BMJ Open

FLUID trial: a hospital-wide open-label cluster cross-over pragmatic comparative effectiveness randomised pilot trial comparing normal saline to Ringer's lactate

Lauralyn Ann McIntyre ,[1,2] Dean A Fergusson ,[3] Tracy McArdle,[3] Alison Fox-Robichaud ,[4] Shane W English ,[5,6] Claudio Martin,[7] John Marshall,[8] Deborah J Cook,[9] Ian D Graham,[6,10] Steven Hawken,[11,12] Colin McCartney,[13] Kusum Menon,[14] Raphael Saginur,[15] Andrew Seely,[16,17] Ian Stiell,[18] Kednapa Thavorn ,[6,19] Charles Weijer,[20] Akshai Iyengar,[15] John Muscedere,[21] Alan J Forster,[22,23] Monica Taljaard ,[6] for the Canadian Critical Care Trials Group

To cite: McIntyre LA, Fergusson DA, McArdle T, *et al*. FLUID trial: a hospital-wide open-label cluster cross-over pragmatic comparative effectiveness randomised pilot trial comparing normal saline to Ringer's lactate. *BMJ Open* 2023;**13**:e067142. doi:10.1136/bmjopen-2022-067142

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-067142).

Received 09 August 2022
Accepted 21 December 2022

For numbered affiliations see end of article.

Correspondence to
Dr Lauralyn Ann McIntyre; lmcintyre@ottawahospital.on.ca

ABSTRACT

Objectives Normal saline (NS) and Ringer's lactate (RL) are the most common crystalloids used for fluid therapy. Despite evidence of possible harm associated with NS (eg, hyperchloremic metabolic acidosis, impaired kidney function and death), few large multi-centre randomised trials have evaluated the effect of these fluids on clinically important outcomes. We conducted a pilot trial to explore the feasibility of a large trial powered for clinically important outcomes.

Design FLUID was a pragmatic pilot cluster randomised cross-over trial.

Setting Four hospitals in the province of Ontario, Canada

Participants All hospitalised adult and paediatric patients with an incident admission to the hospital over the course of each study period.

Interventions A hospital wide policy/strategy which stocked either NS or RL throughout the hospital for 12 weeks before crossing over to the alternate fluid for the subsequent 12 weeks.

Primary and secondary outcome measures The primary feasibility outcome was study fluid protocol adherence. Secondary feasibility outcomes included time to Research Ethics Board (REB) approval and trial initiation. Primary (composite of death or re-admission to hospital in first 90 days of index hospitalisation) and secondary clinical outcomes were analysed descriptively.

Results Among 24 905 included patients, mean age 59.1 (SD 20.5); 13 977 (56.1%) were female and 21 150 (85.0%) had medical or surgical admitting diagnoses. Overall, 96 821 L were administered in the NS arm, and 78 348 L in the RL arm. Study fluid adherence to NS and RL was 93.7% (site range: 91.6%–98.0%) and 79.8% (site range: 72.5%–83.9%), respectively. Time to REB approval ranged from 2 to 48 days and readiness for trial initiation from 51 to 331 days. 5544 (22.3%) patients died or required hospital re-admission in the first 90 days.

Conclusions The future large trial is feasible. Anticipating and addressing logistical challenges during the planning stages will be imperative.

Trial registration number NCT02721485.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The FLUID pilot trial was an innovative pragmatic cluster randomised cross-over trial, with randomisation done at the hospital level and inclusion of all patients.
⇒ The study fluid (normal saline or Ringer's lactate) was the dominant (at least 80%) fluid stocked throughout the entire hospital to ensure patients received the same study fluid from hospital entry to hospital discharge and the addition of run-outs after study period 1 and 2 served to further reduce the possibility of contamination.
⇒ FLUID relied exclusively on health administrative data for the description of patient baseline characteristics and clinical outcome measures.
⇒ The ability to opt out provided treating physicians with autonomy and ultimately their patient trust and was a key requirement for the use of a waiver of patient informed consent in FLUID.
⇒ Although overall study fluid adherence targets were met, specific geographic regions in the hospital were below target. Due to the logistical issues, not all centres initiated the pilot trial at the same time.

INTRODUCTION

Other than the administration of oxygen, crystalloid fluids including normal (0.9%) saline (NS) and Ringer's lactate (RL) are among the most common interventions administered to hospitalised patients.[1 2] These fluids may be

used as a life-saving measure to re-establish haemodynamic stability, for rehydration, to replace fluid losses and to maintain intravascular volume.

In observational studies, NS as compared with RL and other balanced crystalloid fluids have been associated with acute renal injury hypothesised due to its higher chloride concentration and resultant metabolic acidosis that can occur with NS administration.[3–5] However, RL and other balanced crystalloid fluids with buffers have the potential to cause metabolic alkalosis[6 7] and theoretically, cause arrhythmias, tetany, coma and seizures.[8–10] The lactate in RL may accumulate in the setting of liver failure and may influence clinical diagnoses and clinical decision making.[11–13] Moreover, RL has a lower osmolarity in comparison to NS and when administered rapidly in large volumes could theoretically reduce plasma osmolarity and increase the risk of oedema formation,[14] which raises potential concern for patients with cerebral oedema.

Two large single centre multiple cross-over trials conducted in the intensive care unit (ICU), and the emergency department (ED) for patients who did not require admission to the ICU, found that balanced crystalloid fluids as compared with NS were associated with lower major adverse kidney events at 30 days which is a composite outcome of mortality, new renal replacement therapy or persistent renal dysfunction.[2 15] In contrast, two large multi-centre randomised trials (BaSICS, n=11 052 and PLUS, n=5037)[16 17] examined the efficacy of NS as compared with a balanced crystalloid (RL and Plasma-Lyte 148, respectively) on the primary outcome 90-day mortality. Neither of these trials detected differences in 90-day mortality; in BaSICS, the mortality rate was 22.0% versus 21.8%; in PLUS, mortality was 27.2% versus 26.4%. Renal function did not differ between the fluid groups in either trial, although the PLUS trial was stopped early due to recruitment challenges and insufficient funding during the pandemic. In a systematic review of 13 critical care trials to January 2022 and 35 884 participants, there were no detectable differences in renal function. In low risk of bias trials, there was no significant difference in mortality for the 0.9 saline as compared with balanced crystalloid group (28.2% and 27.9%, respectively; relative risk (RR) 0.96 (95% CI 0.91 to 1.01)), nor renal function.[15–28] However, authors concluded that there is a high probability balanced crystalloids reduce death since the CIs ranged from a 9% relative reduction to a 1% relative increase in death.

Crystalloid fluids are not limited to use in the ED or the ICU, but are administered to the majority of patients admitted to the hospital and throughout their care. To address this evidence gap, we designed a cluster cross-over randomised trial to compare a hospital-wide policy/strategy which stocked NS or RL as the main crystalloid resuscitation fluid with the aim to have all admitted patients throughout the hospital receive the same crystalloid fluid from the time they enter hospital to hospital discharge with a primary composite outcome of death or re-admission to hospital in the first 90 days. With the

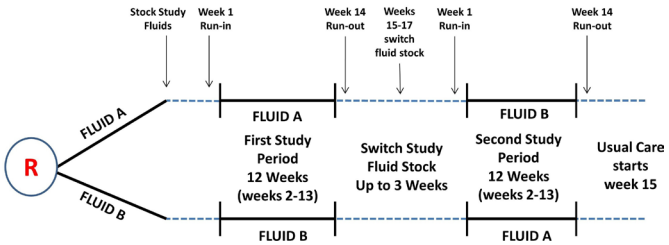

Figure 1 FLUID pilot trial study design: study fluid for the first study period was stocked from 1 to 3 weeks before initiation of the week 1 run-in period. No patients admitted during the week 1 run in-periods were included in the analysis. The week 1 run-in period familiarised hospital staff (physicians, nurses and trainees) with the FLUID operations, including the FLUID automatic substitution order prior to initiation of the two active 12-week study fluid periods (weeks 2–13 post week 1 run-in periods), where all patients with index hospitalisations were included. To ensure patients who were admitted close to the end of each study period received the same study fluid, a run-out period (week 14) was enabled through stocking of the same fluid on all the shelves throughout the hospital for following. No patients admitted during the week 14 run-out period were included in the analysis. We also allowed hospitals up to 3 weeks (weeks 15–17) to swap out the study fluid and cross over to the other study period fluid before the second study period week 1 run-in began. Patients admitted during the swap out time were not included in the analysis. Usual care began week 15 post the second study period.

FLUID design, the evidence generated will apply at the level of the hospital and healthcare system and for the majority of hospitalised patients.

As a necessary first step, our team conducted the FLUID pilot trial to examine feasibility related to study fluid protocol adherence, time to REB approvals and time to readiness to initiate the trial.

METHODS

Study oversight and design

FLUID was designed in collaboration with the FLUID executive committee and endorsed by the Canadian Critical Care Trials Group. The study protocol was published https://dx.doi.org/10.1136%2Fbmjopen-2018-022780.[29]

FLUID was a pragmatic, open-label, hospital-wide cluster randomised cross-over trial (see figure 1) conducted in three tertiary care hospitals and one community hospital in Ontario, Canada. Cluster randomisation was justified in accordance with the Ottawa Statement,[30] because randomising and following each individual patient admitted to the hospital would have been logistically challenging and financially infeasible. Having the same study fluid available throughout the hospital was essential to minimise contamination and maximise adherence, as study patients could be potentially exposed to both fluids across multiple clinical areas, prescribed by various clinicians. FLUID relied exclusively on health administrative data that is housed at the ICES in the province of Ontario, Canada for the description

of patient baseline characteristics and clinical outcome measures. ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyse healthcare and demographic data, without consent, for health system evaluation and improvement.

Patient and public involvement

Our patient partners contributed to the study design (waiver of consent, outcome measures and study implementation). Additional input related to the rationale and justification for waiver of consent was also received from the Patient and Family Advisory Council at the Ottawa Hospital which includes public participation.

Trial preparation and conduct strategies

A standardised strategy for site trial preparation and conduct was implemented and is summarised in detail in the published FLUID protocol *BMJ Open* 2018;8;e022780. doi.1136/bmjopen-2018-022780.[29]

Eligibility criteria for pilot trial

Inclusion criteria at *hospital level*: participating hospitals were required to have a level II or III ICU as these hospitals have the capability of admitting patients that are more severely ill and in turn may receive more fluid administration than hospitals with a level I ICU.[31]

Exclusion criteria at the *hospital level*: we excluded hospitals that had fewer than 6000 acute care admissions per year (<1500 admissions per study period).

Inclusion criteria at *patient level*: adult and paediatric patients admitted to the participating hospitals for the first time in the previous 90 days (index admission) over the duration of each study period were included in FLUID (to avoid exposure and thus potential contamination with either crystalloid fluid in the prior 90 days).

Exclusion criteria at *patient level*: neonates were excluded from FLUID since RL is neither used nor recommended for use in this population.[32] Patients who were readmitted to hospital during study period 1 or 2 were excluded to avoid contamination with previous FLUID exposure. Patients admitted during the run-in or run-out study periods were also excluded.

Study treatments and randomisation

The trial interventions were a hospital policy or strategy of predominantly stocking open label NS (control fluid) or RL (treatment fluid). Both NS and RL with or without the addition of electrolytes were stocked in the hospitals and administered in the usual way as 500 or 1000 mL boluses or continuous intravenous infusions as specified by the treating physicians at the participating hospitals in an open-label fashion. The allocated study fluid was the dominant fluid stocked (at least 80%) throughout the hospital for the duration of both study periods. Other fluid products did not undergo substitution during the study periods.

Participating sites were randomised sequentially. The allocation of hospitals to begin with NS versus RL was determined by computer-generated random numbers at the coordinating centre prepared by a statistician not familiar with the sites. For each study period, week 1 served as a run-in, weeks 2–13 as the study period time during which time all patients with index admissions to the study hospital were included for analysis. Week 14 served as a run-out week during which time the study fluid remained stocked in the hospital for use by patients admitted during weeks 2–13. After the 1-week run-out period, hospitals had up to an additional 3 weeks to crossover to period two study fluid.

Strategies to minimise contamination

The risk of contamination due to non-adherence to the study fluid was minimised through six mechanisms. (1) An automatic substitution order for the study fluid was invoked during the trial study periods: nurses were authorised by the senior management team or by a specific order at each participating hospital to perform an automatic substitution for the study fluid when the alternate fluid had been ordered by the treating physician. The automatic substitution could have been overridden if the treating physician indicated 'no substitution' in the physician's orders. (2) The hospital ward shelves were stocked with at least 80% study fluid for the duration of the study periods. (3) Bright signage prominently placed where NS and RL were stored helped to remind nurses about the automatic substitution. (4) The other resuscitation crystalloid fluid was available only in small quantities (less than 20% available on the shelves of non-trial resuscitation crystalloid fluid). (5) A 1-week run in prior to initiation of study period 1 and 2 to ensure the allocated study fluid was adequately stocked throughout the study hospital and (6) a 1-week run out at conclusion of study period 1 and 2 to minimise the occurrence of patients being exposed to two different kinds of fluids during the same hospitalisation.

Approach to safety

NS and RL are usual care resuscitation crystalloid fluids in clinical use for decades. Thus, participation in this trial posed no greater risk than that of routine care.

In advance of FLUID trial start-up at each participating hospital, several communication strategies were implemented to ensure all key stakeholders (staff physicians, trainees, nurses) were educated about FLUID,[29] *BMJ Open* 2018;8;e022780.doi.1136/bmjopen-2018-022780). These communication strategies ensured that physicians and nurses knew there was a small amount of the non-allocated study fluid available for use throughout the hospital if the treating physician chose to opt out of using the study fluid for a given patient. Opting out occurred if the treating physician had a strong clinical reason to not use the allocated study fluid (eg, severe hyperkalaemia, severe metabolic alkalosis or acidosis, burn injury or severe brain injury).

An independent safety committee reviewed a blinded by group safety analysis of the primary clinical outcome

(death or requirement for hospital re-admission at 90 days) as well as any serious adverse events considered related to the study fluids that were reviewed at morbidity and mortality rounds or reported to safety management committees at participating sites after completion of the pilot trial to determine if there were any serious safety signals.

Outcome measures

Primary feasibility outcome

Adherence to the fluid protocol

Adherence to the study fluid was measured not at the individual patient-level, but according to the aggregate use of the study fluid throughout the hospitals (all hospital wards, monitored units, and departments) using the hospital inventory system; monitoring fluid exposure or adherence according to individual patients was not feasible due to the sheer number of hospital admissions.

Successful adherence to the FLUID protocol was defined as a total of at least 80% of the prescribed study fluid for each study group being administered across all four participating hospitals combined and by individual hospitals over the 12-week study periods. The 80% adherence threshold was agreed to by our research team and the Canadian Critical Care trials group as FLUID was designed as a hospital-wide real world intervention strategy and after accounting for strong clinician preferences and contraindications, and adherence of 80% would be sufficiently high to justify going forward to the large trial. Adherence was monitored at 2-week intervals over the 12-week (weeks 2–13) study periods and described according to each study group across all four participating hospitals combined and according to major fluid user groups (ED, medicine, surgery, operating room (OR), postoperative assessment unit (PACU), obstetrics, ICU.

Secondary feasibility outcomes

Time to REB approval

Although FLUID met ethical criteria for the use of a waiver of consent, REBs may interpret justification for waiver of consent differently which could delay REB approval, and in turn, site allocation and protocol implementation within the scheduled time period. Successful time to REB approval was defined as taking no longer than 3 months from REB submission to receiving written approval from participating REB(s).

Time to readiness for study initiation

Delayed trial initiation may increase the risk of sites dropping out, or cause downstream operational complications such as increased study duration and costs. Successful time to readiness for trial initiation was defined when a hospital took no longer than 3 months from REB approval to trial initiation. The date of commencement of FLUID was confirmed through mutual agreement with the site PIs, logistical services representatives and nurse educators.

Secondary clinical outcomes

All primary and secondary clinical outcomes for the future large FLUID trial were described as a cohort (not by study group) in the pilot trial. The primary clinical outcome for the future large FLUID trial is a composite of death or re-admission to hospital within the first 90 days of the index hospitalisation; both outcomes are clinically important, relevant at the level of the hospital, healthcare system and to patients, and easily obtainable. Importantly, they have both been validated at the Institute for Clinical Evaluative Sciences, are complete and highly accurate (≥99%).[33 34]

Secondary clinical outcomes include death and re-admission to hospital within the first 90 days of the index hospitalisation described as separate variables, requirement for dialysis, need for re-operation, need for re-intubation postoperatively, ED visits within the first 90 days of the index hospitalisation, length of stay in hospital and hospital discharge disposition.

Subgroup analyses

Several predefined subgroups described the primary clinical outcome (death or re-admission to hospital within first 90 days) among patients who were more likely to receive higher exposure to fluids, with greater risk profiles or higher severity of illness. These include age (<18, 18 to ≤65, 66 to ≤80 and >80); sex; type of hospital admission (medical, surgical, pregnancy and childbirth, mental health), trauma, sepsis; elective versus urgent/emergent surgery, and admission to an ICU.

Data collection

All follow-up and collection of data for enrolled patients at the participating hospitals were captured through health administrative data that are housed at the Institute for Clinical Evaluative Sciences. There were no individual patient level data collected by research coordinators in the participating hospitals. The use of data in this project was authorised under section 45 of Ontario's personal health Information Protection Act, which does not require review by a REB. Trial and intervention costs were estimated from the trial budget, financial records and service level agreements. No additional data available. A data dictionary which summarises all administrative databases searched as well as ICD-10 codes for each variable in FLUID is described in online supplemental appendix I.

Analysis

All feasibility outcomes were described across all sites and then at each site. To calculate overall adherence to study fluid, the total use of the allocated study fluid was divided by the total combined use of NS and RL.

All baseline characteristics and clinical outcome data were described using means with SD or medians with IQRs as appropriate for continuous data, and frequencies and proportions for categorical and dichotomous variables. For clinical outcomes, 95% two-sided CIs were included. In accordance with the FLUID pilot protocol,

clinical outcomes were not analysed by study fluid group[29] because the primary objectives were to examine the feasibility of conducting the large trial. Reporting the results by trial arm would be potentially misleading due to the small sample size and four included centres.[35 36] The effect size for the future trial will be based on the minimum clinically important differences as opposed to the effect size observed in the pilot.[35 36]

Sample size

Four hospitals participated in the FLUID pilot trial. The sample size for this pilot was not based on precision or power considerations, but instead, on logistical and feasibility considerations within the constraints of a pilot study.

Preliminary sample size calculations described in the pilot protocol for the large FLUID trial are based on an absolute difference of 1% in the composite outcome of death or re-admission to hospital within 90 days. These calculations include varying within and between cluster correlation co-efficients which are required for cluster RCT sample size calculations.[29] The 1% absolute difference is very small and was agreed to by our FLUID team, the CCCTG and our patient partners as these differences are highly important at the population (hospital or healthcare system) level with thousands of hospital admissions every year.

RESULTS

Enrolment in FLUID commenced in August 2016 and was completed in October 2017. Two of the hospitals were allocated to begin the trial with NS as the control, while the other two were allocated to begin with RL.

A total of 32 154 patients were admitted to the study hospitals over the two 12-week (weeks 2–13) study periods. After excluding non-index admissions during study period 1 and 2 and patients admitted during the run-in and run-out periods, there were a total of 24 905 patients (12 338 in the NS and 12 567 in the RL arms), respectively. A consort flow diagram is shown in figure 2.

Baseline characteristics between the study fluid groups were balanced (see table 1). The mean age was 59.2 (SD 20.5), and 13, 977 (56.1%) were female. The majority of admissions were medical (n=10 773, 43.3%) or surgical (n=10 377, 41.7%).

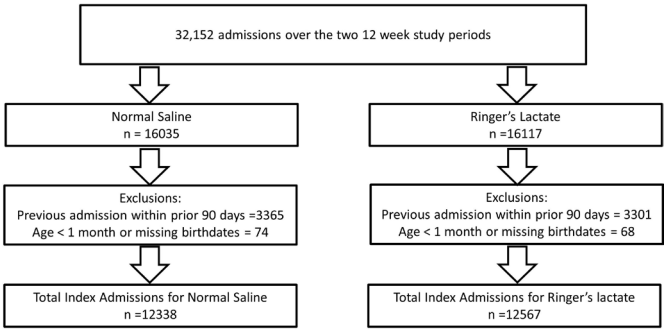

Figure 2 Consort flow diagram.

Primary feasibility outcome

Protocol adherence: The total volume of NS and RL administered according to inventory reports throughout the study period was 96 821 and 78 348 L, respectively. Study fluid adherence targets of at least 80% overall (four sites combined) were met for both the NS and RL arms (93.7% and 79.8%, respectively). Study fluid adherence for all sites combined according to 2-week intervals ranged from 93.2% to 94.3% and 78.4% to 81.1% for the NS and RL groups, respectively. Across the four individual participating sites adherence in the NS and RL arms ranged from 91.6% to 98.0% and 72.5% to 83.9%, respectively (see figures 3–6).

The seven main fluid user groups in seven settings (ED, surgery, medicine, ICU, OR, PACU and obstetrics) accounted for 97.5% and 93.8% of all NS and RL administered throughout the study periods, respectively. Study fluid adherence to NS was highest in the ED (94.8%) and lowest in the OR (86.6%). Overall study fluid adherence to RL was highest in the PACU (96.0%) and lowest on the medicine ward (63.4%) (see figure 3).

Secondary feasibility outcomes

Time to REB approval: Ethical concerns were not raised by the REBs. REB approval was obtained by all four sites in less than 3 months (90 days). On behalf of Clinical Trials Ontario, a provincial REB (Ottawa Health Sciences Network REB (OHSN-REB #: 20150619-01H), CTO - # - (0778) approved the Ottawa Hospital General and Civic Campuses within 48 days from submission and the Hamilton General Hospital within 3 days from submission. The Queensway Carleton Hospital Research Ethics Board (QCH-REB # 16-05) was approved within 20 days from submission.

Time for readiness for study initiation: The target time for readiness for study initiation was set as less than 3 months from REB approval. Two of the four pilot centres met this target and initiated the study at 66 and 51 days after REB approval, respectively. At one centre the trial was initiated after 331 days; a decision was made to delay study initiation at this site until completion of enrolment at a sister hospital due to limited storage space for the large volumes of fluid. At another centre, study initiation was 102 days post-REB approval and purposefully delayed by an additional 12 days to accommodate for ward closures over a major holiday period.

There were no serious adverse events considered related to the study fluid that were reviewed at morbidity and mortality rounds or reported to safety management committees at participating sites and communicated to the site investigator during the pilot trial. The independent safety committee found no reason to suspect harm resulting from either fluid intervention.

Clinical outcomes

The primary composite outcome of death or re-admission to hospital within 90 days of the index admission occurred in 5544 patients (22.6%, 95% CI 21.7 to 22.8). Patients

Table 1 Baseline characteristics

	Total no. of index admissions **N=24 905**	Normal saline **N=12 338**	Ringer's lactate **N=12 567**
Sex, female, n (%)	13 977 (56.1%)	6976 (56.5%)	7001 (55.7%)
Age, mean±SD	59.2±20.5	59.4±20.6	59.0±20.5
Age group, n (%)			
1 month to 18 years	168 (0.7%)	75 (0.6%)	93 (0.7%)
>18 to 65	13 792 (55.4%)	6756 (54.8%)	7036 (56.0%)
>65 to 80	6771 (27.2%)	3368 (27.3%)	3403 (27.1%)
>80	4174 (16.8%)	2139 (17.3%)	2035 (16.2%)
Case mix group, n (%)			
Medicine	10 773 (43.3%)	5449 (44.2%)	5324 (42.4%)
Surgery	10 377 (41.7%)	5080 (41.2%)	5297 (42.2%)
Pregnancy and childbirth	3614 (14.5%)	1744 (14.1%)	1870 (14.9%)
Mental health	141 (0.6%)	65 (0.5%)	76 (0.6%)
Type of surgical admission, n (%)			
Elective	5796 (55.9%)	2852 (56.1%)	2944 (55.6%)
Urgent	4581 (44.2%)	2228 (43.9%)	2353 (44.4%)
Surgical admission <24 hours, n (%)	950 (9.2%)	484 (9.5%)	466 (8.8%)
Severity of illness			
Admission to ICU, n (%)	3034 (12.2%)	1494 (12.1%)	1540 (12.3%)
Infection alone and infection and organ dysfunction, n (%)	2734 (11.0%)	1365 (11.1%)	1369 (10.9%)
Infection alone and infection and organ dysfunction and ICU admission, n (%)	579 (2.3%)	292 (2.4%)	287 (2.3%)
Trauma+ICU, n (%)	176 (0.7%)	92 (0.8%)	84 (0.7%)
Traumatic brain injury, n (%)	121 (0.6%)	68 (0.6%)	53 (0.4%)
Traumatic brain injury+ICU, n (%)	64 (0.3%)	35 (0.3%)	29 (0.2%)
Comorbidities			
Elixhauser comorbidity score, mean±SD	5.3±6.0	5.4±6.1	5.3±6.0
Elixhauser comorbidities, n (%)			
Diabetes, complicated	2819 (11.3%)	1396 (11.3%)	1423 (11.3%)
Hypertension, uncomplicated and complicated	2574 (10.3%)	1207 (9.8%)	1367 (10.9%)
Cardiac arrhythmias	2263 (9.1%)	1143 (9.3%)	1120 (8.9%)
Solid tumour without metastasis	2105 (8.5%)	1004 (8.1%)	1101 (8.8%)
Fluid and electrolyte disorders	1886 (7.6%)	944 (7.7%)	942 (7.5%)
Diabetes, uncomplicated	1374 (5.5%)	686 (5.6%)	688 (5.5%)
Congestive heart failure	1187 (4.8%)	606 (4.9%)	581 (4.6%)
Metastatic cancer	1008 (4.1%)	487 (4.0%)	521 (4.2%)
Chronic pulmonary disease	971 (3.9%)	536 (4.3%)	435 (3.5%)
Other neurological disorders	946 (3.8%)	490 (4.0%)	456 (3.6%)
Peripheral vascular disorders	732 (2.9%)	348 (2.8%)	384 (3.1%)
Coagulopathy	495 (2.0%)	230 (1.9%)	265 (2.1%)
Valvular disease	472 (1.9%)	242 (2.0%)	230 (1.8%)
Obesity	460 (1.9%)	248 (2.0%)	212 (1.7%)
Renal failure	450 (1.8%)	239 (1.9%)	211 (1.7%)
Paralysis	379 (1.5%)	209 (1.7%)	170 (1.4%)
Liver disease	360 (1.5%)	173 (1.4%)	187 (1.5%)

Continued

Table 1 Continued

	Total no. of index admissions N=24 905	Normal saline N=12 338	Ringer's lactate N=12 567
Alcohol abuse	348 (1.4%)	171 (1.4%)	177 (1.4%)
Pulmonary circulation disorders	300 (1.2%)	147 (1.2%)	153 (1.2%)
Depression	253 (1.0%)	105 (1.0%)	148 (1.2%)
Deficiency anaemia	248 (1.0%)	120 (1.0%)	128 (1.0%)
Lymphoma	247 (1.0%)	125 (1.0%)	122 (1.0%)
Drug abuse	199 (0.8%)	96 (0.8%)	103 (0.8%)
Rheumatoid arthritis/collagen vascular diseases	168 (0.7%)	87 (0.7%)	81 (0.6%)
Hypothyroidism	156 (0.6%)	78 (0.6%)	78 (0.6%)
Weight loss	152 (0.6%)	67 (0.5%)	85 (0.7%)
Psychoses	97 (0.4%)	51 (0.4%)	46 (0.4%)
Blood loss anaemia	56 (0.2%)	28 (0.2%)	28 (0.2%)
Peptic ulcer disease excluding bleeding	35 (0.1%)	20 (0.2%)	15 (0.1%)
AIDS/HIV	21 (0.1%)	11 (0.1%)	10 (0.1%)

ICU, intensive care unit; n, number.

were admitted to hospital for a median of 3 days (IQR 1–6) and 3429 patients (13.1%, 95% CI 12.6 to 13.5) were discharged to a facility other than home. Other secondary clinical outcomes and subgroups described according to the primary composite outcome are described in tables 2 and 3, respectively.

DISCUSSION

The FLUID trial design is innovative in its use of a pragmatic cluster randomised cross-over design, a waiver of patient informed consent to include all hospitalised patients, hospital based randomisation and the use of routinely collected electronic administrative health data to determine study outcomes. Our pilot trial confirmed that a large FLUID trial powered to evaluate death or re-admission to hospital within 90 days as the primary outcome is feasible based on study fluid adherence, REB

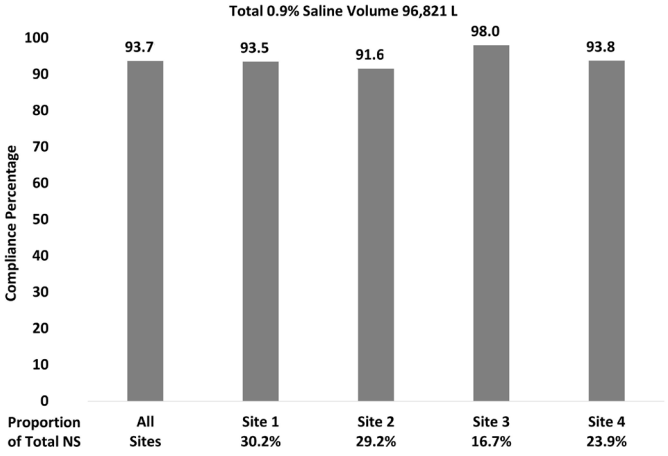

Figure 3 Overall 0.9% saline compliance and by study site: the number (%) over the first histogram bar summarises adherence to 0.9% saline which was calculated by adding the total combined volume of 0.9% saline at all four sites divided by the total combined volume of 0.9% saline and Ringer's lactate at all four sites during the 12-week 0.9% saline study period. The numbers (%) below each histogram bar summarise the proportion of 0.9% saline at each site which was calculated by adding the total volume of 0.9% saline used at each site divided by the total volume of 0.9% saline used at all four sites combined.

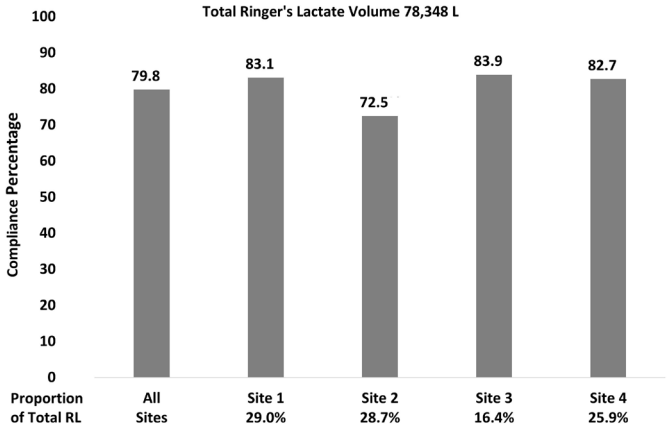

Figure 4 Overall Ringer's lactate (RL) compliance and by study site: the number (%) over the first histogram bar summarises adherence to RL which was calculated by adding the total combined volume of RL at the four sites divided by the total combined volume of 0.9% saline and RL at the four sites during the 12-week 0.9% Ringer's study period. The numbers (%) below each histogram bar summarises the proportion of Ringer's lactate at each site which was calculated by adding the total volume of RL used at each site divided by the total volume of RL used at the four sites combined.

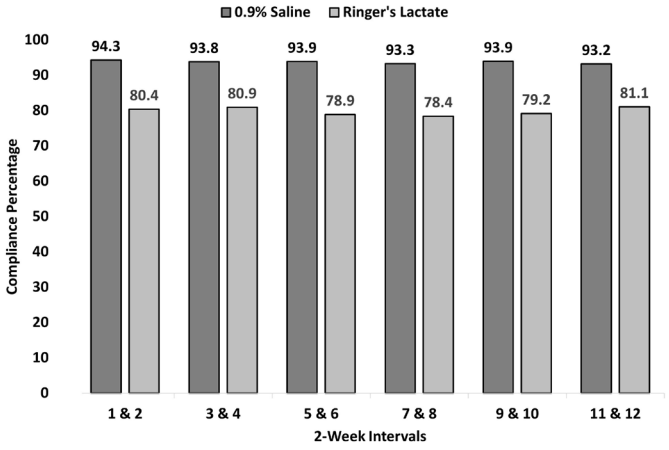

Figure 5 All sites overall study fluid compliance over 2-week intervals: the number (%) over each histogram bar summarises compliance to 0.9% saline and Ringer's lactate for all four sites combined in 2-week intervals over the 12-week study period.

approval time and readiness to initiate the trial. The REB approval target of 3 months was met for all four study sites. However, for three of the four centres, the REB approval process was centralised which avoided delays. In the large trial, a centralised REB process will be implemented where feasible. The FLUID pilot experience allowed our team to identify and address several logistical challenges associated with trial start up (eg, stocking of fluids, holiday closures).

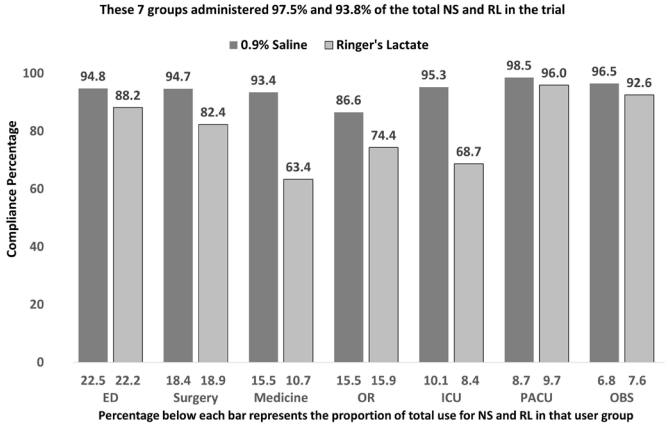

Figure 6 All sites overall study fluid compliance: major fluid user groups: the numbers (%) over the histogram bars summarises adherence to 0.9% saline and Ringer's lactate (RL) for each fluid user group and was calculated by adding the total volume of the allocated study fluid used divided by the total combined volume of 0.9% saline and RL for that fluid user group during each 12-week study period. The numbers (%) below each histogram summarise the proportion of allocated study fluid used for each fluid user group and was calculated by adding the volume of allocated study fluid used by each fluid user group divided by the total volume of allocated study fluid used at all four sites combined. ED, emergency department; ICU, intensive care unit; NS, normal saline; OBS, obstetrics; OR, operating room; PACU, postanaesthetic care unit.

The study fluid interventions were implemented at the hospital level using a hospital policy or strategy, with the aim to answer our study question at the hospital level. Our overall study fluid adherence targets were met. The ability to opt out provided treating physicians with autonomy and ultimately their patient trust and was a key requirement for the use of a waiver of patient informed consent in FLUID. With ethics expertise and guidance on our team, the REBs agreed that FLUID met Tri-Council Guideline criteria[37] which allowed for waiver of consent, which if not granted would have rendered this trial design infeasible. An extensive preparation and tailored education communication plan was developed for each participating hospital prior to the roll out of FLUID. As part of the preparation, collaboration with inventory services ensured at least 80% stocking of the study fluid in every in-patient cart in the participating hospitals and the receipt of inventory reports every 2 weeks related to these carts to facilitate adherence measurements. The trial was designed so that from the point of hospital entry until hospital discharge, whenever a clinician ordered RL or NS, the patient received the allocated study fluid. There was a run-out period at the end of period 1 and 2 to further reduce any contamination that may have occurred for patients who were enrolled near the end of each study period. Overall, prespecified study fluid protocol adherence targets were met. In the future large trial, we will target specific geographic regions in the hospital where adherence in the pilot was less than 80% for additional pretrial communication and educational enhancement strategies (eg, medicine wards).

The generation of recent evidence will help inform the design and subgroup analyses for future large pragmatic balanced crystalloid versus NS crystalloid trials. For example, a subgroup analysis of three trials and 1896 in patients who had sustained traumatic brain injury from a systematic review of 13 critical care trials found the use of balanced crystalloids as compared with NS was associated with a trend toward harm (RR 1.26, 95% CI 0.98 to 1.60),[27] potentially related to the lower osmolarity and risk of cerebral oedema formation with balanced crystalloid fluids. Based on these data, balanced crystalloid versus NS trials going forward need to carefully consider the exclusion of patients with acute brain injury from different causes as well as different severity of injuries. In addition, recent evidence generated from systematic reviews of small trials and subgroup analyses of large trials suggest balanced crystalloids as compared with NS may reduce death from sepsis and time to resolution of diabetic ketoacidosis[27 38] and represent important subgroups to examine in the future large FLUID trial.

The FLUID trial identified potential limitations. Adherence to RL as measured by fluid inventory reports was lower than NS. Reasons include lower adherence by treating clinicians, but could also be explained by the use of NS for non-fluid therapy reasons (eg, medication delivery, catheter patency and flushes, coadministration for blood products, surgical wound washouts

Table 2 Primary composite and secondary outcomes and costs

Primary composite outcome	n (%, 95% CI)
Death or re-admission to hospital within the first 90 days of the index hospitalisation, n (%)	5544 (22.3, 21.7 to 22.8)
Secondary outcomes	
Death within 90 days of index admission, n (%)	1926 (7.7, 7.4 to 8.1)
Re-admission within 90 days of index admission, n (%)	4049 (16.3, 15.8 to 16.7)
Total hospital length of stay	
Mean±SD	6.1±12.1
Median (IQR)	3 (1–6)
New dialysis within 90 days of index admission, n (%)	215 (0.86, 0.75 to 0.98)
ED visit within 90 days of index admission, n (%)	5499 (22.1, 22.0 to 22.6)
Discharge disposition (detailed), n (%)	
Discharged to facility other than home, n (%)	3250 (13.1, 12.6 to 13.5)
Transferred to another facility providing inpatient hospital care or acute care inpatient institution	1080 (4.3, 4.1 to 4.6)
Transferred to a long term or continuing care facility	2072 (8.3, 8.0 to 8.7)
Transferred to other ambulatory care, palliative care/hospice, addiction treatment centre, jails, infants and children (discharged/detained by social services)	98 (0.4, 0.3 to 0.5)
Discharged to a home setting with support services	4711 (19.0, 18.4 to 19.4)
Discharged to home (no support service from an external agency required)	15 807 (63.5, 63.0 to 64.1)
Signed out (against medical advice)	189 (0.9, 0.7 to 0.9)
Died	948 (3.8, 3.6 to 4.0)
90-day total health system and sub-divided costs, calculated 90 days after index date, Mean +/-SD	
Hospital cost (DAD)	
Inpatient cost	12 499.7±185 060.4
Hospital outpatient clinic cost	756.8±934.4
ED cost (NACRS)	431.9±577.4
Dialysis cost (NACRS)	138.9±1600.7
Cancer care cost (NACRS)	303.2±1805.2
Medication cost (ODB)	539.9±2081.6
Outpatient cost (OHIP)	
Physician FFS billings	3139.1±3121.7
Lab billings	38.9±68.1
Non-physician billings	10.8±179.6
FHO/FHN capitation	4.0±7.6
Total cost	18 088.5±221 010.3

%, percentage; DAD, discharge abstract database; ED, emergency department; FHN, family health network; FHO, family health organization; IQR, interquartile range; n, number; NACRS, national ambulatory core reporting system; ODB, Ontario drug benefit; OHIP, Ontario health insurance plan; SD, standard deviation.

and during dialysis). These reasons for lower adherence may have overestimated adherence to NS and underestimated adherence to RL. However, non-adherence will be accounted for in the power calculation for the large trial. Finally, cluster cross-over trials are vulnerable to period effects if the timing of trial initiation and cross-over are not controlled and balanced between the randomisation sequences. Ideally, all sites in the large trial should be randomised either at one time or in batches.[39] Due to the logistical issues, we were unable to initiate all centres at the same time during the pilot trial but will put measures in place to ensure balanced allocations on time in the large trial.

CONCLUSION

The FLUID pilot trial suggests that a future large pragmatic multi-centre trial is feasible. The large trial will

Table 3 Description of composite primary outcome in prespecified subgroups

	N (%, 95% CI)
Sex	
Female	2774 (19.9, 19.2 to 20.5)
Male	2770 (25.4, 24.5 to 26.2)
Age group	
≤18 years (children and adolescents)	20 (11.9, 7.0 to 16.8)
>18 to 65	2149 (15.6, 15.0 to 16.2)
>65 to 80	1811 (26.8, 25.7 to 27.8)
>80	1564 (37.5, 36 to 39.0)
Case mix group	
Medicine	3560 (33.1, 32.2 to 33.9)
Surgery	1699 (16.4, 15.7 to 17.1)
Pregnancy and childbirth	267 (7.4, 6.5 to 8.2)
Mental health	18 (12.8, 7.3 to 18.3)
Type of surgical admission, n (%)	
Elective surgery	677 (11.7, 10.9 to 12.5)
Urgent surgery	1022 (22.3, 21.1 to 23.5)
Surgical admission <24 hours	87 (9.2, 7.3 to 11.0)
Severity of illness	
Admission to intensive care unit	967 (31.9, 30.2 to 33.5)
Infection alone and infection and organ dysfunction	1076 (39.4, 37.5 to 41.2)
Infection alone and infection and organ dysfunction and ICU admission	276 (47.7, 43.6 to 51.7)
Trauma+ICU	77 (43.8, 36.4 to 51.1)
Traumatic brain injury	49 (40.5, 31.8 to 49.2)
Traumatic brain injury+ICU	34 (53.1, 40.9 to 65.4)
New dialysis within 90 days of index admission	51 (57.30, 47.03 to 67.58)

ICU, intensive care unit.

determine whether RL as compared with NS reduces death or requirement for hospital re-admission by an absolute difference of 1%. In contrast to trials that have generated evidence in specific populations with fluid interventions limited to geographic locations in the hospital (ICU, ED), the results of FLUID will apply broadly to patients who are admitted throughout the hospital. As such FLUID will provide important evidence-based guidance at the hospital and system level as to what fluid(s) could be predominantly stocked for use throughout the hospital and the associated healthcare resources required for such supply. Finally, our trial will also inform the usual care arm for future large crystalloid trials of similar design and build capacity for the conduct of similar trials in the future.

Author affiliations
[1]Department of Medicine (Critical Care), Ottawa Hospital Research Institute Clinical Epidemiology Program, Ottawa, Ontario, Canada
[2]Critical Care, Ottawa Hospital General Campus, Ottawa, Ontario, Canada
[3]Clinical Epidemiology, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
[4]Medicine, McMaster University, Hamilton, Ontario, Canada
[5]Medicine (Critical Care), University of Ottawa, Ottawa, Ontario, Canada
[6]Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
[7]Medicine (Critical Care), London Health Sciences Centre, London, Ontario, Canada
[8]Surgery/Critical Care Medicine, St. Michael's Hospital, Toronto, Ontario, Canada
[9]Department of Medicine, McMaster University, Hamilton, Ontario, Canada
[10]Department of Clinical Epidemiology, University of Ottawa, Ottawa, Ontario, Canada
[11]ICES @uOttawa, Institute for Clinical Evaluative Sciences, Ottawa, Ontario, Canada
[12]Clinical Epidemiology, The Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
[13]Anesthesiology, University of Ottawa Faculty of Medicine, Ottawa, Ontario, Canada
[14]Department of Pediatrics, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada
[15]Department of Medicine, The Ottawa Hospital, Ottawa, Ontario, Canada
[16]Epidemiology, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
[17]Surgery, Ottawa Hospital, Ottawa, Ontario, Canada
[18]Department of Emergency Medicine, Ottawa Hospital Research Institute Clinical Epidemiology Program, Ottawa, Ontario, Canada
[19]Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada
[20]Rotman Institute of Philospohy, Western University Faculty of Science, London, Ontario, Canada
[21]Critical Care, Kingston General Hospital, Kingston, Ontario, Canada
[22]Internal Medicine, The Ottawa Hospital, Ottawa, Ontario, Canada
[23]Clinical Epidemiology Program, The Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

Twitter Alison Fox-Robichaud @drfoxrob and John Marshall @DrJohnCMarshall

Acknowledgements We would like to thank the Canadian Critical Care Trials Group (CCCTG) for their assistance with the design and implementation of the FLUID pilot trial and Dr Tsang for her critical review of this manuscript. We would also like to thank Matthieu Laplante, Stuart Meredith and Natalie Ladouceur at the Ottawa Hospital General and Civic campuses, Ellen McDonald, Tracey Reynolds, Dave Wilson at Hamilton Health Sciences Centre, and Melissa Doherty, Alison Giourard, Mark Stinson, Kristian Gunderson at the Queensway Carleton hospital, their contributions related to planning, preparing and conducting a successful roll out of FLUID at our participating hospitals. We would also like to thank the Alies Maybee, our patient partner, as well as the Patient and Family Advisory Council at the Ottawa Hospital for discussions related to waiver of consent. Thank you to Robin Ducharme for her assistance with ICES data definitions and Ewa Sucha and Meltem Tuna for their longstanding work analysing the ICES data. Finally, we would also like to thank all of our clinical staff and logistical services personnel from our participating hospitals for their collective support for FLUID.

Contributors LAM, MT and DAF conceived the project idea. All authors (LAM, MT, DAF, DJC, TM, AF-R, SWE, CMartin, JMarshall, KM, JMuscedere, CW, RS, AI, AJF, IDG, SH, CMcCartney, AS, IS, KT) contributed to the development of the trial protocol. LAM created the initial draft of the manuscript. All authors contributed critical revisions and approved the final version of the manuscript. LAM is the guarantor of this study.

Funding The FLUID pilot trial was funded by the Canadian Institutes for Health Research (2015-0619) and the TOHAMO Innovation Fund Competition (2016-0356) who did not contribute to the design of the FLUID pilot protocol. This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC).

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval The pilot trial was submitted and granted ethical approval through the Ottawa Health Sciences Network Research Ethics Board (REB) Protocol # 21050619 and as board of record on behalf of Clinical Trials Ontario (Project ID number: 0778) and the Queensway Carleton Hospital REB (Study 16-5).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. Not applicable - All clinical data in this manuscript was sourced from a provincial health administrative database in the province of Ontario, Canada (Institute for Clinical Evaluative Sciences). As such, access to any individual level patient data is not available.

ORCID iDs

Lauralyn Ann McIntyre http://orcid.org/0000-0001-7421-1407
Dean A Fergusson http://orcid.org/0000-0002-3389-2485
Alison Fox-Robichaud http://orcid.org/0000-0001-9912-3606
Shane W English http://orcid.org/0000-0002-9477-6146
Kednapa Thavorn http://orcid.org/0000-0003-4738-8447
Monica Taljaard http://orcid.org/0000-0002-3978-8961

REFERENCES

1 Myburgh JA, Mythen MG. Resuscitation fluids. *N Engl J Med* 2013;369:1243–51.
2 Self WH, Semler MW, Wanderer JP, *et al*. Balanced crystalloids versus saline in noncritically ill adults. *N Engl J Med* 2018;378:819–28.
3 Burdett E, Dushianthan A, Bennett-Guerrero E, *et al*. Perioperative buffered versus non-buffered fluid administration for surgery in adults. *Cochrane Database Syst Rev* 2012;12:CD004089.
4 Orbegozo Cortés D, Rayo Bonor A, Vincent JL. Isotonic crystalloid solutions: a structured review of the literature. *Br J Anaesth* 2014;112:968–81.
5 Kawano-Dourado L, Zampieri FG, Azevedo LCP, *et al*. Low- versus high-chloride content intravenous solutions for critically ill and perioperative adult patients: a systematic review and meta-analysis. *Anesth Analg* 2018;126:513–21.
6 Zhou F, Peng Z-Y, Bishop JV, *et al*. Effects of fluid resuscitation with 0.9 % saline versus a balanced electrolyte solution on acute kidney injury in a rat model of sepsis*. *Crit Care Med* 2014;42:e270–8.
7 Yunos NM, Kim IB, Bellomo R, *et al*. The biochemical effects of restricting chloride-rich fluids in intensive care. *Crit Care Med* 2011;39:2419–24.
8 Fitzgibbons LJ, Snoey ER. Severe metabolic alkalosis due to baking soda ingestion: case reports of two patients with unsuspected antacid overdose. *J Emerg Med* 1999;17:57–61.
9 Mennen M, Slovis CM. Severe metabolic alkalosis in the emergency department. *Ann Emerg Med* 1988;17:354–7.
10 Gawarammana IB, Coburn J, Greene S, *et al*. Severe hypokalaemic metabolic alkalosis following ingestion of Gaviscon. *Clin Toxicol (Phila)* 2007;45:176–8.
11 Todd SR, Malinoski D, Muller PJ, *et al*. Lactated Ringer's is superior to normal saline in the resuscitation of uncontrolled hemorrhagic shock. *J Trauma* 2007;62:636–9.
12 Hadimioglu N, Saadawy I, Saglam T, *et al*. The effect of different crystalloid solutions on acid-base balance and early kidney function after kidney transplantation. *Anesth Analg* 2008;107:264–9.
13 Scheingraber S, Rehm M, Sehmisch C, *et al*. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. *Anesthesiology* 1999;90:1265–70.
14 Butscher K, Jamali S, Talib R, *et al*. Effects of different loading solutions on plasma osmolality. *Ann Fr Anesth Reanim* 1996;15:1037–40.
15 Semler MW, Self WH, Wanderer JP, *et al*. Balanced crystalloids versus saline in critically ill adults. *N Engl J Med* 2018;378:829–39.
16 Finfer S, Micallef S, Hammond N, *et al*. Balanced multielectrolyte solution versus saline in critically ill adults. *N Engl J Med* 2022;386:815–26.
17 Zampieri FG, Machado FR, Biondi RS, *et al*. Effect of intravenous fluid treatment with a balanced solution vs 0.9 % saline solution on mortality in critically ill patients: the basics randomized clinical trial. *JAMA* 2021;326:1–12.
18 Waters JH, Gottlieb A, Schoenwald P, *et al*. Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. *Anesth Analg* 2001;93:817–22.
19 Young JB, Utter GH, Schermer CR, *et al*. Saline versus Plasma-Lyte A in initial resuscitation of trauma patients: a randomized trial. *Ann Surg* 2014;259:255–62.
20 Verma B, Luethi N, Cioccari L, *et al*. A multicentre randomised controlled pilot study of fluid resuscitation with saline or Plasma-Lyte 148 in critically ill patients. *Crit Care Resusc* 2016;18:205–12.
21 Semler MW, Wanderer JP, Ehrenfeld JM, *et al*. Balanced crystalloids versus saline in the intensive care unit. The salt randomized trial. *Am J Respir Crit Care Med* 2017;195:1362–72.
22 ESICM lives 2017: 30th ESICM annual congress. september 23-27, 2017. *Intensive Care Med Exp* 2017;5:44.
23 Choosakul S, Harinwan K, Chirapongsathorn S, *et al*. Comparison of normal saline versus lactated ringer's solution for fluid resuscitation in patients with mild acute pancreatitis, a randomized controlled trial. *Pancreatology* 2018;18:507–12.
24 Kunupakan S, Thamrongsa N, *et al*. The effect of fluid resuscitation with normal saline versus ringer's acetate on renal function and host defense in severe sepsis/septic shock patients: a randomised controlled trial (abstrat). The 34th Annual Meeting; Thailand: The Royal College of Physicians of Thailand, 2018
25 Golla R, Kumar S, Dhibhar DP, *et al*. 0.9 % saline V/s Ringe''s lactate for fluid resuscitation in adult sepsis patients in emergency medical services: an open-label randomized controlled trial. *Hong Kong Journal of Emergency Medicine* 2022;29:271–80.
26 Ramanan M, Attokaran A, Murray L, *et al*. Sodium chloride or plasmalyte-148 evaluation in severe diabetic ketoacidosis (SCOPE-

DKA): a cluster, crossover, randomized, controlled trial. *Intensive Care Med* 2021;47:1248–57.
27 Hammond NE, Zampieri FG, Di Tanna GL, *et al*. Balanced crystalloids versus saline in critically ill adults — a systematic review with meta-analysis. *NEJM Evidence* 2022;1:EVIDoa2100010.
28 Young P, Bailey M, Beasley R, *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.
29 McIntyre L, Taljaard M, McArdle T, *et al*. Fluid trial: a protocol for a hospital-wide open-label cluster crossover pragmatic comparative effectiveness randomised pilot trial. *BMJ Open* 2018;8:e022780.
30 Taljaard M, Weijer C, Grimshaw JM, *et al*. The ottawa statement on the ethical design and conduct of cluster randomised trials: precis for researchers and research ethics committees. *BMJ* 2013;346:f2838.
31 Intensive Care, S. and M. Department of Health. *Comprehensive critical care: a review of adult critical care services*. 2011.
32 Friedman JN, Canadian Paediatric Society, Acute Care Committee. Risk of acute hyponatremia in hospitalized children and youth receiving maintenance intravenous fluids. *Paediatr Child Health* 2013;18:102–7.
33 Juurlink D, Preyra C, Croxford R, *et al*. *Canadian institute for health information discharge abstract database: A validation study*. Toronto, Ontario, Canada, 2006.
34 Richards J, Brown A, Homan C. The data quality study of the canadian discharge abstract database. Proceedings of Statistics Canada Symposium 2001; Canadian Institute for Health Information, 2001
35 Eldridge SM, Chan CL, Campbell MJ, *et al*. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *BMJ* 2016;355:i5239.
36 Sim J. Should treatment effects be estimated in pilot and feasibility studies? *Pilot Feasibility Stud* 2019;5:107.
37 Canadian Institutes of Health. *Tri-council policy statement: ethical conduct for research involving humans*. 2014.
38 Alghamdi NA, Major P, Chaudhuri D, *et al*. Saline compared to balanced crystalloid in patients with diabetic ketoacidosis: a systematic review and meta-analysis of randomized controlled trials. *Crit Care Explor* 2022;4:e0613.
39 Hemming K, Taljaard M, Weijer C, *et al*. Use of multiple period, cluster randomised, crossover trial designs for comparative effectiveness research. *BMJ* 2020;371:m3800.