Supplementary Online Content

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eFigure 1. Map of Study Sites

eTable 1. Study Hospital Characteristics

eTable 2. Implementation Framework and Strategy

eFigure 2. Flow Diagram of Study Implementation

eFigure 3. Implementation Team Organizational Chart

eFigure 4. Example of Electronic Health Record Order Set

eFigure 5. Best Practice Alert

eFigure 6. Sample Educational Materials Used for Implementation (Presentation)

eFigure 7. Sample Educational Materials Used for Implementation (Informational Flyer)

eMethods.

eTable 3. ICD-10 Root Codes Occurring in 5% or More of the Study Population as the Primary (First) Discharge Diagnosis

eFigure 8. Forest Plot of Relative Difference in Incidence Rate of MAKE30 for Subgroups

eFigure 9. Observed and Risk-Adjusted Rate of MAKE30 in Patient Subgroups

eFigure 10. Observed and Risk-Adjusted Incidence Rate of MAKE30 by Patient Admission Type

eFigure 11. Observed and Risk-Adjusted Incidence Rate of MAKE30 in Patient Subgroups by Age

This supplementary material has been provided by the authors to give readers additional information about their work.

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Layton Hospital (participating site) is located between Salt Lake City and Ogden, UT and is not depicted on this map. Primary Children’s Hospital was excluded from study participation. St. George Medical Center (participating site) changed titles during the study period so is depicted as Dixie Regional Medical.
**eTable 1. Study Hospital Characteristics**

| Hospital                                      | City               | Beds | Trauma Level | Annual ED Visits | Hospital Type | Education Phase |
|------------------------------------------------|--------------------|------|--------------|------------------|---------------|-----------------|
| Intermountain Medical Center                  | Murray             | 472  | TI           | 95,000           | Tertiary      | 1               |
| Utah Valley                                   | Provo              | 395  | TII          | 49,000           | Tertiary      | 2               |
| McKay-Dee                                     | Ogden              | 321  | TII          | 64,000           | Tertiary      | 2               |
| St. George Medical Center                     | St. George         | 245  | TII          | 52,800           | Tertiary      | 1               |
| The Orthopedic Specialty Hospital            | Murray             | 36   | N/A          |                  | Community     | 1               |
| LDS Hospital                                  | Salt Lake City     | 250  |              | 24,000           | Community     | 1               |
| Logan Regional                                | Logan              | 146  | TIII         | 26,400           | Community     | 2               |
| Riverton                                      | Riverton           | 97   | TIII         | 25,000           | Community     | 1               |
| American Fork                                 | American Fork      | 89   | TIV          | 31,000           | Community     | 2               |
| Alta View                                     | Sandy              | 71   | TIII         | 21,000           | Community     | 1               |
| Cedar City                                    | Cedar City         | 48   |              | 19,000           | Community     | 1               |
| Park City                                     | Park City          | 37   | TIV          | 11,700           | Community     | 2               |
| Sevier Valley                                 | Richfield          | 29   |              | 7,600            | Rural         | 1               |
| Cassia Regional                               | Burley, ID         | 25   |              | 11,000           | Rural         | 2               |
| Orem Community                                | Orem               | 24   |              | 7,000            | Rural         | 2               |
| Fillmore Community                            | Fillmore           | 19   |              | 1,700            | Rural         | 1               |
| Heber Valley                                  | Heber              | 19   |              | 7,200            | Rural         | 2               |
| Delta Community                               | Delta              | 18   |              | 2,500            | Rural         | 1               |
| Sanpete Valley                                | Mt. Pleasant       | 18   |              | 5,200            | Rural         | 1               |
| Bear River Valley                             | Tremonton          | 16   | TIV          | 6,200            | Rural         | 2               |
| Garfield Memorial                             | Panguitch          | 14   |              | 2,600            | Rural         | 1               |
| Layton                                        | Layton             | 50   | TIV          | 5,000            | Rural         | 2               |
| Implementation steps                          | Descriptions                                                                 | Examples                                                                                     | Adaptations                      |
|----------------------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|----------------------------------|
| Identify key clinical leverage points        | The team identified key places to intervene in the clinical workflow to drive improvement. | Knowledge/Acceptance: Physician/APP/Nurse/Pharmacist education Workflow: EHR IVF orders        | Pop up alert                     |
| Identify actors and performance objectives   | Actors were identified in the clinical workflow process with assigned performance objectives to support adherence to the clinical leverage points. | Clinical leaders- Letter of support Clinical champion- review orders for targeted substitutions Supply chain- order/stock LR to support anticipated increase in demand | Front line clinician champions identified to address slow adopters |
| Select from known implementation strategies and link to barriers | The team designed interventions to influence previously identified barriers to prescribing LR. This specific step allowed the team to logically follow previous steps, identifying interventions that will be more effective for influencing implementation and producing a final logic model depicting relationships. | Scale up strategy- provide access to LR (supply chain/stock bedside carts etc.) Implementation process strategy- Engage key stakeholders/clinical champions Dissemination strategy- evidence based intervention (EBI) distributed to clinicians | Interventions were adapted to improve acceptance |
| Produce protocol and implementation materials | The team created design documents, draft content, pretest and refine content, and produce final materials to achieve action targets. This design document not only supports the development of implementation plan but can also help evaluation and potential adaptation of future interventions. | Action Targets: Proportion of fluids delivered -LR Incidence of MAKE-30 Evidence-based intervention (EBI) materials created tailored to clinical discipline Expert reviewed targeted order substitutions | Final materials were tailored to specific disciplines. |
| Implement across system                      | We developed the mechanisms for which we expected the implementation strategies to work and allowed us to determine future relationships. This included working within the constraints of our EHR rules and development processes. | Phase1: Hospital group 1 education (all hospitals nurse/pharmacy education) Phase 2: All hospitals EHR order substitutions/alert Phase 3: Hospital group 2 education | Sustain effects with EHR-embedded solutions. |
| Evaluate                                     | The team developed mechanisms for monitoring the implementation outcome. Performance feedback provided to ordering clinicians performing below the target 75% LR proportion of fluids prescribed. | A dashboard to monitor the implementation outcome using the lead measure: IV fluid prescribing. | Email to clinicians falling below target of 75%. |
First Education Intervention: indicates education using standard communication channels (e.g., Department meetings, email, huddle boards, etc.) for physicians, advanced practice clinicians, and pharmacists at the 12 hospitals designated in eTable1 as Phase 1. A mandatory computer-based training module was required of nurses in phase 1 and phase 2 hospitals during this Phase 1.

EHR intervention: Hospitals in Phase 1 and Phase 2 had EHR modifications turned on to encourage LR prescribing.

Second Education Intervention: Hospitals in Phase 2 received education using standard communication channels.

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**eFigure 4.** Example of Electronic Health Record Order Set

Lactated Ringer’s fluids are pre-selected in this order set for emergency department patients with diabetic ketoacidosis as part of the implementation process. Normal saline is still an option, but ordering it requires first de-selecting lactated Ringer’s and then selecting normal saline.
eFigure 5. Best Practice Alert

LR Is Better

Literature shows a potential morbidity and mortality benefit to using LR instead of NS.

Consider switching your NS order to LR unless contraindicated.

Patients at risk of cerebral edema should not receive hypotonic crystalloid solutions like LR.

Alert Action:
- Cancel NS order
- Proceed with NS order

Add orders for:
- LR bolus

OK
**Background**

- **Context:** Comparison of Natural Saline (NS) vs. Lactated Ringers (LR) for fluid resuscitation in critically ill patients.
- **Objective:** To assess the effectiveness of NS vs. LR in reducing mortality, ICU length of stay, and cost.
- **Methods:** Randomized controlled trial design. 100 patients were randomized to either NS or LR.

**Significance**

- **Main finding:** No significant difference in mortality, ICU length of stay, or cost between NS and LR groups.
- **Implications:** NS may be a cost-effective alternative to LR for fluid resuscitation in critically ill patients.

**Implementation**

- **Vision:** To translate research findings into clinical practice.
- **Roles:** Physician-led initiative, interdisciplinary team.
- **Context:** Large hospital setting with high patient turnover.

**Benefits to Patients**

- Reduced cost of fluid resuscitation.
- Improved patient outcomes with NS.
- Enhanced patient satisfaction.

**References**

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**eFigure 7. Sample Educational Materials Used for Implementation (Informational Flyer)**

**Quick-Fact Sheet for Lactated Ringer Transition – Physicians**

**Background**
While Normal Saline (NS) is currently the most commonly used intravenous fluid, recent literature has shown support for the use of Balanced Crystalloids (BC) (including Lactated Ringer’s and Plasmalyte) instead. Concerns continue to rise around NS causing acute kidney injury, hyperchloremic metabolic acidosis, and worsening of mortality. BC are designed to closer mimic the body’s natural electrolyte and solute compositions as shown in Table 1.

**Table 1: Composition of Fluids**

| Fluid Type       | Na⁺  | K⁺  | Ca²⁺ | Mg²⁺ | Cl⁻  | Lactate | Osmol | pH  |
|------------------|------|-----|------|------|------|---------|-------|-----|
| Plasma           | 140  | 4   | 2.3  | 1    | 104  | <1      | 285   | 7.4 |
| Normal Saline    | 154  |     |      |      | 154  | 308     | 5     |     |
| Lactated Ringer’s (LR) | 130  | 4   | 1.5  |      | 109  | 28      | 274   | 6.5 |
| Plasmalyte       | 140  | 5   |      | 1.5  | 98   | 295     |       |     |

Two recent trials present convincing evidence for the use of BC over NS:
- **SMART Tria**: ICU patients using BC experienced significantly less major adverse kidney events at day 30 compared with those given NS; greatest benefit was in those with sepsis and chronic RRT
- **SALT-ED Tria**: Non-ICU patients using BC experienced significantly less major adverse kidney events at day 30 compared with those given NS; greatest benefit was in those with renal dysfunction at baseline and elevated serum chloride

**Significance**
Lactated Ringer’s benefits:
- Little risk of harm
- Potential to prevent mortality, persistent kidney disease, and new need for renal therapy
- Increased cost-effectiveness at $0.16/1000mL less when compared to NS

Consequently, Intermountain Healthcare will alter system-wide guidelines and electronic order-sets to make LR the default resuscitation fluid with NS made as a second line/alternative option.

**Implementation**
- **Population**: Inclusion: 118,000 adults ≥18; enrolled in the ED and continuing if admitted to the hospital for medicine, surgery, trauma, or the ICU
- **Exclusion**: Patients with TBI, intra-cerebral hemorrhage, cerebral vascular accident, transient ischemic attack, hyponatremia, hypercalcemia, and other who may benefit from NS
- **Where**: 21 hospitals with staggered start times by region based on resources, practice patterns of physicians, supply chain, and overall system efficiencies
- **When**: 2019
- **Additional Physician Role**: Provide feedback regarding implementation structure

**Goals of Implementation**
- **Objective**: Assess the clinical, hospital admission, and expenditure impact of institutional replacement of NS to LR.
- **Primary Efficacy Outcomes**: Major adverse kidney events at 30 days; composite of death at any cause; new renal replacement therapy or persistent renal dysfunction
- **Secondary Efficacy Outcomes**: Hospital admission; hospital readmission and/or mortality within 30 days of initial ED enrollment
- **Cost-Centered Outcomes**: Costs of care before and after intervention

**Impact**
This study aligns with Intermountain Healthcare’s vision to provide the highest quality of care at the lowest possible cost. While immediate cost savings may not be profound, the real benefit will be synergistic with potential improvement to patient outcomes. Additionally, this study will enroll 10 times as many patients as previous studies, contributing meaningfully to the field’s literature.

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There were 51 encounters with more than 24,000 mL received in 24 hours that were excluded due to implausible fluid volumes. Baseline serum creatinine values were obtained from up to one year prior to the date of admission for the index encounter. Baseline serum creatinine was calculated in cases where no value was available using the following formula:

\[
\text{Creatinine} = 0.74 - 0.2 \left( \text{if female} \right) + 0.08 \left( \text{if Black} \right) + 0.003 \times \text{age (in years)}
\]

Normal saline included fluids with 0.83-0.9% sodium chloride with or without dextrose or potassium chloride. Lactated Ringer’s (LR) included LR with or without dextrose as well as an alternative proprietary balanced crystalloid solution (Plasma-Lyte). Bolus or maintenance infusions but not diluent or carrier fluids were included when calculating fluid administration volumes. The proportion of fluids received that were LR by volume (mL) was calculated with following formula:

\[
\text{Proportion BC} = \frac{\text{Lactated Ringer's volume} + \text{PlasmaLyte}}{\text{Normal Saline volume} + \text{Lactated Ringer's volume} + \text{PlasmaLyte}}
\]

Sepsis was identified per Sepsis-3 criteria\(^\text{17}\) as the combination acute organ failure (Sequential Organ Failure Assessment score ≥2 points above pre-ED baseline) plus confirmed or suspected infection (based on collection of body fluid cultures and administration of an IV antimicrobial or oral vancomycin, fidaxomicin, or oseltamivir) prior to ED departure using an internally validated electronic data warehouse query.

Data analysis

We used a quasi-experimental analysis strategy, segmented linear regression, to support more robust causal inference from this non-randomized trial. For our effectiveness outcome, we first obtained the weekly adjusted MAKE\(^\text{30}\) (or other outcome) using binomial regression.

\[
\text{MAKE}\text{30} = \beta_z \times (\text{Age} + \text{Sex} + \text{Race/Ethnicity} + \text{Charlson} + \text{APS} + \text{Baseline Dialysis} + \text{Baseline Creatinine})
\]

Variables in the model were Age (years); Sex (Male or Female); Race/Ethnicity (self-reported race/ethnicity, categorized as Hispanic/Latino, non-Hispanic American Indian/Alaska Native, non-Hispanic Asian, non-Hispanic Black, multiple races, non-Hispanic Native Hawaiian/Pacific Islander, non-Hispanic White, or unknown); Charlson comorbidity score (integers from 0 to 20); Acute physiology score (APS Score, integers from 0 to 52); Baseline Dialysis use (present/absent); and Baseline Creatinine (in mg/dL). \(\beta_z\) represents the vector of coefficients for each variable. Risk adjusted models were then calibrated to predict MAKE\(^\text{30}\) at the same rate that was observed during the study. Formulas for weekly standardized MAKE\(^\text{30}\):

\[
\text{Adjusted MAKE}\text{30 rate} = \frac{\text{Observed weekly rate}}{\text{Estimated weekly rate}} \times \text{Observed rate during study period}
\]

\[
\text{Observed weekly rate} = \frac{\text{Number of MAKE}\text{30 outcomes among week's patients}}{\text{Number of patients for week}}
\]

\[
\text{Estimated weekly rate} = \frac{\text{Risk adjusted MAKE}\text{30 outcomes among week's patients}}{\text{Number of patients for week}}
\]

\[
\text{Observed rate for study period} = \frac{\text{Number of MAKE}\text{30 outcomes during study period}}{\text{Number of patients during study period}}
\]
The Clopper-Pearson method was used to calculate 95% confidence intervals for the weekly risk-adjusted MAKE30 outcome. We then performed segmented linear regression based on fractional binomial regression to obtain interrupted time series estimates for the association between the intervention and the effectiveness outcomes according to the following formula.

\[
\frac{\text{Number of patients} \times \text{Adjusted MAKE30 rate}}{\text{Number of patients}} = \beta_0 + \beta_{\text{pre}}(\text{time}) + \beta_{\text{step}}(\text{Post Implementation}) + \beta_{\text{post}}(\text{timeAfter})
\]

In this formula, \text{time} is the integer count of weeks during study period from 1 to 69; \text{Post Implementation} is binary where 0 represents pre-implementation and 1 represents post implementation; \text{timeAfter} is the integer count of weeks during the post-implementation phase of the study from 0 for weeks pre-implementation and 1 to 33 weeks post-implementation; and \text{rate of Adjusted MAKE30} and \text{# patients} are week-specific rates and counts, respectively, from the cohort for a total of 69 datapoints. The week-on-week trend for the outcome pre- and post-intervention is obtained from coefficients \(\beta_{\text{pre}}\) and \(\beta_{\text{post}}\), respectively, while the step-off effect is provided by the coefficient \(\beta_{\text{step}}\). Absolute and relative risk difference was calculated with regard to the final week of the study per the following formulas:

\[
\text{Absolute risk difference} = \text{Estimated MAKE30 with intervention} - \text{Estimated MAKE30 without intervention}
\]

\[
\text{Relative risk difference} = \frac{\text{Estimated MAKE30 with intervention} - \text{Estimated MAKE30 without intervention}}{\text{Estimated MAKE30 without intervention}}
\]

We used a similar segmented linear regression approach based on beta regression with a logit link to obtain interrupted times series estimates of the association between implementation interventions and the proportion of LR received:

\[
\text{Proportion LR} = \beta_0 + \beta_{\text{pre1}}(\text{time}) + \beta_{\text{pre2}}(\text{time Education1}) + \beta_{\text{step}}(\text{Post Implementation}) + \beta_{\text{post}}(\text{time Education2})
\]

In this formula, \text{time} and \text{Post Implementation} are the same as the MAKE30 model above, and \text{time Education1} and \text{time Education2} is the integer count of weeks after the educational interventions from 0 during pre-education time frames and 1 to 47 for \text{time Education1} and 1 to 21 for \text{time Education2}. The binary variable, \text{Post Implementation}, allows for analyzing and immediate change, or step-off, of the intervention. The time variables that count whole weeks from a specific time point (e.g., \text{time}, \text{timeAfter}, \text{time Education1}, \text{time Education2}) permit an analysis of trend, or slope during the period where the time count is greater than zero. Coefficients provide trend and step-off effect estimates analogous to the prior equation.

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**eTable 3. ICD-10 Root Codes Occurring in 5% or More of the Study Population as the Primary (First) Discharge Diagnosis**

| Truncated ICD10 | ICD10 Description                                                                 | n (%)          |
|-----------------|-----------------------------------------------------------------------------------|----------------|
| R10             | Abdominal and pelvic pain                                                         | 12230 (8.2%)   |
| O80             | Encounter for full-term uncomplicated delivery                                     | 5728 (3.9%)    |
| R11             | Nausea and vomiting                                                                | 4276 (2.9%)    |
| N20             | Calculus of kidney and ureter                                                      | 4142 (2.8%)    |
| R51             | Headache                                                                          | 3263 (2.2%)    |
| Z98             | Other postprocedural states                                                        | 2739 (1.8%)    |
| R07             | Pain in throat and chest                                                          | 2722 (1.8%)    |
| N39             | Other disorders of urinary system                                                  | 2531 (1.7%)    |
| J18             | Pneumonia, unspecified organism                                                    | 2524 (1.7%)    |
| K52             | Other and unsp noninfective gastroenteritis and colitis                           | 2380 (1.6%)    |
| R55             | Syncope and collapse                                                               | 2320 (1.6%)    |
| Z96             | Presence of other functional implants                                              | 2199 (1.5%)    |
| A41             | Other sepsis                                                                       | 2178 (1.5%)    |
| R42             | Dizziness and giddiness                                                           | 1932 (1.3%)    |
| F10             | Alcohol related disorders                                                          | 1849 (1.2%)    |
| M17             | Osteoarthritis of knee                                                             | 1773 (1.2%)    |
| G43             | Migraine                                                                          | 1692 (1.1%)    |
| J96             | Respiratory failure, not elsewhere classified                                     | 1649 (1.1%)    |
| J10             | Influenza due to other identified influenza virus                                  | 1403 (0.9%)    |
| E11             | Type 2 diabetes mellitus                                                           | 1314 (0.9%)    |
| S72             | Fracture of femur                                                                  | 1280 (0.9%)    |
| K80             | Cholelithiasis                                                                     | 1257 (0.8%)    |
| K92             | Other diseases of digestive system                                                 | 1239 (0.8%)    |
| I63             | Cerebral infarction                                                                | 1231 (0.8%)    |
| N12             | Tubulo-interstitial nephritis, not spcf as acute or chronic                        | 1229 (0.8%)    |
| K56             | Paralytic ileus and intestinal obstruction without hernia                          | 1225 (0.8%)    |
| K57             | Diverticular disease of intestine                                                  | 1220 (0.8%)    |
| I48             | Atrial fibrillation and flutter                                                    | 1160 (0.8%)    |
| M54             | Dorsalgia                                                                         | 1150 (0.8%)    |
| R19             | Oth symptoms and signs involving the dgstv sys and abdomen                         | 1127 (0.8%)    |
| R53             | Malaise and fatigue                                                                | 1105 (0.7%)    |
| L03             | Cellulitis and acute lymphangitis                                                  | 1083 (0.7%)    |
| M16             | Osteoarthrosis of hip                                                               | 1061 (0.7%)    |
| R65             | Symp and signs specifically assoc w sys inflam and infect                          | 1047 (0.7%)    |
| R50             | Fever of other and unknown origin                                                  | 970 (0.7%)     |
| E87             | Other disorders of fluid, electrolyte and acid-base balance                        | 963 (0.6%)     |
| K85             | Acute pancreatitis                                                                 | 958 (0.6%)     |
| Z34             | Encounter for supervision of normal pregnancy                                      | 957 (0.6%)     |
| I21             | Acute myocardial infarction                                                        | 949 (0.6%)     |
| Z3A             | Weeks of gestation                                                                 | 943 (0.6%)     |
| E86             | Volume depletion                                                                   | 909 (0.6%)     |
| B34             | Viral infection of unspecified site                                                | 899 (0.6%)     |
| G93             | Other disorders of brain                                                           | 859 (0.6%)     |
| R00             | Abnormalities of heart beat                                                        | 855 (0.6%)     |
| Code | Description                                                                 | Count | Percentage |
|------|------------------------------------------------------------------------------|-------|------------|
| O82  | Encounter for cesarean delivery without indication                            | 836   | (0.6%)     |
| N17  | Acute kidney failure                                                          | 812   | (0.5%)     |
| E66  | Overweight and obesity                                                        | 808   | (0.5%)     |
| N83  | Noninflammatory disorder of ovary, fallop and broad ligament                 | 802   | (0.5%)     |
| I10  | Essential (primary) hypertension                                               | 763   | (0.5%)     |
| R56  | Convulsions, not elsewhere classified                                          | 755   | (0.5%)     |
| F41  | Other anxiety disorders                                                       | 712   | (0.5%)     |

**eFigure 8.** Forest Plot of Relative Difference in Incidence Rate of MAKE30 for Subgroups

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**eFigure 9.** Observed and Risk-Adjusted Rate of MAKE30 in Patient Subgroups

Figures depict major adverse kidney outcomes at 30 days (MAKE30, a composite of persistent renal dysfunction, new renal replacement therapy, and mortality at 30 days) among patients admitted in the indicated week for patients who are A) female or B) male or who have C) sepsis absent or D) sepsis present during their admission.
eFigure 10. Observed and Risk-Adjusted Incidence Rate of MAKE30 by Patient Admission Type

Figures depict major adverse kidney outcomes at 30 days (MAKE30, a composite of persistent renal dysfunction, new renal replacement therapy, and mortality at 30 days) among patients admitted in the indicated whose highest level of care was A) intensive care unit (ICU), B) emergency department (ED), C) inpatient surgery, and D) inpatient.
eFigure 11. Observed and Risk-Adjusted Incidence Rate of MAKE30 in Patient Subgroups by Age

Figures depict major adverse kidney outcomes at 30 days (MAKE30, a composite of persistent renal dysfunction, new renal replacement therapy, and mortality at 30 days) among patients admitted in the indicated week for patient age subgroups: A) 18 to 29 years, B) 30 to 49 years, C) 50 to 59 years, D) 60 to 69 years, E) 70 to 79 years, and F) ≥80 years.