('per protocol'). We will repeat the primary analysis comparing MAKE30 between study groups in the intention to treat population excluding those who remained in the intensive care unit through a crossover in crystalloid assignment or were transferred between study ICUs.

(5) Sensitivity analysis including only each patient's first admission to a participating intensive care unit during the study period. We will repeat the primary analysis

comparing MAKE30 between study groups in the intention to treat population including only the first ICU admission in the study for each patient.

Corrections for multiple testing

All of the additional secondary analyses will be considered hypothesis-generating and no corrections for multiple comparisons will be performed.

Handling of Missing Data

Of the components of the MAKE30 primary outcome, data regarding in-hospital mortality and receipt of new renal replacement therapy are not anticipated to be missing for any patients[14,22]. In contrast, the persistent renal dysfunction component of MAKE30 may suffer from missing data for serum creatinine value at baseline or between enrollment and hospital discharge. In a pilot study of 974 patients in the same hospital, 31 patients (3.2%) had no measured serum creatinine between enrollment and hospital discharge[14]. Of these 31 patients, 6 (19.4%) died within hours of ICU admission and qualified for the MAKE30 outcome via the in-hospital mortality criteria. The remaining 25 (80.6%) were low acuity ICU patients with a normal creatinine value measured in the 24 hours prior to ICU admission who were discharged from the hospital within 48 hours without another serum creatinine measurement. Of these, 24 had a subsequent outpatient serum creatinine value measured in the next 90 days, all of which were in the normal range. Thus, patients without a serum creatinine measurement between enrollment and hospital discharge, who do not experience in-hospital mortality or new RRT, will be classified as having not experienced the MAKE30 outcome.

With regard to missing data for baseline serum creatinine, in the same pilot study 595 of 974 patients (61.0%) had a measured serum creatinine value between 12 months and 24 hours prior to hospital admission[14]. Of those without such a measurement, 259 of 379 (68.3%) had a value measured between 24 hours prior to hospital admission and study enrollment. Only 120 of 974 patients (12.3%) did not have an available serum creatinine value prior to enrollment. For the main analysis, patients without a measured serum creatinine value between 12 months prior to hospital

admission and enrollment will have a baseline creatinine value estimated using a previously-described three-variable formula[29]. Multiple alternative approaches to missing baseline creatinine data will be explored in sensitivity analyses including use of complete cases, multivariable single imputation, and use of the first creatinine after enrollment or the highest or lowest creatinine during the study (see Appendix 5).

Post hoc analyses.

In the event that investigators or reviewers introduce analyses in addition to those described above, these will be clearly delimitated as *post hoc* and will be considered hypothesis-generating.

PRESENTATION OF THE RESULTS

After completion of enrollment and data analysis, the results of the trial will be communicated to the public through manuscript publication and submission of the results to clinicaltrials.gov. Submission for publication will include public access to the full study protocol and statistical code. Authorship will be based on the International Committee of Medical Journal Editors guidelines and professional writers will not be used.

The flow of patients through the study will be presented in a flow diagram (Figure 2). Baseline characteristics will be presented by treatment group, as shown in Table 1 and Table E2. The volume of isotonic crystalloid administered, other fluids, and blood products administered over time will be presented by treatment group (Table E3). Serum values for sodium, potassium, chloride, bicarbonate, blood urea nitrogen, and creatinine will be presented in figures displaying serum values over time by group and in tables detailing the incidence of abnormal values (Table E4). Clinical and renal outcomes will be reported by treatment group, as shown in Table 2. For the primary analysis of the primary outcome, we will present the unadjusted frequency and proportion of MAKE30 in each study group as well as the adjusted odds ratio, 95% confidence interval, and *P* value derived from the generalized linear mixed-effects model. Indications for new renal replacement therapy will be displayed as in Table E5. Heterogeneity of treatment effect analyses will be displayed as loess curves or partial

effect plots for continuous variables and forest plots for categorical variables.

DISCUSSION

Upon completion, SMART will provide the most comprehensive data to date on the comparative effects of saline versus balanced crystalloids among critically ill adults. Given that isotonic crystalloid administration represents the most common intervention provided to hospitalized patients, saline and balanced crystalloids are the only available options for isotonic crystalloid administration, and the relationship between saline and acute kidney injury and death remains unclear, the results of SMART will have immediate implications for the care of a broad population of acutely ill patients. Results showing superior clinical outcomes in the balanced crystalloids group would provide compelling evidence that balanced solutions should be considered the preferred isotonic crystalloid for most acutely ill patients. Better clinical outcomes with saline would cement 0.9% sodium chloride as the first line isotonic intravenous fluid and end the current debate about optimal crystalloid composition. In this comparative effectiveness trial of thousands of critically ill adults, a finding of no difference between groups would still have important implications for clinical care and future research. In a trial powered to detect absolute risk reductions as small as 2% in clinical outcomes, no difference between groups would imply that the effect of crystalloid choice for the majority of ICU patients is minimal and any future research would need to focus on select subpopulations.

While designing SMART, we weighed the relative advantages and disadvantages of multiple study designs, including a blinded, patient-level randomized trial. A major challenge to controlled studies of fluid administration in critical illness is the ability to enroll patients prior to the period of highest fluid exposure. As the majority of fluid is administered as part of resuscitation in the emergency department and first 12 hours of ICU admission, we selected a cluster-level-allocation design that would allow enrollment immediately upon presentation and coordination between study ICUs and the emergency department to maximize exposure to the assigned crystalloid and minimize exposure to the non-assigned crystalloid. By basing study group assignment at the unit level, we ensured delivery of the assigned crystalloid even among unstable patients for

whom fluid was being administered immediately upon presentation, since the assigned crystalloid would be the fluid most readily available in the study unit. The enrollment of all adults admitted to the participating ICUs examines the effects of saline versus balanced crystalloids in a real-world, clinical environment improving the generalizability of the study findings. Coupling group assignment at the level of the ICU with relatively short periods (one month) and frequent crossovers (at least eleven in each unit) balances baseline characteristics and co-interventions better than a simple cluster-randomized trial or before-after trial with the same number of units, decreasing confounding by seasonal change or trends in usual care over time. Although blinding of treating clinicians and study personnel to the assigned intervention would be ideal, a prior pilot trial of the same topic found high rates of provider awareness of crystalloid assignment despite blinding, perhaps due to the overt effect of the study crystalloids on clinically available laboratory values such as serum chloride and bicarbonate[13]. Use of an objective, patient-centered primary outcome abstracted automatically from the EHR increases the pragmatic nature of the design and diminishes the risk of observer bias.

Several potential threats to the validity of our trial exist. Including all patients admitted to each study ICU may produce a patient population with limited average exposure to the study interventions[13,14]. Based on our preliminary data from the same units prior to this study, however, we anticipate that more than 90% of enrolled patients will receive isotonic crystalloid and at least 25% of patients will receive more than 4 liters of isotonic crystalloid, which is comparable or greater than that received in prior positive ICU fluid trials[30]. Additionally, we have pre-specified analyses to evaluate for a ‘dose-response’ relationship between the volume of isotonic crystalloid administered and clinical outcomes with saline vs balanced crystalloid. Similarly, the broad enrollment criteria may produce a study population at relatively low risk for adverse clinical outcomes. The anticipated incidence of the primary outcome of 15%, however, is comparable to that of other large ICU fluid management trials[30,31]. Treating clinicians are aware of study group assignment which may permit a treatment bias in which clinicians administer less isotonic crystalloid and/or more non-isotonic crystalloids when assigned to one of the fluid groups. For this reason, we will record

and report not only use of isotonic crystalloid but non-isotonic crystalloid, colloid, and blood product during the trial. Group assignment at the level of the cluster with multiple cluster-level crossovers introduces the possibility for intra-cluster correlation, inter-period correlation, and intra-cluster intra-period correlation which may confound the relationship between group assignment and clinical outcome. In preparatory analyses using data from more than 10,000 patients admitted in the year prior to the trial, we have found the effect of intra-cluster correlation to be minimized by the short periods and frequent crossovers and the effects of intra-period correlation and intra-cluster intra-period correlation to be small. Our primary analysis uses a generalized linear mixed-effects model to account for these aspects of the study structure. In the absence of a washout period, there will be carryover of crystalloid administration from one group assignment into the other, but based on pilot data we anticipate the volume of non-assigned crystalloid received as a result of carryover will be low[14], and we pre-specify secondary analyses to address the effects of carryover. Finally, although MAKE30 is a recommended outcome for clinical trials involving AKI[23,32], use of a composite outcome presents potential challenges. Unlike death and new receipt of renal replacement therapy, whether persistent renal dysfunction on hospital discharge is a patient-centered outcome remains a point of discussion. Persistent renal dysfunction also relies on the availability of serum creatinine measurements at baseline and before hospital discharge – potentially requiring imputation of missing data for one component of the composite primary outcome. Perhaps most importantly, although death, new receipt of renal replacement therapy, and persistent renal dysfunction are weighted equally in the MAKE30 composite outcome, they a may not represent equivalent outcomes to patients or providers. To address this we will provide data on the MAKE30 outcome overall and each of its separate components.

TRIAL STATUS

In summary, SMART is an ongoing pragmatic cluster-level-allocation, cluster-level-crossover trial that will compare saline to balanced crystalloids with regard to major adverse kidney events among critically ill adults. Patient enrollment began June 1, 2015, and enrollment is scheduled for completion on April 30, 2017.

LIST OF ABBREVIATIONS

CTSA	Clinical and Translational Science Award
CONSORT	Consolidated Standards of Reporting Trials
dL	deciliter
DSMB	data and safety monitoring board
ED	emergency department
EHR	electronic health record
IRB	institutional review board
ICU	intensive care unit
IV	intravenous
KDIGO	Kidney Disease Improving Global Outcomes
L	liter
MAKE30	Major Adverse Kidney Event by Day 30
mg	milligram
ml	milliliter
RRT	renal replacement therapy
SMART	Isotonic Solutions and Major Adverse Renal Events Trial

DECLARATIONS

Ethics Approval and Consent to Participate: The trial was approved by the Vanderbilt University Medical Center Institutional Review Board (IRB) with waiver of informed consent (IRB#141349).

Availability of Data and Material: A file containing the de-identified data needed to replicate the primary analysis will be submitted as a supporting file at the time of submission of the main manuscript for the trial. The complete dataset developed during the current study will be available from the corresponding author upon reasonable request.

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Authors' contributions:

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Acquisition of data: M.W.S., J.P.W., J.M.E.

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Drafting of the initial manuscript: M.W.S., L.W., T.W.R.

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M.W.S., L.W., D.W.B., and T.W.R. will have complete access to the final trial dataset.

REFERENCES

1. Finfer S, Liu B, Taylor C, Bellomo R, Billot L, Cook D, et al. Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. Crit. Care Lond. Engl. 2010;14:R185.

2. Yunos NM, Kim IB, Bellomo R, Bailey M, Ho L, Story D, et al. The biochemical effects of restricting chloride-rich fluids in intensive care. Crit. Care Med. 2011;39:2419–24.

3. Smith RJ, Reid DA, Delaney EF, Santamaria JD. Fluid therapy using a balanced crystalloid solution and acid-base stability after cardiac surgery. Crit. Care Resusc. J. Australas. Acad. Crit. Care Med. 2010;12:235–41.

4. Wilcox CS. Regulation of renal blood flow by plasma chloride. J. Clin. Invest. 1983;71:726–35.

5. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann. Surg. 2012;256:18–24.

6. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA J. Am. Med. Assoc. 2012;308:1566–72.

7. Raghunathan K, Shaw A, Nathanson B, Stürmer T, Brookhart A, Stefan MS, et al. Association Between the Choice of IV Crystalloid and In-Hospital Mortality Among Critically Ill Adults With Sepsis. Crit. Care Med. 2014;

8. Rochwerg B, Alhazzani W, Sindi A, Heels-Ansdell D, Thabane L, Fox-Robichaud A, et al. Fluid Resuscitation in Sepsis: A Systematic Review and Network Meta-analysis. Ann. Intern. Med. 2014;

9. Shaw AD, Raghunathan K, Peyerl FW, Munson SH, Paluszkiewicz SM, Schermer CR. Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS. Intensive Care Med. 2014;40:1897–905.

10. Shaw AD, Bagshaw SM, Goldstein SL, Scherer LA, Duan M, Schermer CR, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. Ann. Surg. 2012;255:821–9.

11. Sen A, Keener CM, Sileanu FE, Foldes E, Clermont G, Murugan R, et al. Chloride Content of Fluids Used for Large-Volume Resuscitation Is Associated With Reduced Survival. Crit. Care Med. 2016;

12. Krajewski ML, Raghunathan K, Paluszkiewicz SM, Schermer CR, Shaw AD. Meta-analysis of high- versus low-chloride content in perioperative and critical care fluid resuscitation. Br. J. Surg. 2015;102:24–36.

13. Young P, Bailey M, Beasley R, Henderson S, Mackle D, McArthur C, et al. Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit: The SPLIT Randomized Clinical Trial. JAMA. 2015;1–10.

14. Semler MW, Wanderer JP, Ehrenfeld JM, Stollings JL, Self WH, Siew ED, et al. Balanced Crystalloids versus Saline in the Intensive Care Unit: The SALT Randomized Trial. Am. J. Respir. Crit. Care Med. 2016;

15. Young P. Saline Is the Solution for Crystalloid Resuscitation. Crit. Care Med. 2016;44:1538–40.

16. Semler MW, Rice TW. Saline Is Not the First Choice for Crystalloid Resuscitation Fluids. Crit. Care Med. 2016;44:1541–4.

17. Dellinger RP. Crystalloids for Fluid Resuscitation in Sepsis: Where Is the Balance? Ann. Intern. Med. 2014;

18. Ware JH, Hamel MB. Pragmatic trials--guides to better patient care? N. Engl. J. Med. 2011;364:1685–7.

19. Noto MJ, Domenico HJ, Byrne DW, Talbot T, Rice TW, Bernard GR, et al. Chlorhexidine bathing and health care-associated infections: a randomized clinical trial. JAMA. 2015;313:369–78.

20. Myburgh JA, Mythen MG. Resuscitation fluids. N. Engl. J. Med. 2013;369:1243–51.

21. Lorenzo M, Davis JW, Negin S, Kaups K, Parks S, Brubaker D, et al. Can Ringer's lactate be used safely with blood transfusions? Am. J. Surg. 1998;175:308–10.

22. Semler MW, Rice TW, Shaw AD, Siew ED, Self WH, Kumar AB, et al. Identification of Major Adverse Kidney Events Within the Electronic Health Record. J. Med. Syst. 2016;40:167.

23. Palevsky PM, Molitoris BA, Okusa MD, Levin A, Waikar SS, Wald R, et al. Design of clinical trials in acute kidney injury: report from an NIDDK workshop on trial methodology. Clin. J. Am. Soc. Nephrol. CJASN. 2012;7:844–50.

24. Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit. Care Lond. Engl. 2013;17:R25.

25. Závada J, Hoste E, Cartin-Ceba R, Calzavacca P, Gajic O, Clermont G, et al. A comparison of three methods to estimate baseline creatinine for RIFLE classification. Nephrol. Dial. Transplant. Off. Publ. Eur. Dial. Transpl. Assoc. - Eur. Ren. Assoc. 2010;25:3911–8.

26. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney inter.

2012;2(Suppl):8.

27. Parienti J-J, Kuss O. Cluster-crossover design: a method for limiting clusters level effect in community-intervention studies. Contemp. Clin. Trials. 2007;28:316–23.

28. Turner RM, White IR, Croudace T, PIP Study Group. Analysis of cluster randomized cross-over trial data: a comparison of methods. Stat. Med. 2007;26:274–89.

29. Zavada J, Hoste E, Cartin-Ceba R, Calzavacca P, Gajic O, Clermont G, et al. A comparison of three methods to estimate baseline creatinine for RIFLE classification. Nephrol. Dial. Transplant. 2010;25:3911–8.

30. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N. Engl. J. Med. 2012;367:1901–11.

31. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N. Engl. J. Med. 2004;350:2247–56.

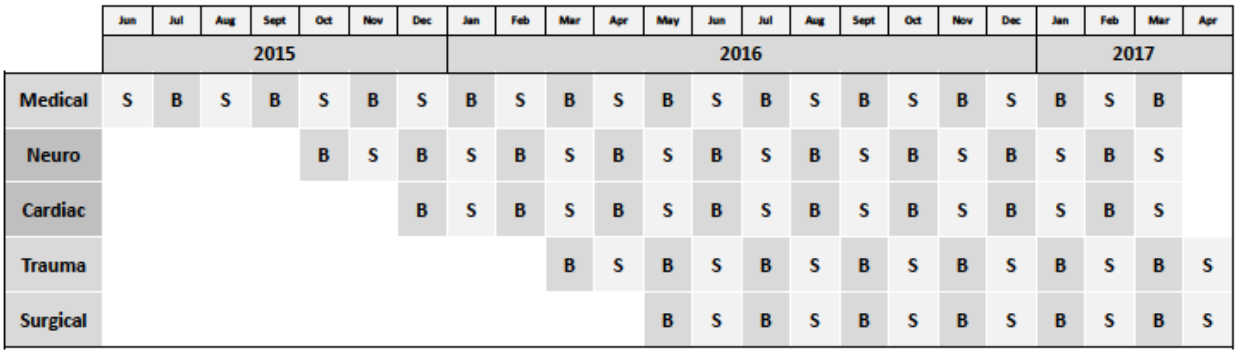
32. Weisbord SD, Gallagher M, Kaufman J, Cass A, Parikh CR, Chertow GM, et al. Prevention of contrast-induced AKI: a review of published trials and the design of the prevention of serious adverse events following angiography (PRESERVE) trial. Clin. J. Am. Soc. Nephrol. CJASN. 2013;8:1618–31.

33. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann. Intern. Med. 2009;150:604–12.

FIGURES

Figure 1.

Crystalloid assignment during the trial. During each month of the study, each ICU is assigned to use either 0.9% saline (S) or balanced crystalloids (B).

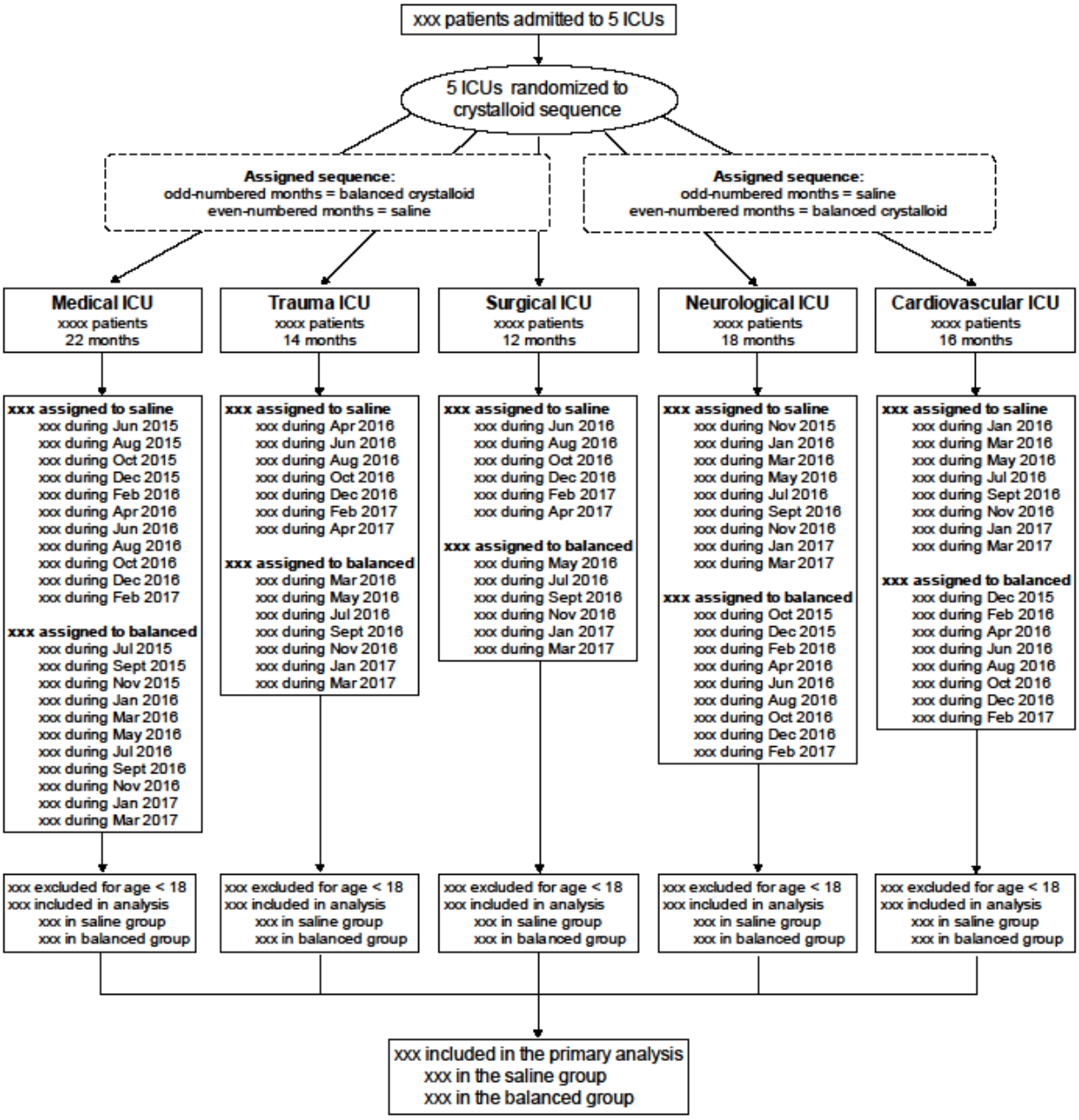


	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr
	2015							2016												2017			
Medical	S	B	S	B	S	B	S	B	S	B	S	B	S	B	S	B	S	B	S	B	S	B	
Neuro					B	S	B	S	B	S	B	S	B	S	B	S	B	S	B	S	B	S	
Cardiac							B	S	B	S	B	S	B	S	B	S	B	S	B	S	B	S	
Trauma										B	S	B	S	B	S	B	S	B	S	B	S	B	S
Surgical												B	S	B	S	B	S	B	S	B	S	B	S

Figure 2.

Flow diagram of the progress of patients through the trial.

ICU = intensive care unit.



TABLES

Table 1. Patient characteristics at baseline.

Patient Characteristics	Saline (n =)	Balanced (n =)
Age, median [IQR], years	--	--
Men, No. (%)	--	--
Caucasian, No. (%)	--	--
Weight, median [IQR], kg	--	--
Body mass index, median [IQR], kg/m^2	--	--
Renal comorbidities, No. (%)		
Chronic kidney disease, stage III or greater	--	--
Prior renal replacement therapy receipt	--	--
Source of admission to ICU, No. (%)		
Emergency department	--	--
Transfer from another hospital	--	--
Hospital ward	--	--
Another ICU within the hospital	--	--
Operating room	--	--
Outpatient	--	--
Study ICU, No. (%)		
Medical	--	--
Surgical	--	--
Cardiac	--	--
Neuro	--	--
Trauma	--	--
Admitting diagnosis, No. (%)	--	--
Sepsis or septic shock	--	--
Traumatic brain injury		
Mechanical ventilation, No. (%)	--	--
Vasopressors, No. (%)	--	--
UHC expected mortality, mean (95% CI), %	--	--
Serum creatinine, median [IQR], mg/dL		
Lowest in 12 months prior to hospitalization	--	--
No. (%) of patients	--	--
Lowest between hospitalization and ICU admission	--	--
No. (%) of patients	--	--
Estimated by three-variable formula	--	--
No. (%) of patients	--	--
Study baseline	--	--
Acute kidney injury, stage II or greater	--	--

Table 2. Clinical Outcomes.

Outcome	Saline (n =)	Balanced (n =)	Adjusted OR (95% CI)	Adjusted *P* Value
Primary Outcome				
Major Adverse Kidney Event within 30 days, No. (%)	--	--	--	--
Secondary Clinical Outcomes				
In-hospital mortality, No. (%)				
Before ICU discharge	--	--	--	--
Before 30 days	--	--	--	--
Before 60 days	--	--	--	--
ICU-free days, median [IQR]	--	--	--	--
Mean ± SD	--	--		
Ventilator-free days, median [IQR]	--	--	--	--
Mean ± SD	--	--		
Vasopressor-free days, median [IQR]	--	--	--	--
Mean ± SD	--	--		
Renal replacement therapy-free days, median [IQR]	--	--	--	--
Mean ± SD	--	--		
Secondary Renal Outcomes				
Serum creatinine, mg/dL				
Highest before discharge or day 30, median [IQR], mg/dL	--	--	--	--
Change from baseline to highest value, median [IQR], mg/dL	--	--	--	--
Final value before discharge or 30 days, median [IQR], mg/dL	--	--	--	--
Among survivors, median [IQR], mg/dL	--	--	--	--
Final creatinine > 200% baseline, No. (%)	--	--	--	--
Among survivors to hospital discharge	--	--	--	--
Among survivors to hospital discharge without new RRT	--	--	--	--
Acute kidney injury, stage II or greater, No. (%)	--	--	--	--
Developing after enrollment	--	--	--	--
Receipt of new renal replacement therapy, No. (%)	--	--	--	--
Duration of in-hospital receipt, median [IQR], days	--	--	--	--
Continued receipt after hospital discharge, No. (%)	--	--	--	--

SUPPLEMENTAL TABLES

Table E1. Composition of the study fluids.

	Sodium	Potassium	Calcium	Magnesium	Chloride	Acetate	Lactate	Gluconate	Osmolarity
Plasma	135–145	4.5–5.0	2.2–2.6	0.8–1.0	94–111		1–2		275–295
0.9% saline	154				154				308
Lactated Ringer's	130	4.0	2.7		109		28		273
Plasma-Lyte A®	140	5.0		3.0	98	27		23	294

All values are in mEq/L except calculated osmolarity, which is in mOsm/L. 0.9% saline is "Sodium Chloride Injection, USP", Lactated Ringer's is "Lactated Ringer's Injection, USP", and Plasma-Lyte A® is "Multiple Electrolyte Injection, Type 1, USP", all from Baxter Healthcare Corporation in Deerfield, IL, USA.

Table E2. Elixhauser comorbidity index.

	Saline	Balanced
Comorbidity, No. (%)	**(n =)**	**(n =)**
Congestive heart failure	--	--
Cardiac arrhythmias	--	--
Valvular disease	--	--
Pulmonary circulation disorders	--	--
Hypertension, uncomplicated	--	--
Hypertension, complicated	--	--
Paralysis	--	--
Other neurological disorders	--	--
Chronic pulmonary disease	--	--
Diabetes, uncomplicated	--	--
Diabetes, complicated	--	--
Hypothyroidism	--	--
Renal failure	--	--
Liver disease	--	--
Peptic ulcer disease excluding bleeding	--	--
Acquired immunodeficiency syndrome	--	--
Lymphoma	--	--
Metastatic cancer	--	--
Solid tumor without metastasis	--	--
Rheumatoid arthritis / collagen vascular disease	--	--
Coagulopathy	--	--
Obesity	--	--
Weight loss	--	--
Fluid and electrolyte disorders	--	--
Blood loss anemia	--	--
Deficiency anemias	--	--
Alcohol abuse	--	--
Drug abuse	--	--
Psychoses	--	--
Depression	--	--

Table E3. Intravenous fluids and blood products.

	Saline	Balanced Crystalloid	
	(n =)	(n =)	*P* value
0.9% sodium chloride, median [IQR]; mean ± SD, mL			
Prior to enrollment on Day 0	--	--	--
Cumulative volume from enrollment through day 3	--	--	--
Cumulative volume from enrollment through day 7	--	--	--
Cumulative volume from enrollment through day 14	--	--	--
Cumulative volume from enrollment through day 30	--	--	--
Cumulative volume from enrollment through ICU transfer	--	--	--
Prior to an ICU crossover in fluid assignment	--	--	--
After an ICU crossover in fluid assignment	--	--	--
Cumulative volume from ICU transfer to hospital discharge	--	--	--
Lactated Ringer's, median [IQR]; mean ± SD, mL			
Prior to enrollment on Day 0	--	--	--
Cumulative volume from enrollment through day 3	--	--	--
Cumulative volume from enrollment through day 7	--	--	--
Cumulative volume from enrollment through day 14	--	--	--
Cumulative volume from enrollment through day 30	--	--	--
Cumulative volume from enrollment through ICU transfer	--	--	--
Cumulative volume from ICU transfer to hospital discharge	--	--	--
Plasma-Lyte A®, median [IQR]; mean ± SD, mL			
Prior to enrollment on Day 0	--	--	--
Cumulative volume from enrollment through day 3	--	--	--
Cumulative volume from enrollment through day 7	--	--	--
Cumulative volume from enrollment through day 14	--	--	--
Cumulative volume from enrollment through day 30	--	--	--
Cumulative volume from enrollment through ICU transfer	--	--	--
Cumulative volume from ICU transfer to hospital discharge	--	--	--
Balanced crystalloid, median [IQR]; mean ± SD, mL			
Prior to enrollment on Day 0	--	--	--
Cumulative volume from enrollment through day 3	--	--	--
Cumulative volume from enrollment through day 7	--	--	--
Cumulative volume from enrollment through day 14	--	--	--
Cumulative volume from enrollment through day 30	--	--	--
Cumulative volume from enrollment through ICU transfer	--	--	--
Prior to an ICU crossover in fluid assignment	--	--	--
After an ICU crossover in fluid assignment	--	--	--
Cumulative volume from ICU transfer to hospital discharge	--	--	--
"Hypotonic" crystalloid, median [IQR]; mean ± SD, mL			
Prior to enrollment on Day 0	--	--	--
Cumulative volume from enrollment through day 3	--	--	--
Cumulative volume from enrollment through day 7	--	--	--

Cumulative volume from enrollment through day 14	--	--	--
Cumulative volume from enrollment through day 30	--	--	--
Cumulative volume from enrollment through ICU transfer	--	--	--
Cumulative volume from ICU transfer to hospital discharge	--	--	--
Human albumin solutions, median [IQR]; mean ± SD, mL			
Prior to enrollment on Day 0	--	--	--
Cumulative volume from enrollment through day 3	--	--	--
Cumulative volume from enrollment through day 7	--	--	--
Cumulative volume from enrollment through day 14	--	--	--
Cumulative volume from enrollment through day 30	--	--	--
Cumulative volume from enrollment through ICU transfer	--	--	--
Cumulative volume from ICU transfer to hospital discharge	--	--	--
Blood products, median [IQR]; mean ± SD, mL			
Prior to enrollment on Day 0	--	--	--
Cumulative volume from enrollment through day 3	--	--	--
Cumulative volume from enrollment through day 7	--	--	--
Cumulative volume from enrollment through day 14	--	--	--
Cumulative volume from enrollment through day 30	--	--	--
Cumulative volume from enrollment through ICU transfer	--	--	--
Cumulative volume from ICU transfer to hospital discharge	--	--	--

Table E4. Serum laboratory values.

	Saline	Balanced	
Laboratory value	**(n =)**	**(n =)**	***P* value**
Serum sodium, mmol/L			
Highest between enrollment and day 30, median [IQR]	--	--	--
Lowest between enrollment and day 30, median [IQR]	--	--	--
>145 between enrollment and day 30, No. (%)	--	--	--
< 135 between enrollment and day 30, No. (%)	--	--	--
Serum potassium, mmol/L			
Highest between enrollment and day 30, median [IQR]	--	--	--
Lowest between enrollment and day 30, median [IQR]	--	--	--
> 5.0 between enrollment and day 30, No. (%)	--	--	--
< 3.0 between enrollment and day 30, No. (%)	--	--	--
Serum chloride, mmol/L			
Highest between enrollment and day 30, median [IQR]	--	--	--
Lowest between enrollment and day 30, median [IQR]	--	--	--
> 110 between enrollment and day 30, No. (%)	--	--	--
< 90 between enrollment and day 30, No. (%)	--	--	--
Serum bicarbonate, mmol/L			
Highest between enrollment and day 30, median [IQR]	--	--	--
Lowest between enrollment and day 30, median [IQR]	--	--	--
> 30 between enrollment and day 30, No. (%)	--	--	--
< 20 between enrollment and day 30, No. (%)	--	--	--

Table E5. Indications for new renal replacement therapy.

	Saline	Balanced	
Indication, No. (%)	**(n =)**	**(n =)**	***P* Value**
Oliguria	--	--	--
Hyperkalemia with serum potassium > 6.5 mEq/L	--	--	--
Acidemia with pH < 7.20	--	--	--
Blood urea nitrogen > 70 mg/dL	--	--	--
Serum creatinine > 3.39 mg/dL	--	--	--
Organ edema	--	--	--
Other renal failure–related indication	--	--	--
Other non–renal failure–related indication	--	--	--

Appendix 1: The SMART Investigators

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American Society of Health-System Pharmacists, Bethesda, MD – Seth Strawbridge (Clinical Informatics).

*Denotes members of the Writing Committee.

Appendix 2: Denifitions of Study Variables

Fluids

Intravenous fluid – For the SMART study, intravenous fluid will be defined as the intravenous administration of any formulation of any volume at any rate of 0.9% sodium chloride, Lactated Ringer's, Plasma-Lyte A®; 0.45% sodium chloride, 0.225% sodium chloride, dextrose in water, 20% or 5% human albumin solution, gelatins, dextrans, or hydroxyethyl starches. This will include fluid given as a bolus, fluid given as maintenance infusions, fluid given as flushes, fluid given as 'piggy-back' infusions for IV medications, fluid given through pressure-bag systems, fluid given as a part of thermodilution of pulmonary artery catheters, and fluid given to maintain the patency of peripheral venous access. This will not include carrier fluid for medications and oral fluids.

Isotonic crystalloid – For the SMART study, the term isotonic crystalloid will be used to refer to any of 0.9% sodium chloride, Lactated Ringer's, or Plasma-Lyte A®. Use of the term isotonic crystalloid is intended to distinguish these three fluids from colloid solutions and from significantly hypotonic (0.45% sodium chloride) or hypertonic (3% sodium chloride) crystalloid solutions, rather than to imply that the tonicities of 0.9% sodium chloride, Lactated Ringer's, or Plasma-Lyte A® are precisely comparable to extracellular fluid.

Saline – Saline will refer to 0.9% sodium chloride.

Balanced Crystalloid – For the SMART study, Lactated Ringer's or Plasma-Lyte A® will be referred to as balanced crystalloids.

Renal Function

Baseline serum creatinine – The value for baseline serum creatinine will be determined in a hierarchical approach. The lowest serum creatinine between 12 months

and 24 h prior to hospital admission will be used when available. If no such creatinine value is available, the lowest creatinine value between 24 h prior to hospital admission and the time of ICU admission will be used. If no creatinine value is available between 12 months prior to hospital admission and the time of ICU admission, a baseline creatinine value will be estimated using a previously-described three-variable formula [creatinine = 0.74 − 0.2 (if female) + 0.08 (if African American) + 0.003 × age (in years)][25].

Acute kidney injury, stage II or greater – Stage II or greater acute kidney injury will be defined according to Kidney Disease Improving Global Outcomes (KDIGO) creatinine criteria[26] as a creatinine value between enrollment and the first of hospital discharge or 30 days at least 200% of the baseline value OR both (1) greater than 4.0 mg/dL and (2) increased at least 0.3 mg/dL from baseline. Patients may have acute kidney injury present at the time of first creatinine measurement after enrollment (prevalent AKI) or acute kidney injury developing during the study (incident AKI). Incident AKI will be defined as any creatinine value between enrollment and discharge or 30 days that is (1) increased at least 0.3 mg/dL from a preceding post-enrollment value AND (2) at least 200% of the baseline value, at least 200% of a preceding post-enrollment value, or at least 4.0 mg/dL.

Chronic kidney disease stage III or greater – Chronic kidney disease stage III or greater will be defined as a glomerular filtration rate less than 60 ml/min per 1.73 m^2 as calculated by the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation[33] using the patient's baseline creatinine value.

Outcomes

Major Adverse Kidney Events within 30 days (MAKE30). The MAKE30 composite outcome will be considered to have occurred when patients meet one or more of the following criteria in the 30 days after enrollment: (1) in-hospital mortality, (2) receipt of new renal replacement therapy (RRT), or (3) persistent renal dysfunction. Patients who

have received RRT prior to enrollment will be ineligible to meet the new RRT or persistent renal dysfunction criteria but will remain eligible to meet criteria for in-hospital mortality.

In-hospital mortality – In-hospital mortality will be defined as death from any cause prior to hospital discharge censored at 30 days after ICU admission (30-day in-hospital mortality).

Receipt of new renal replacement therapy – Receipt of new RRT will be defined as receipt of any modality of RRT between ICU admission and the first of (1) hospital discharge or (2) 30 days in a patient not known to have received RRT prior to ICU admission.

Persistent renal dysfunction – Persistent renal dysfunction will be defined as a final serum creatinine value before hospital discharge (censored at 30 days after enrollment) that is ≥
200% of the baseline creatinine value.

ICU-free days – Intensive care unit-free days to day 28 (ICU-free days) will be defined as the number of days from the time of the patient's physical transfer out of the ICU until day 28 after enrollment. Patients who die prior to day 28 after enrollment will receive a value of 0 for ICU-free days. Patients who are never transferred out of the ICU prior to day 28 after enrollment will receive a value of 0 for ICU-free days. Patients who are transferred out of the ICU, return to the ICU, and are not subsequently transferred out of the ICU again before day 28 after enrollment will receive a value of 0 for ICU-free days. For patients who are transferred out of the ICU, are readmitted to the ICU, and are subsequently transferred out of the ICU again prior to day 28 after enrollment, ICU-free days will be awarded based on the time of the final transfer out of the ICU prior to day 28 after enrollment.

Ventilator-free days – Ventilator-free days to day 28 (VFDs) will be defined as the

number of days from the time of initiating unassisted breathing until day 28 after enrollment. Patients who die prior to day 28 after enrollment will receive a value of 0 for VFDs. Patients who never achieve unassisted breathing prior to day 28 after enrollment will receive a value of 0 for VFDs. Patients who achieve unassisted breathing, return to assisted breathing, and do not again achieve unassisted breathing before day 28 after enrollment will receive a value of 0 for VFDs. For patients who achieve unassisted breathing, return to assisted breathing, and subsequently achieve unassisted breathing again prior to day 28 after enrollment, VFDs will be awarded based on the time of the final initiation of unassisted breathing prior to day 28 after enrollment. Survivors who never experience assisted breathing will receive 28 VFDs.

Vasopressor-free days – Vasopressor-free days to day 28 will be defined as the number of days from the time of vasopressor cessation until day 28 after enrollment. Patients who die prior to day 28 after enrollment will receive a value of 0 for vasopressor-free days. Patients who never cease to receive vasopressors prior to day 28 after enrollment will receive a value of 0 for vasopressor-free days. Patients who achieve vasopressor cessation, return to receiving vasopressors, and do not again achieve vasopressor cessation before day 28 after enrollment will receive a value of 0 for vasopressor-free days. For patients who achieve vasopressor cessation, return to receiving vasopressors, and subsequently achieve cessation of vasopressors again prior to day 28 after enrollment, vasopressor-free days will be awarded based on the time of the final cessation of vasopressors prior to day 28 after enrollment. Survivors who never receive vasopressors will receive 28 vasopressor-free days.

Renal replacement therapy-free days – Renal replacement therapy-free days to day 28 (RRT-free days) will be defined as the number of days from the time the final RRT treatment until day 28 after enrollment. Patients who die prior to day 28 after enrollment will receive a value of 0 for RRT-free days. Patients who continue to receive RRT through day 28 after enrollment will receive a value of 0 for RRT-free days. Patients who achieve RRT cessation, return to receiving RRT, and do not again achieve RRT cessation before day 28 after enrollment will receive a value of 0 for RRT-free days.

For patients who achieve RRT cessation, return to receiving RRT, and subsequently achieve cessation of RRT again prior to day 28 after enrollment, RRT-free days will be awarded based on the time of the final RRT treatment prior to day 28 after enrollment. Survivors who never receive RRT will receive 28 RRT-free days.

Appendix 3: Sample Size Estimation and Re-estimation

Initial Sample Size Justification (Initial Protocol)

In clinical practice, the use of balanced intravenous fluids instead of chloride-rich fluids is an intervention with no increased cost and both types of fluids are equally available to the practitioner. Therefore any difference between treatment groups is clinically meaningful in regards to the MAKE30 primary endpoint. In previous studies using the MAKE30 composite endpoint in critically ill patients, the development of this endpoint occurred at a rate of 22%. SMART-MED is anticipated to enroll between 3,000 and 3,600 patients over the one year study period. Barring logistical difficulties, SMART-SURG is anticipated to enroll between 5,000 and 6,500 patients over the one year study period. Enrollment of 8,000 patients in the SMART study overall would allow detection of a difference of 2.6% in the incidence of the primary endpoint with 80% power using a type I error of 0.05.

Revised Sample Size Justification (Protocol Revision 5/10/16)

The initial protocol called for a study duration of 12 months in 5 units (60 unit-months) based on an anticipated MAKE30 event rate of 22.0%. This event rate was based on prior observational data[24], but was not specific to the study institution.

We have subsequently conducted a pilot trial in the medical ICU and examined a small amount of observational data regarding the incidence of MAKE30 in the non-medical ICUs. These data suggest (1) variation in the rate of MAKE30 between ICUs and (2) an overall rate of MAKE30 in the range of 15-17%, lower than anticipated in our initial power calculation. In order to retain adequate power to detect a relative risk reduction in the initially specified range, we plan to increase the duration of the study to include a total of 82 unit-months over a calendar period of two years.

Based on data from the year prior we anticipate the total enrollment in SMART to be around 14,000 and the overall rate of MAKE30 to be around 15%, resulting in a detectible absolute risk reduction of 1.9% or relative risk reduction of 12%. The largest prior trial of saline versus balanced crystalloids reported a point estimate for the relative risk reduction in favor of balanced crystalloids of 12%[13].

Appendix 4: Interim Analyses

Interim Analysis (Initial Protocol)

Enrollment will occur over an expected one year period in which all Vanderbilt ICUs are randomly assigned to one month blocks of alternating balanced fluids only or 0.9% saline only. Blocks will be only one month in length to minimize the effect of seasonal variability.

Thirty days after the conclusion of the sixth month of the study, the DSMB will review one interim analysis to determine if further study is warranted. The stopping boundary for efficacy will be met if (1) the difference in the incidence of the primary outcome (MAKE30) between groups is greater than or equal to 2.6% with a p value less than 0.001 AND (2) the p value is less than 0.001 for either death or new renal replacement therapy. As even small differences between groups would be clinically meaningful and given the importance to determine with as much certainty as possible whether balanced fluids are superior to chloride-rich fluids, there will not be a futility stopping boundary.

Interim Analyses (Protocol Revision 5/10/16)

With the initial trial duration scheduled for 12 months in 5 ICUs (60 ICU-months), we planned for a single interim analysis by the DSMB 6 months after trial initiation. As part of the amendment to increase the duration of the study to 82 ICU-months over almost two calendar years, the DSMB will conduct a second interim analysis midway between the initial interim analysis and the revised study stop date. This second interim analysis will include all patients enrolled through July 31st 2016 and will use the same stopping criteria as used the first interim analysis. Specifically, the stopping boundary for efficacy will be met if (1) the difference in the incidence of the primary outcome (MAKE30) between groups is greater than or equal to 2.6% with a p value less than 0.001 AND (2) the p value is less than 0.001 for either death or new renal replacement therapy. As even small differences between groups would be clinically meaningful and given the importance to determine with as much certainty as possible whether balanced fluids are superior to chloride-rich fluids, there will not be a futility stopping boundary.

Appendix 5: Handling of Missing Baseline Serum Creatinine Values

For patients without a measured serum creatinine between 12 months prior to hospital admission and enrollment, baseline creatinine value for the primary analysis will be estimated using a previously-described three-variable formula [creatinine = 0.74 − 0.2 (if female) + 0.08 (if African American) + 0.003 × age (in years)][25]. Multiple sensitivity analyses will employ alternative approaches to estimating missing baseline creatinine values:

1) A 'complete cases' analysis will be performed in which patients without a measured creatinine value between 12 months prior to hospital admission and enrollment will be excluded.
2) Missing baseline serum creatinine values will be imputed by multivariable single imputation using the R function aregImpute in Hmisc package with 5 imputations. The imputation model will include age, gender, race, group assignment, source of admission, primary diagnosis, receipt of mechanical ventilation, vasopressor receipt, prior hemodialysis, total fluids received in 30 days, UHC expected mortality, overall mortality, new RRT received, minimum creatinine value, maximum creatinine value, and final study creatinine value. Continuous variables will be transformed via cubic splines with 3 to 5 knots.
3) Simple imputation will be performed in which first serum creatinine value after enrollment is used as the baseline creatinine.
4) Simple imputation will be performed in which the highest serum creatinine value between enrollment and 30 days is used as the baseline creatinine.
5) Simple imputation will be performed in which the lowest serum creatinine value between enrollment and 30 days is used as the baseline creatinine.

Statistical Analysis Plan Publication

The Statistical Analysis Plan described in this document represents the final Statistical Analysis Plan for the SMART trial, and supersedes any prior versions. Any analyses not contained in this document that are performed by investigators or requested by reviewers will be considered *post hoc*. This Statistical Analysis Plan was:

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Trials

STUDY PROTOCOL Open Access

Balanced crystalloids versus saline in the intensive care unit: study protocol for a cluster-randomized, multiple-crossover trial

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Abstract

Background: Saline, the intravenous fluid most commonly administered to critically ill adults, contains a high chloride content, which may be associated with acute kidney injury and death. Whether using balanced crystalloids rather than saline decreases the risk of acute kidney injury and death among critically ill adults remains unknown.

Methods: The Isotonic Solutions and Major Adverse Renal Events Trial (SMART) is a pragmatic, cluster-level allocation, cluster-level crossover trial being conducted between 1 June 2015 and 30 April 2017 in five intensive care units at Vanderbilt University Medical Center in Nashville, TN, USA. SMART compares saline (0.9% sodium chloride) with balanced crystalloids (clinician's choice of lactated Ringer's solution or Plasma-Lyte A®). Each intensive care unit is assigned to provide either saline or balanced crystalloids each month, with the assigned crystalloid alternating monthly over the course of the trial. All adults admitted to participating intensive care units during the study period are enrolled and followed until hospital discharge or 30 days after enrollment. The anticipated enrollment is approximately 14,000 patients. The primary outcome is Major Adverse Kidney Events within 30 days—the composite of in-hospital death, receipt of new renal replacement therapy, or persistent renal dysfunction (discharge creatinine ≥200% of baseline creatinine). Secondary clinical outcomes include in-hospital mortality, intensive care unit-free days, ventilator-free days, vasopressor-free days, and renal replacement therapy-free days. Secondary renal outcomes include new renal replacement therapy receipt, persistent renal dysfunction, and incidence of stage 2 or higher acute kidney injury.

Discussion: This ongoing pragmatic trial will provide the largest and most comprehensive comparison to date of clinical outcomes with saline versus balanced crystalloids among critically ill adults.

Trial registration: For logistical reasons, SMART was prospectively registered separately for the medical ICU (SMART-MED; ClinicalTrials.gov identifier: NCT02444988; registered on 11 May 2015; date of first patient enrollment: 1 June 2015) and the nonmedical ICUs (SMART-SURG; ClinicalTrials.gov identifier: NCT02547779; registered on 9 September 2015; date of first patient enrollment: 1 October 2015).

Keywords: Intravenous fluids, Crystalloid, Saline, Renal failure, Pragmatic trial

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Background

The administration of intravenous (IV) fluid is ubiquitous in the care of the critically ill [1]. Globally, 0.9% sodium chloride (saline) is the most common resuscitation fluid, but recent data have associated saline with hyperchloremia [2, 3], metabolic acidosis and renal vasoconstriction [4, 5], acute kidney injury (AKI) and renal replacement therapy (RRT) [6], and increased mortality [7, 8]. Although several observational studies [7, 9–11], a before-and-after trial [6], and meta-analyses [8, 12] suggested increased rates of AKI, RRT receipt, and death with saline compared with balanced crystalloids, researchers in two recent randomized pilot trials found no difference between crystalloids in any patient outcome [13, 14]. The number of patients enrolled in these pilot trials was insufficient to exclude small but potentially clinically meaningful differences in patient outcomes between saline and balanced crystalloids. Thus, the optimal choice of isotonic crystalloid for the treatment of critically ill adults remains unknown [15, 16]. To determine the impact of balanced crystalloids compared with saline on clinical outcomes among critically ill adults, a large, prospective, controlled trial is needed [13, 17].

The aim of the present trial is to compare the effect of balanced crystalloids with that of saline on the development of major adverse kidney events (the composite of death, new RRT, or persistent renal dysfunction) among intensive care unit (ICU) patients. Secondary aims are to evaluate the effect of balanced crystalloids with that of saline on laboratory values (serum chloride, serum bicarbonate, serum creatinine), organ injury (AKI, receipt of RRT), and additional clinical outcomes (ventilator-free days, ICU-free days, in-hospital mortality). We hypothesize that use of balanced crystalloids among ICU patients will reduce the incidence of major adverse kidney events.

Methods

This manuscript was written in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (see SPIRIT checklist in Additional file 1 and Fig. 1) [18].

Design

The Isotonic Solutions and Major Adverse Renal Events Trial (SMART) is a prospective, unblinded, pragmatic, cluster-level allocation, cluster-level crossover trial being conducted between 1 June 2015 and 30 April 2017 in five ICUs at Vanderbilt University Medical Center in Nashville, TN, USA. SMART compares saline (0.9% sodium chloride) with balanced crystalloids (lactated Ringer's solution and Plasma-Lyte A® [Baxter Healthcare, Deerfield, IL, USA]) with regard to the primary outcome of Major Adverse Kidney Events within 30 days (MAKE30)—the composite of in-hospital death, receipt of new RRT, or persistent renal dysfunction (discharge creatinine ≥200% of baseline creatinine). Consistent with the concept of a pragmatic clinical trial [19, 20], the eligibility criteria are broad, the sample size is large, and study procedures are embedded into routine care and executed by clinical personnel. The trial was approved by the Vanderbilt University Medical Center Institutional Review Board (IRB) with waiver of informed consent (IRB 141349). The trial was registered with ClinicalTrials.gov prior to initiation of patient enrollment (ClinicalTrials.gov identifiers: NCT02444988, NCT02547779). An independent data and safety monitoring board (DSMB) is monitoring the progress and safety of the trial. The trial is investigator-initiated with funding provided by the Vanderbilt Institute for Clinical and Translational Research through a Clinical and Translational Science Award from the National Center for Advancing Translational Sciences (UL1 TR000445).

Study sites and period

SMART is being conducted in five academic ICUs at Vanderbilt University Medical Center: a 34-bed medical ICU, a 22-bed neurological and neurosurgical ICU, a 27-bed cardiovascular ICU, a 31-bed trauma ICU, and a 22-bed surgical ICU. Participating ICUs began enrollment sequentially over the first year of the study (Fig. 2). Each ICU will enroll patients for at least 12 months and will enroll participants for an equal number of saline and balanced crystalloid months.

Population

All adults (aged ≥18 years) admitted to a participating ICU at Vanderbilt University Medical Center during the study period are enrolled at the time of ICU admission. Enrolled patients who are discharged from the hospital are eligible again if they are admitted to a participating ICU again during the study period.

Consent

Saline, lactated Ringer's solution, and Plasma-Lyte A® are all IV crystalloids currently used in the routine care of patients admitted to the ICUs at Vanderbilt University Medical Center. Currently, no high-quality data suggest that choice of crystalloid affects clinical outcomes among critically ill adults. During the SMART trial, each time a study crystalloid is ordered, the study confirms that the treating clinician does not feel that a specific study crystalloid is required for the safe treatment of that specific patient at that specific point in time (see

	STUDY PERIOD						
	Enrolment & Allocation	On-study					Termination
TIMEPOINT**	ICU admission	ICU day 1	ICU day 2	ICU day 3	ICU txfr	Ward	30 days after enrollment
ENROLMENT:	X						
Eligibility screen	X						
Allocation	X						
INTERVENTIONS:							
Balanced crystalloids	←	—	—	—	→		
Screening for contraindications	X	X	X	X	X		
0.9% saline	←	—	—	—	→		
Screening for contra-indications	X	X	X	X	X		
ASSESSMENTS:							
Baseline variables	X						
Intravenous fluid receipt		X	X	X	X	X	
Serum electrolytes and creatinine		X	X	X	X	X	
Receipt of invasive support		X	X	X	X	X	
Clinical outcomes							X

Baseline variables include: pre-study renal function; demographic characteristics, admitting location and diagnosis, and severity of illness at enrollment. Intravenous fluid receipt includes: receipt of intravenous crystalloids, other fluids, and blood products. Receipt of invasive support includes: receipt of RRT, mechanical ventilation, and vasopressors. Clinical outcomes include: vital status, ongoing receipt of RRT, and serum creatinine at hospital discharge.

Fig. 1 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist. Enrollment, interventions, and assessments. *ICU* Intensive care unit

Study interventions section below). The trial is felt to pose minimal risk because (1) exposure to the study crystalloids occurs only for patients whose treating clinician has already decided to administer an IV crystalloid, (2) all of the crystalloid solutions examined are already used in routine practice in the study environment, (3) no definitive prior data suggest clinical outcomes are better with one crystalloid relative to the others, and (4) the study confirms with every crystalloid order that the treating clinician does not feel any one crystalloid type is required for safe treatment of the patient. Given the minimal risk, the focus of the study on crystalloid use at an ICU level, as well as the impracticability of consenting each patient admitted to each ICU prior to the first administration of crystalloid, a waiver of informed consent was granted by the Vanderbilt University Medical Center IRB (IRB 141349).

Randomization and allocation

During each month of the study, each ICU is assigned to either saline or balanced crystalloids. So that each ICU would experience an equal number of months assigned to saline and balanced crystalloids while minimizing monthly imbalances in the hospital's overall use of each crystalloid, we generated two sequences of study group assignment: (1) saline during odd-numbered months and balanced crystalloid during even-numbered months or (2) balanced crystalloid during odd-numbered months and saline during even-numbered months. We planned for three ICUs to be assigned to one sequence and the remaining two ICUs to the opposite sequence. To facilitate the early administration of the assigned crystalloid in the ED and operating room prior to the patient's physical arrival in the ICU, a single, computer-generated, simple randomization was performed in which the three ICUs that admit the majority of patients from the ED (medical ICU, trauma ICU, and surgical ICU) were randomized en bloc to one sequence of crystalloid group assignments, and the two ICUs that admit the majority of patients from the operating room (neurological ICU and cardiac ICU) were randomized en bloc to the opposite sequence of crystalloid group assignments (Figs. 2 and 3).

Concealment and blinding

Because available laboratory values overtly reflect the crystalloid being used, and because prior studies have

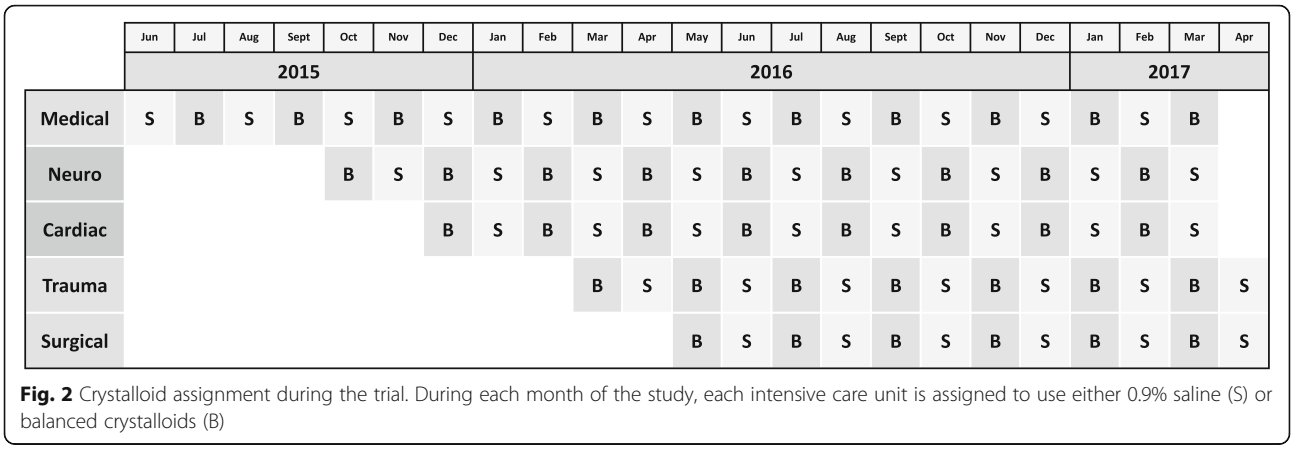

Fig. 2 Crystalloid assignment during the trial. During each month of the study, each intensive care unit is assigned to use either 0.9% saline (S) or balanced crystalloids (B)

shown high levels of provider awareness of crystalloid assignment despite attempts at blinding [13], patients, clinicians, and investigators are not blinded to crystalloid assignment. All study data, including the objective primary outcome, will be electronically extracted from the medical record in an automated manner unaffected by study group assignment.

Study interventions

Study protocol determines only the choice of IV isotonic crystalloid: 0.9% sodium chloride (saline group) versus the treating clinician's preference of lactated Ringer's solution or Plasma-Lyte A® (balanced crystalloid group). The composition of each crystalloid solution is displayed in Additional file 2: Table S1. Lactated Ringer's solution and Plasma-Lyte A® are the balanced crystalloids commonly available in the United States [21]. Lactated Ringer's solution and Plasma-Lyte A® both offer a significantly lower chloride content than saline, but other minor differences in composition lead some clinicians to prefer one balanced crystalloid or the other for particular patients; for example, some clinicians prefer Plasma-Lyte A® over lactated Ringer's solution for patients receiving blood transfusions [22]. Allowing clinicians to select either lactated Ringer's solution or Plasma-Lyte A® when a balanced crystalloid is assigned is anticipated to improve compliance with balanced crystalloid assignment and emulate how balanced crystalloids are used in practice while maintaining relevant comparator groups consisting of crystalloid with a higher chloride content (saline) versus crystalloids with a lower chloride content (lactated Ringer's solution and Plasma-Lyte A®). Decisions regarding crystalloid rate, volume, and additive content are deferred to treating clinicians.

Delivery of the assigned crystalloid to patients occurs via interventions in pharmacy supply and clinician order entry. Each month, the dispensing cabinets within the ICUs are stocked with 1000-ml bags of the assigned crystalloid. Additionally, any order for IV crystalloid for a patient located in a study ICU triggers an advisor application within the electronic order entry system. The advisor application informs providers about the study, asks about relative contraindications to the assigned crystalloid, and (if relative contraindications are not present) guides providers to order the assigned crystalloid. Accepted relative contraindications for patients assigned to balanced crystalloid include hyperkalemia and brain injury. The severity of hyperkalemia and brain injury at which saline will be used in favor of balanced crystalloids is determined by the treating clinician. The nonassigned crystalloid is also made available via the pharmacy if a formal statement is submitted that the attending physician feels the nonassigned crystalloid is required for the safe treatment of a specific patient.

Although the study is focused on crystalloid use in the ICU, crystalloid administration prior to ICU admission in the emergency department (ED) or operating room may introduce contamination and limit separation between study arms. Therefore, between 1 January 2016 and 30 April 2017, the Vanderbilt University Medical Center ED is coordinating their crystalloid use with the medical, surgical, and trauma ICUs such that patients admitted to those units from the ED begin receiving the assigned crystalloid during evaluation and management in the ED (ClinicalTrials.gov identifier: NCT02614040). Clinical outcomes of patients treated with study crystalloids in the ED and hospitalized outside the ICU will be recorded and reported separately. Similarly, to the extent that it is logistically feasible, for patients identified in the operating room as coming from or being admitted to one of the participating ICUs, the request is made that they receive the fluid assigned to the corresponding ICU during their operative procedure. Fluid administered prior to enrollment by the emergency medical system and outside hospitals, as well as fluid administered after discharge from the ICU, is not controlled by the study.

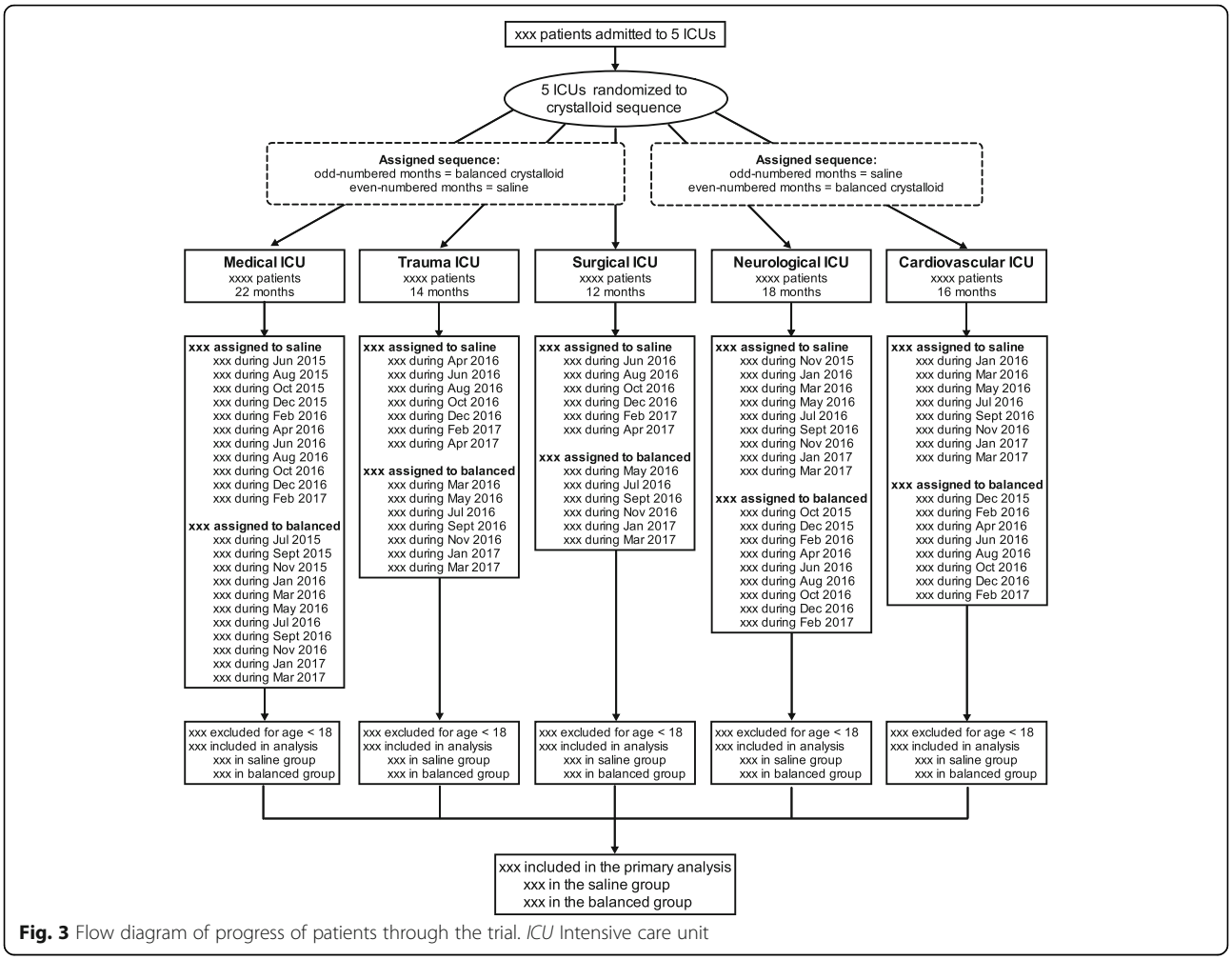

Fig. 3 Flow diagram of progress of patients through the trial. *ICU* Intensive care unit

Each day patients receive the crystalloid to which their ICU is currently assigned. The necessity that an IV crystalloid be clinically available at all times precluded the use of washout periods, and patients who remain in the ICU through a crossover (i.e., from one calendar month to another) may potentially be exposed to both types of crystalloid. Although this introduces the potential for contamination of study groups, in a pilot trial at the same institution, the total volume of nonassigned crystalloid administered because of the lack of a washout period was <125 ml per patient [14]. As described in the Statistical analysis section below, patients will be analyzed in the group to which they were assigned at the time of study enrollment in an intention-to-treat fashion. For example, a patient admitted to an ICU during a month assigned to saline will be analyzed in the saline group even if that patient remains in the ICU after the ICU switches assignment to balanced crystalloids.

Data collection

In this pragmatic trial, we are using data collected in routine clinical care and electronically extracted from the electronic health record (EHR) (see Additional file 2). All data are stored confidentially in an institutional patient data management system. Data collected include prestudy renal function; demographic characteristics, admitting location and diagnosis, and severity of illness at enrollment; receipt of IV crystalloids, other fluids, and blood products; serum electrolyte and creatinine values; receipt of RRT, mechanical ventilation, and vasopressors; and vital status and serum creatinine at hospital discharge. Electronic extraction of these data from the EHR has previously been validated against the reference standard of two-physician manual chart review [23]. For all patients who receive new RRT, study personnel will perform manual chart review to confirm the absence of prior RRT and identify the indication for RRT.

Primary outcome

The primary outcome will be the proportion of patients meeting one or more criteria for MAKE30: in-hospital mortality, receipt of new RRT, or persistent renal dysfunction defined as a final inpatient serum creatinine value ≥200% of baseline [23–25]. In-hospital mortality will be defined as death due to any cause prior to hospital discharge censored at 30 days after ICU admission. Receipt of new RRT will be defined as receipt of any modality of RRT between ICU admission and the first of hospital discharge or 30 days among patients not known to have received RRT prior to ICU admission. Persistent renal dysfunction will be defined as a final serum creatinine value before hospital discharge (censored at 30 days after enrollment) ≥200% of the baseline creatinine value. The value for baseline serum creatinine will be determined using a previously described hierarchical approach [23]. The lowest serum creatinine between 12 months and 24 h prior to hospital admission will be used when available. If no such creatinine value is available, the lowest creatinine value between 24 h prior to hospital admission and the time of ICU admission will be used. If no creatinine value is available between 12 months prior to hospital admission and the time of ICU admission, a baseline creatinine value will be estimated using a previously described formula [creatinine = 0.74 – 0.2 (if female) + 0.08 (if African American) + 0.003 × age (in years)] [26]. Patients known to have received RRT prior to enrollment will be considered ineligible to meet criteria for new RRT or persistent renal dysfunction, but they may qualify for MAKE30 by experiencing in-hospital mortality.

Secondary outcomes

Secondary outcomes will include additional clinical outcomes, additional renal outcomes, and biochemical outcomes. Additional clinical outcomes will include in-hospital mortality before ICU discharge, before 30 days, and before 60 days, as well as ICU-free days, ventilator-free days, vasopressor-free days, and RRT-free days, all through 28 days after enrollment. Additional renal outcomes will include new RRT receipt, persistent renal dysfunction, stage 2 or higher AKI according to Kidney Disease: Improving Global Outcomes (KDIGO) creatinine criteria [27], highest serum creatinine value, change from baseline creatinine to highest creatinine, final serum creatinine value before hospital discharge, and duration of new RRT. Biochemical outcomes will include serum values for sodium, potassium, chloride, bicarbonate, blood urea nitrogen, and creatinine from enrollment through day 30.

Power calculation

On the basis of data from the study ICUs in the 1 year prior to the trial, we anticipate the planned study duration (Fig. 2) will result in enrollment of around 14,000 patients with an overall rate of MAKE30 around 15%. Enrollment of 14,000 patients will provide 90% power at an α level of 0.05 to detect an absolute difference between the saline and balanced crystalloid groups in MAKE30 of 1.9%, as well as a relative risk reduction of 12%, which is comparable to the 12% relative risk reduction for in-hospital mortality reported in a recent pilot trial [13] (additional details in Additional file 2).

Data and safety monitoring board and interim analysis

A DSMB was appointed to oversee the conduct of the trial and review two interim analyses. The DSMB is comprised of two academic intensivists outside the study institution who are experienced in the conduct of clinical trials in critical illness. The first interim analysis occurred 6 months after study initiation, examining patients enrolled between 1 June 2015 and 30 November 2015. The second interim analysis occurred halfway between the first interim analysis and the end of the trial, examining patients enrolled between 1 June 2015 and 31 July 2016 (additional details in Additional file 2). Both interim analyses used the same stopping criteria:

> *The stopping boundary for efficacy will be met if (1) the unadjusted difference in the incidence of the primary outcome (MAKE30) between study groups is greater than or equal to 2.6% with a P value less than 0.001 and (2) the P value is less than 0.001 for the difference between study groups in the incidence of either in-hospital mortality or receipt of new RRT. Because even small differences between groups would be clinically meaningful, and given the importance of determining with as much certainty as possible whether balanced crystalloids are superior to saline, a futility stopping boundary will not be employed. Use of the conservative Haybittle-Peto boundary* ($P < 0.001$) *will allow the final analysis to be performed using an unchanged level of significance* ($P = 0.05$).

At the time of submission of the manuscript of this report, both interim analyses had been completed, and the DSMB had recommended continuing the trial to completion. In addition, the DSMB is available to evaluate adverse events or serious adverse events during the conduct of the trial. In cases of serious adverse events, the DSMB has the ability to pause the trial to investigate possible safety issues and suggest changes to the design of the study to abrogate any safety issues.

Statistical analysis principles

All analyses will be performed using R version 3.2.0 software (R Foundation for Statistical Computing, Vienna, Austria). To maximize transparency and

reproducibility, a complete version of the R code that will be used to analyze the final study data is available in Additional file 3. This ensures that (1) statistical reviewers or external investigators will be able to replicate the prespecified analysis of the trial independently and (2) any changes or additions to the statistical analysis introduced by investigators or reviewers after completion of enrollment will be evident as differences between the prespecified code and the analysis code included with the final publication.

All analyses will be conducted at the level of the individual patient during an individual hospitalization in an intention-to-treat fashion unless otherwise specified. Continuous variables will be reported as mean ± SD, mean and 95% CI, or median and IQR; categorical variables will be reported as frequencies and proportions. Between-group comparisons will be made with the Mann-Whitney rank-sum test for continuous variables, the chi-square test for categorical variables, generalized estimating equations for repeatedly measured variables, and generalized linear mixed-effects models for analyses of the primary and secondary outcomes. A two-sided P value <0.05 will be considered statistically significant.

Analytic rationale

In the setting of a large, pragmatic trial enrolling every adult admitted to the five participating ICUs, the SMART study population will contain a wide spectrum of (1) exposure to the study intervention, (2) baseline risk of the primary outcome, and (3) physiologically distinct patient subgroups. The primary and secondary analyses evaluate the effect of the intervention overall and across the spectrum of exposure to crystalloid, baseline risk of MAKE30, and patient subgroups.

Primary analysis

To account for the cluster-level allocation, cluster-level crossover structure of the trial, the primary analysis will be an intention-to-treat comparison of the primary outcome of MAKE30 between the saline and balanced crystalloid groups using a generalized linear mixed-effects model including fixed effects (group assignment, age, sex, race, source of admission, mechanical ventilation, vasopressor receipt, diagnosis of sepsis, and diagnosis of traumatic brain injury) and random effects (ICU) (additional details in Additional file 2) [28, 29].

Main secondary analysis

Anticipating (1) a wide range in the total volume of crystalloid received by study participants and (2) the potential for greater difference in outcomes between study groups among those patients who receive larger volumes of crystalloid, the main secondary analysis will compare the proportion of patients experiencing MAKE30 in the saline and balanced crystalloid groups, accounting for patients' overall volume of isotonic crystalloid received. For this analysis, we will construct a logistic regression model with MAKE30 as the outcome and independent variables of study group, total isotonic crystalloid received between enrollment and 30 days, and the interaction between the two (as a cross-product term). This will allow us to determine whether any volume of crystalloid receipt exists at which use of balanced crystalloids decreases the risk of MAKE30 compared with saline.

Given that total crystalloid receipt is a variable that emerges after enrollment, we will perform sensitivity analyses (1) using total crystalloid receipt in the 72 h after enrollment (before incident AKI or death are likely to have affected isotonic crystalloid administration), (2) replacing the actual total crystalloid receipt with predicted total crystalloid receipt based on a multivariable linear regression model using patient and ICU characteristics available at the time of enrollment derived from crystalloid administration in the study ICUs in the 1 year prior to the trial, and (3) comparing outcomes between study groups among a modified intention-to-treat population of patients who received at least 500 ml of any study crystalloid in the 72 h after enrollment.

Additional secondary analyses

We will perform the following additional secondary analyses:

1. *Comparison of secondary outcomes between study groups.*
2. *Effect modification by severity of illness and prespecified subgroups.* Using generalized linear mixed-effects modeling, we will examine the interaction between crystalloid assignment and the following baseline variables with respect to the primary outcome of MAKE30 in the intention-to-treat population:

a. Source of admission to the ICU (ED, operating room, transfer from another hospital, hospital ward, other)
b. Study ICU (medical, surgical, cardiac, neurological, trauma) (Because cluster cannot be treated as a random effect for this subgroup, we will use logistic regression modeling.)
c. Sepsis or septic shock (yes, no)
d. Traumatic brain injury (yes, no)
e. Receipt of mechanical ventilation (yes, no)
f. Receipt of vasopressors (yes, no)
g. Category of renal dysfunction at the time of enrollment (no renal dysfunction, AKI, chronic kidney disease, end-stage renal disease receiving RRT)

h. Risk of in-hospital mortality as predicted by baseline University HealthSystem Consortium expected in-hospital mortality (continuous variable ranging from 0.0 to 1.0)

3. *Sensitivity analysis excluding patients admitted in the week prior to a crossover ("washout").* We will repeat the primary analysis comparing MAKE30 between study groups in the intention-to-treat population excluding those admitted in the 7 days prior to a crossover in ICU crystalloid assignment (simulating a washout period). Prior data from the study ICUs suggest that less than 10% of patients remain in the ICU for longer than 7 days [14]. Excluding those admitted within 7 days of a crossover in ICU crystalloid assignment will allow use of a baseline factor to exclude the majority of patients who would go on to experience a crossover in crystalloid assignment because of the study design.
4. *Sensitivity analysis excluding patients who were transferred between ICUs or remained in the ICU through a crossover ("per protocol").* We will repeat the primary analysis comparing MAKE30 between study groups in the intention-to-treat population excluding those who remained in the ICU through a crossover in crystalloid assignment or who were transferred between study ICUs.
5. *Sensitivity analysis including only each patient's first admission to a participating ICU during the study period.* We will repeat the primary analysis comparing MAKE30 between study groups in the intention-to-treat population including only the first ICU admission in the study for each patient.

Corrections for multiple testing

All of the additional secondary analyses will be considered hypothesis-generating, and no corrections for multiple comparisons will be performed.

Handling of missing data

Of the components of the MAKE30 primary outcome, data regarding in-hospital mortality and receipt of new RRT are not anticipated to be missing for any patients [14, 23]. In contrast, the persistent renal dysfunction component of MAKE30 may suffer from missing data for serum creatinine value at baseline or between enrollment and hospital discharge. In a pilot study of 974 patients in the same hospital, 31 patients (3.2%) had no measured serum creatinine between enrollment and hospital discharge [14]. Of these 31 patients, 6 (19.4%) died within hours of ICU admission and qualified for the MAKE30 outcome via the in-hospital mortality criteria. The remaining 25 (80.6%) were low-acuity ICU patients with a normal creatinine value measured in the 24 h prior to ICU admission who were discharged from the hospital within 48 h without another serum creatinine measurement. Of these, 24 had a subsequent outpatient serum creatinine value measured in the next 90 days, all of which measurements were in the normal range. Thus, patients without a serum creatinine measurement between enrollment and hospital discharge who do not experience in-hospital mortality or new RRT will be classified as not having experienced the MAKE30 outcome.

With regard to missing data for baseline serum creatinine, in the same pilot study, 595 (61.0%) of 974 patients had a measured serum creatinine value between 12 months and 24 h prior to hospital admission [14]. Of those without such a measurement, 259 (68.3%) of 379 had a value measured between 24 h prior to hospital admission and study enrollment. Only 120 (12.3%) of 974 patients did not have an available serum creatinine value prior to enrollment. For the main analysis, patients without a measured serum creatinine value between 12 months prior to hospital admission and enrollment will have a baseline creatinine value estimated using a previously described three-variable formula [26]. Multiple alternative approaches to missing baseline creatinine data will be explored in sensitivity analyses, including use of complete cases, multivariable single imputation, and use of the first creatinine after enrollment or the highest or lowest creatinine during the study (see Additional file 2).

Post hoc analyses

In the event that investigators or reviewers introduce analyses in addition to those described above, these will be clearly delimitated as post hoc and will be considered hypothesis-generating.

Presentation of the results

After completion of enrollment and data analysis, the results of the trial will be communicated to the public through manuscript publication and submission of the results to the ClinicalTrials.gov database. Submission for publication will include public access to the full study protocol and statistical code. Authorship will be based on the International Committee of Medical Journal Editors guidelines, and professional writers will not be used.

The flow of patients through the study will be presented in a flow diagram (Fig. 3). Baseline characteristics will be presented by treatment group, as shown in Table 1 and Additional file 2: Table S2. The volume of isotonic crystalloid administered, other fluids, and blood products administered over time will be presented by treatment group (Additional file 2: Table S3). Serum values for sodium, potassium, chloride, bicarbonate, blood urea nitrogen, and creatinine will be presented in figures displaying serum values over time by group and

Table 1 Patient characteristics at baseline

Patient characteristics	Saline (*n* =)	Balanced (*n* =)
Age, years, median [IQR]	–	–
Male sex, *n* (%)	–	–
White race, *n* (%)	–	–
Weight, kg, median [IQR]	–	–
Body mass index, kg/m^2, median [IQR]	–	–
Renal comorbidities, *n* (%)		
Chronic kidney disease, stage 3 or higher	–	–
Prior RRT receipt	–	–
Source of admission to ICU, *n* (%)		
Emergency department	–	–
Transfer from another hospital	–	–
Hospital ward	–	–
Another ICU within the hospital	–	–
Operating room	–	–
Outpatient	–	–
Study ICU, *n* (%)		
Medical	–	–
Surgical	–	–
Cardiac	–	–
Neuro	–	–
Trauma	–	–
Admitting diagnosis, *n* (%)	–	–
Sepsis or septic shock	–	–
Traumatic brain injury		
Mechanical ventilation, *n* (%)	–	–
Vasopressors, *n* (%)	–	–
UHC expected mortality, %, mean (95% CI)	–	–
Serum creatinine, mg/dl, median [IQR]		
Lowest in 12 months prior to hospitalization	–	–
No. (%) of patients	–	–
Lowest between hospitalization and ICU admission	–	–
No. (%) of patients	–	–
Estimated by three-variable formula	–	–
No. (%) of patients	–	–
Study baseline	–	–
Acute kidney injury, stage 2 or higher	–	–

ICU Intensive care unit, *UHC* University HealthSystem Consortium

in tables detailing the incidence of abnormal values (Additional file 2: Table S4). Clinical and renal outcomes will be reported by treatment group, as shown in Table 2. For the primary analysis of the primary outcome, we will present the unadjusted frequency and proportion of MAKE30 in each study group, as well as the adjusted OR, 95% CI, and *P* value derived from the generalized linear mixed-effects model. Indications for new RRT are displayed as in Additional file 2: Table S5. Heterogeneity of treatment effect analyses will be displayed as locally weighted scatterplot smoothing (LOESS) curves or partial effect plots for continuous variables and forest plots for categorical variables.

Discussion

Upon completion, SMART will provide the most comprehensive data to date on the comparative effects of saline versus balanced crystalloids among critically ill adults. Given that isotonic crystalloid administration represents the most common intervention provided to hospitalized patients, saline and balanced crystalloids are the only available options for isotonic crystalloid administration, and also that the relationship between saline and AKI and death remains unclear, the results of SMART will have immediate implications for the care of a broad population of acutely ill patients. Results showing superior clinical outcomes in the balanced crystalloids group would provide compelling evidence that balanced solutions should be considered the preferred isotonic crystalloid for most acutely ill patients. Better clinical outcomes with saline would cement 0.9% sodium chloride as the first-line isotonic IV fluid and end the current debate about optimal crystalloid composition. In this comparative effectiveness trial of thousands of critically ill adults, a finding of no difference between groups would still have important implications for clinical care and future research. In a trial powered to detect absolute risk reductions as small as 2% in clinical outcomes, no difference between groups would imply that the effect of crystalloid choice for the majority of ICU patients is minimal, and any future research would need to be focused on select subpopulations.

While designing SMART, we weighed the relative advantages and disadvantages of multiple study designs, including a blinded, patient-level randomized trial. A major challenge to controlled studies of fluid administration in critical illness is the ability to enroll patients prior to the period of highest fluid exposure. Because the majority of fluid is administered as part of resuscitation in the ED and during the first 12 h of ICU admission, we selected a cluster-level allocation design that would allow enrollment immediately upon presentation and coordination between study ICUs and the ED to maximize exposure to the assigned crystalloid and minimize exposure to the nonassigned crystalloid. By basing study group assignment at the unit level, we ensured delivery of the assigned crystalloid even among unstable patients for whom fluid was being administered immediately upon presentation, because the assigned crystalloid would be the fluid most readily available in the study unit. The enrollment of all adults admitted to the participating ICUs examines the effects of saline

Table 2 Clinical outcomes

Outcome	Saline (*n* =)	Balanced (*n* =)	Adjusted OR (95% CI)	Adjusted *P* value
Primary outcome				
Major Adverse Kidney Event within 30 days, *n* (%)	–	–	–	–
Secondary clinical outcomes				
In-hospital mortality, *n* (%)				
Before ICU discharge	–	–	–	–
Before 30 days	–	–	–	–
Before 60 days	–	–	–	–
ICU-free days, median [IQR]	–	–	–	–
Mean ± SD	–	–		
Ventilator-free days, median [IQR]	–	–	–	–
Mean ± SD	–	–		
Vasopressor-free days, median [IQR]	–	–	–	–
Mean ± SD	–	–		
RRT-free days, median [IQR]	–	–	–	–
Mean ± SD	–	–		
Secondary renal outcomes				
Serum creatinine, mg/dl				
Highest before discharge or day 30, mg/dl, median [IQR]	–	–	–	–
Change from baseline to highest value, mg/dl, median [IQR]	–	–	–	–
Final value before discharge or 30 days, mg/dl, median [IQR]	–	–	–	–
Among survivors, mg/dl, median [IQR]	–	–	–	–
Final creatinine ≥200% baseline, *n* (%)	–	–	–	–
Among survivors to hospital discharge	–	–	–	–
Among survivors to hospital discharge without new RRT	–	–	–	–
Acute kidney injury, stage 2 or higher, *n* (%)	–	–	–	–
Developing after enrollment	–	–	–	–
Receipt of new RRT, No. (%)	–	–	–	–
Duration of in-hospital receipt, days, median [IQR]	–	–	–	–
Continued receipt after hospital discharge, *n* (%)	–	–	–	–

ICU Intensive care unit, *RRT* Renal replacement therapy

versus balanced crystalloids in a real-world clinical environment, improving the generalizability of the study findings. Coupling group assignment at the level of the ICU with relatively short periods (1 month) and frequent crossovers (at least 11 in each unit) balances baseline characteristics and cointerventions better than a simple cluster-randomized trial or before-and-after trial with the same number of units, decreasing confounding by seasonal change or trends in usual care over time. Although blinding of treating clinicians and study personnel to the assigned intervention would be ideal, researchers in a prior pilot trial of the same topic found high rates of provider awareness of crystalloid assignment despite blinding, perhaps owing to the overt effect of the study crystalloids on clinically available laboratory values such as serum chloride and bicarbonate [13]. Use of an objective, patient-centered primary outcome abstracted automatically from the EHR increases the pragmatic nature of the design and diminishes the risk of observer bias.

Several potential threats to the validity of our trial exist. Including all patients admitted to each study ICU may produce a patient population with limited average exposure to the study interventions [13, 14]. On the basis of our preliminary data from the same units prior to this study, however, we anticipate that more than 90% of enrolled patients will receive isotonic crystalloid and at least 25% of patients will receive more than 4 L of isotonic crystalloid, which is comparable to or greater than that received in prior positive ICU fluid trials [30]. Additionally, we have prespecified analyses to evaluate for a dose-response relationship between

the volume of isotonic crystalloid administered and clinical outcomes with saline versus balanced crystalloid. Similarly, the broad enrollment criteria may produce a study population at relatively low risk for adverse clinical outcomes. The anticipated incidence of the primary outcome of 15%, however, is comparable to that of other large ICU fluid management trials [30, 31]. Treating clinicians are aware of study group assignment, which may permit a treatment bias in which clinicians administer less isotonic crystalloid and/or more nonisotonic crystalloids when assigned to one of the fluid groups. For this reason, we will record and report use of not only isotonic crystalloid but also nonisotonic crystalloid, colloid, and blood products during the trial. Group assignment at the level of the cluster with multiple cluster-level crossovers introduces the possibility for intracluster correlation, interperiod correlation, and intracluster intraperiod correlation, which may confound the relationship between group assignment and clinical outcome. In preparatory analyses using data from more than 10,000 patients admitted in the 1 year prior to the trial, we found the effect of intracluster correlation to be minimized by the short periods and frequent crossovers and the effects of intraperiod correlation and intracluster intraperiod correlation to be small (see Additional file 2: Supplemental methods). Our primary analysis uses a generalized linear mixed-effects model to account for these aspects of the study structure. In the absence of a washout period, there will be carryover of crystalloid administration from one group assignment into the other; however, on the basis of pilot data, we anticipate the volume of nonassigned crystalloid received as a result of carryover will be low [14], and we prespecify secondary analyses to address the effects of carryover. Finally, although MAKE30 is a recommended outcome for clinical trials involving AKI [24, 32], use of a composite outcome presents potential challenges. Unlike death and new receipt of RRT, whether persistent renal dysfunction on hospital discharge is a patient-centered outcome remains a point of discussion. Persistent renal dysfunction also relies on the availability of serum creatinine measurements at baseline and before hospital discharge, potentially requiring imputation of missing data for one component of the composite primary outcome. Perhaps most important, although death, new receipt of RRT, and persistent renal dysfunction are weighted equally in the MAKE30 composite outcome, they may not represent equivalent outcomes to patients or providers. To address this, we will provide data on the MAKE30 outcome overall and for each of its separate components.

Trial status

SMART is an ongoing, pragmatic, cluster-level allocation, cluster-level crossover trial that will compare saline to balanced crystalloids with regard to major adverse kidney events among critically ill adults. Patient enrollment began on 1 June 2015, and enrollment is scheduled for completion on 30 April 2017.

Additional files

Additional file 1: SPIRIT 2013 checklist: recommended items to address in a clinical trial protocol and related documents. (DOC 122 kb)

Additional file 2: This file contains supplemental tables and methods, including additional details regarding electronic health record-based data collection, power calculation, development of the model for the primary analysis, interim analyses, and handling of missing data for baseline creatinine. (DOCX 88 kb)

Additional file 3: This file contains a .pdf version of the R code that will be used to analyze the final study data. (PDF 118 kb)

Abbreviations

AKI: Acute kidney injury; DSMB: Data and safety monitoring board; ED: Emergency department; EHR: Electronic health record; ICU: Intensive care unit; IRB: Institutional review board; IV: Intravenous; KDIGO: Kidney Disease: Improving Global Outcomes; LOESS: Locally weighted scatterplot smoothing; MAKE30: Major Adverse Kidney Events within 30 days; RRT: Renal replacement therapy; SMART: Isotonic Solutions and Major Adverse Renal Events Trial; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; UHC: University HealthSystem Consortium

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Availability of data and materials

A file containing the de-identified data needed to replicate the primary analysis will be submitted as a supporting file at the time of submission of the

main manuscript reporting the trial. The complete dataset developed during the present study is available from the corresponding author upon reasonable request.

Authors' contributions

MWS, EDS, ADS, GRB, and TWR conceived of and designed the study. MWS, WHS, JLS, ABK, AH, ODG, AKM, EDS, and TWR executed the study. MWS, JPW, and JME acquired data. MWS, LW, DWB, and TWR devised the statistical approach. MWS, LW, and TWR drafted the initial manuscript. MWS, WHS, LW, DWB, JPW, JME, JLS, ABK, AH, ODG, AKM, EDS, ADS, GRB, and TWR critically revised and approved the manuscript. MWS, WHS, JLS, ABK, AH, ODG, AKM, ADS, GRB, TWR MWS, LW, and DWB supervised the study. MWS, LW, DWB, and TWR will have complete access to the final trial dataset. All authors read and approved the final manuscript.

Competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors Uniform Disclosure Form for Potential Conflicts of Interest. ADS reported consulting for Baxter International Inc. in 2014–2015. The other authors declare that they have no competing interests. Outside the submitted work, WHS reported receiving grants from bioMérieux, Affinium Pharmaceuticals, Astute Medical, B·R·A·H·M·S GmbH/Thermo Fisher, Pfizer, Rapid Pathogen Screening, Ferring Pharmaceuticals, Gilead Sciences, Venaxis, sphingotec GmbH, and BioAegis Inc., as well as receiving personal fees from BioFire Diagnostics, Venaxis Inc., Abbott Point of Care, and Cempra Pharmaceuticals. AKM reported receiving grants from AtoxBio Ltd, Cubist Pharmaceuticals Inc., Bayer HealthCare Pharmaceuticals Inc., and Fresenius Kabi, as well as doing consulting for AtoxBio Ltd. TWR reported serving on an advisory board for Avisa Pharma, LLC, and as director of medical affairs for Cumberland Pharmaceuticals, Inc.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The trial was approved by the Vanderbilt University Medical Center Institutional Review Board (IRB) with waiver of informed consent (IRB 141349).

Publisher's Note

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References

1. Finfer S, Liu B, Taylor C, Bellomo R, Billot L, Cook D, et al. Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. Crit Care. 2010;14:R185.
2. Yunos NM, Kim IB, Bellomo R, Bailey M, Ho L, Story D, et al. The biochemical effects of restricting chloride-rich fluids in intensive care. Crit Care Med. 2011; 39:2419–24.
3. Smith RJ, Reid DA, Delaney EF, Santamaria JD. Fluid therapy using a balanced crystalloid solution and acid–base stability after cardiac surgery. Crit Care Resusc. 2010;12:235–41.
4. Wilcox CS. Regulation of renal blood flow by plasma chloride. J Clin Invest. 1983;71:726–35.
5. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and Plasma-Lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg. 2012;256:18–24.
6. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA. 2012; 308:1566–72.
7. Raghunathan K, Shaw A, Nathanson B, Stürmer T, Brookhart A, Stefan MS, et al. Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis. Crit Care Med. 2014;42:1585–91.
8. Rochwerg B, Alhazzani W, Sindi A, Heels-Ansdell D, Thabane L, Fox-Robichaud A, et al. Fluid resuscitation in sepsis: a systematic review and network meta-analysis. Ann Intern Med. 2014;161:347–55.
9. Shaw AD, Raghunathan K, Peyerl FW, Munson SH, Paluszkiewicz SM, Schermer CR. Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS. Intensive Care Med. 2014;40: 1897–905.
10. Shaw AD, Bagshaw SM, Goldstein SL, Scherer LA, Duan M, Schermer CR, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. Ann Surg. 2012; 255:821–9.
11. Sen A, Keener CM, Sileanu FE, Foldes E, Clermont G, Murugan R, et al. Chloride content of fluids used for large-volume resuscitation is associated with reduced survival. Crit Care Med. 2017;45:e146–53.
12. Krajewski ML, Raghunathan K, Paluszkiewicz SM, Schermer CR, Shaw AD. Meta-analysis of high- versus low-chloride content in perioperative and critical care fluid resuscitation. Br J Surg. 2015;102:24–36.
13. Young P, Bailey M, Beasley R, Henderson S, Mackle D, McArthur C, et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: the SPLIT randomized clinical trial. JAMA. 2015;314:1701–10.
14. Semler MW, Wanderer JP, Ehrenfeld JM, Stollings JL, Self WH, Siew ED, et al. Balanced crystalloids versus saline in the intensive care unit: the SALT randomized trial. Am J Respir Crit Care Med. doi:10.1164/rccm.201607-1345OC.
15. Young P. Saline is the solution for crystalloid resuscitation. Crit Care Med. 2016;44:1538–40.
16. Semler MW, Rice TW. Saline is not the first choice for crystalloid resuscitation fluids. Crit Care Med. 2016;44:1541–4.
17. Dellinger RP. Crystalloids for fluid resuscitation in sepsis: where is the balance? Ann Intern Med. 2014;161:372–3.
18. Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ. 2013;346:e7586.
19. Ware JH, Hamel MB. Pragmatic trials—guides to better patient care? N Engl J Med. 2011;364:1685–7.
20. Noto MJ, Domenico HJ, Byrne DW, Talbot T, Rice TW, Bernard GR, et al. Chlorhexidine bathing and health care-associated infections: a randomized clinical trial. JAMA. 2015;313:369–78.
21. Myburgh JA, Mythen MG. Resuscitation fluids. N Engl J Med. 2013;369:1243–51.
22. Lorenzo M, Davis JW, Negin S, Kaups K, Parks S, Brubaker D, et al. Can Ringer's lactate be used safely with blood transfusions? Am J Surg. 1998;175:308–10.
23. Semler MW, Rice TW, Shaw AD, Siew ED, Self WH, Kumar AB, et al. Identification of major adverse kidney events within the electronic health record. J Med Syst. 2016;40:167.
24. Palevsky PM, Molitoris BA, Okusa MD, Levin A, Waikar SS, Wald R, et al. Design of clinical trials in acute kidney injury: report from an NIDDK workshop on trial methodology. Clin J Am Soc Nephrol. 2012;7:844–50.
25. Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care. 2013;17:R25.
26. Závada J, Hoste E, Cartin-Ceba R, Calzavacca P, Gajic O, Clermont G, et al. A comparison of three methods to estimate baseline creatinine for RIFLE classification. Nephrol Dial Transplant. 2010;25:3911–8.
27. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int. 2012;2 Suppl:1–138.

28. Parienti JJ, Kuss O. Cluster-crossover design: a method for limiting clusters level effect in community-intervention studies. Contemp Clin Trials. 2007;28:316–23.
29. Turner RM, White IR, Croudace T, PIP Study Group. Analysis of cluster randomized cross-over trial data: a comparison of methods. Stat Med. 2007;26:274–89.
30. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367:1901–11.
31. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350:2247–56.
32. Weisbord SD, Gallagher M, Kaufman J, Cass A, Parikh CR, Chertow GM, et al. Prevention of contrast-induced AKI: a review of published trials and the design of the Prevention of Serious Adverse Events following Angiography (PRESERVE) trial. Clin J Am Soc Nephrol. 2013;8:1618–31.

Isotonic Solutions and Major Adverse Renal Events Trial (SMART)

Statistical Analysis Plan Revision Sequence

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4/30/2017 Completion of enrollment for SMART Trial

6/30/2017 Completion of 60-day follow-up

**No changes occurred between the Original and Final Statistical Analysis Plans*