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# The FLUID Trial: A Hospital – Wide Open - Label Cluster Cross-Over Pragmatic Comparative Effectiveness Randomized Pilot Trial

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# The FLUID Trial: A Hospital-Wide Open-Label Cluster Cross-Over Pragmatic Comparative Effectiveness Randomized Pilot Trial

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**Keywords:**

fluid therapy, normal saline, Ringer's lactate, randomized trial, pragmatic, comparative effectiveness

## Strengths and limitations of this study

- The FLUID pilot trial was an innovative pragmatic cluster randomized cross-over trial, with randomization done at the hospital level and inclusion of all patients by using routinely collected health administrative data.
- The study fluid (NS or RL) was the dominant (at least 80%) fluid stocked throughout the hospital to ensure patients received the same study fluid from hospital entry to hospital discharge.
- The addition of run-outs after study period 1 and 2 served to further reduce the possibility of contamination.
- 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 inititated the pilot trial at the same time

ABSTRACT

**Introduction:** 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 (e.g. hyperchloremic metabolic acidosis, impaired kidney function and death), few large multi-centre randomized 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.

**Methods:** FLUID was a pragmatic pilot cluster randomized cross-over trial in which four hospitals were randomized to a hospital policy/strategy of stocking either NS or RL throughout the hospital for all patients (adult and pediatric, excluding neonates) for 12 weeks, before crossing over to the alternate fluid for the subsequent 12 weeks. Clinical data were obtained through provincial health administrative data held at the Institute for Clinical Evaluative Sciences (ICES). 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 hospitalization) and secondary clinical outcomes were analyzed 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 litres (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 2-48 days and readiness for trial initiation from 51-331 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.

## 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 hospitalized patients [1, 2]. These fluids may be used as a life-saving measure to re-establish hemodynamic stability, for rehydration, to replace fluid losses and to maintain intravascular volume.

In observational studies, NS as compared to RL and other balanced crystalloid fluids have been associated with acute renal injury hypothesized 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 edema formation [14], which raises potential concern for patients with cerebral edema.

Recently, two large multi-centre randomized trials (BaSICS, n=11,052 and PLUS, n=5037) [15, 16] examined the efficacy of NS as compared to a balanced crystalloid (Ringer's lactate 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, authors did not detect differences in renal function. In low risk of bias trials, authors also did not detect

a significant difference in mortality for the 0.9 saline as compared to balanced crystalloid group (mortality in NS versus Balanced Crystalloid groups: 28.2% and 27.9%; Relative Risk 0.96 (95% Confidence Interval: 0.91 – 1.01), nor renal function.[17] However, authors also concluded that there is a high probability balanced crystalloids reduce death since the confidence intervals ranged from a 9% relative reduction to a 1% relative increase in death.

Crystalloid fluids are not limited to use in the intensive care unit, but are administered to the majority of patients admitted to hospital and throughout their care. Hence, we designed a cluster cross-over randomized trial to compare a hospital-wide policy/strategy which stocked NS or RL as the main crystalloid resuscitation fluid with a primary composite outcome of death or re-admission to hospital in the first 90 days, aiming to have patients receive the same crystalloid fluid from entry to hospital to their hospital discharge. As a necessary first step, our team conducted the FLUID pilot trial to examine feasibility related to study fluid protocol adherence, time to research ethics board (REB) approvals, and time to readiness to initiate the trial.

## METHODS

### 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).

## 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 [18] and is registered with clinicaltrials.gov (NCT02721485).

FLUID was a pragmatic, open-label, hospital-wide cluster randomized cross-over trial (see Figure 1) conducted in three tertiary care hospitals and one community hospital in Ontario, Canada. Cluster randomization was justified in accordance with the Ottawa Statement [19], because randomizing 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 minimize contamination and maximize 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 analyze health care and demographic data, without consent, for health system evaluation and improvement.

## Patient and Public Partnership:

Our patient partner 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.

**Trial Preparation and Conduct Strategies:**

A standardized strategy for site trial preparation and conduct was implemented and is summarized in detail in the published FLUID protocol BMJ Open 2018;8;e022780.doi.1136/bmjopen-2018-022780.[18]

**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 [20].

Exclusion criteria at *hospital level:* We excluded hospitals that had fewer than 6,000 acute care admissions per year (< 1,500 admissions per study period).

Inclusion criteria at *patient level:* Adult and pediatric 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 [21]. Patients who were re-admitted 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 Randomization

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 randomized 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 one served as a run-in, weeks two to 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 two to 13. After the one week run-out period, hospitals had up to an additional three weeks to cross-over to period two study fluid.

## Strategies to Minimize Contamination

The risk of contamination due to non-adherence to the study fluid was minimized through six mechanisms. (1) An automatic substitution order for the study fluid was invoked during the trial study periods: nurses were authorized 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 minimize the occurrence of patients being exposed to two different kinds of fluids during the same hospitalization.

**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 [18] (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 (e.g., severe hyperkalemia, 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 4 participating hospitals combined and by individual hospitals over the 12 week study periods. Adherence was monitored at two week intervals over the 12-week (weeks 2 – 13) study periods and described according to each study group across all 4 participating hospitals combined and according to major fluid user groups (Emergency Department (ED), Medicine, Surgery, Operating Room (OR), Post Operative Assessment Unit (PACU), Obstetrics, Intensive Care Unit (ICU).

## Secondary Feasibility Outcomes

**Time to Research Ethics Board (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 three 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 three 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 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%) [22, 23].

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, emergency department visits within the first 90 days of the index hospitalisation, length of stay in hospital and hospital discharge disposition.

**Subgroup Analyses**

Several pre-defined 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 authorized under section 45 of Ontario's personal health Information Protection Act, which does not require review by a Research Ethics Board. Trial and intervention costs were estimated from the trial budget, financial records, and service level agreements. No additional data available. A data dictionary which summarizes all administrative databases searched as well as ICD 10 codes for each variable in FLUID is described in the Supplementary 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 standard deviations or medians with interquartile ranges as appropriate for continuous data, and frequencies and proportions for categorical and dichotomous variables. For clinical outcomes, 95% two-sided confidence intervals were included. In accordance with the FLUID pilot protocol, clinical outcomes were not analyzed by study fluid group [18] because the primary objectives were to examine the feasibility of conducting the large trial. Preliminary sample size calculations which include varying within and between cluster correlation co-efficients which are required for cluster RCT sample size calculations are summarized in the FLUID pilot protocol [18].

## 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.

## 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 (Standard Deviation (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%).

Table 1 Baseline Characteristics

| | **Total # Index Admissions** N=24,905 | **Normal Saline** N=12,338 | **Ringers Lactate** N =12,567 |
|---|---|---|---|
| Sex, female, n (%) | 13,977 (56.1%) | 6,976 (56.5%) | 7,001 (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%) | 6,756 (54.8%) | 7,036 (56.0%) |
| >65 to 80 | 6,771 (27.2%) | 3,368 (27.3%) | 3,403 (27.1%) |
| >80 | 4,174 (16.8%) | 2,139 (17.3%) | 2,035 (16.2%) |
| **Case Mix Group n (%)** | | | |
| Medicine | 10,773 (43.3%) | 5,449 (44.2%) | 5,324 (42.4%) |
| Surgery | 10,377 (41.7%) | 5,080 (41.2%) | 5,297 (42.2%) |
| Pregnancy and Childbirth | 3,614 (14.5%) | 1,744 (14.1%) | 1,870 (14.9%) |
| Mental Health | 141 (0.6%) | 65 (0.5%) | 76 (0.6%) |
| **Type of surgical admission, n (%)** | | | |
| Elective | 5,796 (55.9%) | 2,852 (56.1%) | 2,944 (55.6%) |

| | Total # Index Admissions N=24,905 | Normal Saline N=12,338 | Ringers Lactate N =12,567 |
|---|---|---|---|
| Urgent | 4,581 (44.2%) | 2,228 (43.9%) | 2,353 (44.4%) |
| Surgical admission <24 hours, n (%) | 950 (9.2%) | 484 (9.5%) | 466 (8.8%) |
| **Severity of Illness** | | | |
| Admission to ICU, n (%) | 3,034 (12.2%) | 1,494 (12.1%) | 1,540 (12.3%) |
| Infection Alone and Infection and Organ Dysfunction, n (%) | 2,734 (12.0%) | 1,365 (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 | 2,819 (11.3%) | 1,396 (11.3%) | 1,423 (11.3%) |
| Hypertension, uncomplicated & complicated | 2,574 (10.3%) | 1,207 (9.8%) | 1,367 (10.9%) |
| Cardiac arrhythmias | 2,263 (9.1%) | 1,143 (9.3%) | 1,120 (8.9%) |
| Solid tumour without metastasis | 2,105 (8.5%) | 1,004 (8.1%) | 1,101 (8.8%) |
| Fluid and electrolyte disorders | 1,886 (7.6%) | 944 (7.7%) | 942 (7.5%) |
| Diabetes, uncomplicated | 1,374 (5.5%) | 686 (5.6%) | 688 (5.5%) |
| Congestive heart failure | 1,187 (4.8%) | 606 (4.9%) | 581 (4.6%) |
| Metastatic cancer | 1,008 (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%) |
| 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%) |

| | Total # Index Admissions N=24,905 | Normal Saline N=12,338 | Ringers Lactate N =12,567 |
|---|---|---|---|
| Deficiency anemia | 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 anemia | 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%) |

Legend: ICU = intensive care unit, SD = standard deviation, n = number

**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 litres respectively. Study fluid adherence targets of at least 80% overall (4 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 two 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 4 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% CIs: 21.7 – 22.8). Patients were admitted to hospital for a median of 3 days (interquartile range 1-6) and 3429 patients (13.1%, 95% CIs: (95% CI: 12.6 , 13.5) were discharged to a facility other than home. Other secondary clinical outcomes and sub-groups described according to the primary composite outcome are described in Tables 2 and 3 respectively.

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 hospitalization, n (%) | 5544 (22.3%, 95% CI: 21.7 , 22.8) |
| **Secondary Outcomes** | |
| Death within 90 days of index admission, n (%) | 1926 (7.7%, 95% CI: 7.4 , 8.1) |
| Re-admission within 90 days of index admission, n (%) | 4049 (16.3%, 95% CI: 15.8 , 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%, 95% CI: 0.75 , 0.98) |
| ED visit within 90 days of index admission, n (%) | 5499 (22.1%, 95% CI: 22.0 , 22.6) |
| **Discharge Disposition (detailed), n (%)** | |
| Discharged to facility other than home, n (%) | 3250 (13.1%, 95% CI: 12.6 , 13.5) |
| Transferred to another facility providing inpatient hospital care or acute care inpatient institution | 1080 (4.3%, 95% CI: 4.1 , 4.6) |
| Transferred to a long term or continuing care facility | 2072 (8.3%, 95% CI: 8.0 , 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%, 95% CI: 0.3 , 0.5) |
| Discharged to a home setting with support services | 4711 (19.0%, 95% CI: 18.4 , 19.4) |
| Discharged to home (no support service from an external agency required) | 15807 (63.5%, 95% CI: 63.0 , 64.1) |
| Signed out (against medical advice) | 189 (0.9%, 95% CI: 0.7 , 0.9) |

| | |
|---|---|
| Died | 948 (3.8%, 95% CI: 3.6 , 4.0) |
| **90-day total health system and sub-divided costs, mean ± SD**<br>** cost is calculated 90 days after index date | |
| Hospital cost (DAD) | |
| Inpatient cost | 12,499.7 ± 18,506.4 |
| Hospital outpatient clinic cost | 756.8 ± 934.4 |
| ED cost (NACRS) | 431.9 ± 577.4 |
| Dialysis cost (NACRS) | 138.9 ± 1,600.7 |
| Cancer care cost (NACRS) | 303.2 ± 1,805.2 |
| Medication cost (ODB) | 539.9 ± 2,081.6 |
| Outpatient cost (OHIP) | |
| Physician FFS billings | 3,139.1 ± 3,121.7 |
| 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 ± 22,101.3 |

Legend: n = number, SD = standard deviation, IQR = interquartile range, CI = confidence interval

Table 3 Description of Composite Primary Outcome in Pre-specified Subgroups

| | N (%, 95% CI) |
|---|---|
| **Sex** | |
| Female | 2774 (19.9%, 95% CI: 19.2 , 20.5) |
| Male | 2770 (25.4%, 95% CI: 24.5 , 26.2) |
| **Age Group** | |
| <=18 years (children & adolescents) | 20 (11.9%, 95% CI: 7.0 , 16.8) |
| >18 to 65 | 2149 (15.6%, 95% CI: 15.0 , 16.2) |
| >65 to 80 | 1811 (26.8%, 95% CI: 25.7 , 27.8) |
| >80 | 1564 (37.5%, 95% CI: 36 , 39.0) |
| **Case Mix Group** | |
| Medicine | 3560 (33.1%, 95% CI: 32.2 , 33.9) |
| Surgery | 1699 (16.4%, 95% CI: 15.7 , 17.1) |
| Pregnancy and Childbirth | 267 (7.4%, 95% CI: 6.5 , 8.2) |

| | |
|---|---|
| Mental Health | 18 (12.8%, 95% CI: 7.3 , 18.3) |
| **Type of Surgical Admission, n (%)** | |
| Elective Surgery | 677 (11.7%, 95% CI: 10.9 , 12.5) |
| Urgent Surgery | 1022 (22.3%, 95% CI: 21.1 , 23.5) |
| Surgical Admission <24 hours | 87 (9.2%, 95% CI: 7.3 , 11.0) |
| **Severity of Illness** | |
| Admission to Intensive Care Unit | 967 (31.9%, 95% CI: 30.2 , 33.5) |
| Infection Alone and Infection and Organ Dysfunction | 1076 (39.4%, 95% CI: 37.5 , 41.2) |
| Infection Alone and Infection and Organ Dysfunction and ICU admission | 276 (47.7%, 95% CI: 43.6 , 51.7) |
| Trauma + ICU | 77 (43.8%, 95% CI: 36.4 , 51.1) |
| Traumatic Brain Injury | 49 (40.5%, 95% CI: 31.8 , 49.2) |
| Traumatic Brain Injury + ICU | 34 (53.1%, 95% CI: 40.9 , 65.4) |
| New dialysis within 90 days of index admission | 51 (57.30%, 95% CI: 47.03 , 67.58) |

Legend: ICU = intensive care unit, % = percent; CI = Confidence Interval

## DISCUSSION

The FLUID trial design is innovative in its use of a pragmatic cluster randomized cross-over design, a waiver of patient informed consent to include all hospitalized patients, hospital based randomization, 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 approval time, and readiness to initiate the trial. The REB approval target of 3 months was met for all 4 study sites. However, for three of the four centres, the REB approval process was centralized which avoided delays. In the large trial, a centralized 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).

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 [24] 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, pre-specifed 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 pre-trial communication and educational enhancement strategies (e.g. medicine wards).

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 (e.g., medication delivery, catheter patency and flushes, coadministration for blood products, surgical wound washouts, and during dialysis). These reasons for lower adherence may have overestimated adherence to NS and underestimated adherence to RL. 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 randomization sequences. Ideally, all sites in the large trial should be randomized either at one time or in batches [25]. 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 multicentre trial is feasible. The large trial will determine whether RL as compared to NS reduces death or requirement for hospital re-admission by an absolute difference of 1%. FLUID will provide important guidance as to what fluid(s) could be predominantly stocked for use throughout the hospital and the associated healthcare resources required for such supply. 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.

**Authors Contributions:** LM, MT and DF conceived the project idea. All authors (LM, MT, DF, DC, DF, TM, AFR, SE, CM, JM, KM, JMu, DC, CW, RS, AI, AF, IG, SH, CMc, AS, IS, KT, DF) contributed to the development of the trial protocol. LM created the initial draft of the manuscript. All authors contributed critical revisions and approved the final version of the manuscript.

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## REFERENCE LIST

1. Myburgh, J.A. and M.G. Mythen, *Resuscitation Fluids.* N Engl J Med, 2013. **369**(13): p. 1243-1251.

2. Self, W.H., et al., *Balanced Crystalloids versus Saline in Noncritically Ill Adults.* N Engl J Med, 2018. **378**(9): p. 819-828.

3. Burdett, E., et al., *Perioperative buffered versus non-buffered fluid administration for surgery in adults.* Cochrane.Database.Syst.Rev., 2012. **12**: p. CD004089.

4. Orbegozo, C.D., B.A. Rayo, and J.L. Vincent, *Isotonic crystalloid solutions: a structured review of the literature.* British Journal of Anaesthesia, 2014. **112**(6): p. 968-981.

5. Kawano-Dourado, L., 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**(2): p. 513-521.

6. Zhou, F., 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**(4): p. e270-e278.

7. Yunos, N.M., et al., *The biochemical effects of restricting chloride-rich fluids in intensive care.* Crit Care Med., 2011. **39**(11): p. 2419-2424.

8. Fitzgibbons, L.J. and E.R. Snoey, *Severe metabolic alkalosis due to baking soda ingestion: case reports of two patients with unsuspected antacid overdose.* The Journal of Emergency Medicine, 1999. **17**(1): p. 57-61.

9. Mennen, M. and C.M. Slovis, *Severe metabolic alkalosis in the emergency department.* Annals of Emergency Medicine, 1988. **17**(4): p. 354-357.

10. Gawarammana, I.B., et al., *Severe hypokalaemic metabolic alkalosis following ingestion of gaviscon.* Clin.Toxicol.(Phila), 2007. **45**(2): p. 176-178.

11. Todd, S.R., et al., *Lactated Ringer's is superior to normal saline in the resuscitation of uncontrolled hemorrhagic shock.* Journal of Trauma, 2007. **62**(3): p. 636-639.

12. Hadimioglu, N., et al., *The effect of different crystalloid solutions on acid-base balance and early kidney function after kidney transplantation.* Anesthesia and Analgesia, 2008. **107**(1): p. 264-269.

13. Scheingraber, S., et al., *Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery.* Anesthesiology, 1999. **90**(5): p. 1265-1270.

14. Butscher, K., et al., *[Effects of different loading solutions on plasma osmolality].* Annales Francaises d'Anesthesie et de Reanimation, 1996. **15**(7): p. 1037-1040.

15. Finfer, S., et al., *Balanced Multielectrolyte Solution versus Saline in Critically Ill Adults.* N Engl J Med, 2022.

16. Zampieri, F.G., 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**(9): p. 1-12.

17. Hammond Naomi, E., et al., *Balanced Crystalloids versus Saline in Critically Ill Adults — A Systematic Review with Meta-Analysis.* NEJM Evidence, 2022. **1**(2): p. EVIDoa2100010.

18. McIntyre, L., et al., *FLUID trial: a protocol for a hospital-wide open-label cluster crossover pragmatic comparative effectiveness randomised pilot trial.* BMJ Open, 2018. **8**(8): p. e022780.

19. Taljaard, M., et al., *The Ottawa Statement on the ethical design and conduct of cluster randomised trials: precis for researchers and research ethics committees.* British Medical Journal, 2013. **346**: p. f2838.

20. Intensive Care, S. and M. Department of Health, *Comprehensive Critical Care: a review of adult critical care services*. 2011.

21. Friedman, J.N., *Risk of acute hyponatremia in hospitalized children and youth receiving maintenance intravenous fluids.* Paediatr.Child Health, 2013. **18**(2): p. 102-107.

22. Juurlink, D., et al., *Canadian Institute for Health Information Discharge Abstract Database: A Validation Study*. 2006, The Institute for Clinical Evaluative Sciences (ICES): Toronto, Ontario, Canada.

23. Richards, J., A. Brown, and C. Homan, *The Data Quality Study of the Canadian Discharge Abstract Database.* Canadian Institute for Health Information, 2001. **Proceedings of Statistics Canada Symposium 2001**.

24. Canadian Institutes of Health, R., et al., *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*. 2014.

25. Hemming, K., et al., *Use of multiple period, cluster randomised, crossover trial designs for comparative effectiveness research.* Bmj, 2020. **371**: p. m3800.

## Figure Legends

**Legend Figure 1: FLUID Pilot Trial Study Design**: Study fluid for the first study period was stocked from 1–3 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 familiarized 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 hospitalizations 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.

**Legend Figure 2: Consort Flow Diagram**

Legend Figure 3: Overall 0.9% Saline Compliance and by Study Site: The number (%) over the first histogram bar summarizes adherence to 0.9% saline which was calculated by adding the total combined volume of 0.9% saline at all 4 sites divided by the total combined volume of 0.9% saline and Ringer's lactate at all 4 sites during the 12-week 0.9% saline study period. The numbers (%) below each histogram bar summarize 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 4 sites combined.

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

**Legend Figure 5: All Sites Overall Study Fluid Compliance Over 2-Week Intervals**: The number (%) over each histogram bar summarizes compliance to 0.9% saline and Ringer's lactate for all 4 sites combined in 2-week intervals over the 12-week study period.

**Legend Figure 6: All Sites Overall Study Fluid Compliance: Major Fluid User Groups**: The numbers (%) over the histogram bars summarizes adherence to 0.9% saline and Ringer's lactate 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 Ringer's lactate for that fluid user group during each 12-week study period. The numbers (%) below each histogram summarize 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 4 sites combined. Abbreviations: ED = Emergency Department, OR = Operating Room, ICU = Intensive Care Unit, PACU = Post Anesthetic Care Unit, OBS = Obstetrics

**Figure 1: FLUID Pilot Trial Study Design**

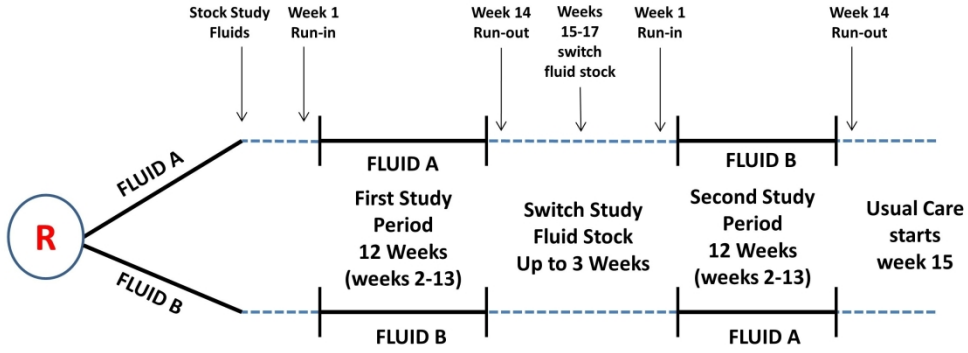


Figure 1

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**Figure 2: Consort Flow Diagram**

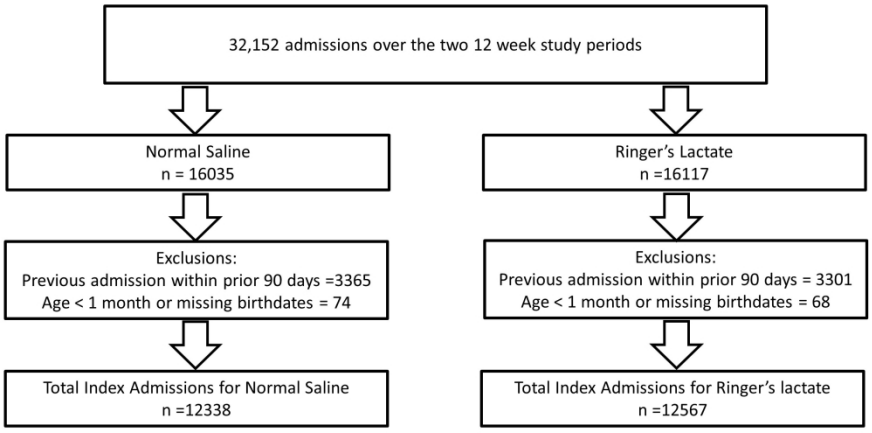


Figure 2

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**Figure 3: 0.9% Saline Compliance: Overall and by Site**

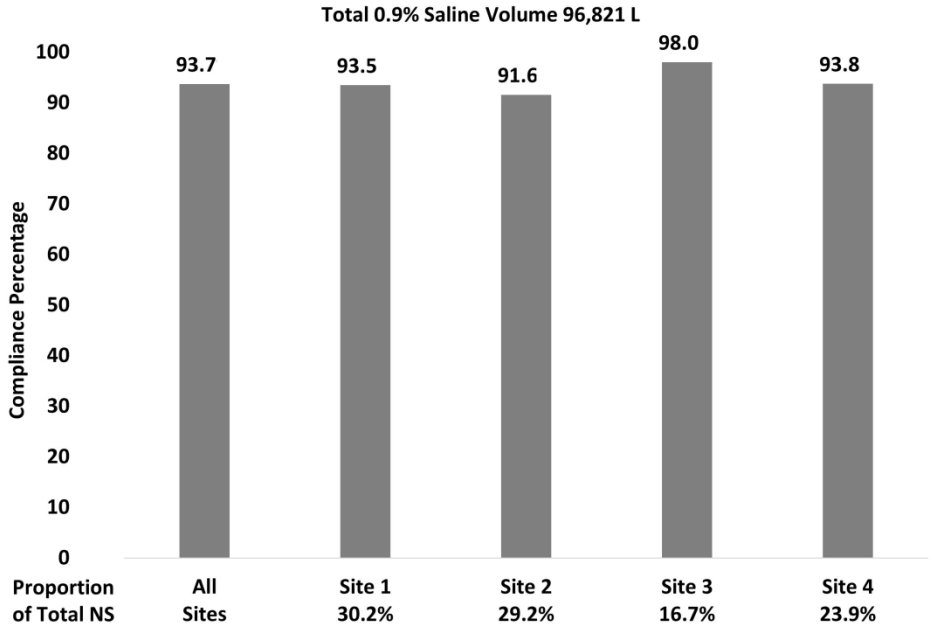


Figure 3

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**Figure 4: Ringer's Lactate Compliance: Overall and by Site**

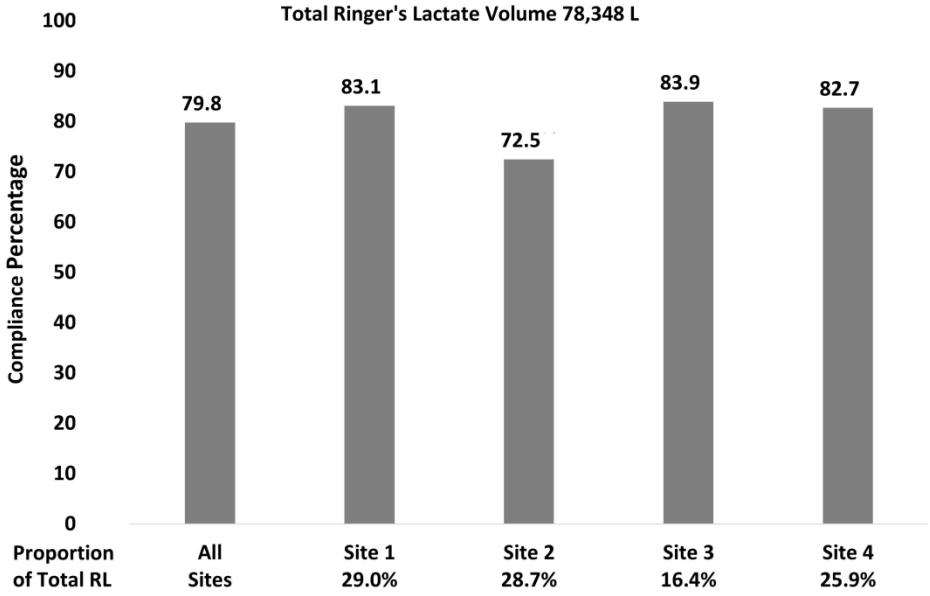


Figure 4

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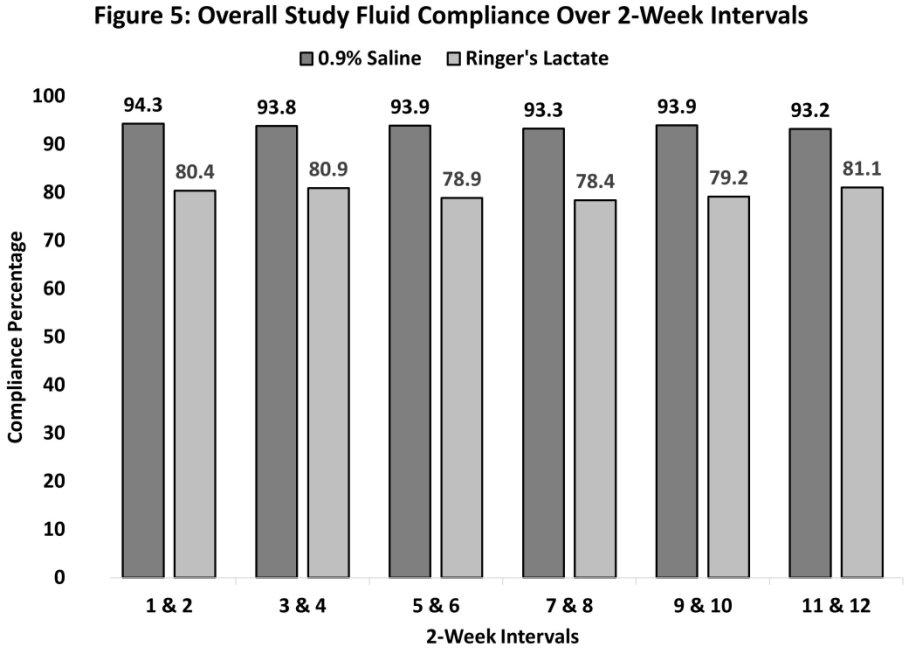


Figure 5

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**Figure 6: All Sites Overall Study Fluid Compliance: Major Fluid User Groups**

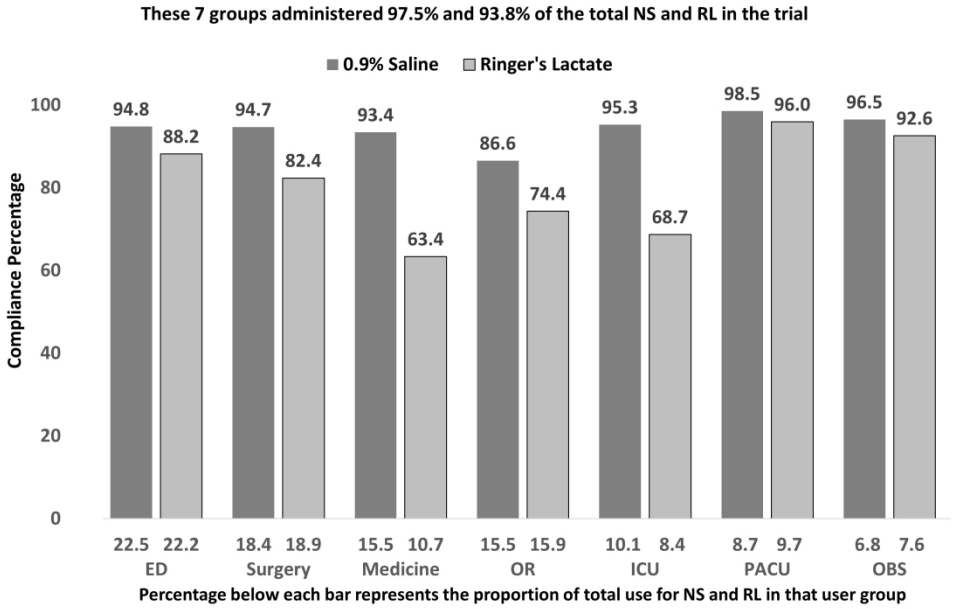


Figure 6

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# Supplementary Appendix I

## The FLUID Trial: A Hospital-Wide Open-Label Cluster Cross-Over Pragmatic Comparative Effectiveness Randomized Pilot Trial

**Table of Contents**

## Summary

This document defines the codes utilized for variables utilized in the trial dataset. Data was obtained using Ontario's population-based health administrative databases at the Institute for Clinical Evaluative Sciences (ICES). ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. Trained coders review all hospital charts upon discharge to record appropriate diagnosis codes and their characteristics. Coders follow the Canadian Coding Standards developed by the Canadian Institute for Health Information (CIHI).[1] These datasets were linked using unique encoded identifiers and analyzed at ICES.

Databases utilized for variables include:

- Registered Persons Database (RPDB)
- Discharge Abstract Database (DAD)
- Ontario Mental Health Reporting System (OMHRS)
- National Ambulatory Care Reporting System (NACRS)
- Ontario Health Insurance Plan (OHIP)
- Same Day Surgery (SDS)

Calculation of Costing may also include information from:

- Ontario Drug Benefit (ODP)
- OHIP lab claims (all OHIP billings have a fee code beginning with 'L')
- OHIP physician billings
- Home Care Services (OACCAC HCD)
- Complex & Continuing Care (CCRS)
- National Rehabilitation System (NRS)
- Continuing Care Reporting System (CCRS)
- Home Care Services (OACCAC HCD)
- FHO/FHN capitation
- Long term Care
- Hospital outpatient clinic
- NACRS ED visits
- NACRS visits to dialysis clinics
- BACRS visits to cancer clinics
- NDFP chemotherapy drugs
- Assistive Device Programs

**Table 1. Baseline Characteristics**

## 1. Demographics

| RPDB Code | Definition |
|---|---|
| Gender | The sex of the patient as recorded |
| Age | Birthdate subtracted from date of index hospital admission |

## 2. Case Mix Group (CMG)

A CMG is a numbered cell/group to which an acute care inpatient is assigned. CMG+ CIHI grouping methodology that categorizes acute care patients based on similarities of diagnosis and/or interventions, length of stay (LOS) and resource use.

| Database | CMG cell |
|---|---|
| DAD | Medicine |
| DAD | Surgery |
| DAD | Pregnancy & Childbirth |
| OMHRS, DAD | Mental Health |

## 3. Type of Surgical Admission

| Database | Category | Definition |
|---|---|---|
| DAD | L (elective) | Non-emergent surgery |
| DAD | U (urgent) | Urgent/emergent |
| DAD | Surgical admission < 24 hrs | The number of surgical admissions < 24 hrs using a calculated length of hospital stay by admit date/time and discharge date/time |

## 4. Severity of Illness

### A. Admission to ICU

Special Care Units (SCU) identify location of critical care

| Database | SCU 1-6 Code | Unit |
|---|---|---|
| DAD | 10 | Medical Intensive Care Unit |
| DAD | 20 | Surgical Intensive Care Nursing Unit |
| DAD | 25 | Trauma Intensive Care Nursing Unit |
| DAD | 30 | Combined Medical/Surgical Intensive Care Nursing Unit |
| DAD | 35 | Burn Intensive Care Nursing Unit |
| DAD | 40 | Cardiac Intensive Care Nursing Unit Surgery |
| DAD | 45 | Coronary Intensive Care Nursing Unit Medical |
| DAD | 60 | Neurosurgery Intensive Care Nursing Unit |
| DAD | 70 | Paediatric Intensive Care Nursing Unit |
| DAD | 80 | Respirology Intensive Care Nursing Unit |

### B. Infection Alone and Infection and Organ Dysfunction

All patients admitted to the entire hospital (including ICU (SCU location code)) with a code for Infection alone (ICD 10 infection code) and Infection and organ dysfunction (ICD 10 infection code + ICD 10 organ dysfunction code and/or a Canadian Classification of Health Interventions (CCI) code listed below).

### C. Infection Alone and Infection and Organ Dysfunction and ICU admission

All patients admitted to the ICU (SCU location code) who have an infection alone code (ICD 10 infection code) and infection and organ dysfunction (ICD 10 infection code + ICD 10 organ dysfunction code and/or CCI code listed below)

**ICD 10 Infection Codes**

| ICD-10 | Definition |
|---|---|
| A039 | Shigellosis, unspecified |
| A021 | Salmonella sepsis |
| A207 | Septicaemic plague |
| A217 | Generalized tularaemia |
| A227 | Anthrax sepsis |
| A239 | Brucellosis, unspecified |
| A241 | Acute and fulminating melioidosis |
| A267 | Erysipelothrix sepsis |
| A280 | Pasteurellosis |
| A282 | Extraintestinal yersiniosis |
| A327 | Listerial sepsis |
| A392 | Acute meningococcaemia |
| A393 | Chronic meningococcaemia |
| A394 | Meningococcaemia, unspecified |
| A40 | Streptococcal septicaemia |
| A400 | Sepsis due to streptococcus, group A |
| A401 | Sepsis due to streptococcus, group B |
| A402 | Sepsis due to streptococcus, group D |
| A403 | Sepsis due to Streptococcus pneumoniae |
| A408 | Other streptococcal sepsis |
| A409 | Streptococcal sepsis, unspecified |

| ICD-10 | Definition |
|---|---|
| A41 | Other septicaemia |
| A410 | Sepsis due to Staphylococcus aureus |
| A411 | Sepsis due to other specified staphylococcus |
| A412 | Sepsis due to unspecified staphylococcus |
| A413 | Sepsis due to Haemophilus influenzae |
| A414 | Sepsis due to anaerobes |
| A4150 | Sepsis due to Escherichia coli [E.coli] |
| A4151 | Sepsis due to Pseudomonas |
| A4152 | Sepsis due to Serratia |
| A4158 | Sepsis due to other Gram-negative organisms |
| A4159 | Gram-negative septicaemia, unspecified |
| A4180 | Sepsis due to Enterococcus |
| A4188 | Other specified sepsis |
| A419 | Sepsis, unspecified |
| A047 | Enterocolitis due to Clostridium difficile |
| A427 | Actinomycotic sepsis |
| A4880 | Necrotizing fasciitis |
| A480 | Gas gangrene |
| A482 | Nonpneumonic Legionnaires' disease [Pontiac fever] |
| A483 | Toxic shock syndrome |
| A87 | Viral meningitis |
| B007 | Disseminated herpesviral disease |
| B377 | Candidal sepsis |
| B9548 | Other streptococcus as the cause of diseases classified to other chapters |
| B956 | Staphylococcus aureus as the cause of diseases classified to other chapters |
| B962 | Escherichia coli [E. coli] as the cause of diseases classified to other chapters |
| J189 | Pneumonia, unspecified |
| J440 | Chronic obstructive pulmonary disease with acute lower respiratory infection |
| N390 | Urinary tract infection, site not specified |
| P36 | Bacterial sepsis of newborn |
| P360 | Sepsis of newborn due to streptococcus, group B |
| P361 | Sepsis of newborn due to other and unspecified streptococci |
| P362 | Sepsis of newborn due to Staphylococcus aureus |
| P363 | Sepsis of newborn due to other and unspecified staphylococci |
| P364 | Sepsis of newborn due to Escherichia coli |
| P365 | Sepsis of newborn due to anaerobes |
| P368 | Other bacterial sepsis of newborn |
| P369 | Bacterial sepsis of newborn, unspecified |
| P352 | Congenital herpesviral [herpes simplex] infection |
| P372 | Neonatal (disseminated) listeriosis |
| P375 | Neonatal candidiasis |

**ICD-10 Organ Dysfunction Codes and CCI Codes**

| | |
|---|---|
| R572 | Septic shock |
| J960 | Acute respiratory failure |
| J969 | Respiratory failure, unspecified |
| J80 | Adult respiratory distress syndrome |
| R092 | Respiratory arrest |
| R570 | Cardiogenic shock |
| R571 | Hypovolaemic shock |
| R578 | Other shock |

| | |
|---|---|
| R57.9 | Shock, unspecified |
| I951 | Orthostatic hypotension |
| I958 | Other hypotension |
| I959 | Hypotension, unspecified |
| N170 | Acute renal failure with tubular necrosis |
| N171 | Acute renal failure with acute cortical necrosis |
| N172 | Acute renal failure with medullary necrosis |
| N178 | Other acute renal failure |
| N179 | Acute renal failure, unspecified |
| K720 | Acute and subacute hepatic failure |
| K729 | Hepatic failure, unspecified |
| K763 | Infarction of liver |
| F050 | Delirium not superimposed on dementia, so described |
| F059 | Delirium, unspecified |
| G931 | Anoxic brain damage, not elsewhere classified |
| G934 | Other and unspecified encephalopathy |
| G93.80 | Metabolic encephalopathy |
| D69.5 | Secondary thrombocytopenia |
| D69.6 | Thrombocytopenia, unspecified |
| D65 | Disseminated intravascular coagulation |
| **Intervention Codes (CCI)** | |
| GZ.31.CA-ND | Ventilation, respiratory system NEC invasive per orifice approach by endotracheal intubation and positive pressure |
| GZ.31CR-ND | Ventilation, respiratory system NEC invasive per orifice with incision approach for intubation through tracheostomy positive pressure |
| GZ.31GP-ND | Ventilation, respiratory system NEC invasive percutaneous transluminal approach (e.g. transtracheal jet) through needle and positive pressure |

### D. Trauma and ICU

Presence of an ICD-10 trauma code in the range S00-T14, plus any external cause code from range W00 – X59 and admission to an intensive care unit (SCU location code)

| ICD-10 | Definition |
|---|---|
| S00 - S09 | Injuries to the head |
| S10-S19 | Injuries to the neck |
| S20-S29 | Injuries to the thorax |
| S30-S39 | Injuries to the abdomen, lower back, lumbar spine, pelvis and external genitalia |
| S40-S49 | Injuries to the shoulder and upper arm |
| S50-S59 | Injuries to the elbow and forearm |
| S60-S69 | Injuries to the wrist, hand and fingers |
| S70-S79 | Injuries to the hip and thigh |
| S80-S89 | Injuries to the knee and lower leg |
| S90-S99 | Injuries to the ankle and foot |
| T00 | Superficial injuries involving multiple body regions |
| T000 | Superficial injuries involving head with neck |
| T001 | Superficial injuries involving thorax with abdomen, lower back and pelvis |
| T002 | Superficial injuries involving multiple regions of upper limb(s) |
| T003 | Superficial injuries involving multiple regions of lower limb(s) |
| T006 | Superficial injuries involving multiple regions of upper limb(s) with lower limb(s) |

| ICD-10 | Definition |
|---|---|
| T008 | Superficial injuries involving other combinations of body regions |
| T009 | Multiple superficial injuries, unspecified |
| T01 | Open wounds involving multiple body regions |
| T0100 | Open wound involving head with neck, uncomplicated |
| T0101 | Open wound involving head with neck, complicated |
| T0110 | Open wounds involving thorax with abdomen, lower back and pelvis, uncomplicated |
| T0111 | Open wounds involving thorax with abdomen, lower back and pelvis, complicated |
| T0120 | Open wounds involving multiple regions of upper limb(s), uncomplicated |
| T0121 | Open wounds involving multiple regions of upper limb(s), complicated |
| T0130 | Open wounds of multiple regions of lower limb(s), uncomplicated |
| T0131 | Open wounds of multiple regions of lower limb(s), complicated |
| T0160 | Open wounds involving multiple regions of upper limb(s) with lower limb(s), uncomplicated |
| T0161 | Open wounds involving multiple regions of upper limb(s) with lower limb(s), complicated |
| T0180 | Open wounds involving other combinations of body regions, uncomplicated |
| T0181 | Open wounds involving other combinations of body regions, complicated |
| T0190 | Multiple open wounds of unspecified site, uncomplicated |
| T0191 | Multiple open wounds of unspecified site, complicated |
| T02 | Fractures involving multiple body regions |
| T0200 | Fractures involving head with neck, closed |
| T0201 | Fractures involving head with neck, open |
| T0210 | Fractures involving thorax with lower back and pelvis, closed |
| T0211 | Fractures involving thorax with lower back and pelvis, open |
| T0220 | Fractures involving multiple regions of one upper limb, closed |
| T0221 | Fractures involving multiple regions of one upper limb, open |
| T0230 | Fractures involving multiple regions of one lower limb, closed |
| T0231 | Fractures involving multiple regions of one lower limb, open |
| T0240 | Fractures involving multiple regions of both upper limbs, closed |
| T0241 | Fractures involving multiple regions of both upper limbs, open |
| T0250 | Fractures involving multiple regions of both lower limbs, closed |
| T0251 | Fractures involving multiple regions of both lower limbs, open |
| T0260 | Fractures involving multiple regions of upper limb(s) with lower limb(s), closed |
| T0261 | Fractures involving multiple regions of upper limb(s) with lower limb(s), open |
| T0270 | Fractures involving thorax with lower back and pelvis with limb(s), closed |
| T0271 | Fractures involving thorax with lower back and pelvis with limb(s), open |
| T0280 | Fractures involving other combinations of body regions, closed |
| T0281 | Fractures involving other combinations of body regions, open |
| T0290 | Multiple fractures, unspecified, closed |
| T0291 | Multiple fractures, unspecified, open |
| T03 | Dislocations, sprains and strains involving multiple body regions |
| T030 | Dislocations, sprains and strains involving head with neck |
| T031 | Dislocations, sprains and strains involving thorax with lower back and pelvis |
| T032 | Dislocations, sprains and strains involving multiple regions of upper limb(s) |
| T033 | Dislocations, sprains and strains involving multiple regions of lower limb(s) |
| T034 | Dislocations, sprains and strains involving multiple regions of upper limb(s) with lower limb(s) |
| T038 | Dislocations, sprains and strains involving other combinations of body regions |
| T039 | Multiple dislocations, sprains and strains, unspecified |
| T04 | Crushing injuries involving multiple body regions |
| T040 | Crushing injuries involving head with neck |
| T041 | Crushing injuries involving thorax with abdomen, lower back and pelvis |
| T042 | Crushing injuries involving multiple regions of upper limb(s) |
| T043 | Crushing injuries involving multiple regions of lower limb(s) |

| ICD-10 | Definition |
|---|---|
| T044 | Crushing injuries involving multiple regions of upper limb(s) with lower limb(s) |
| T047 | Crushing injuries of thorax with abdomen, lower back and pelvis with limb(s) |
| T048 | Crushing injuries involving other combinations of body regions |
| T049 | Multiple crushing injuries, unspecified |
| T05 | Traumatic amputations involving multiple body regions |
| T050 | Traumatic amputation of both hands |
| T051 | Traumatic amputation of one hand and other arm [any level, except hand] |
| T052 | Traumatic amputation of both arms [any level] |
| T053 | Traumatic amputation of both feet |
| T054 | Traumatic amputation of one foot and other leg [any level, except foot] |
| T055 | Traumatic amputation of both legs [any level] |
| T056 | Traumatic amputation of upper and lower limbs, any combination [any level] |
| T058 | Traumatic amputations involving other combinations of body regions |
| T059 | Multiple traumatic amputations, unspecified |
| T06 | Other injuries involving multiple body regions, not elsewhere classified |
| T060 | Injuries of brain and cranial nerves with injuries of nerves and spinal cord at neck level |
| T061 | Injuries of nerves and spinal cord involving other multiple body regions |
| T062 | Injuries of nerves involving multiple body regions |
| T063 | Injuries of blood vessels involving multiple body regions |
| T064 | Injuries of muscles and tendons involving multiple body regions |
| T065 | Injuries of intrathoracic organs with intra-abdominal and pelvic organs |
| T068 | Other specified injuries involving multiple body regions |
| T07 | Unspecified multiple injuries |
| T08 | Fracture of spine, level unspecified |
| T080 | Fracture of spine, level unspecified, closed |
| T081 | Fracture of spine, level unspecified, open |
| T09 | Other injuries of spine and trunk, level unspecified |
| T090 | Superficial injury of trunk, level unspecified |
| T091 | Open wound of trunk, level unspecified |
| T095 | Injury of unspecified muscle and tendon of trunk |
| T098 | Other specified injuries of trunk, level unspecified |
| T099 | Unspecified injury of trunk, level unspecified |
| T10 | Fracture of upper limb, level unspecified |
| T100 | Fracture of upper limb, level unspecified, closed |
| T101 | Fracture of upper limb, level unspecified, open |
| T11 | Other injuries of upper limb, level unspecified |
| T110 | Superficial injury of upper limb, level unspecified |
| T111 | Open wound of upper limb, level unspecified |
| T112 | Dislocation, sprain and strain of unspecified joint and ligament of upper limb, level unspecified |
| T113 | Injury of unspecified nerve of upper limb, level unspecified |
| T114 | Injury of unspecified blood vessel of upper limb, level unspecified |
| T115 | Injury of unspecified muscle and tendon of upper limb, level unspecified |
| T116 | Traumatic amputation of upper limb, level unspecified |
| T118 | Other specified injuries of upper limb, level unspecified |
| T119 | Unspecified injury of upper limb, level unspecified |
| T12 | Fracture of lower limb, level unspecified |
| T120 | Fracture of lower limb, level unspecified, closed |
| T1200 | Fracture of lower limb, level unspecified, closed |
| T1201 | Fracture of lower limb, level unspecified, open |
| T121 | Fracture of lower limb, level unspecified, open |
| T13 | Other injuries of lower limb, level unspecified |

| ICD-10 | Definition |
|---|---|
| T130 | Superficial injury of lower limb, level unspecified |
| T131 | Open wound of lower limb, level unspecified |
| T132 | Dislocation, sprain and strain of unspecified joint and ligament of lower limb, level unspecified |
| T133 | Injury of unspecified nerve of lower limb, level unspecified |
| T134 | Injury of unspecified blood vessel of lower limb, level unspecified |
| T135 | Injury of unspecified muscle and tendon of lower limb, level unspecified |
| T136 | Traumatic amputation of lower limb, level unspecified |
| T138 | Other specified injuries of lower limb, level unspecified |
| T139 | Unspecified injury of lower limb, level unspecified |
| T14 | Injury of unspecified body region |
| T140 | Superficial injury of unspecified body region |
| T141 | Open wound of unspecified body region |
| T1420 | Fracture of unspecified body region, closed |
| T1421 | Fracture of unspecified body region, open |
| T143 | Dislocation, sprain and strain of unspecified body region |
| T144 | Injury of nerve(s) of unspecified body region |
| T145 | Injury of blood vessel(s) of unspecified body region |
| T146 | Injury of muscles and tendons of unspecified body region |
| T147 | Crushing injury and traumatic amputation of unspecified body region |
| T148 | Other injuries of unspecified body region |
| T149 | Injury, unspecified |
| W00 | Fall on same level involving ice and snow |
| W01 | Fall on same level from slipping, tripping and stumbling |
| W02 | Fall involving skates, skis, sport boards and rollerblades |
| W0200 | Fall involving ice skates |
| W0201 | Fall involving skis |
| W0202 | Fall involving roller skates/in-line skates |
| W0203 | Fall involving skateboard |
| W0204 | Fall involving snowboard |
| W0208 | Fall other specified |
| W03 | Other fall on same level due to collision with, or pushing by, another person |
| W04 | Fall while being carried or supported by other persons |
| W05 | Fall involving wheelchair and other types of walking devices |
| W0500 | Fall involving wheelchair |
| W0501 | Fall involving adult walker |
| W0502 | Fall involving baby walker |
| W0503 | Fall involving stroller/carriage |
| W0504 | Fall involving shopping cart |
| W0508 | Fall involving other specified walking devices |
| W0509 | Fall involving unspecified walking devices |
| W06 | Fall involving bed |
| W07 | Fall involving chair |
| W08 | Fall involving other furniture |
| W09 | Fall involving playground equipment |
| W0901 | Fall involving swing |
| W0902 | Fall involving slide |
| W0903 | Fall involving teeter totter |
| W0904 | Fall involving monkey bars |
| W0905 | Fall involving trampoline |
| W0908 | Fall involving other playground equipment |
| W0909 | Fall involving unspecified playground equipment |

| ICD-10 | Definition |
|---|---|
| W10 | Fall on and from stairs and steps |
| W11 | Fall on and from ladder |
| W12 | Fall on and from scaffolding |
| W13 | Fall from, out of or through building or structure |
| W14 | Fall from tree |
| W15 | Fall from cliff |
| W16 | Diving or jumping into water causing injury other than drowning or submersion |
| W17 | Other fall from one level to another |
| W18 | Other fall on same level |
| W19 | Unspecified fall |
| W20 | Struck by thrown, projected or falling object |
| W21 | Striking against or struck by sports equipment |
| W2100 | Striking against or struck by ball |
| W2101 | Striking against or struck by bat |
| W2102 | Striking against or struck by hockey stick |
| W2103 | Striking against or struck by hockey puck |
| W2108 | Striking against or struck by other specified sport equipment |
| W2109 | Striking against or struck by other unspecified sport equipment |
| W22 | Striking against or struck by other objects |
| W2200 | Striking against or struck by/while skiing/snowboarding |
| W2201 | Striking against or struck while tobogganing |
| W2202 | Striking against or struck by/playing hockey |
| W2203 | Striking against or struck by/playing football/rugby |
| W2204 | Striking against or struck by/playing soccer |
| W2205 | Striking against or struck by/playing baseball |
| W2207 | Striking against or struck by/in other sports/recreation |
| W2208 | Striking against or struck by/in non-sports |
| W2209 | Striking against or struck by unspecified |
| W23 | Caught, crushed, jammed or pinched in or between objects |
| W24 | Contact with lifting and transmission devices, not elsewhere classified |
| W25 | Contact with sharp glass |
| W26 | Contact with knife, sword or dagger |
| W27 | Contact with nonpowered hand tool |
| W28 | Contact with powered lawnmower |
| W29 | Contact with other powered hand tools and household machinery |
| W30 | Contact with agricultural machinery |
| W31 | Contact with other and unspecified machinery |
| W32 | Handgun discharge |
| W33 | Rifle, shotgun and larger firearm discharge |
| W34 | Discharge from other and unspecified firearms |
| W3400 | Discharge from BB gun |
| W3401 | Discharge from air gun |
| W3408 | Discharge from other specified firearm |
| W3409 | Discharge from unspecified firearm |
| W35 | Explosion and rupture of boiler |
| W36 | Explosion and rupture of gas cylinder |
| W37 | Explosion and rupture of pressurized tyre, pipe or hose |
| W38 | Explosion and rupture of other specified pressurized devices |
| W39 | Discharge of firework |
| W40 | Explosion of other materials |
| W41 | Exposure to high-pressure jet |

| ICD-10 | Definition |
|---|---|
| W42 | Exposure to noise |
| W43 | Exposure to vibration |
| W44 | Foreign body entering into or through eye or natural orifice |
| W45 | Foreign body or object entering through skin |
| W4500 | Body piercing |
| W4509 | Foreign body or object entering through skin |
| W46 | Contact with hypodermic needle |
| W49 | Exposure to other and unspecified inanimate mechanical forces |

### E. Traumatic Brain Injury

Presence of a traumatic brain injury (TBI) ICD-10 code for all hospital admissions (including ICU (SCU location code)

### F. Traumatic Brain Injury and ICU admission

Presence of a traumatic brain injury ICD-10 and admission to an intensive care unit (SCU location code)

| ICD-10 | Definition |
|---|---|
| S06 | Intracranial injury |
| S060 | Concussion |
| S06000 | Concussion without loss of consciousness without open intracranial wound |
| S06001 | Concussion without loss of consciousness with open intracranial wound |
| S06010 | Concussion with brief loss of consciousness without open intracranial wound |
| S06011 | Concussion with brief loss of consciousness with open intracranial wound |
| S06020 | Concussion with moderate loss of consciousness without open intracranial wound |
| S06021 | Concussion with moderate loss of consciousness with open intracranial wound |
| S06030 | Concussion with prolonged loss of consciousness with return to pre-existing level of consciousness without open intracranial wound |
| S06031 | Concussion with prolonged loss of consciousness with return to pre-existing level of consciousness with open intracranial wound |
| S06040 | Concussion with prolonged loss of consciousness without return to pre-existing level of consciousness without open intracranial wound |
| S06041 | Concussion with prolonged loss of consciousness without return to pre-existing level of consciousness with open intracranial wound |
| S06090 | Concussion with loss of consciousness of unspecified duration without open intracranial wound |
| S06091 | Concussion with loss of consciousness of unspecified duration with open intracranial wound |
| S061 | Traumatic cerebral oedema |
| S06100 | Traumatic cerebral oedema without loss of consciousness without open intracranial wound |
| S06101 | Traumatic cerebral oedema without loss of consciousness with open intracranial wound |
| S06110 | Traumatic cerebral oedema with brief loss of consciousness without open intracranial wound |
| S06111 | Traumatic cerebral oedema with brief loss of consciousness with open intracranial wound |
| S06120 | Traumatic cerebral oedema with moderate loss of consciousness without open intracranial wound |
| S06121 | Traumatic cerebral oedema with moderate loss of consciousness with open intracranial wound |
| S06130 | Traumatic cerebral oedema with prolonged loss of consciousness with return to pre-existing level of consciousness without open intracranial wound |
| S06131 | Traumatic cerebral oedema with prolonged loss of consciousness with return to pre-existing level of consciousness with open intracranial wound |
| S06140 | Traumatic cerebral oedema with prolonged loss of consciousness without return to pre-existing level of consciousness without open intracranial wound |
| S06141 | Traumatic cerebral oedema with prolonged loss of consciousness without return to pre-existing level of consciousness with open intracranial wound |

| ICD-10 | Definition |
|---|---|
| S06190 | Traumatic cerebral oedema with loss of consciousness of unspecified duration without open intracranial wound |
| S06191 | Traumatic cerebral oedema with loss of consciousness of unspecified duration with open intracranial wound |
| S06200 | Diffuse brain injury without loss of consciousness without open intracranial wound |
| S06201 | Diffuse brain injury without loss of consciousness with open intracranial wound |
| S06210 | Diffuse brain injury with brief loss of consciousness without open intracranial wound |
| S06211 | Diffuse brain injury with brief loss of consciousness with open intracranial wound |
| S06220 | Diffuse brain injury with moderate loss of consciousness without open intracranial wound |
| S06221 | Diffuse brain injury with moderate loss of consciousness with open intracranial wound |
| S06230 | Diffuse brain injury with prolonged loss of consciousness with return to pre-existing level of consciousness without open intracranial wound |
| S06231 | Diffuse brain injury with prolonged loss of consciousness with return to pre-existing level of consciousness with open intracranial wound |
| S06240 | Diffuse brain injury with prolonged loss of consciousness without return to pre-existing level of consciousness without open intracranial wound |
| S06241 | Diffuse brain injury with prolonged loss of consciousness without return to pre-existing level of consciousness with open intracranial wound |
| S0625 | Diffuse brain injury without open intracranial wound |
| S0626 | Diffuse brain injury with open intracranial wound |
| S06290 | Diffuse brain injury with loss of consciousness of unspecified duration without open intracranial wound |
| S06291 | Diffuse brain injury with loss of consciousness of unspecified duration with open intracranial wound |
| S06300 | Focal brain injury without loss of consciousness, without open intracranial wound |
| S06301 | Focal brain injury without loss of consciousness, with open intracranial wound |
| S06310 | Focal brain injury with brief loss of consciousness without open intracranial wound |
| S06311 | Focal brain injury with brief loss of consciousness with open intracranial wound |
| S06320 | Focal brain injury with moderate loss of consciousness without open intracranial wound |
| S06321 | Focal brain injury with moderate loss of consciousness with open intracranial wound |
| S06330 | Focal brain injury with prolonged loss of consciousness with return to pre-existing level of consciousness without open intracranial wound |
| S06331 | Focal brain injury with prolonged loss of consciousness with return to pre-existing level of consciousness with open intracranial wound |
| S06340 | Focal brain injury with prolonged loss of consciousness without return to pre-existing level of consciousness without open intracranial wound |
| S06341 | Focal brain injury with prolonged loss of consciousness without return to pre-existing level of consciousness with open intracranial wound |
| S0635 | Focal brain injury without open intracranial wound |
| S0636 | Focal brain injury with open intracranial wound |
| S06390 | Focal brain injury with loss of consciousness of unspecified duration without open intracranial wound |
| S06391 | Focal brain injury with loss of consciousness of unspecified duration with open intracranial wound |
| S064 | Epidural haemorrhage |
| S06400 | Epidural haemorrhage without loss of consciousness without open intracranial wound |
| S06401 | Epidural haemorrhage without loss of consciousness with open intracranial wound |
| S06410 | Epidural haemorrhage with brief loss of consciousness without open intracranial wound |
| S06411 | Epidural haemorrhage with brief loss of consciousness with open intracranial wound |
| S06420 | Epidural haemorrhage with moderate loss of consciousness without open intracranial wound |
| S06421 | Epidural haemorrhage with moderate loss of consciousness with open intracranial wound |
| S06430 | Epidural haemorrhage with prolonged loss of consciousness without open intracranial wound |
| S06431 | Epidural haemorrhage with prolonged loss of consciousness with open intracranial wound |
| S06440 | Epidural haemorrhage with prolonged loss of consciousness without return to pre-existing level of consciousness without open intracranial wound |
| S06441 | Epidural haemorrhage with prolonged loss of consciousness without return to pre-existing level of consciousness with open intracranial wound |

| ICD-10 | Definition |
|---|---|
| S06490 | Epidural haemorrhage with loss of consciousness of unspecified duration without open intracranial wound |
| S06491 | Epidural haemorrhage with loss of consciousness of unspecified duration with open intracranial wound |
| S065 | Traumatic subdural haemorrhage |
| S06500 | Traumatic subdural haemorrhage without loss of consciousness without open intracranial wound |
| S06501 | Traumatic subdural haemorrhage without loss of consciousness with open intracranial wound |
| S06510 | Traumatic subdural haemorrhage with brief loss of consciousness without open intracranial wound |
| S06511 | Traumatic subdural haemorrhage with brief loss of consciousness with open intracranial wound |
| S06520 | Traumatic subdural haemorrhage with moderate loss of consciousness without open intracranial wound |
| S06521 | Traumatic subdural haemorrhage with moderate loss of consciousness with open intracranial wound |
| S06530 | Traumatic subdural haemorrhage with prolonged loss of consciousness with return to pre-existing level of consciousness without open intracranial wound |
| S06531 | Traumatic subdural haemorrhage with prolonged loss of consciousness with return to pre-existing level of consciousness with open intracranial wound |
| S06540 | Traumatic subdural haemorrhage with prolonged loss of consciousness without return to pre-existing level of consciousness without open intracranial wound |
| S06541 | Traumatic subdural haemorrhage with prolonged loss of consciousness without return to pre-existing level of consciousness with open intracranial wound |
| S06590 | Traumatic subdural haemorrhage with loss of consciousness of unspecified duration without open intracranial wound |
| S06591 | Traumatic subdural haemorrhage with loss of consciousness of unspecified duration with open intracranial wound |
| S066 | Traumatic subarachnoid haemorrhage |
| S06600 | Traumatic subarachnoid haemorrhage without loss of consciousness without open intracranial wound |
| S06601 | Traumatic subarachnoid haemorrhage without loss of consciousness with open intracranial wound |
| S06610 | Traumatic subarachnoid haemorrhage with brief loss of consciousness without intracranial wound |
| S06611 | Traumatic subarachnoid haemorrhage with brief loss of consciousness with intracranial wound |
| S06620 | Traumatic subarachnoid haemorrhage with moderate loss of consciousness without open intracranial wound |
| S06621 | Traumatic subarachnoid haemorrhage with moderate loss of consciousness with open intracranial wound |
| S06630 | Traumatic subarachnoid haemorrhage with prolonged loss of consciousness with return to pre-existing level of consciousness without open intracranial wound |
| S06631 | Traumatic subarachnoid haemorrhage with prolonged loss of consciousness with return to pre-existing level of consciousness with open intracranial wound |
| S06640 | Traumatic subarachnoid haemorrhage with prolonged loss of consciousness without return to pre-existing level of consciousness without open intracranial wound |
| S06641 | Traumatic subarachnoid haemorrhage with prolonged loss of consciousness without return to pre-existing level of consciousness with open intracranial wound |
| S06690 | Traumatic subarachnoid haemorrhage with loss of consciousness of unspecified duration without open intracranial wound |
| S06691 | Traumatic subarachnoid haemorrhage with loss of consciousness of unspecified duration with open intracranial wound |
| S06800 | Other intracranial injuries without loss of consciousness without open intracranial wound |
| S06801 | Other intracranial injuries without loss of consciousness with open intracranial wound |
| S06810 | Other intracranial injuries with brief loss of consciousness without open intracranial wound |
| S06811 | Other intracranial injuries with brief loss of consciousness with open intracranial wound |
| S06820 | Other intracranial injuries with moderate loss of consciousness without open intracranial wound |
| S06821 | Other intracranial injuries with moderate loss of consciousness with open intracranial wound |
| S06830 | Other intracranial injuries with prolonged loss of consciousness with return to pre-existing level of consciousness without open intracranial wound |
| S06831 | Other intracranial injuries with prolonged loss of consciousness with return to pre-existing level of consciousness with open intracranial wound |
| S06840 | Other intracranial injuries with prolonged loss of consciousness without return to pre-existing level of consciousness without open intracranial wound |

| ICD-10 | Definition |
|---|---|
| S06841 | Other intracranial injuries with prolonged loss of consciousness without return to pre-existing level of consciousness with open intracranial wound |
| S0685 | Other intracranial injuries without open intracranial wound |
| S0686 | Other intracranial injuries with open intracranial wound |
| S06890 | Other intracranial injuries with loss of consciousness of unspecified duration without open intracranial wound |
| S06891 | Other intracranial injuries with loss of consciousness of unspecified duration with open intracranial wound |
| S069 | Intracranial injury, unspecified |
| S06900 | Intracranial injury, unspecified without loss of consciousness without open intracranial wound |
| S06901 | Intracranial injury, unspecified without loss of consciousness with open intracranial wound |
| S06910 | Intracranial injury, unspecified with brief loss of consciousness without open intracranial wound |
| S06911 | Intracranial injury, unspecified with brief loss of consciousness with open intracranial wound |
| S06920 | Intracranial injury, unspecified with moderate loss of consciousness without open intracranial wound |
| S06921 | Intracranial injury, unspecified with moderate loss of consciousness with open intracranial wound |
| S06930 | Intracranial injury, unspecified with prolonged loss of consciousness with return to pre-existing level of consciousness without open intracranial wound |
| S06931 | Intracranial injury, unspecified with prolonged loss of consciousness with return to pre-existing level of consciousness with open intracranial wound |
| S06940 | Intracranial injury, unspecified with prolonged loss of consciousness without return to pre-existing level of consciousness without open intracranial wound |
| S06941 | Intracranial injury, unspecified with prolonged loss of consciousness without return to pre-existing level of consciousness with open intracranial wound |
| S06990 | Intracranial injury, unspecified with loss of consciousness of unspecified duration without open intracranial wound |
| S06991 | Intracranial injury, unspecified without loss of consciousness with open intracranial wound |

## 5. Comorbidities

### A. Elixhauser Comorbidity Index Codes

The Elixhauser Comorbidity Index is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data, such as hospital abstracts data. Each comorbidity category is dichotomous -- it is either present or it is not. The Index can be used to predict hospital resource use and in-hospital mortality.[2]

**Table 2 Primary Composite and Secondary Clinical Outcomes and Costs**

### 1. Primary Composite Outcome

### A. Death or re-admission to hospital within first 90 days of index admission

| Database | Definition |
|---|---|
| RPDB | Verified if death date subtracted from index admission date is ≤ 90 days |
| DAD | Index hospital admission date compared to any subsequent admission to an Ontario hospital within 90 days |

### 2. Secondary Outcomes

### A. Death

| Database | Definition |
|---|---|
| RPDB | Verified if death date subtracted from index admission date is ≤ 90 days |

| Database | Definition |
|---|---|
| DAD | Index hospital admission date compared to any subsequent admission to an Ontario hospital within 90 days |

### B. Total hospital length of stay

| Database | Definition |
|---|---|
| DAD | Calculated from discharge date of index admission from admit date of index hospital admission |

### C. New Dialysis Within 90 Days of Index Hospital Admission

This variable identifies patients who did not require dialysis within 90 days prior to the index hospital admission and subsequently required any form of dialysis within 90 days of the index hospital admission

| OHIP Billing Code | Definitions |
|---|---|
| **Hemodialysis** | |
| R849 | Haemodialysis - Initial and acute (includes both medical and surgical components) |
| G323 | Haemodialysis - Acute, repeat - for the first 3 services |
| G325 | Haemodialysis - Medical component alone |
| G326 | Dialysis - Chronic, contin. haemodialysis or haemofiltration each |
| G860 | Chronic dialysis weekly team fee - Hospital haemodialysis |
| G333 | Home/self dialysis |
| G862 | Chronic dialysis weekly team fee - Hospital self-care haemodialysis or satellite haemodialysis. |
| G863 | Chronic dialysis weekly team fee - Independent health facility haemodialysis |
| G865 | Home Hemodialysis |
| G866 | Chronic dialysis weekly team fee - Intermittent haemodialysis - at an auxiliary treatment centre (per treatment, maximum 2 per patient per 7-day period referred to above) |
| **Peritoneal Dialysis** | |
| G330 | Peritoneal dialysis - Acute (up to 48 hours) includes stylette cannula insertion (temporary) |
| G331 | Peritoneal dialysis - Repeat acute (up to 48 hours) - for the first 3 services |
| G333 | Home/self dialysis |
| G861 | Chronic dialysis weekly team fee - Hospital peritoneal dialysis |

| | |
|---|---|
| G864 | Chronic dialysis weekly team fee – Home peritoneal dialysis |
| **Continuous Renal Replacement Therapy** | |
| G083 | Haemodialysis - Continuous venovenous haemodialysis - initial and acute (for the first 3 services) |
| G091 | Haemodialysis - Continuous arteriovenous haemodialysis - initial and acute (for the first 3 services) |
| G085 | Haemodialysis - Continuous venovenous haemofiltration - initial and acute (for the first 3 services) |
| G295 | Haemodialysis - Continuous arteriovenous haemofiltration - initial and acute (for the first 3 services) |
| G082 | CVVHD, initial and acute X 3 |
| G092 | Continuous haemodiafiltration - Continuous arteriovenous haemodiafiltration - initial and acute (for the first 3 services) |
| G093 | Haemodiafiltration - Contin. Init & Acute (repeatx3) |
| G094 | Continuous haemodiafiltration - Chronic, continuous haemodiafiltration |
| G090 | Slow continuous ultrafiltration - Venovenous slow continuous ultrafiltration - initial and acute (for the first 3 services) |
| G294 | Continuous haemodiafiltration - Chronic, continuous haemodiafiltration |
| G095 | Slow Continuous Ultra Filtration - Initial & Acute (repeat) |
| G096 | Slow continuous ultrafiltration - Chronic, slow continuous ultrafiltration |

### D. Emergency Department visit within 90 days of index admission

| Database | Definition |
|---|---|
| NACRS | Registration date of the first ED visit to any hospital in Ontario within 90 days of index admission |

### E. Discharge Disposition of the Index Hospitalization

| Database | Discharge Disposition code | Definition |
|---|---|---|
| DAD | 01 | Transferred to another facility providing inpatient hospital care or acute care inpatient institution |
| DAD | 02 | Transferred to a long term or continuing care facility |
| DAD | 03 | Transferred to other ambulatory care, palliative care/hospice, addiction treatment centre, jails, infants and children discharged/detained by social services) |
| DAD | 04 | Discharged to a home setting with support services |
| DAD | 05 | Discharged to home (no support service from an external agency required) |
| DAD | 06 | Signed out (against medical advice) |
| RPDB | | Died |

### 3. 90-day total health system and sub-divided costs, mean ± SD

Direct health care costs were derived from provincial health administrative data available at ICES. ICES uses the GETCOST macro designed to compute individual-level healthcare cost for any requested time period. Cost is calculated 90 days after index hospital admission.[3]

**Reference List**

1. Information CIHI. Canadian Coding Standards for Version 2018 ICD-10-CA and CCI. Ottawa, Ontario, Canada2018:767.
2. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care 1998;36:8-27.
3. Wodchis W, Bushmeneva K, Nikitovic M, McKillop I. Health System Performance Research Network, Guidelines on Person-Level Costing. Using Administrative Databases in Ontario 2013;1:71.

# CONSORT 2010 checklist of information to include when reporting a randomised trial*

| Section/Topic | Item No | Checklist item | Reported on page No |
|---|---|---|---|
| **Title and abstract** | | | |
| | 1a | Identification as a randomised trial in the title | 1 |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | 4 |
| **Introduction** | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | 5, 6 |
| | 2b | Specific objectives or hypotheses | |
| **Methods** | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | 7 |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | N/A |
| Participants | 4a | Eligibility criteria for participants | 8 |
| | 4b | Settings and locations where the data were collected | 9 |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 9,10 |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | 11, 12 |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | N/A |
| Sample size | 7a | How sample size was determined | 14 |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | N/A |
| Randomisation: | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | 9 |
| | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | 9 |
| Allocation concealment mechanism | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | 9 |
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | 9 |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those | N/A |

| | | | |
|---|---|---|---|
| | | assessing outcomes) and how | |
| | 11b | If relevant, description of the similarity of interventions | 5, 10 |
| Statistical methods | 12a | Statistical methods used to compare groups for primary and secondary outcomes | 14 |
| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | 15 |
| **Results** | | | |
| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | Figure 2 |
| | 13b | For each group, losses and exclusions after randomisation, together with reasons | Figure 2 |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | 15 |
| | 14b | Why the trial ended or was stopped | N/A |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics for each group | Table 1 |
| Numbers analysed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | Table 2 |
| Outcomes and estimation | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | Table 2 |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | Table 3 |
| Harms | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) | 10, 11 |
| **Discussion** | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | 22 |
| Generalisability | 21 | Generalisability (external validity, applicability) of the trial findings | 22 |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | 22 |
| **Other information** | | | |
| Registration | 23 | Registration number and name of trial registry | NCT02721485 |
| Protocol | 24 | Where the full trial protocol can be accessed, if available | BMJ open |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders | CIHR, TOHAMO |

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

# The FLUID Trial: A Hospital – Wide Open - Label Cluster Cross-Over Pragmatic Comparative Effectiveness Randomized Pilot Trial Comparing Normal Saline to Ringer's Lactate



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|---|---|
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# The FLUID Trial: A Hospital-Wide Open-Label Cluster Cross-Over Pragmatic Comparative Effectiveness Randomized Pilot Trial Comparing Normal Saline to Ringer's Lactate

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Word Count: 4270

**Keywords:**

fluid therapy, normal saline, Ringer's lactate, randomized trial, pragmatic, comparative effectiveness

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 (e.g. hyperchloremic metabolic acidosis, impaired kidney function and death), few large multi-centre randomized 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 randomized cross-over trial.

**Setting:** Four hospitals in the province of Ontario, Canada

**Participants:** All hospitalized adult and pediatric 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 hospitalization) and secondary clinical outcomes were analyzed 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 litres (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 2-48 days and readiness for trial initiation from 51-331 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.

**Registration**: clinicaltrials.gov (NCT02721485).

## Strengths and limitations of this study

- The FLUID pilot trial was an innovative pragmatic cluster randomized cross-over trial, with randomization done at the hospital level and inclusion of all patients
- The study fluid (NS or RL) 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 hospitalized patients [1, 2]. These fluids may be used as a life-saving measure to re-establish hemodynamic stability, for rehydration, to replace fluid losses and to maintain intravascular volume.

In observational studies, NS as compared to RL and other balanced crystalloid fluids have been associated with acute renal injury hypothesized 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 edema formation [14], which raises potential concern for patients with cerebral edema.

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 to NS were associated with lower Major Adverse Kidney Events (MAKE) 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 randomized trials (BaSICS, n=11,052 and PLUS, n=5037) [16, 17] examined the efficacy of NS as compared to a balanced crystalloid (Ringer's lactate 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 to balanced crystalloid group (28.2% and 27.9% respectively; Relative Risk 0.96 (95% Confidence Interval: 0.91 – 1.01)), nor renal function[15-28] However, authors concluded that there is a high probability balanced crystalloids reduce death since the confidence intervals ranged from a 9% relative reduction to a 1% relative increase in death.

Crystalloid fluids are not limited to use in the emergency department or the intensive care unit, but are administered to the majority of patients admitted to hospital and throughout their care. To address this evidence gap, we designed a cluster cross-over randomized 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 FLUID design, the evidence generated will apply at the level of the hospital and health care system and for the majority of hospitalized patients.

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

## METHODS

### 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).

### 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] and is registered with clinicaltrials.gov (NCT02721485).

FLUID was a pragmatic, open-label, hospital-wide cluster randomized cross-over trial (see Figure 1) conducted in three tertiary care hospitals and one community hospital in Ontario, Canada. Cluster randomization was justified in accordance with the Ottawa Statement [30], because randomizing 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 minimize contamination and maximize 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 analyze health care 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 standardized strategy for site trial preparation and conduct was implemented and is summarized 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 *hospital level:* We excluded hospitals that had fewer than 6,000 acute care admissions per year (< 1,500 admissions per study period).

Inclusion criteria at *patient level:* Adult and pediatric 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 re-admitted 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 Randomization**

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 randomized 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 one served as a run-in, weeks two to 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 two to 13. After the one week run-out period, hospitals had up to an additional three weeks to cross-over to period two study fluid.

**Strategies to Minimize Contamination**

The risk of contamination due to non-adherence to the study fluid was minimized through six mechanisms. (1) An automatic substitution order for the study fluid was invoked during the trial study periods: nurses were authorized 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 minimize the occurrence of patients being exposed to two different kinds of fluids during the same hospitalization.

**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 (e.g., severe hyperkalemia, 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 4 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 two-week intervals over the 12-week (weeks 2 – 13) study periods and described according to each study group across all 4 participating hospitals combined and according to major fluid user groups (Emergency Department (ED), Medicine, Surgery, Operating Room (OR), Post Operative Assessment Unit (PACU), Obstetrics, Intensive Care Unit (ICU).

**Secondary Feasibility Outcomes**

**Time to Research Ethics Board (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 three 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 three 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, emergency department visits within the first 90 days of the index hospitalisation, length of stay in hospital and hospital discharge disposition.

## Subgroup Analyses

Several pre-defined 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 authorized under section 45 of Ontario's personal health Information Protection Act, which does not require review by a Research Ethics Board. Trial and intervention costs were estimated from the trial budget, financial records, and service level agreements. No additional data available. A data dictionary which summarizes all administrative databases searched as well as ICD 10 codes for each variable in FLUID is described in the Supplementary 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 standard deviations or medians with interquartile ranges as appropriate for continuous data, and frequencies and proportions for categorical and dichotomous variables. For clinical outcomes, 95% two-sided confidence intervals were included. In accordance with the FLUID pilot protocol, clinical outcomes were not analyzed 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 4 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 health care 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 (Standard Deviation (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%).

Table 1 Baseline Characteristics

| | Total # Index Admissions N=24,905 | Normal Saline N=12,338 | Ringers Lactate N =12,567 |
|---|---|---|---|
| Sex, female, n (%) | 13,977 (56.1%) | 6,976 (56.5%) | 7,001 (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%) | 6,756 (54.8%) | 7,036 (56.0%) |
| >65 to 80 | 6,771 (27.2%) | 3,368 (27.3%) | 3,403 (27.1%) |
| >80 | 4,174 (16.8%) | 2,139 (17.3%) | 2,035 (16.2%) |
| **Case Mix Group n (%)** | | | |
| Medicine | 10,773 (43.3%) | 5,449 (44.2%) | 5,324 (42.4%) |
| Surgery | 10,377 (41.7%) | 5,080 (41.2%) | 5,297 (42.2%) |
| Pregnancy and Childbirth | 3,614 (14.5%) | 1,744 (14.1%) | 1,870 (14.9%) |
| Mental Health | 141 (0.6%) | 65 (0.5%) | 76 (0.6%) |
| **Type of surgical admission, n (%)** | | | |
| Elective | 5,796 (55.9%) | 2,852 (56.1%) | 2,944 (55.6%) |
| Urgent | 4,581 (44.2%) | 2,228 (43.9%) | 2,353 (44.4%) |
| Surgical admission <24 hours, n (%) | 950 (9.2%) | 484 (9.5%) | 466 (8.8%) |
| **Severity of Illness** | | | |
| Admission to ICU, n (%) | 3,034 (12.2%) | 1,494 (12.1%) | 1,540 (12.3%) |
| Infection Alone and Infection and Organ Dysfunction, n (%) | 2,734 (12.0%) | 1,365 (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%) |

| | Total # Index Admissions N=24,905 | Normal Saline N=12,338 | Ringers Lactate N =12,567 |
|---|---|---|---|
| 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 | 2,819 (11.3%) | 1,396 (11.3%) | 1,423 (11.3%) |
| Hypertension, uncomplicated & complicated | 2,574 (10.3%) | 1,207 (9.8%) | 1,367 (10.9%) |
| Cardiac arrhythmias | 2,263 (9.1%) | 1,143 (9.3%) | 1,120 (8.9%) |
| Solid tumour without metastasis | 2,105 (8.5%) | 1,004 (8.1%) | 1,101 (8.8%) |
| Fluid and electrolyte disorders | 1,886 (7.6%) | 944 (7.7%) | 942 (7.5%) |
| Diabetes, uncomplicated | 1,374 (5.5%) | 686 (5.6%) | 688 (5.5%) |
| Congestive heart failure | 1,187 (4.8%) | 606 (4.9%) | 581 (4.6%) |
| Metastatic cancer | 1,008 (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%) |
| 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 anemia | 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%) |

| | Total # Index Admissions N=24,905 | Normal Saline N=12,338 | Ringers Lactate N =12,567 |
|---|---|---|---|
| Blood loss anemia | 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%) |

Legend: ICU = intensive care unit, SD = standard deviation, n = number

**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 litres respectively. Study fluid adherence targets of at least 80% overall (4 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 two 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 4 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% CIs: 21.7 – 22.8). Patients were admitted to hospital for a median of 3 days (interquartile range 1-6) and 3429 patients (13.1%, 95% CIs: (95% CI: 12.6 , 13.5) were discharged to a facility other than home. Other secondary clinical outcomes and sub-groups described according to the primary composite outcome are described in Tables 2 and 3 respectively.

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 hospitalization, n (%) | 5544 (22.3%, 95% CI: 21.7 , 22.8) |
| **Secondary Outcomes** | |
| Death within 90 days of index admission, n (%) | 1926 (7.7%, 95% CI: 7.4 , 8.1) |
| Re-admission within 90 days of index admission, n (%) | 4049 (16.3%, 95% CI: 15.8 , 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%, 95% CI: 0.75 , 0.98) |
| ED visit within 90 days of index admission, n (%) | 5499 (22.1%, 95% CI: 22.0 , 22.6) |
| **Discharge Disposition (detailed), n (%)** | |
| Discharged to facility other than home, n (%) | 3250 (13.1%, 95% CI: 12.6 , 13.5) |
| Transferred to another facility providing inpatient hospital care or acute care inpatient institution | 1080 (4.3%, 95% CI: 4.1 , 4.6) |
| Transferred to a long term or continuing care facility | 2072 (8.3%, 95% CI: 8.0 , 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%, 95% CI: 0.3 , 0.5) |
| Discharged to a home setting with support services | 4711 (19.0%, 95% CI: 18.4 , 19.4) |
| Discharged to home (no support service from an external agency required) | 15807 (63.5%, 95% CI: 63.0 , 64.1) |
| Signed out (against medical advice) | 189 (0.9%, 95% CI: 0.7 , 0.9) |

| | |
|---|---|
| Died | 948 (3.8%, 95% CI: 3.6 , 4.0) |
| **90-day total health system and sub-divided costs, mean ± SD**<br>** cost is calculated 90 days after index date | |
| Hospital cost (DAD) | |
| Inpatient cost | 12,499.7 ± 18,506.4 |
| Hospital outpatient clinic cost | 756.8 ± 934.4 |
| ED cost (NACRS) | 431.9 ± 577.4 |
| Dialysis cost (NACRS) | 138.9 ± 1,600.7 |
| Cancer care cost (NACRS) | 303.2 ± 1,805.2 |
| Medication cost (ODB) | 539.9 ± 2,081.6 |
| Outpatient cost (OHIP) | |
| Physician FFS billings | 3,139.1 ± 3,121.7 |
| 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 ± 22,101.3 |

Legend: n = number, SD = standard deviation, IQR = interquartile range, CI = confidence interval

Table 3 Description of Composite Primary Outcome in Pre-specified Subgroups

| | N (%, 95% CI) |
|---|---|
| **Sex** | |
| Female | 2774 (19.9%, 95% CI: 19.2 , 20.5) |
| Male | 2770 (25.4%, 95% CI: 24.5 , 26.2) |
| **Age Group** | |
| <=18 years (children & adolescents) | 20 (11.9%, 95% CI: 7.0 , 16.8) |
| >18 to 65 | 2149 (15.6%, 95% CI: 15.0 , 16.2) |
| >65 to 80 | 1811 (26.8%, 95% CI: 25.7 , 27.8) |
| >80 | 1564 (37.5%, 95% CI: 36 , 39.0) |
| **Case Mix Group** | |
| Medicine | 3560 (33.1%, 95% CI: 32.2 , 33.9) |
| Surgery | 1699 (16.4%, 95% CI: 15.7 , 17.1) |
| Pregnancy and Childbirth | 267 (7.4%, 95% CI: 6.5 , 8.2) |

| | |
|---|---|
| Mental Health | 18 (12.8%, 95% CI: 7.3 , 18.3) |
| **Type of Surgical Admission, n (%)** | |
| Elective Surgery | 677 (11.7%, 95% CI: 10.9 , 12.5) |
| Urgent Surgery | 1022 (22.3%, 95% CI: 21.1 , 23.5) |
| Surgical Admission <24 hours | 87 (9.2%, 95% CI: 7.3 , 11.0) |
| **Severity of Illness** | |
| Admission to Intensive Care Unit | 967 (31.9%, 95% CI: 30.2 , 33.5) |
| Infection Alone and Infection and Organ Dysfunction | 1076 (39.4%, 95% CI: 37.5 , 41.2) |
| Infection Alone and Infection and Organ Dysfunction and ICU admission | 276 (47.7%, 95% CI: 43.6 , 51.7) |
| Trauma + ICU | 77 (43.8%, 95% CI: 36.4 , 51.1) |
| Traumatic Brain Injury | 49 (40.5%, 95% CI: 31.8 , 49.2) |
| Traumatic Brain Injury + ICU | 34 (53.1%, 95% CI: 40.9 , 65.4) |
| New dialysis within 90 days of index admission | 51 (57.30%, 95% CI: 47.03 , 67.58) |

Legend: ICU = intensive care unit, % = percent; CI = Confidence Interval

## DISCUSSION

The FLUID trial design is innovative in its use of a pragmatic cluster randomized cross-over design, a waiver of patient informed consent to include all hospitalized patients, hospital based randomization, 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 approval time, and readiness to initiate the trial. The REB approval target of 3 months was met for all 4 study sites. However, for three of the four centres, the REB approval process was centralized which avoided delays. In the large trial, a centralized 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).

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, pre-specified 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 pre-trial communication and educational enhancement strategies (e.g. medicine wards).

The generation of recent evidence will help inform the design and sub-group analyses for future large pragmatic balanced crystalloid versus NS crystalloid trials. For example, a sub-group analysis of 3 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 to normal saline was associated with a trend toward harm (RR 1.26, 95% CI: 0.98 – 1.60)[27], potentially related to the lower osmolarity and risk of cerebral edema 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 sub-group analyses of large trials suggest balanced crystalloids as compared to NS may reduce death from sepsis and time to resolution of diabetic ketoacidosis[27, 38] and represent important sub-groups 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 (e.g., medication delivery, catheter patency and flushes, coadministration for blood products, surgical wound washouts, 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 randomization sequences. Ideally, all sites in the large trial should be randomized 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 determine whether RL as compared to 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.

**Authors Contributions:** LM, MT and DF conceived the project idea. All authors (LM, MT, DF, DC, DF, TM, AFR, SE, CM, JM, KM, JMu, DC, CW, RS, AI, AF, IG, SH, CMc, AS, IS, KT, DF) contributed to the development of the trial protocol. LM created the initial draft of the manuscript. All authors contributed critical revisions and approved the final version of the manuscript.

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**Data availability statement:** All data relevant to the study are included in the article or uploaded as supplementary information

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## Figure Legends

**Legend Figure 1: FLUID Pilot Trial Study Design**: Study fluid for the first study period was stocked from 1–3 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 familiarized 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 hospitalizations 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.

**Legend Figure 2: Consort Flow Diagram**

Legend Figure 3: Overall 0.9% Saline Compliance and by Study Site: The number (%) over the first histogram bar summarizes adherence to 0.9% saline which was calculated by adding the total combined volume of 0.9% saline at all 4 sites divided by the total combined volume of 0.9% saline and Ringer's lactate at all 4 sites during the 12-week 0.9% saline study period. The numbers (%) below each histogram bar summarize 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 4 sites combined.

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

**Legend Figure 5: All Sites Overall Study Fluid Compliance Over 2-Week Intervals**: The number (%) over each histogram bar summarizes compliance to 0.9% saline and Ringer's lactate for all 4 sites combined in 2-week intervals over the 12-week study period.

**Legend Figure 6: All Sites Overall Study Fluid Compliance: Major Fluid User Groups**: The numbers (%) over the histogram bars summarizes adherence to 0.9% saline and Ringer's lactate 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 Ringer's lactate for that fluid user group during each 12-week study period. The numbers (%) below each histogram summarize 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 4 sites combined. Abbreviations: ED = Emergency Department, OR = Operating Room, ICU = Intensive Care Unit, PACU = Post Anesthetic Care Unit, OBS = Obstetrics

## Reference List:


1. Myburgh, J.A. and M.G. Mythen, *Resuscitation Fluids.* The New England Journal of Medicine, 2013. **369**(13): p. 1243-1251.
2. Self, W.H., et al., *Balanced Crystalloids versus Saline in Noncritically Ill Adults.* N Engl J Med, 2018. **378**(9): p. 819-828.
3. Burdett, E., et al., *Perioperative buffered versus non-buffered fluid administration for surgery in adults.* Cochrane.Database.Syst.Rev., 2012. **12**: p. CD004089.
4. Orbegozo, C.D., B.A. Rayo, and J.L. Vincent, *Isotonic crystalloid solutions: a structured review of the literature.* British Journal of Anaesthesia, 2014. **112**(6): p. 968-981.
5. Kawano-Dourado, L., 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**(2): p. 513-521.
6. Zhou, F., 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**(4): p. e270-e278.
7. Yunos, N.M., et al., *The biochemical effects of restricting chloride-rich fluids in intensive care.* Crit Care Med., 2011. **39**(11): p. 2419-2424.
8. Fitzgibbons, L.J. and E.R. Snoey, *Severe metabolic alkalosis due to baking soda ingestion: case reports of two patients with unsuspected antacid overdose.* The Journal of Emergency Medicine, 1999. **17**(1): p. 57-61.
9. Mennen, M. and C.M. Slovis, *Severe metabolic alkalosis in the emergency department.* Annals of Emergency Medicine, 1988. **17**(4): p. 354-357.
10. Gawarammana, I.B., et al., *Severe hypokalaemic metabolic alkalosis following ingestion of gaviscon.* Clin.Toxicol.(Phila), 2007. **45**(2): p. 176-178.
11. Todd, S.R., et al., *Lactated Ringer's is superior to normal saline in the resuscitation of uncontrolled hemorrhagic shock.* Journal of Trauma, 2007. **62**(3): p. 636-639.
12. Hadimioglu, N., et al., *The effect of different crystalloid solutions on acid-base balance and early kidney function after kidney transplantation.* Anesthesia and Analgesia, 2008. **107**(1): p. 264-269.
13. Scheingraber, S., et al., *Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery.* Anesthesiology, 1999. **90**(5): p. 1265-1270.
14. Butscher, K., et al., *[Effects of different loading solutions on plasma osmolality].* Annales Francaises d'Anesthesie et de Reanimation, 1996. **15**(7): p. 1037-1040.
15. Semler, M.W., et al., *Balanced Crystalloids versus Saline in Critically Ill Adults.* N Engl J Med, 2018. **378**(9): p. 829-839.
16. Finfer, S., et al., *Balanced Multielectrolyte Solution versus Saline in Critically Ill Adults.* N Engl J Med, 2022.
17. Zampieri, F.G., 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**(9): p. 1-12.
18. Waters, J.H., et al., *Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study.* Anesthesia and Analgesia, 2001. **93**(4): p. 817-822.
19. Young, J.B., et al., *Saline versus Plasma-Lyte A in initial resuscitation of trauma patients: a randomized trial.* Annals of Surgery, 2014. **259**(2): p. 255-262.
20. Verma, B., 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**: p. 205-212.
21. Semler, M.W., et al., *Balanced Crystalloids versus Saline in the Intensive Care Unit. The SALT Randomized Trial.* Am J Respir Crit Care Med, 2017. **195**(10): p. 1362-1372.

22. Ratanart, R., *ESICM LIVES 2017 : 30th ESICM Annual Congress. September 23-27, 2017 (0400).* Intensive Care Med Exp, 2017. **5**(Suppl 2).
23. Choosakul, 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**(5): p. 507-512.
24. Kunupakan, S., 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)*, in *The 34th Annual Meeting The Royal College of Physicians of Thailand*. 2018: Thailand.
25. Golla, R., et al., *0.9% saline V/S Ringer'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, 2020. **29**(5): p. 271-280.
26. Ramanan, M., 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**(11): p. 1248-1257.
27. Hammond Naomi, E., et al., *Balanced Crystalloids versus Saline in Critically Ill Adults — A Systematic Review with Meta-Analysis.* NEJM Evidence, 2022. **1**(2): p. EVIDoa2100010.
28. Young, P., 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.* Journal of the American Medical Association, 2015: p. 1-10.
29. McIntyre, L., et al., *FLUID trial: a protocol for a hospital-wide open-label cluster crossover pragmatic comparative effectiveness randomised pilot trial.* BMJ Open, 2018. **8**(8): p. e022780.
30. Taljaard, M., et al., *The Ottawa Statement on the ethical design and conduct of cluster randomised trials: precis for researchers and research ethics committees.* British Medical Journal, 2013. **346**: p. f2838.
31. Intensive Care, S. and M. Department of Health, *Comprehensive Critical Care: a review of adult critical care services*. 2011.
32. Friedman, J.N., *Risk of acute hyponatremia in hospitalized children and youth receiving maintenance intravenous fluids.* Paediatr.Child Health, 2013. **18**(2): p. 102-107.
33. Juurlink, D., et al., *Canadian Institute for Health Information Discharge Abstract Database: A Validation Study*. 2006, The Institute for Clinical Evaluative Sciences (ICES): Toronto, Ontario, Canada.
34. Richards, J., A. Brown, and C. Homan, *The Data Quality Study of the Canadian Discharge Abstract Database.* Canadian Institute for Health Information, 2001. **Proceedings of Statistics Canada Symposium 2001**.
35. Eldridge, S.M., et al., *CONSORT 2010 statement: extension to randomised pilot and feasibility trials.* Bmj, 2016. **355**: p. i5239.
36. Sim, J., *Should treatment effects be estimated in pilot and feasibility studies?* Pilot Feasibility Stud, 2019. **5**: p. 107.
37. Canadian Institutes of Health, R., et al., *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*. 2014.
38. Alghamdi, N.A., 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**(1): p. e0613.
39. Hemming, K., et al., *Use of multiple period, cluster randomised, crossover trial designs for comparative effectiveness research.* Bmj, 2020. **371**: p. m3800.

**Figure 1: FLUID Pilot Trial Study Design**

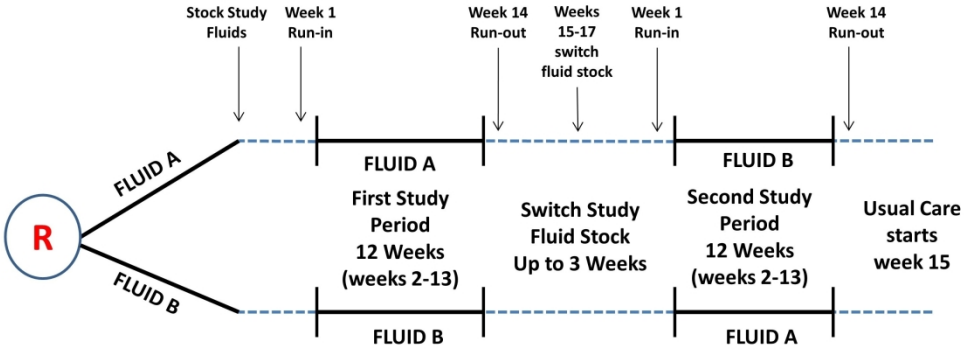


Figure 1

254x129mm (300 x 300 DPI)

**Figure 2: Consort Flow Diagram**

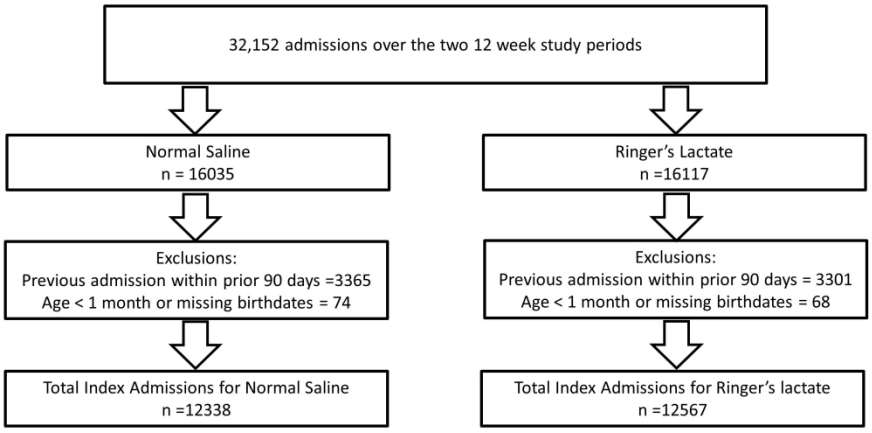


Figure 2

265x155mm (300 x 300 DPI)

**Figure 3: 0.9% Saline Compliance: Overall and by Site**

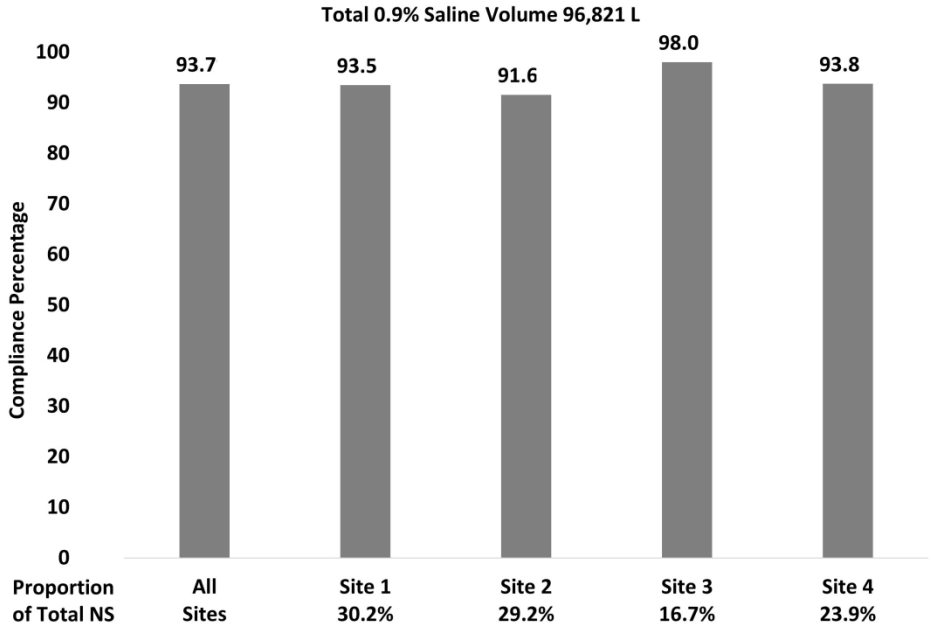


Figure 3

251x190mm (300 x 300 DPI)

**Figure 4: Ringer's Lactate Compliance: Overall and by Site**

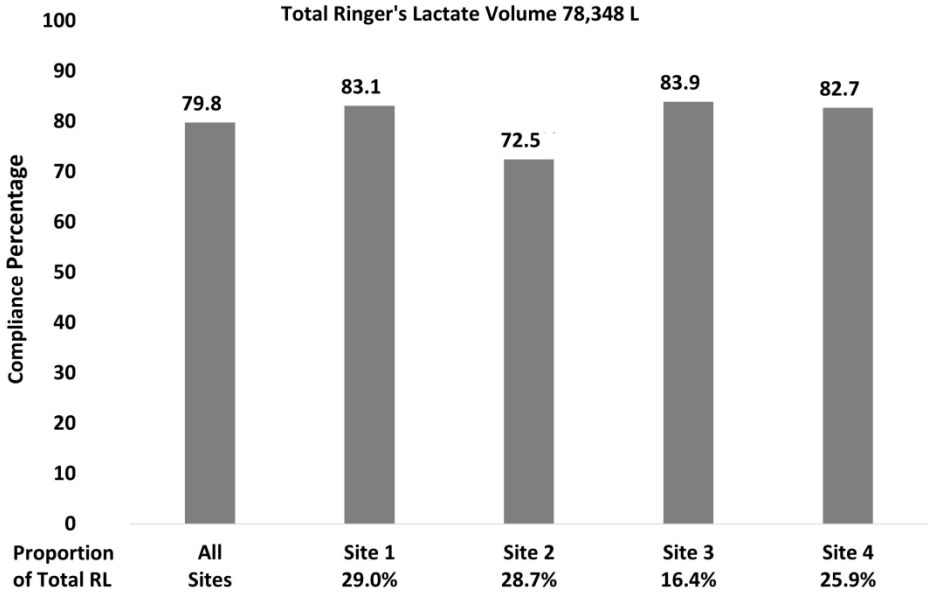


Figure 4

252x190mm (300 x 300 DPI)

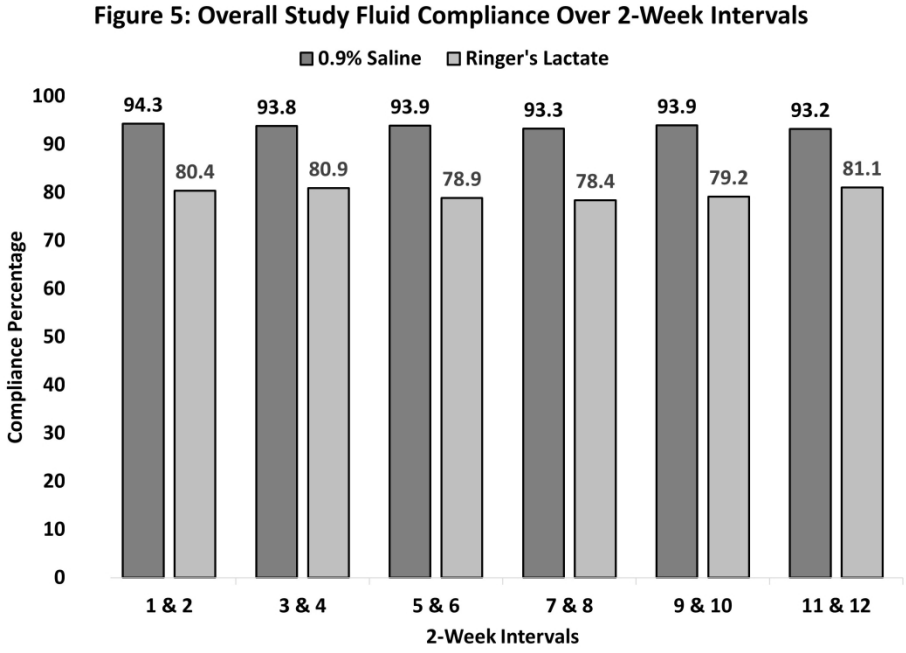


Figure 5

257x190mm (300 x 300 DPI)

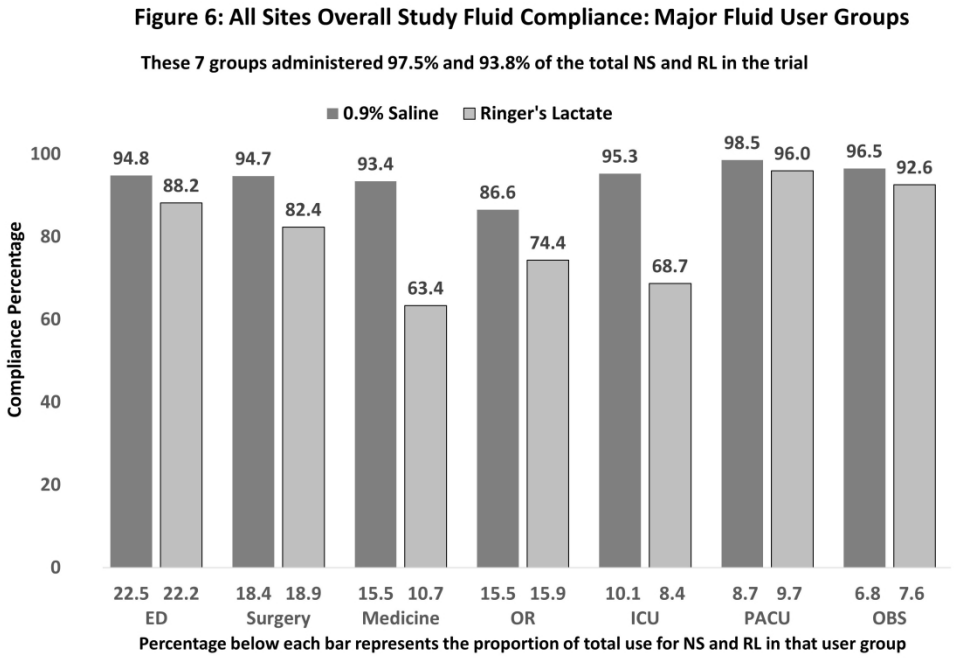


Figure 6

279x190mm (300 x 300 DPI)

# Supplementary Appendix I

## The FLUID Trial: A Hospital-Wide Open-Label Cluster Cross-Over Pragmatic Comparative Effectiveness Randomized Pilot Trial

**Table of Contents**

## Summary

This document defines the codes utilized for variables utilized in the trial dataset. Data was obtained using Ontario's population-based health administrative databases at the Institute for Clinical Evaluative Sciences (ICES). ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. Trained coders review all hospital charts upon discharge to record appropriate diagnosis codes and their characteristics. Coders follow the Canadian Coding Standards developed by the Canadian Institute for Health Information (CIHI).[1] These datasets were linked using unique encoded identifiers and analyzed at ICES.

Databases utilized for variables include:

- Registered Persons Database (RPDB)
- Discharge Abstract Database (DAD)
- Ontario Mental Health Reporting System (OMHRS)
- National Ambulatory Care Reporting System (NACRS)
- Ontario Health Insurance Plan (OHIP)
- Same Day Surgery (SDS)

Calculation of Costing may also include information from:

- Ontario Drug Benefit (ODP)
- OHIP lab claims (all OHIP billings have a fee code beginning with 'L')
- OHIP physician billings
- Home Care Services (OACCAC HCD)
- Complex & Continuing Care (CCRS)
- National Rehabilitation System (NRS)
- Continuing Care Reporting System (CCRS)
- Home Care Services (OACCAC HCD)
- FHO/FHN capitation
- Long term Care
- Hospital outpatient clinic
- NACRS ED visits
- NACRS visits to dialysis clinics
- BACRS visits to cancer clinics
- NDFP chemotherapy drugs
- Assistive Device Programs

**Table 1. Baseline Characteristics**

## 1. Demographics

| RPDB Code | Definition |
|---|---|
| Gender | The sex of the patient as recorded |
| Age | Birthdate subtracted from date of index hospital admission |

## 2. Case Mix Group (CMG)

A CMG is a numbered cell/group to which an acute care inpatient is assigned. CMG+ CIHI grouping methodology that categorizes acute care patients based on similarities of diagnosis and/or interventions, length of stay (LOS) and resource use.

| Database | CMG cell |
|---|---|
| DAD | Medicine |
| DAD | Surgery |
| DAD | Pregnancy & Childbirth |
| OMHRS, DAD | Mental Health |

## 3. Type of Surgical Admission

| Database | Category | Definition |
|---|---|---|
| DAD | L (elective) | Non-emergent surgery |
| DAD | U (urgent) | Urgent/emergent |
| DAD | Surgical admission < 24 hrs | The number of surgical admissions < 24 hrs using a calculated length of hospital stay by admit date/time and discharge date/time |

## 4. Severity of Illness

### A. Admission to ICU

Special Care Units (SCU) identify location of critical care

| Database | SCU 1-6 Code | Unit |
|---|---|---|
| DAD | 10 | Medical Intensive Care Unit |
| DAD | 20 | Surgical Intensive Care Nursing Unit |
| DAD | 25 | Trauma Intensive Care Nursing Unit |
| DAD | 30 | Combined Medical/Surgical Intensive Care Nursing Unit |
| DAD | 35 | Burn Intensive Care Nursing Unit |
| DAD | 40 | Cardiac Intensive Care Nursing Unit Surgery |
| DAD | 45 | Coronary Intensive Care Nursing Unit Medical |
| DAD | 60 | Neurosurgery Intensive Care Nursing Unit |
| DAD | 70 | Paediatric Intensive Care Nursing Unit |
| DAD | 80 | Respirology Intensive Care Nursing Unit |

### B. Infection Alone and Infection and Organ Dysfunction

All patients admitted to the entire hospital (including ICU (SCU location code)) with a code for Infection alone (ICD 10 infection code) and Infection and organ dysfunction (ICD 10 infection code + ICD 10 organ dysfunction code and/or a Canadian Classification of Health Interventions (CCI) code listed below).

### C. Infection Alone and Infection and Organ Dysfunction and ICU admission

All patients admitted to the ICU (SCU location code) who have an infection alone code (ICD 10 infection code) and infection and organ dysfunction (ICD 10 infection code + ICD 10 organ dysfunction code and/or CCI code listed below)

**ICD 10 Infection Codes**

| ICD-10 | Definition |
|---|---|
| A039 | Shigellosis, unspecified |
| A021 | Salmonella sepsis |
| A207 | Septicaemic plague |
| A217 | Generalized tularaemia |
| A227 | Anthrax sepsis |
| A239 | Brucellosis, unspecified |
| A241 | Acute and fulminating melioidosis |
| A267 | Erysipelothrix sepsis |
| A280 | Pasteurellosis |
| A282 | Extraintestinal yersiniosis |
| A327 | Listerial sepsis |
| A392 | Acute meningococcaemia |
| A393 | Chronic meningococcaemia |
| A394 | Meningococcaemia, unspecified |
| A40 | Streptococcal septicaemia |
| A400 | Sepsis due to streptococcus, group A |
| A401 | Sepsis due to streptococcus, group B |
| A402 | Sepsis due to streptococcus, group D |
| A403 | Sepsis due to Streptococcus pneumoniae |
| A408 | Other streptococcal sepsis |
| A409 | Streptococcal sepsis, unspecified |

| ICD-10 | Definition |
|---|---|
| A41 | Other septicaemia |
| A410 | Sepsis due to Staphylococcus aureus |
| A411 | Sepsis due to other specified staphylococcus |
| A412 | Sepsis due to unspecified staphylococcus |
| A413 | Sepsis due to Haemophilus influenzae |
| A414 | Sepsis due to anaerobes |
| A4150 | Sepsis due to Escherichia coli [E.coli] |
| A4151 | Sepsis due to Pseudomonas |
| A4152 | Sepsis due to Serratia |
| A4158 | Sepsis due to other Gram-negative organisms |
| A4159 | Gram-negative septicaemia, unspecified |
| A4180 | Sepsis due to Enterococcus |
| A4188 | Other specified sepsis |
| A419 | Sepsis, unspecified |
| A047 | Enterocolitis due to Clostridium difficile |
| A427 | Actinomycotic sepsis |
| A4880 | Necrotizing fasciitis |
| A480 | Gas gangrene |
| A482 | Nonpneumonic Legionnaires' disease [Pontiac fever] |
| A483 | Toxic shock syndrome |
| A87 | Viral meningitis |
| B007 | Disseminated herpesviral disease |
| B377 | Candidal sepsis |
| B9548 | Other streptococcus as the cause of diseases classified to other chapters |
| B956 | Staphylococcus aureus as the cause of diseases classified to other chapters |
| B962 | Escherichia coli [E. coli] as the cause of diseases classified to other chapters |
| J189 | Pneumonia, unspecified |
| J440 | Chronic obstructive pulmonary disease with acute lower respiratory infection |
| N390 | Urinary tract infection, site not specified |
| P36 | Bacterial sepsis of newborn |
| P360 | Sepsis of newborn due to streptococcus, group B |
| P361 | Sepsis of newborn due to other and unspecified streptococci |
| P362 | Sepsis of newborn due to Staphylococcus aureus |
| P363 | Sepsis of newborn due to other and unspecified staphylococci |
| P364 | Sepsis of newborn due to Escherichia coli |
| P365 | Sepsis of newborn due to anaerobes |
| P368 | Other bacterial sepsis of newborn |
| P369 | Bacterial sepsis of newborn, unspecified |
| P352 | Congenital herpesviral [herpes simplex] infection |
| P372 | Neonatal (disseminated) listeriosis |
| P375 | Neonatal candidiasis |

**ICD-10 Organ Dysfunction Codes and CCI Codes**

| | |
|---|---|
| R572 | Septic shock |
| J960 | Acute respiratory failure |
| J969 | Respiratory failure, unspecified |
| J80 | Adult respiratory distress syndrome |
| R092 | Respiratory arrest |
| R570 | Cardiogenic shock |
| R571 | Hypovolaemic shock |
| R578 | Other shock |

| | |
|---|---|
| R57.9 | Shock, unspecified |
| I951 | Orthostatic hypotension |
| I958 | Other hypotension |
| I959 | Hypotension, unspecified |
| N170 | Acute renal failure with tubular necrosis |
| N171 | Acute renal failure with acute cortical necrosis |
| N172 | Acute renal failure with medullary necrosis |
| N178 | Other acute renal failure |
| N179 | Acute renal failure, unspecified |
| K720 | Acute and subacute hepatic failure |
| K729 | Hepatic failure, unspecified |
| K763 | Infarction of liver |
| F050 | Delirium not superimposed on dementia, so described |
| F059 | Delirium, unspecified |
| G931 | Anoxic brain damage, not elsewhere classified |
| G934 | Other and unspecified encephalopathy |
| G93.80 | Metabolic encephalopathy |
| D69.5 | Secondary thrombocytopenia |
| D69.6 | Thrombocytopenia, unspecified |
| D65 | Disseminated intravascular coagulation |
| **Intervention Codes (CCI)** | |
| GZ.31.CA-ND | Ventilation, respiratory system NEC invasive per orifice approach by endotracheal intubation and positive pressure |
| GZ.31CR-ND | Ventilation, respiratory system NEC invasive per orifice with incision approach for intubation through tracheostomy positive pressure |
| GZ.31GP-ND | Ventilation, respiratory system NEC invasive percutaneous transluminal approach (e.g. transtracheal jet) through needle and positive pressure |

### D. Trauma and ICU

Presence of an ICD-10 trauma code in the range S00-T14, plus any external cause code from range W00 – X59 and admission to an intensive care unit (SCU location code)

| ICD-10 | Definition |
|---|---|
| S00 - S09 | Injuries to the head |
| S10-S19 | Injuries to the neck |
| S20-S29 | Injuries to the thorax |
| S30-S39 | Injuries to the abdomen, lower back, lumbar spine, pelvis and external genitalia |
| S40-S49 | Injuries to the shoulder and upper arm |
| S50-S59 | Injuries to the elbow and forearm |
| S60-S69 | Injuries to the wrist, hand and fingers |
| S70-S79 | Injuries to the hip and thigh |
| S80-S89 | Injuries to the knee and lower leg |
| S90-S99 | Injuries to the ankle and foot |
| T00 | Superficial injuries involving multiple body regions |
| T000 | Superficial injuries involving head with neck |
| T001 | Superficial injuries involving thorax with abdomen, lower back and pelvis |
| T002 | Superficial injuries involving multiple regions of upper limb(s) |
| T003 | Superficial injuries involving multiple regions of lower limb(s) |
| T006 | Superficial injuries involving multiple regions of upper limb(s) with lower limb(s) |

| ICD-10 | Definition |
|---|---|
| T008 | Superficial injuries involving other combinations of body regions |
| T009 | Multiple superficial injuries, unspecified |
| T01 | Open wounds involving multiple body regions |
| T0100 | Open wound involving head with neck, uncomplicated |
| T0101 | Open wound involving head with neck, complicated |
| T0110 | Open wounds involving thorax with abdomen, lower back and pelvis, uncomplicated |
| T0111 | Open wounds involving thorax with abdomen, lower back and pelvis, complicated |
| T0120 | Open wounds involving multiple regions of upper limb(s), uncomplicated |
| T0121 | Open wounds involving multiple regions of upper limb(s), complicated |
| T0130 | Open wounds of multiple regions of lower limb(s), uncomplicated |
| T0131 | Open wounds of multiple regions of lower limb(s), complicated |
| T0160 | Open wounds involving multiple regions of upper limb(s) with lower limb(s), uncomplicated |
| T0161 | Open wounds involving multiple regions of upper limb(s) with lower limb(s), complicated |
| T0180 | Open wounds involving other combinations of body regions, uncomplicated |
| T0181 | Open wounds involving other combinations of body regions, complicated |
| T0190 | Multiple open wounds of unspecified site, uncomplicated |
| T0191 | Multiple open wounds of unspecified site, complicated |
| T02 | Fractures involving multiple body regions |
| T0200 | Fractures involving head with neck, closed |
| T0201 | Fractures involving head with neck, open |
| T0210 | Fractures involving thorax with lower back and pelvis, closed |
| T0211 | Fractures involving thorax with lower back and pelvis, open |
| T0220 | Fractures involving multiple regions of one upper limb, closed |
| T0221 | Fractures involving multiple regions of one upper limb, open |
| T0230 | Fractures involving multiple regions of one lower limb, closed |
| T0231 | Fractures involving multiple regions of one lower limb, open |
| T0240 | Fractures involving multiple regions of both upper limbs, closed |
| T0241 | Fractures involving multiple regions of both upper limbs, open |
| T0250 | Fractures involving multiple regions of both lower limbs, closed |
| T0251 | Fractures involving multiple regions of both lower limbs, open |
| T0260 | Fractures involving multiple regions of upper limb(s) with lower limb(s), closed |
| T0261 | Fractures involving multiple regions of upper limb(s) with lower limb(s), open |
| T0270 | Fractures involving thorax with lower back and pelvis with limb(s), closed |
| T0271 | Fractures involving thorax with lower back and pelvis with limb(s), open |
| T0280 | Fractures involving other combinations of body regions, closed |
| T0281 | Fractures involving other combinations of body regions, open |
| T0290 | Multiple fractures, unspecified, closed |
| T0291 | Multiple fractures, unspecified, open |
| T03 | Dislocations, sprains and strains involving multiple body regions |
| T030 | Dislocations, sprains and strains involving head with neck |
| T031 | Dislocations, sprains and strains involving thorax with lower back and pelvis |
| T032 | Dislocations, sprains and strains involving multiple regions of upper limb(s) |
| T033 | Dislocations, sprains and strains involving multiple regions of lower limb(s) |
| T034 | Dislocations, sprains and strains involving multiple regions of upper limb(s) with lower limb(s) |
| T038 | Dislocations, sprains and strains involving other combinations of body regions |
| T039 | Multiple dislocations, sprains and strains, unspecified |
| T04 | Crushing injuries involving multiple body regions |
| T040 | Crushing injuries involving head with neck |
| T041 | Crushing injuries involving thorax with abdomen, lower back and pelvis |
| T042 | Crushing injuries involving multiple regions of upper limb(s) |
| T043 | Crushing injuries involving multiple regions of lower limb(s) |

| ICD-10 | Definition |
|---|---|
| T044 | Crushing injuries involving multiple regions of upper limb(s) with lower limb(s) |
| T047 | Crushing injuries of thorax with abdomen, lower back and pelvis with limb(s) |
| T048 | Crushing injuries involving other combinations of body regions |
| T049 | Multiple crushing injuries, unspecified |
| T05 | Traumatic amputations involving multiple body regions |
| T050 | Traumatic amputation of both hands |
| T051 | Traumatic amputation of one hand and other arm [any level, except hand] |
| T052 | Traumatic amputation of both arms [any level] |
| T053 | Traumatic amputation of both feet |
| T054 | Traumatic amputation of one foot and other leg [any level, except foot] |
| T055 | Traumatic amputation of both legs [any level] |
| T056 | Traumatic amputation of upper and lower limbs, any combination [any level] |
| T058 | Traumatic amputations involving other combinations of body regions |
| T059 | Multiple traumatic amputations, unspecified |
| T06 | Other injuries involving multiple body regions, not elsewhere classified |
| T060 | Injuries of brain and cranial nerves with injuries of nerves and spinal cord at neck level |
| T061 | Injuries of nerves and spinal cord involving other multiple body regions |
| T062 | Injuries of nerves involving multiple body regions |
| T063 | Injuries of blood vessels involving multiple body regions |
| T064 | Injuries of muscles and tendons involving multiple body regions |
| T065 | Injuries of intrathoracic organs with intra-abdominal and pelvic organs |
| T068 | Other specified injuries involving multiple body regions |
| T07 | Unspecified multiple injuries |
| T08 | Fracture of spine, level unspecified |
| T080 | Fracture of spine, level unspecified, closed |
| T081 | Fracture of spine, level unspecified, open |
| T09 | Other injuries of spine and trunk, level unspecified |
| T090 | Superficial injury of trunk, level unspecified |
| T091 | Open wound of trunk, level unspecified |
| T095 | Injury of unspecified muscle and tendon of trunk |
| T098 | Other specified injuries of trunk, level unspecified |
| T099 | Unspecified injury of trunk, level unspecified |
| T10 | Fracture of upper limb, level unspecified |
| T100 | Fracture of upper limb, level unspecified, closed |
| T101 | Fracture of upper limb, level unspecified, open |
| T11 | Other injuries of upper limb, level unspecified |
| T110 | Superficial injury of upper limb, level unspecified |
| T111 | Open wound of upper limb, level unspecified |
| T112 | Dislocation, sprain and strain of unspecified joint and ligament of upper limb, level unspecified |
| T113 | Injury of unspecified nerve of upper limb, level unspecified |
| T114 | Injury of unspecified blood vessel of upper limb, level unspecified |
| T115 | Injury of unspecified muscle and tendon of upper limb, level unspecified |
| T116 | Traumatic amputation of upper limb, level unspecified |
| T118 | Other specified injuries of upper limb, level unspecified |
| T119 | Unspecified injury of upper limb, level unspecified |
| T12 | Fracture of lower limb, level unspecified |
| T120 | Fracture of lower limb, level unspecified, closed |
| T1200 | Fracture of lower limb, level unspecified, closed |
| T1201 | Fracture of lower limb, level unspecified, open |
| T121 | Fracture of lower limb, level unspecified, open |
| T13 | Other injuries of lower limb, level unspecified |

| ICD-10 | Definition |
|---|---|
| T130 | Superficial injury of lower limb, level unspecified |
| T131 | Open wound of lower limb, level unspecified |
| T132 | Dislocation, sprain and strain of unspecified joint and ligament of lower limb, level unspecified |
| T133 | Injury of unspecified nerve of lower limb, level unspecified |
| T134 | Injury of unspecified blood vessel of lower limb, level unspecified |
| T135 | Injury of unspecified muscle and tendon of lower limb, level unspecified |
| T136 | Traumatic amputation of lower limb, level unspecified |
| T138 | Other specified injuries of lower limb, level unspecified |
| T139 | Unspecified injury of lower limb, level unspecified |
| T14 | Injury of unspecified body region |
| T140 | Superficial injury of unspecified body region |
| T141 | Open wound of unspecified body region |
| T1420 | Fracture of unspecified body region, closed |
| T1421 | Fracture of unspecified body region, open |
| T143 | Dislocation, sprain and strain of unspecified body region |
| T144 | Injury of nerve(s) of unspecified body region |
| T145 | Injury of blood vessel(s) of unspecified body region |
| T146 | Injury of muscles and tendons of unspecified body region |
| T147 | Crushing injury and traumatic amputation of unspecified body region |
| T148 | Other injuries of unspecified body region |
| T149 | Injury, unspecified |
| W00 | Fall on same level involving ice and snow |
| W01 | Fall on same level from slipping, tripping and stumbling |
| W02 | Fall involving skates, skis, sport boards and rollerblades |
| W0200 | Fall involving ice skates |
| W0201 | Fall involving skis |
| W0202 | Fall involving roller skates/in-line skates |
| W0203 | Fall involving skateboard |
| W0204 | Fall involving snowboard |
| W0208 | Fall other specified |
| W03 | Other fall on same level due to collision with, or pushing by, another person |
| W04 | Fall while being carried or supported by other persons |
| W05 | Fall involving wheelchair and other types of walking devices |
| W0500 | Fall involving wheelchair |
| W0501 | Fall involving adult walker |
| W0502 | Fall involving baby walker |
| W0503 | Fall involving stroller/carriage |
| W0504 | Fall involving shopping cart |
| W0508 | Fall involving other specified walking devices |
| W0509 | Fall involving unspecified walking devices |
| W06 | Fall involving bed |
| W07 | Fall involving chair |
| W08 | Fall involving other furniture |
| W09 | Fall involving playground equipment |
| W0901 | Fall involving swing |
| W0902 | Fall involving slide |
| W0903 | Fall involving teeter totter |
| W0904 | Fall involving monkey bars |
| W0905 | Fall involving trampoline |
| W0908 | Fall involving other playground equipment |
| W0909 | Fall involving unspecified playground equipment |

| ICD-10 | Definition |
|---|---|
| W10 | Fall on and from stairs and steps |
| W11 | Fall on and from ladder |
| W12 | Fall on and from scaffolding |
| W13 | Fall from, out of or through building or structure |
| W14 | Fall from tree |
| W15 | Fall from cliff |
| W16 | Diving or jumping into water causing injury other than drowning or submersion |
| W17 | Other fall from one level to another |
| W18 | Other fall on same level |
| W19 | Unspecified fall |
| W20 | Struck by thrown, projected or falling object |
| W21 | Striking against or struck by sports equipment |
| W2100 | Striking against or struck by ball |
| W2101 | Striking against or struck by bat |
| W2102 | Striking against or struck by hockey stick |
| W2103 | Striking against or struck by hockey puck |
| W2108 | Striking against or struck by other specified sport equipment |
| W2109 | Striking against or struck by other unspecified sport equipment |
| W22 | Striking against or struck by other objects |
| W2200 | Striking against or struck by/while skiing/snowboarding |
| W2201 | Striking against or struck while tobogganing |
| W2202 | Striking against or struck by/playing hockey |
| W2203 | Striking against or struck by/playing football/rugby |
| W2204 | Striking against or struck by/playing soccer |
| W2205 | Striking against or struck by/playing baseball |
| W2207 | Striking against or struck by/in other sports/recreation |
| W2208 | Striking against or struck by/in non-sports |
| W2209 | Striking against or struck by unspecified |
| W23 | Caught, crushed, jammed or pinched in or between objects |
| W24 | Contact with lifting and transmission devices, not elsewhere classified |
| W25 | Contact with sharp glass |
| W26 | Contact with knife, sword or dagger |
| W27 | Contact with nonpowered hand tool |
| W28 | Contact with powered lawnmower |
| W29 | Contact with other powered hand tools and household machinery |
| W30 | Contact with agricultural machinery |
| W31 | Contact with other and unspecified machinery |
| W32 | Handgun discharge |
| W33 | Rifle, shotgun and larger firearm discharge |
| W34 | Discharge from other and unspecified firearms |
| W3400 | Discharge from BB gun |
| W3401 | Discharge from air gun |
| W3408 | Discharge from other specified firearm |
| W3409 | Discharge from unspecified firearm |
| W35 | Explosion and rupture of boiler |
| W36 | Explosion and rupture of gas cylinder |
| W37 | Explosion and rupture of pressurized tyre, pipe or hose |
| W38 | Explosion and rupture of other specified pressurized devices |
| W39 | Discharge of firework |
| W40 | Explosion of other materials |
| W41 | Exposure to high-pressure jet |

| ICD-10 | Definition |
|---|---|
| W42 | Exposure to noise |
| W43 | Exposure to vibration |
| W44 | Foreign body entering into or through eye or natural orifice |
| W45 | Foreign body or object entering through skin |
| W4500 | Body piercing |
| W4509 | Foreign body or object entering through skin |
| W46 | Contact with hypodermic needle |
| W49 | Exposure to other and unspecified inanimate mechanical forces |

### E. Traumatic Brain Injury

Presence of a traumatic brain injury (TBI) ICD-10 code for all hospital admissions (including ICU (SCU location code)

### F. Traumatic Brain Injury and ICU admission

Presence of a traumatic brain injury ICD-10 and admission to an intensive care unit (SCU location code)

| ICD-10 | Definition |
|---|---|
| S06 | Intracranial injury |
| S060 | Concussion |
| S06000 | Concussion without loss of consciousness without open intracranial wound |
| S06001 | Concussion without loss of consciousness with open intracranial wound |
| S06010 | Concussion with brief loss of consciousness without open intracranial wound |
| S06011 | Concussion with brief loss of consciousness with open intracranial wound |
| S06020 | Concussion with moderate loss of consciousness without open intracranial wound |
| S06021 | Concussion with moderate loss of consciousness with open intracranial wound |
| S06030 | Concussion with prolonged loss of consciousness with return to pre-existing level of consciousness without open intracranial wound |
| S06031 | Concussion with prolonged loss of consciousness with return to pre-existing level of consciousness with open intracranial wound |
| S06040 | Concussion with prolonged loss of consciousness without return to pre-existing level of consciousness without open intracranial wound |
| S06041 | Concussion with prolonged loss of consciousness without return to pre-existing level of consciousness with open intracranial wound |
| S06090 | Concussion with loss of consciousness of unspecified duration without open intracranial wound |
| S06091 | Concussion with loss of consciousness of unspecified duration with open intracranial wound |
| S061 | Traumatic cerebral oedema |
| S06100 | Traumatic cerebral oedema without loss of consciousness without open intracranial wound |
| S06101 | Traumatic cerebral oedema without loss of consciousness with open intracranial wound |
| S06110 | Traumatic cerebral oedema with brief loss of consciousness without open intracranial wound |
| S06111 | Traumatic cerebral oedema with brief loss of consciousness with open intracranial wound |
| S06120 | Traumatic cerebral oedema with moderate loss of consciousness without open intracranial wound |
| S06121 | Traumatic cerebral oedema with moderate loss of consciousness with open intracranial wound |
| S06130 | Traumatic cerebral oedema with prolonged loss of consciousness with return to pre-existing level of consciousness without open intracranial wound |
| S06131 | Traumatic cerebral oedema with prolonged loss of consciousness with return to pre-existing level of consciousness with open intracranial wound |
| S06140 | Traumatic cerebral oedema with prolonged loss of consciousness without return to pre-existing level of consciousness without open intracranial wound |
| S06141 | Traumatic cerebral oedema with prolonged loss of consciousness without return to pre-existing level of consciousness with open intracranial wound |

| ICD-10 | Definition |
|---|---|
| S06190 | Traumatic cerebral oedema with loss of consciousness of unspecified duration without open intracranial wound |
| S06191 | Traumatic cerebral oedema with loss of consciousness of unspecified duration with open intracranial wound |
| S06200 | Diffuse brain injury without loss of consciousness without open intracranial wound |
| S06201 | Diffuse brain injury without loss of consciousness with open intracranial wound |
| S06210 | Diffuse brain injury with brief loss of consciousness without open intracranial wound |
| S06211 | Diffuse brain injury with brief loss of consciousness with open intracranial wound |
| S06220 | Diffuse brain injury with moderate loss of consciousness without open intracranial wound |
| S06221 | Diffuse brain injury with moderate loss of consciousness with open intracranial wound |
| S06230 | Diffuse brain injury with prolonged loss of consciousness with return to pre-existing level of consciousness without open intracranial wound |
| S06231 | Diffuse brain injury with prolonged loss of consciousness with return to pre-existing level of consciousness with open intracranial wound |
| S06240 | Diffuse brain injury with prolonged loss of consciousness without return to pre-existing level of consciousness without open intracranial wound |
| S06241 | Diffuse brain injury with prolonged loss of consciousness without return to pre-existing level of consciousness with open intracranial wound |
| S0625 | Diffuse brain injury without open intracranial wound |
| S0626 | Diffuse brain injury with open intracranial wound |
| S06290 | Diffuse brain injury with loss of consciousness of unspecified duration without open intracranial wound |
| S06291 | Diffuse brain injury with loss of consciousness of unspecified duration with open intracranial wound |
| S06300 | Focal brain injury without loss of consciousness, without open intracranial wound |
| S06301 | Focal brain injury without loss of consciousness, with open intracranial wound |
| S06310 | Focal brain injury with brief loss of consciousness without open intracranial wound |
| S06311 | Focal brain injury with brief loss of consciousness with open intracranial wound |
| S06320 | Focal brain injury with moderate loss of consciousness without open intracranial wound |
| S06321 | Focal brain injury with moderate loss of consciousness with open intracranial wound |
| S06330 | Focal brain injury with prolonged loss of consciousness with return to pre-existing level of consciousness without open intracranial wound |
| S06331 | Focal brain injury with prolonged loss of consciousness with return to pre-existing level of consciousness with open intracranial wound |
| S06340 | Focal brain injury with prolonged loss of consciousness without return to pre-existing level of consciousness without open intracranial wound |
| S06341 | Focal brain injury with prolonged loss of consciousness without return to pre-existing level of consciousness with open intracranial wound |
| S0635 | Focal brain injury without open intracranial wound |
| S0636 | Focal brain injury with open intracranial wound |
| S06390 | Focal brain injury with loss of consciousness of unspecified duration without open intracranial wound |
| S06391 | Focal brain injury with loss of consciousness of unspecified duration with open intracranial wound |
| S064 | Epidural haemorrhage |
| S06400 | Epidural haemorrhage without loss of consciousness without open intracranial wound |
| S06401 | Epidural haemorrhage without loss of consciousness with open intracranial wound |
| S06410 | Epidural haemorrhage with brief loss of consciousness without open intracranial wound |
| S06411 | Epidural haemorrhage with brief loss of consciousness with open intracranial wound |
| S06420 | Epidural haemorrhage with moderate loss of consciousness without open intracranial wound |
| S06421 | Epidural haemorrhage with moderate loss of consciousness with open intracranial wound |
| S06430 | Epidural haemorrhage with prolonged loss of consciousness without open intracranial wound |
| S06431 | Epidural haemorrhage with prolonged loss of consciousness with open intracranial wound |
| S06440 | Epidural haemorrhage with prolonged loss of consciousness without return to pre-existing level of consciousness without open intracranial wound |
| S06441 | Epidural haemorrhage with prolonged loss of consciousness without return to pre-existing level of consciousness with open intracranial wound |

| ICD-10 | Definition |
|---|---|
| S06490 | Epidural haemorrhage with loss of consciousness of unspecified duration without open intracranial wound |
| S06491 | Epidural haemorrhage with loss of consciousness of unspecified duration with open intracranial wound |
| S065 | Traumatic subdural haemorrhage |
| S06500 | Traumatic subdural haemorrhage without loss of consciousness without open intracranial wound |
| S06501 | Traumatic subdural haemorrhage without loss of consciousness with open intracranial wound |
| S06510 | Traumatic subdural haemorrhage with brief loss of consciousness without open intracranial wound |
| S06511 | Traumatic subdural haemorrhage with brief loss of consciousness with open intracranial wound |
| S06520 | Traumatic subdural haemorrhage with moderate loss of consciousness without open intracranial wound |
| S06521 | Traumatic subdural haemorrhage with moderate loss of consciousness with open intracranial wound |
| S06530 | Traumatic subdural haemorrhage with prolonged loss of consciousness with return to pre-existing level of consciousness without open intracranial wound |
| S06531 | Traumatic subdural haemorrhage with prolonged loss of consciousness with return to pre-existing level of consciousness with open intracranial wound |
| S06540 | Traumatic subdural haemorrhage with prolonged loss of consciousness without return to pre-existing level of consciousness without open intracranial wound |
| S06541 | Traumatic subdural haemorrhage with prolonged loss of consciousness without return to pre-existing level of consciousness with open intracranial wound |
| S06590 | Traumatic subdural haemorrhage with loss of consciousness of unspecified duration without open intracranial wound |
| S06591 | Traumatic subdural haemorrhage with loss of consciousness of unspecified duration with open intracranial wound |
| S066 | Traumatic subarachnoid haemorrhage |
| S06600 | Traumatic subarachnoid haemorrhage without loss of consciousness without open intracranial wound |
| S06601 | Traumatic subarachnoid haemorrhage without loss of consciousness with open intracranial wound |
| S06610 | Traumatic subarachnoid haemorrhage with brief loss of consciousness without intracranial wound |
| S06611 | Traumatic subarachnoid haemorrhage with brief loss of consciousness with intracranial wound |
| S06620 | Traumatic subarachnoid haemorrhage with moderate loss of consciousness without open intracranial wound |
| S06621 | Traumatic subarachnoid haemorrhage with moderate loss of consciousness with open intracranial wound |
| S06630 | Traumatic subarachnoid haemorrhage with prolonged loss of consciousness with return to pre-existing level of consciousness without open intracranial wound |
| S06631 | Traumatic subarachnoid haemorrhage with prolonged loss of consciousness with return to pre-existing level of consciousness with open intracranial wound |
| S06640 | Traumatic subarachnoid haemorrhage with prolonged loss of consciousness without return to pre-existing level of consciousness without open intracranial wound |
| S06641 | Traumatic subarachnoid haemorrhage with prolonged loss of consciousness without return to pre-existing level of consciousness with open intracranial wound |
| S06690 | Traumatic subarachnoid haemorrhage with loss of consciousness of unspecified duration without open intracranial wound |
| S06691 | Traumatic subarachnoid haemorrhage with loss of consciousness of unspecified duration with open intracranial wound |
| S06800 | Other intracranial injuries without loss of consciousness without open intracranial wound |
| S06801 | Other intracranial injuries without loss of consciousness with open intracranial wound |
| S06810 | Other intracranial injuries with brief loss of consciousness without open intracranial wound |
| S06811 | Other intracranial injuries with brief loss of consciousness with open intracranial wound |
| S06820 | Other intracranial injuries with moderate loss of consciousness without open intracranial wound |
| S06821 | Other intracranial injuries with moderate loss of consciousness with open intracranial wound |
| S06830 | Other intracranial injuries with prolonged loss of consciousness with return to pre-existing level of consciousness without open intracranial wound |
| S06831 | Other intracranial injuries with prolonged loss of consciousness with return to pre-existing level of consciousness with open intracranial wound |
| S06840 | Other intracranial injuries with prolonged loss of consciousness without return to pre-existing level of consciousness without open intracranial wound |

| ICD-10 | Definition |
|---|---|
| S06841 | Other intracranial injuries with prolonged loss of consciousness without return to pre-existing level of consciousness with open intracranial wound |
| S0685 | Other intracranial injuries without open intracranial wound |
| S0686 | Other intracranial injuries with open intracranial wound |
| S06890 | Other intracranial injuries with loss of consciousness of unspecified duration without open intracranial wound |
| S06891 | Other intracranial injuries with loss of consciousness of unspecified duration with open intracranial wound |
| S069 | Intracranial injury, unspecified |
| S06900 | Intracranial injury, unspecified without loss of consciousness without open intracranial wound |
| S06901 | Intracranial injury, unspecified without loss of consciousness with open intracranial wound |
| S06910 | Intracranial injury, unspecified with brief loss of consciousness without open intracranial wound |
| S06911 | Intracranial injury, unspecified with brief loss of consciousness with open intracranial wound |
| S06920 | Intracranial injury, unspecified with moderate loss of consciousness without open intracranial wound |
| S06921 | Intracranial injury, unspecified with moderate loss of consciousness with open intracranial wound |
| S06930 | Intracranial injury, unspecified with prolonged loss of consciousness with return to pre-existing level of consciousness without open intracranial wound |
| S06931 | Intracranial injury, unspecified with prolonged loss of consciousness with return to pre-existing level of consciousness with open intracranial wound |
| S06940 | Intracranial injury, unspecified with prolonged loss of consciousness without return to pre-existing level of consciousness without open intracranial wound |
| S06941 | Intracranial injury, unspecified with prolonged loss of consciousness without return to pre-existing level of consciousness with open intracranial wound |
| S06990 | Intracranial injury, unspecified with loss of consciousness of unspecified duration without open intracranial wound |
| S06991 | Intracranial injury, unspecified without loss of consciousness with open intracranial wound |

## 5. Comorbidities

### A. Elixhauser Comorbidity Index Codes

The Elixhauser Comorbidity Index is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data, such as hospital abstracts data. Each comorbidity category is dichotomous -- it is either present or it is not. The Index can be used to predict hospital resource use and in-hospital mortality.[2]

**Table 2 Primary Composite and Secondary Clinical Outcomes and Costs**

## 1. Primary Composite Outcome

### A. Death or re-admission to hospital within first 90 days of index admission

| Database | Definition |
|---|---|
| RPDB | Verified if death date subtracted from index admission date is ≤ 90 days |
| DAD | Index hospital admission date compared to any subsequent admission to an Ontario hospital within 90 days |

## 2. Secondary Outcomes

### A. Death

| Database | Definition |
|---|---|
| RPDB | Verified if death date subtracted from index admission date is ≤ 90 days |

| Database | Definition |
|---|---|
| DAD | Index hospital admission date compared to any subsequent admission to an Ontario hospital within 90 days |

### B. Total hospital length of stay

| Database | Definition |
|---|---|
| DAD | Calculated from discharge date of index admission from admit date of index hospital admission |

### C. New Dialysis Within 90 Days of Index Hospital Admission

This variable identifies patients who did not require dialysis within 90 days prior to the index hospital admission and subsequently required any form of dialysis within 90 days of the index hospital admission

| OHIP Billing Code | Definitions |
|---|---|
| **Hemodialysis** | |
| R849 | Haemodialysis - Initial and acute (includes both medical and surgical components) |
| G323 | Haemodialysis - Acute, repeat - for the first 3 services |
| G325 | Haemodialysis - Medical component alone |
| G326 | Dialysis - Chronic, contin. haemodialysis or haemofiltration each |
| G860 | Chronic dialysis weekly team fee - Hospital haemodialysis |
| G333 | Home/self dialysis |
| G862 | Chronic dialysis weekly team fee - Hospital self-care haemodialysis or satellite haemodialysis. |
| G863 | Chronic dialysis weekly team fee - Independent health facility haemodialysis |
| G865 | Home Hemodialysis |
| G866 | Chronic dialysis weekly team fee - Intermittent haemodialysis - at an auxiliary treatment centre (per treatment, maximum 2 per patient per 7-day period referred to above) |
| **Peritoneal Dialysis** | |
| G330 | Peritoneal dialysis - Acute (up to 48 hours) includes stylette cannula insertion (temporary) |
| G331 | Peritoneal dialysis - Repeat acute (up to 48 hours) - for the first 3 services |
| G333 | Home/self dialysis |
| G861 | Chronic dialysis weekly team fee - Hospital peritoneal dialysis |

| | |
|---|---|
| G864 | Chronic dialysis weekly team fee – Home peritoneal dialysis |
| **Continuous Renal Replacement Therapy** | |
| G083 | Haemodialysis - Continuous venovenous haemodialysis - initial and acute (for the first 3 services) |
| G091 | Haemodialysis - Continuous arteriovenous haemodialysis - initial and acute (for the first 3 services) |
| G085 | Haemodialysis - Continuous venovenous haemofiltration - initial and acute (for the first 3 services) |
| G295 | Haemodialysis - Continuous arteriovenous haemofiltration - initial and acute (for the first 3 services) |
| G082 | CVVHD, initial and acute X 3 |
| G092 | Continuous haemodiafiltration - Continuous arteriovenous haemodiafiltration - initial and acute (for the first 3 services) |
| G093 | Haemodiafiltration - Contin. Init & Acute (repeatx3) |
| G094 | Continuous haemodiafiltration - Chronic, continuous haemodiafiltration |
| G090 | Slow continuous ultrafiltration - Venovenous slow continuous ultrafiltration - initial and acute (for the first 3 services) |
| G294 | Continuous haemodiafiltration - Chronic, continuous haemodiafiltration |
| G095 | Slow Continuous Ultra Filtration - Initial & Acute (repeat) |
| G096 | Slow continuous ultrafiltration - Chronic, slow continuous ultrafiltration |

### D. Emergency Department visit within 90 days of index admission

| Database | Definition |
|---|---|
| NACRS | Registration date of the first ED visit to any hospital in Ontario within 90 days of index admission |

### E. Discharge Disposition of the Index Hospitalization

| Database | Discharge Disposition code | Definition |
|---|---|---|
| DAD | 01 | Transferred to another facility providing inpatient hospital care or acute care inpatient institution |
| DAD | 02 | Transferred to a long term or continuing care facility |
| DAD | 03 | Transferred to other ambulatory care, palliative care/hospice, addiction treatment centre, jails, infants and children discharged/detained by social services) |
| DAD | 04 | Discharged to a home setting with support services |
| DAD | 05 | Discharged to home (no support service from an external agency required) |
| DAD | 06 | Signed out (against medical advice) |
| RPDB | | Died |

### 3. 90-day total health system and sub-divided costs, mean ± SD

Direct health care costs were derived from provincial health administrative data available at ICES. ICES uses the GETCOST macro designed to compute individual-level healthcare cost for any requested time period. Cost is calculated 90 days after index hospital admission.[3]

**Reference List**

1. Information CIHI. Canadian Coding Standards for Version 2018 ICD-10-CA and CCI. Ottawa, Ontario, Canada2018:767.
2. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care 1998;36:8-27.
3. Wodchis W, Bushmeneva K, Nikitovic M, McKillop I. Health System Performance Research Network, Guidelines on Person-Level Costing. Using Administrative Databases in Ontario 2013;1:71.

# CONSORT 2010 checklist of information to include when reporting a randomised trial*

| Section/Topic | Item No | Checklist item | Reported on page No |
|---|---|---|---|
| **Title and abstract** | | | |
| | 1a | Identification as a randomised trial in the title | 1 |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | 4 |
| **Introduction** | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | 5, 6 |
| | 2b | Specific objectives or hypotheses | |
| **Methods** | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | 7 |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | N/A |
| Participants | 4a | Eligibility criteria for participants | 8 |
| | 4b | Settings and locations where the data were collected | 9 |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 9,10 |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | 11, 12 |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | N/A |
| Sample size | 7a | How sample size was determined | 14 |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | N/A |
| Randomisation: | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | 9 |
| | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | 9 |
| Allocation concealment mechanism | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | 9 |
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | 9 |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those | N/A |

| | | | |
|---|---|---|---|
| | | assessing outcomes) and how | |
| | 11b | If relevant, description of the similarity of interventions | 5, 10 |
| Statistical methods | 12a | Statistical methods used to compare groups for primary and secondary outcomes | 14 |
| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | 15 |
| **Results** | | | |
| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | Figure 2 |
| | 13b | For each group, losses and exclusions after randomisation, together with reasons | Figure 2 |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | 15 |
| | 14b | Why the trial ended or was stopped | N/A |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics for each group | Table 1 |
| Numbers analysed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | Table 2 |
| Outcomes and estimation | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | Table 2 |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | Table 3 |
| Harms | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) | 10, 11 |
| **Discussion** | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | 22 |
| Generalisability | 21 | Generalisability (external validity, applicability) of the trial findings | 22 |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | 22 |
| **Other information** | | | |
| Registration | 23 | Registration number and name of trial registry | NCT02721485 |
| Protocol | 24 | Where the full trial protocol can be accessed, if available | BMJ open |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders | CIHR, TOHAMO |

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.