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FLUID: A Cross-Over Trial of Hospital Wide Ringer's Lactate vs Normal Saline

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NIH PRAGMATIC TRIALS COLLABORATORY

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The Ottawa Hospital RESEARCH INSTITUTE | L'Hôpital d'Ottawa INSTITUT DE RECHERCHE

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Funders, Registration, and Protocols/SAP

Funders:

Canadian Institutes for Health Research

The Ottawa Hospital Academic Medical Organization

Trial Registration:

FLUID Pilot (NCT: 02721485)

FLUID Trial (NCT: 04512950)

Protocol for Pilot trial:

McIntyre, LA et al, BMJ Open 2018:8;e022780

Protocol and Statistical Analysis Plan:

Shaw, J et al, JMIR Research Protocols 2023:12;e51783

Why care about the resuscitation crystalloid crystalloid question…..

- Other than oxygen, the most common intervention that we administer to patients

- Despite many decades using these fluids, dearth of evidence…..

  until the last decade!

Major Complications, Mortality, and Resource Utilizatio[illegible]er
Open Abdominal Surgery

0.9% Saline Compared to Plasma-Lyte

Hyperchloremia After Noncardiac Surge[illegible]
Independently Associated with Increa[illegible]
and Mortality: A Propensity-Matc[illegible]

Is hyperchloremia asso[illegible]n critically ill patients? A prospe[illegible]

A compari[illegible]nbalanced crystalloid solutions in surger[illegible]

Association Between a Chloride-Liberal vs Chloride-Restrictive Intravenous Fluid Administration Strategy and Kidney Injury in Critically Ill Adults

[illegible]ed Ringer Is Associated With Reduced [illegible]rtality and Less Acute Kidney Injury in Critically [illegible]ll Patients: A Retrospective Cohort Analysis*

Shaw et al, Ann Surg, 2012; 255; McCluskey et al Anesth Anal, 2013; 117; Boniatti et al, J Crit Care, 2011; 26; Yunos, JAMA 2012; 308 (15)

Followed by large single centre and multi-centre trials

Balanced Crystalloids versus Saline
In Critically Ill Adults

Semler, M et al, NEJM, 2018;378(9)

Balanced Multielectrolyte Solution versus
Saline in Critically Ill Adults

Finfer, S et al, NEJM, 2022;386(9)

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

Zampiere, F et al, JAMA, 2021;326(9)

Balanced Crystalloids versus Saline in the Intensive Care Unit
The SALT Randomized Trial

Semler, MW et al. Am J Respir Crit Care Med. 2017;195(10)

Effect of a Buffered Crystalloid Solution vs Saline on Acute
Kidney Injury Among Patients in the Intensive Care Unit
The SPLIT Randomized Clinical Trial

Young, P et al. JAMA, 2015;314(16)

Systematic review of RCTs in the critically ill

- Balanced crystalloids versus saline critically ill
- Primary outcome 90-day mortality in low risk of bias trials
- N=13 trials, 35,884
- N= 6 low risk of bias trials (34, 4500)

Study	BSS Deaths	BSS Alive	Saline Deaths	Saline Alive	Risk Ratio with 95% CI	Weight (%)
Low						
Young (2014)[37]	3	19	4	20	0.82 [0.21, 3.25]	2.0
Young (2015)[38]	87	1065	95	1015	0.88 [0.67, 1.17]	14.1
Semler (2017)[34]	87	433	83	371	0.92 [0.70, 1.20]	14.3
Semler (2018)[14]	928	7014	975	6885	0.94 [0.87, 1.02]	18.4
Zampieri (2021)[39]	1381	3849	1439	3851	0.97 [0.91, 1.03]	18.6
Finfer (2021)[17]	530	1903	530	1883	0.99 [0.89, 1.10]	18.1
Heterogeneity: T^2=0.00, I^2=12.08%, H^2=1.14					0.96 [0.91, 1.01]	
Test of $\theta_i=\theta_j$: Q(5)=1.18, P=0.95						

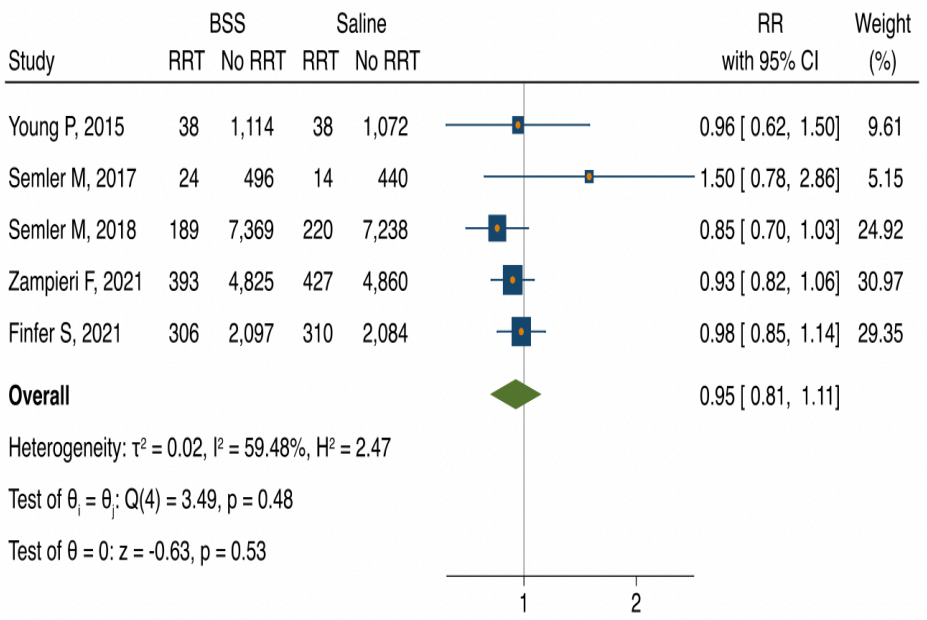
Zampieri et al, Lancet Resp Med, 2023

BSS:17.4%

NS:18.2%

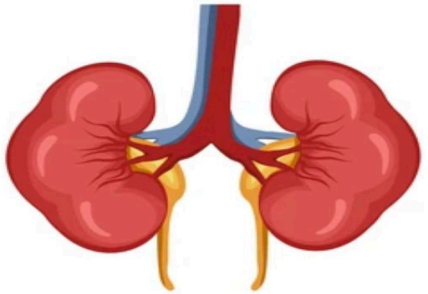
Hammond et al, NEJM Evid 2022; 2(1): 1 - 12

Risk of new Renal Replacement Therapy
Low risk of bias trials (N = 34,460)

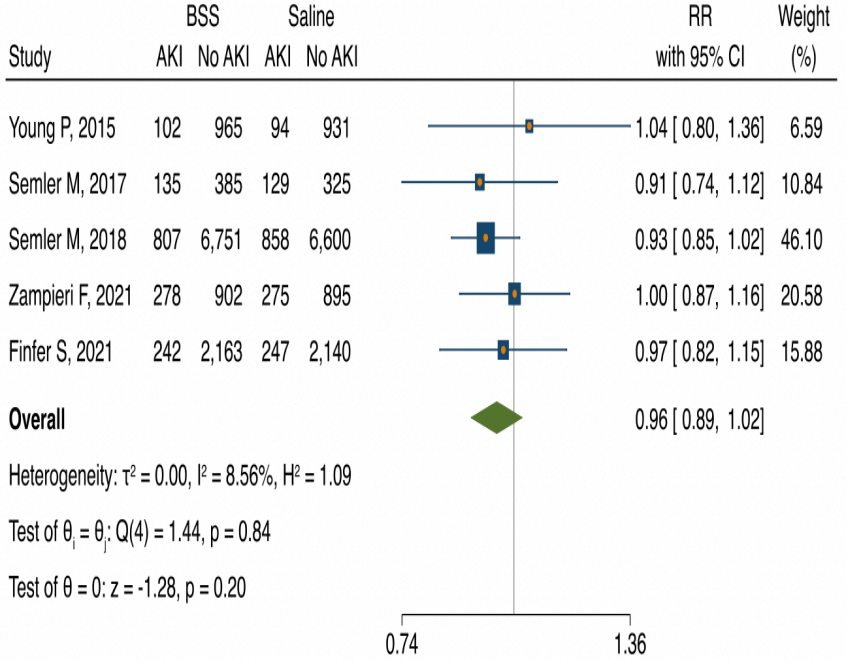


BSS: 5.6%

NS:6.0%



Risk of new Acute Kidney Injury
Low risk of bias trials (n = 33,034)

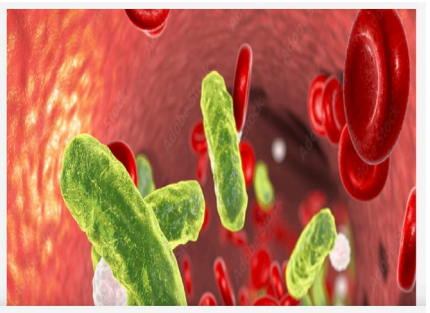


BSS: 12.3%

NS: 13.5%

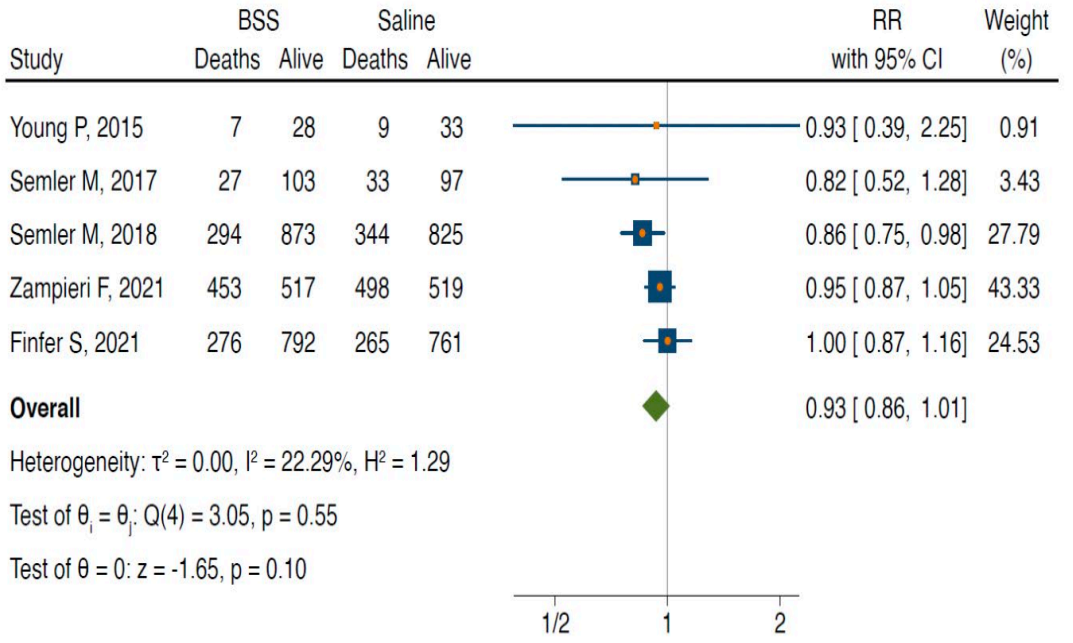
Hammond et al, NEJM Evid 2022; 2(1): 1 - 12

What about the evidence for sepsis? 5 low risk of bias trials (N = 4667)



- Higher risk of death due to severity of illness
- More metabolic acidosis
- More acute renal injury

- Receipt +++ fluid

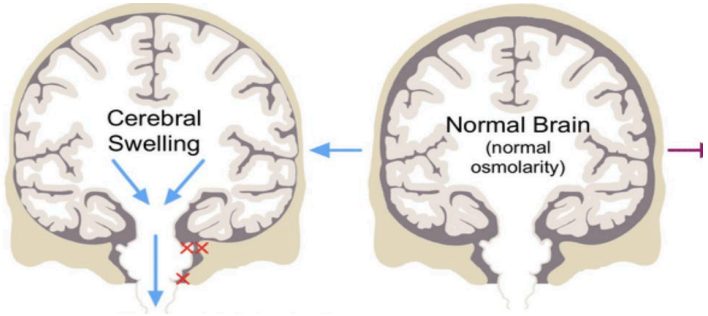


BSS: 31.4%

NS:34.0%

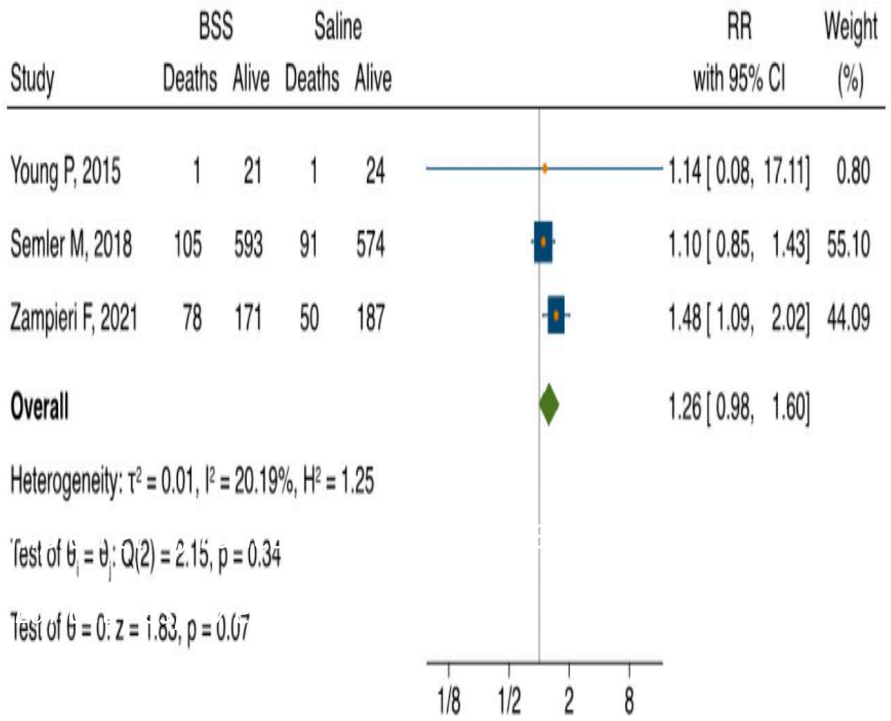
Hammond et al, NEJM Evid 2022; 2(1): 1 - 12

What about the evidence for traumatic brain injury
3 Low risk of bias trials (N = 1806)



- Breakdown of blood brain barrier
- Concern over osmolar shifts
- ? less cerebral edema with NS

Crystalloid	Na mmol/L	Osmolality mmol/Kg
Normal Saline	154	308
Ringer's Lactate	130	271
Plasmalyte 148	140	298



BSS: 19.0%

NS: 15.3%

Hammond et al, NEJM Evid 2022; 2(1): 1 - 12

Some conclusions based on existing evidence for the critically ill

- Current accumulation of the evidence base is centered on the critically ill

- Clinical outcome differences are very small in critically ill
  - Potential exceptions are sub populations including sepsis and traumatic brain injury

Back in 2015…..

- We started thinking about the FLUID trial….

What question does FLUID address?

- Crystalloid fluids ‘touch’ nearly all patients who are admitted to hospital
  - FLUID examines the effect of NS versus RL across all hospitalized patients
- FLUID addresses this study question at the level of the hospital/health care system
- From when patients present to hospital until their hospital discharge/death

What is the FLUID study question?

Does a hospital policy/strategy of a predominantly universal supply of Ringer's Lactate as compared to Normal Saline reduce death or re-admission to hospital within 90 days of the index hospital admission

Pilot Trial: Is it feasible to conduct a hospital wide pragmatic pilot cluster randomized cross-over trial in four Ontario hospitals?

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FLUID

Why is the question important?

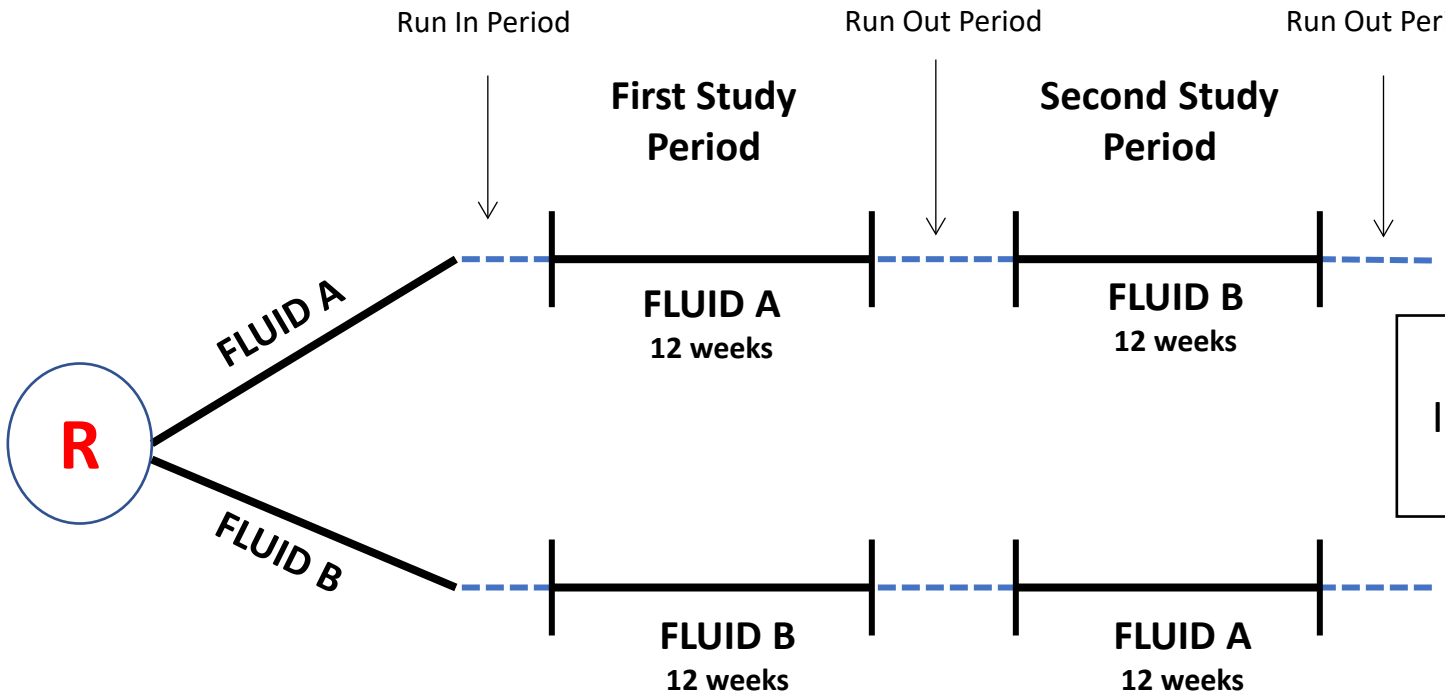
- Small but clinically important differences in outcomes between fluids are relevant
  - 0.5% reduction in death = 2500 lives saved in Ontario
- May have implications for resource use/cost to hospitals and health care system
  - 0.5% decrease hospital re-admission = $5 million savings

Costs of NS versus RL at the level of Ontario health care system

	NS	RL
@ per 1 litre bag	$1.30	$1.66
Cost for 19 million 1 L bags in Ontario	26 million	31.5 million

@ approximate costs at Ottawa hospital

FLUID Pilot Study Design



All Clinical Data Measured at Institute for Clinical Evaluative Science (ICES)

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McIntyre, L et al, BMJ Open 2023;13:e067142

Primary/Secondary Feasibility Outcomes

Primary Outcome:

- Adherence to study fluid (≥ 80% adherence)

Secondary Outcomes:

- Time to Research Ethics Board approval (≤ 3 months)
- Time to readiness for study initiation (≤ 3 months from REB approval to trial initiation)

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McIntyre, L et al, BMJ Open 2023;13:e067142

How did we examine study fluid adherence?

- Logistical service inventory reports

- Calculation:

  study fluid/(total study fluid + non study fluid)

EX: for Normal Saline study period

Normal Saline/ (Normal Saline + Ringer's Lactate)

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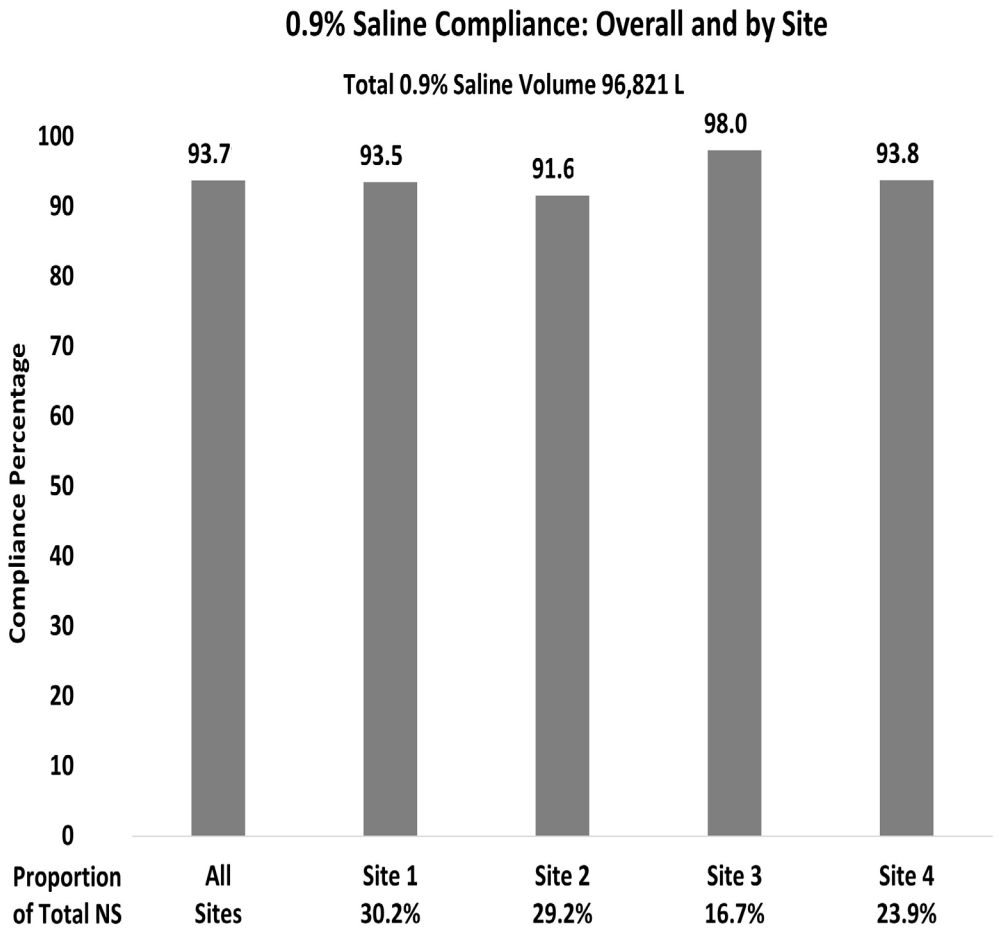
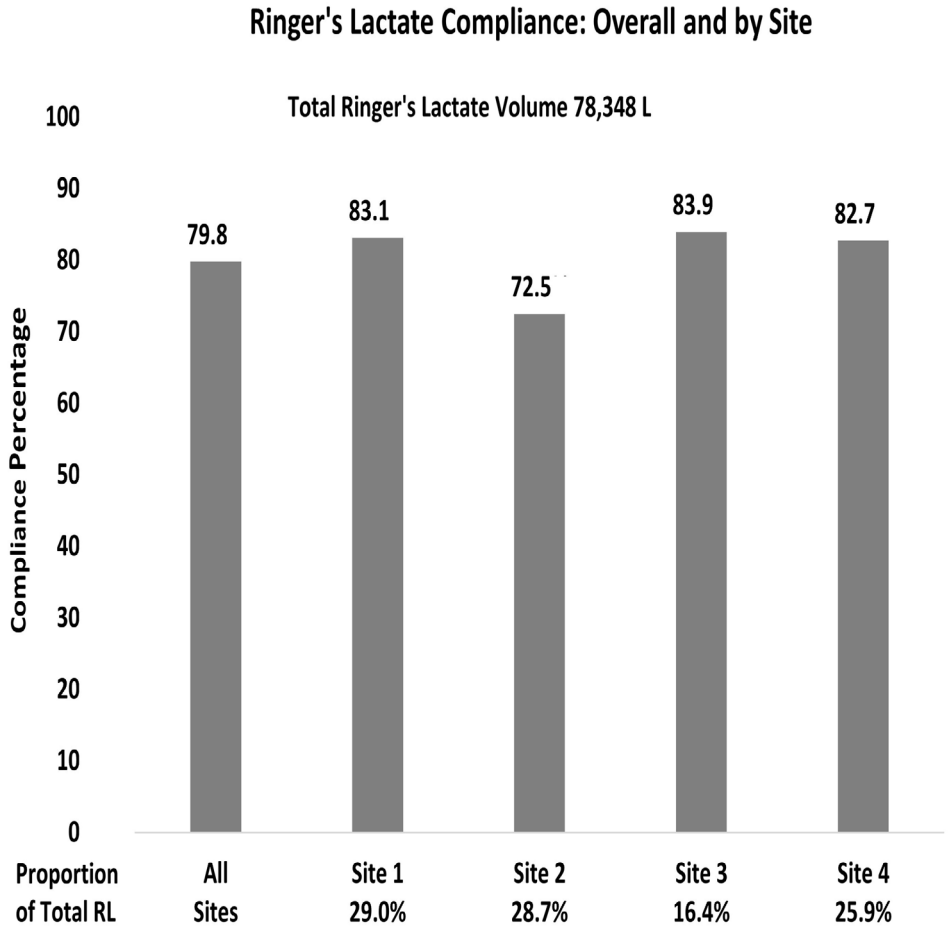
McIntyre, L et al, BMJ Open 2023;13:e067142

Assessment by Independent Safety Committee

- At the end of the pilot trial
- Blinded review safety analysis of the primary clinical endpoint
- Assessment of any other SAE considered related to the study fluids at morbidity and mortality rounds or reported to safety management committees that were reported to the site lead investigator

Results: Study Fluid Adherence





McIntyre, L et al, BMJ Open 2023;13:e067142

Secondary Feasibility Outcomes

Time to REB approval target ≤ 3 months from submission

- All four sites ≤ 3 months

Time to readiness for study initiation target ≤ 3 months from REB approval

- 2/4 sites within 51 and 66 days
- One site delay 102 days - to accommodate for ward closures over a major holiday period
- One site delay 331 days - waited for sister hospital to complete study due to limited storage space for the large volumes of fluid

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McIntyre, L et al, BMJ Open 2023;13:e067142

Knowledge gained from FLUID pilot

- Large trial feasible
- No safety signals
- Attention to logistical challenges
- Focus communication/education tools

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FLUID Methods

Setting/Design:

Pragmatic hospital-wide randomized cluster crossover trial at academic and community hospitals in the province of Ontario, Canada

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FLUID Methods

Inclusion Criteria:

Hospital level:

- Level II or III intensive care units in Ontario, Canada
- At least 6,000 acute care patient admissions per year

Patient level:

- All adult and pediatric patients with an index admission to hospital

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FLUID Methods

Exclusion Criteria

Patient level:

- Neonates (RL is neither used nor recommended for this population)
- Admissions during the run-in or run-out study periods
- Admission to an Ontario hospital in the prior 90 days
- Missing birthdate

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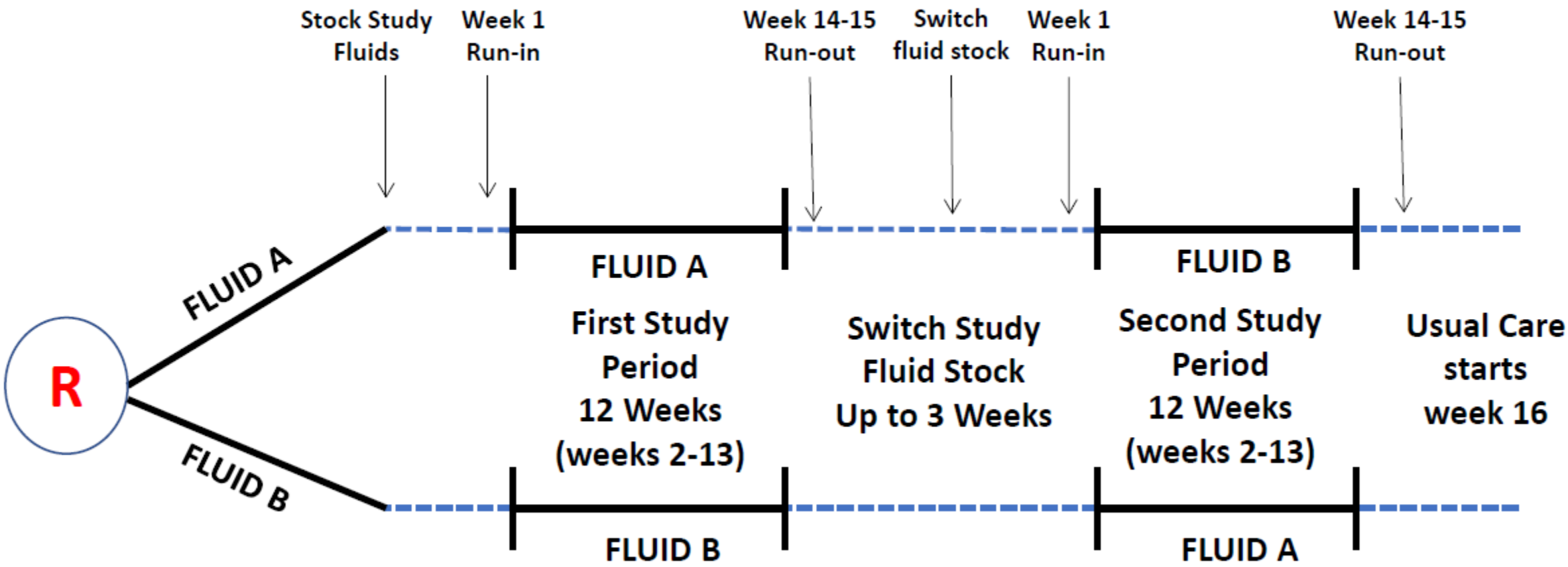
FLUID Trial Design



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FLUID Intervention and Comparison

- Whenever a physician order was written for NS or RL in volumes of 500 or 1000 mls as boluses or infusions the order was substituted for the study fluid
- No substitution for other fluids (ex: D5W, D10W, 1/2NS, 2/3 and 1/3)

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FLUID Outcome Measures

Primary Outcome:

Composite of death or re-admission to hospital within 90 days of index hospital admission

Secondary Outcomes:

Death within 90 days of index hospital admission

Re-admission to hospital within 90 days of index hospital admission

Initiation of dialysis within 90 days of index hospital admission

Incident emergency department visit within 90 days of the index hospital admission

Hospital length of stay

Discharge to a facility other than home

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Pre-Specified Subgroups:

- Age
  - 1 month – 18 years
  - > 18 – 65 years
  - > 65 – 80 years
  - > 80 years
- Sex
  - Male vs female
- Case mix group
  - Medicine
  - Surgery
  - Mental health
  - Pregnancy and childbirth
- Elixhauser co-morbidity index
  - Quartile 1
  - Quartile 2
  - Quartile 3
  - Quartile 4

- Type of surgery
  - Emergent
  - Urgent
  - Elective
- ICU admission within 1 day after hospital admission
- Infection alone
- Infection with ICU admission
- Infection + organ dysfunction
- Infection + organ dysfunction with ICU admission
- Trauma with Injury Severity Score >= 12
- Trauma with injury Severity Score >= 12 with ICU admission
- Traumatic brain injury
- Traumatic brain injury with ICU admission

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Data Collection

- No individual patient data collection
- All clinical data in FLUID obtained through provincial health database called ICES

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Strategies to maximize adherence to study fluid

- Education and communication

- Very small amount of non-study fluid stocked on wards/OR/PACU/ICU/ED in participating hospitals
  - ≤ 20% of fluid stock on all shelves of hospital

Fluid Orders:

- *Paper:* education of nurses to substitute study fluid if NS or RL is written in the doctors' orders
- *Computerized:* automatic substitution

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Ethics: Waiver of Consent

- NS and RL are usual care fluids
- Risk of being in trial no greater than the receipt of usual care
- Impracticable (feasibility and cost) to consent all patients in hospital
- All data from ICES – no collection of individual patient level data
- Physician autonomy to opt an individual patient out (ex: acute brain injury)

Taljaard, M et al, BMJ, 2013
Tri-council Policy Statement: Article 3.7A and B

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Approach to Safety:

- Participating hospitals monitored serious adverse events by means of routinely scheduled safety committee meetings or morbidity and mortality rounds.
- Principal investigators at each site reported any serious adverse event related to the administration of trial fluids to the coordinating centre.

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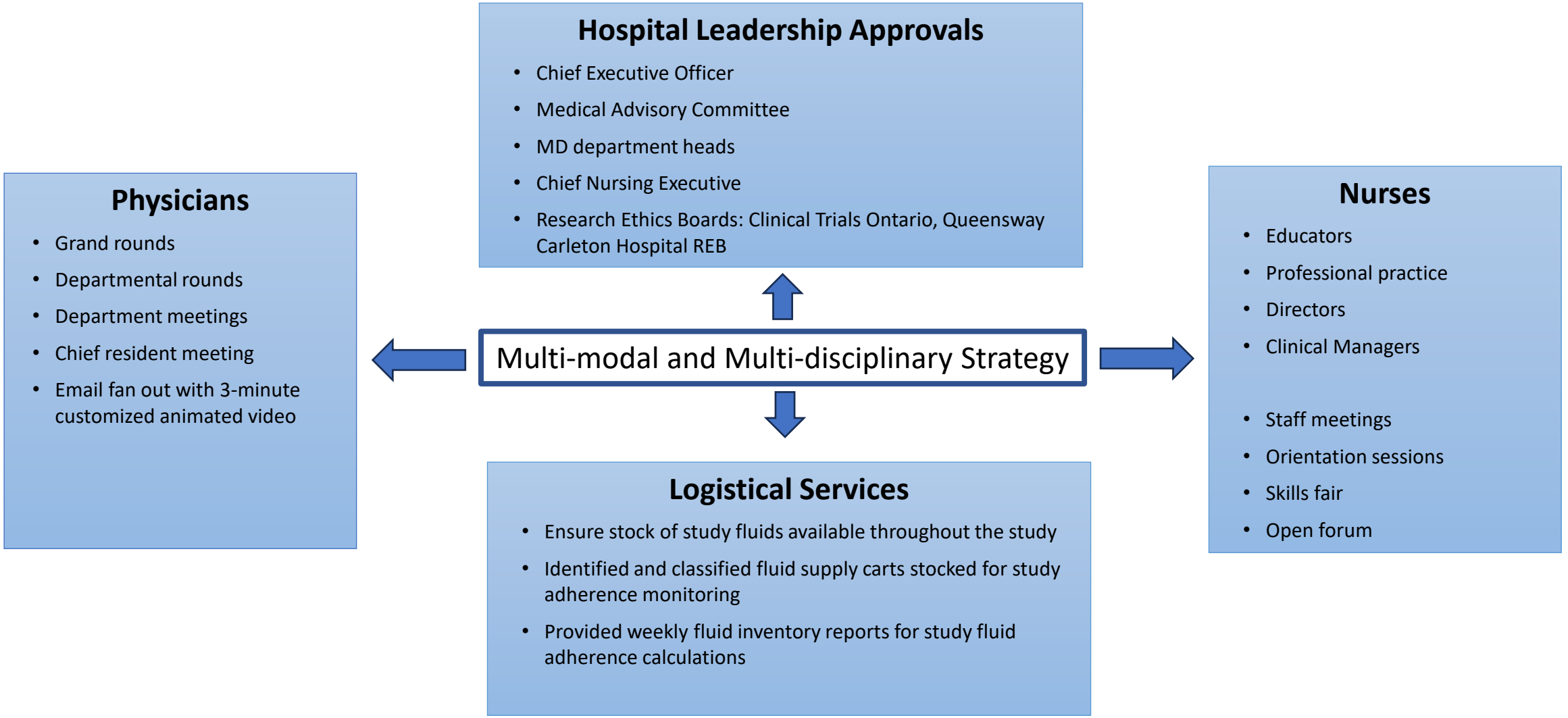
Trial Approval/Collaboration/Communication



FLUID

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SAMPLE SIZE CALCULATION APPROACH

- Two key parameters for a cluster randomized cross-over trial:
  - Within-period intracluster correlation coefficient (ICC)
  - Between-period ICC [or alternatively, the Cluster Autocorrelation Coefficient (CAC)]

- Estimated using historical primary outcome data (numerator and denominator) for all hospitals and all patients across Ontario on a monthly basis

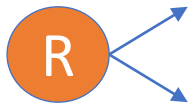
Hooper R, Teerenstra S, de Hoop E, Eldridge S. Sample size calculation for stepped wedge and other longitudinal cluster randomised trials. Stat Med 2016;35(26):4718-4728.

SAMPLE SIZE PARAMETERS

- Within-period ICC ≈ 0.006

Exactly what we observed in the trial!

- Cluster Autocorrelation Coefficient ≈ 1 (used CAC=0.95 to be slightly more conservative)
- Average of 1500 patients per hospital per month
- Target difference = 0.01 (Normal Saline = 0.16 versus Ringer's Lactate = 0.15)
- Requires only 6 hospitals to reach 80% power at 5% significance



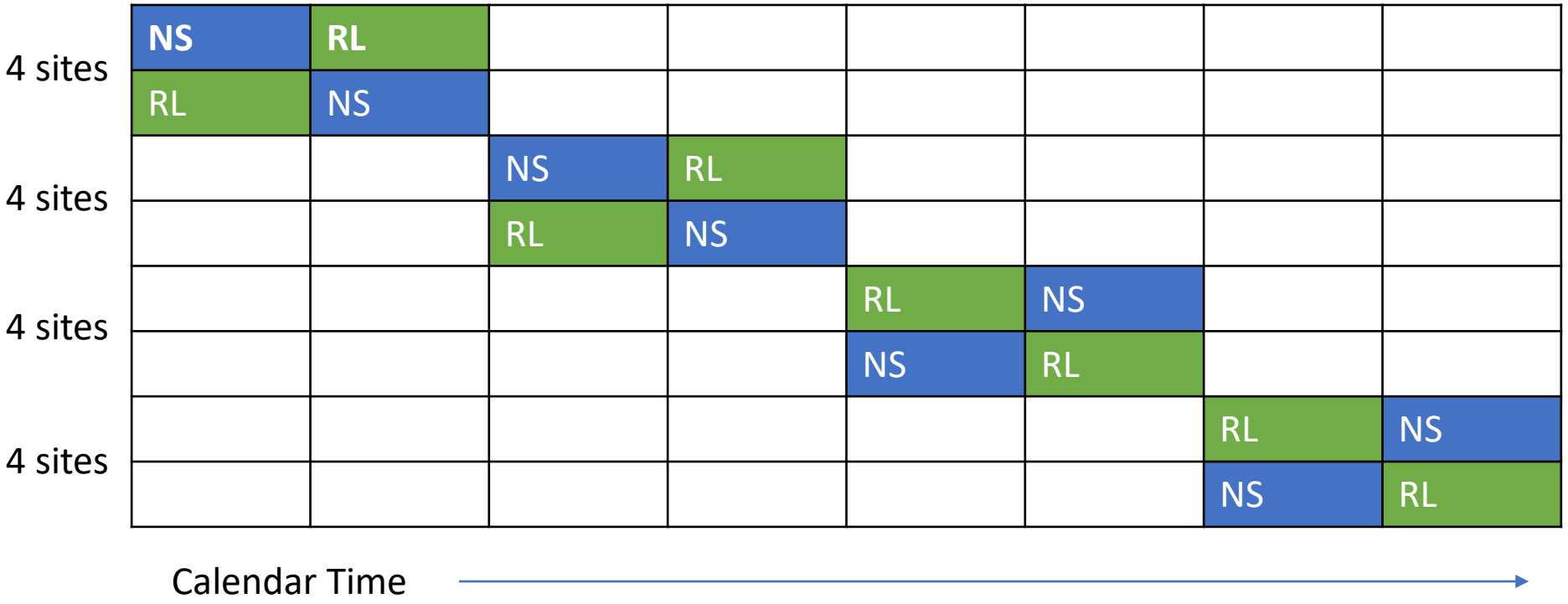
Month	1	2	3	4	5	6
3 clusters	NS	NS	NS	RL	RL	RL
3 clusters	RL	RL	RL	NS	NS	NS

SAMPLE SIZE ADJUSTMENTS

- But… small number of clusters is not desirable!
- Applied some sample size adjustments
  - Allowed for 6% non-adherence in NS and 19% in RL
  - Added 2 clusters as a small sample correction
  - Added 2 clusters to account for variation in cluster sizes
- Target number of hospitals: 16
- Larger number of hospitals will also help counterbalance concerns due to seasonal variation in sequential randomization

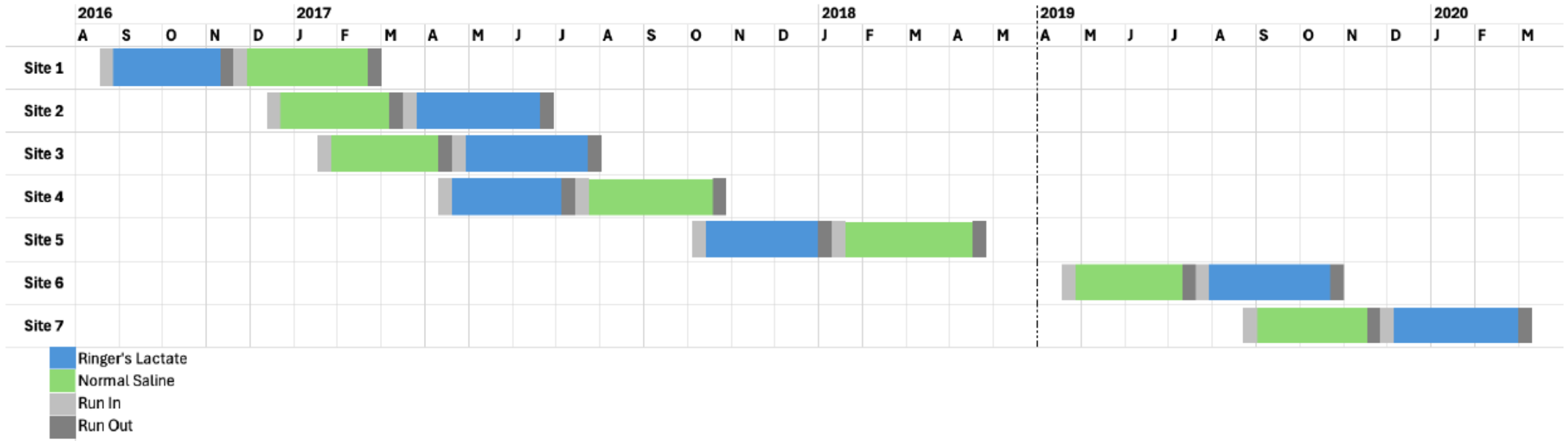
PLANNED (IDEAL) DESIGN

- Sites randomized in batches



ACHIEVED DESIGN

Figure S1: Sequential Trial Initiation in FLUID



METHOD OF ANALYSIS

- Choosing an appropriate analysis method for a cluster randomized trial with a small number of clusters is challenging
  - Individual-level analysis using a hierarchical model is a popular method
  - Requires at 50-80 clusters to yield an acceptable type I error rate
- Used unweighted linear regression of cluster summary measures as recommended by Morgan et al. (2017)

Morgan KE, Forbes AB, Keogh RH, Jairath V, Kahan BC. Choosing appropriate analysis methods for cluster randomised cross-over trials with a binary outcome. Stat Med. 2017 Jan 30;36(2):318-333.

ADVANTAGES AND DISADVANTAGES

- Advantages:
  - Robust to small number of clusters
  - Easy to implement
  - Readily yields estimates on absolute risk difference or relative risk scales
- Disadvantages
  - Can be less powerful than individual-level analysis when cluster sizes vary
  - Requires two-stage approach to adjust for patient-level covariates

COVARIATE ADJUSTMENT

- Pre-specified covariates: age, sex, type of admission ("case-mix group"), comorbidity index, ICU admission within 1 day
- Stage 1:
  - Ordinary (patient-level) logistic regression, adjusting for covariates, but ignoring hospital and treatment
  - Calculate residuals (e.g., observed minus expected # events for absolute risk difference)
- Stage 2:
  - Summarize residuals at hospital-period level and analyze using standard linear regression
  - Indicator for treatment, period, and hospital

SENSITIVITY ANALYSES FOR PERIOD EFFECTS

- Primary analysis used period as a categorical variable ("period 1" vs. "period 2")
- Additional analyses used calendar time as a continuous variable
  - Simple linear term
  - Three-knot restricted cubic spline

- Reassuring that results were virtually identical

FLUID Trial Results

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FLUID Trial Results

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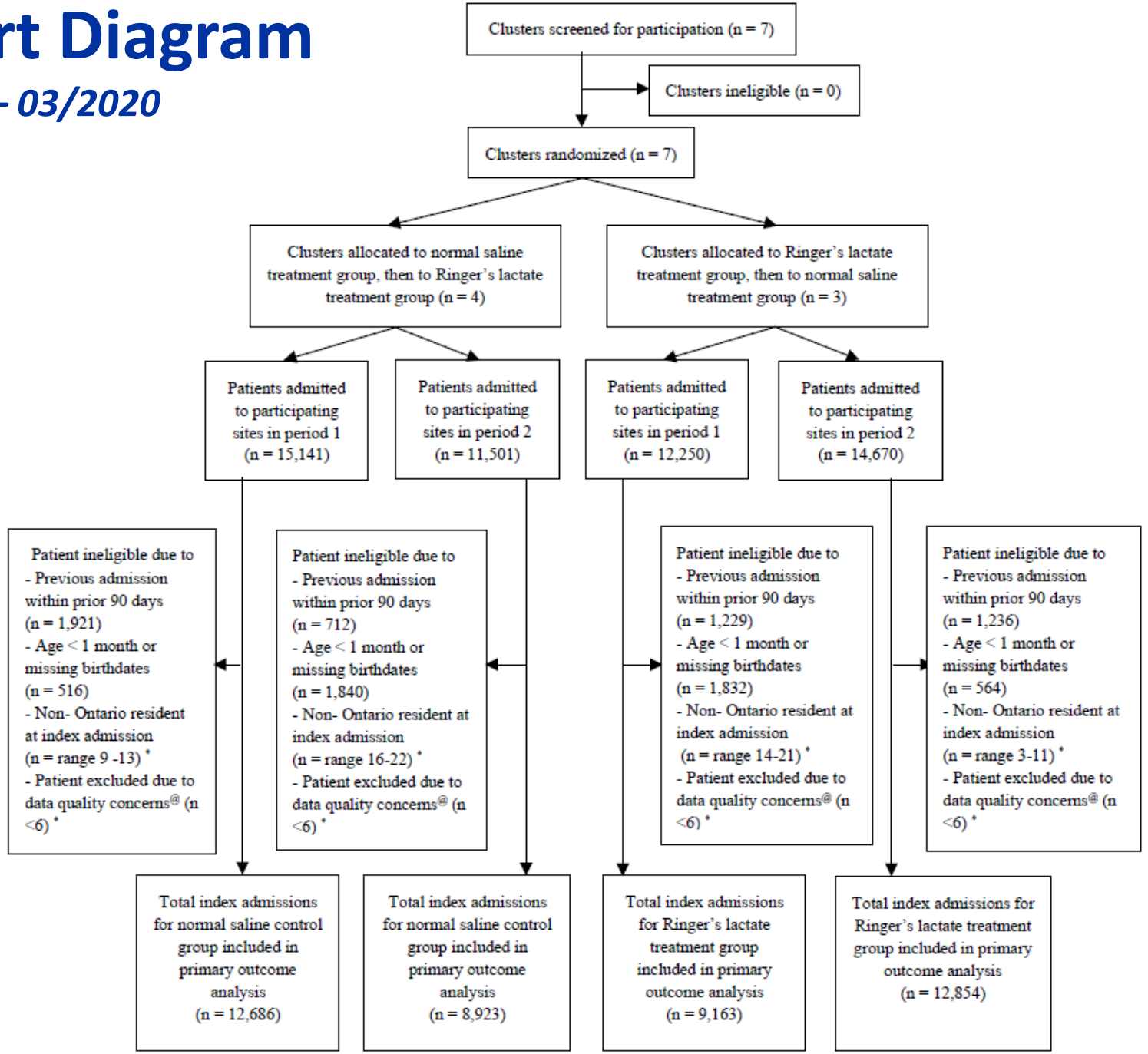
FLUID Consort Diagram

Recruitment: 08/2016 – 03/2020



Baseline characteristics

Characteristic	Ringer's Lactate (N = 22,017)	Normal Saline (N = 21,609)
Age – yr, Mean (SD)	58.5 (20.6)	58.7 (20.8)
Female sex – no./total no. (%)	12,682 (57.6)	12,623 (58.4)
Place of residence – no/total no. (%)@		
Rural	2,221 (10.1)	2,092 (9.7)
Urban	19,743 (89.7)	19,471 (90.1)
Missing data	53 (0.2%)	46 (0.2%)
Income Quintiles – no./total no. (%)!		
1	4,874 (22.1)	4,828 (22.3)
2	4,549 (20.7)	4,574 (21.2)
3	4,362 (19.8)	4,267 (19.7)
4	4,066 (18.5)	4,094 (18.9)
5	4,087 (18.6)	3,778 (17.5)
Missing data	79 (0.4%)	68 (0.3%)

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Baseline characteristics

Characteristic	Ringer's Lactate (N = 22,017)	Normal Saline (N = 21,609)
Case Mix Group – no./total no. (%)		
Medicine	8,787 (39.9)	9,011 (41.7)
Surgery	9,379 (42.6)	8,804 (40.7)
Pregnancy and Childbirth	3,706 (16.8)	3,670 (17.0)
Mental Health	145 (0.7)	124 (0.6)
Elixhauser Co-morbidity Score		
Median (Q1-3)	0 (0-5)	0 (0-5)
Elixhauser Quartiles		
Quartile 1	1,399 (6.4)	1,185 (5.5)
Quartile 2	12,671 (57.6)	12,482 (57.8)
Quartile 3	2,219 (10.1)	2,090 (9.7)
Quartile 4	5,728 (26.0)	5,852 (27.1)

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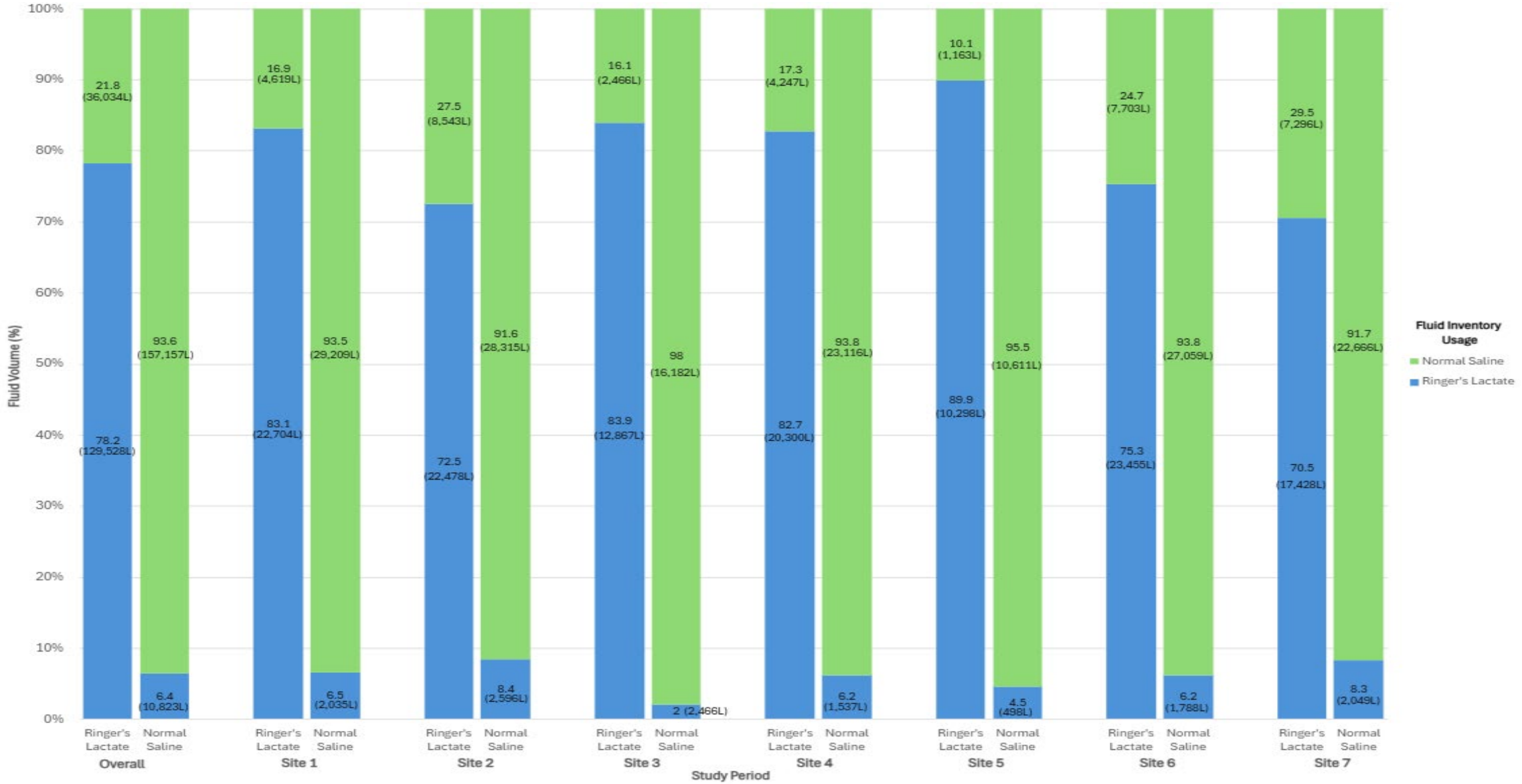
Adherence and Volumes of Study Fluid Administered



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Cluster-level Analyses of Primary and Secondary Outcomes

Outcome	Ringer's Lactate N = 7 hospitals (mean, SD)	Normal Saline N = 7 hospitals (mean, SD)	Adjusted Mean Difference* (95% CI)	P value	Adjusted Relative Difference (95%CI)
Primary Outcome					
Composite of death or readmission within 90 days of index admission (%)	20.3 (3.5)	21.4 (3.3)	- 0.53 (-1.85 to 0.79)	0.35	0.97 (0.90 to 1.05)
Other Secondary Outcomes					
Death within 90 days of index admission (%)	6.9 (1.2)	7.6 (1.7)	- 0.26 (- 0.95 to 0.43)		0.97 (0.89 to 1.07)
Re-admission to hospital within 90 days of index admission (%)	15.1 (2.9)	15.4 (2.1)	- 0.06 (-1.78 to 1.67)		0.99 (0.87 to 1.11)
Emergency Department visits (incident) within 90 days of index admission (%)	21.2 (3.1)	21.0 (2.3)	0.28 (-2.51 to 3.06)		1.01 (0.88 to 1.15)
Initiation of dialysis within 90 days of index hospital admission (%)	0.5 (0.3)	0.6 (0.5)	- 0.12 (-0.34 to 0.11)		0.99 (0.56 to 1.77)
Hospital Length of stay (hours)	164.7 (34.7)	172.3 (34.2)	- 0.002 (- 0.006 to 0.002)		NA
Discharge to a facility other than home (%)	15.4 (4.8)	16.2 (4.6)	- 0.49 (-1.59 to 0.62)		0.96 (0.90 to 1.03)

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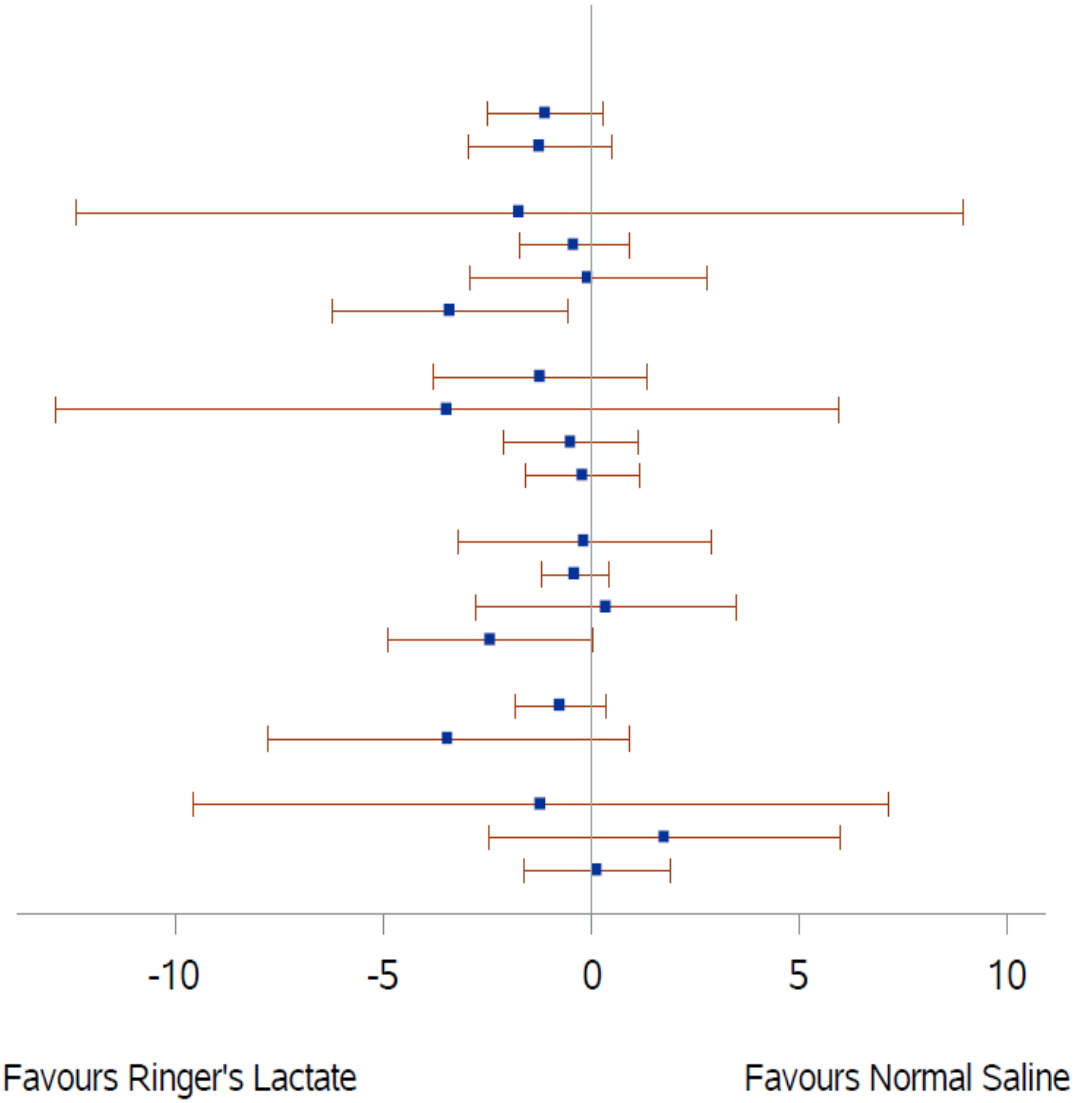
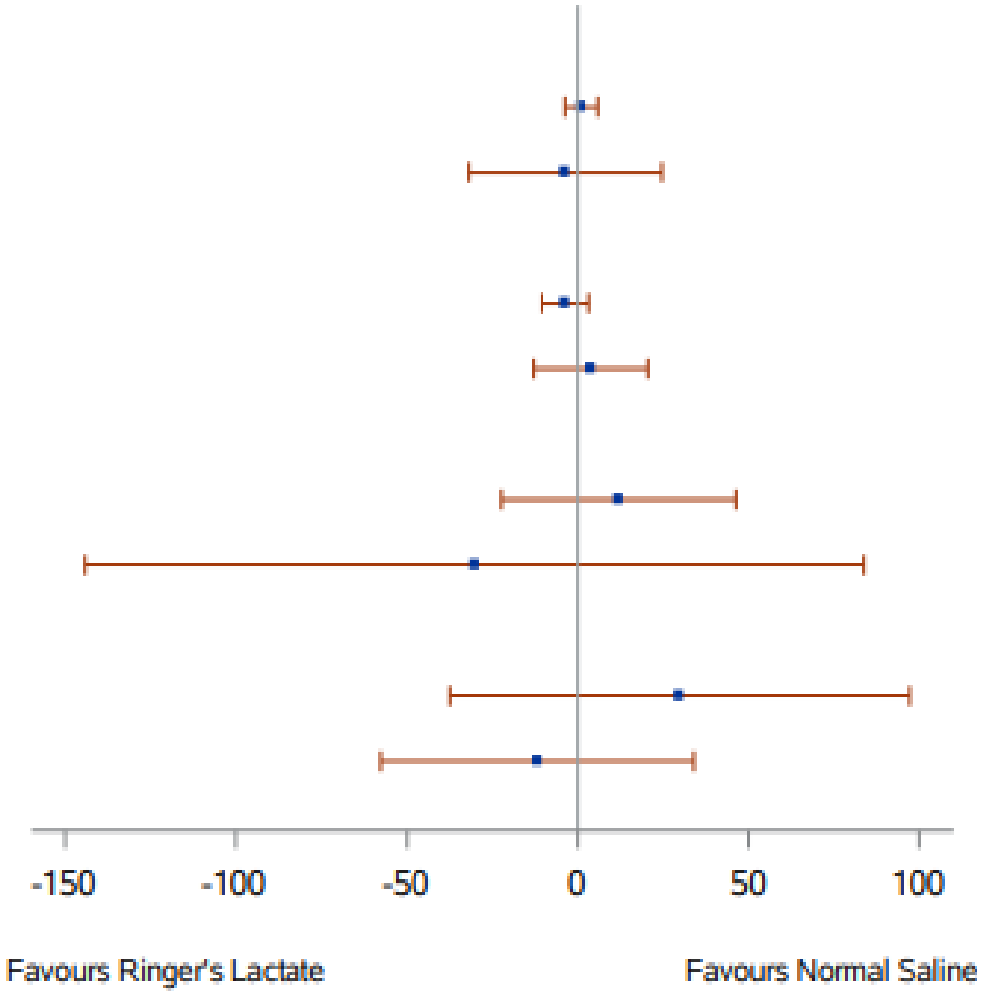
Pre-Specified Subgroup Analyses

Subgroup	Number of patients	Ringer's Lactate (N=22,017) Mean (SD)	Normal Saline (N=21,609) Mean (SD)	RD (95% CI)
Sex				
1. Female	25305	18.2 (3.9)	19.4 (4.6)	-1.11 (-2.49, 0.28)
2. Male	18321	23.7 (3.2)	25.0 (3.2)	-1.25 (-2.98, 0.48)
Age				
1. 1 month to 18 years	198	8.7 (4.8)	10.4 (10.3)	-1.74 (-12.4, 8.92)
2. >18 to 65 years	24650	14.1 (4.4)	14.6 (3.7)	-0.43 (-1.75, 0.89)
3. >65 to 80 years	11693	24.9 (4.5)	25.0 (5.8)	-0.08 (-2.92, 2.76)
4. >80 years	7085	34.9 (1.7)	38.3 (2.5)	-3.41 (-6.25, -0.56)
Case mix group				
1. Medical	17798	31.4 (4.8)	32.7 (3.9)	-1.23 (-3.80, 1.34)
2. Mental health	269	14.5 (6.3)	16.9 (9.3)	-3.48 (-12.9, 5.96)
3. Pregnancy and childbirth	7376	7.1 (3.2)	12.5 (16.9)	-0.50 (-2.13, 1.13)
4. Surgery	18183	14.9 (3.7)	15.2 (3.9)	-0.21 (-1.58, 1.17)
Elixhauser quartiles				
1	2584	14.7 (5.6)	15.1 (5.4)	-0.18 (-3.23, 2.87)
2	25153	13.3 (2.8)	13.8 (2.9)	-0.40 (-1.21, 0.40)
3	4309	27.3 (2.9)	27.3 (3.1)	0.35 (-2.77, 3.47)
4	11580	36.0 (4.4)	38.2 (5.0)	-2.43 (-4.89, 0.04)
ICU within 1 day				
1. No	39254	19.6 (3.7)	20.4 (3.3)	-0.76 (-1.84, 0.33)
2. Yes	4372	31.6 (6.8)	35.1 (7.0)	-3.45 (-7.80, 0.90)
Type of surgery				
1. Emergent	627	7.1 (10.1)	8.3 (3.6)	-1.22 (-9.59, 7.15)
2. Urgent	1008	13.0 (2.1)	11.4 (3.8)	1.76 (-2.46, 5.98)
3. Elective	11484	12.3 (4.4)	12.3 (4.6)	0.14 (-1.61, 1.88)



Additional Pre-Specified Subgroup Analyses

Subgroup	Number of patients	Ringer's Lactate (N=22,017) Mean (SD)	Normal Saline (N=21,609) Mean (SD)	RD (95% CI)
Infection alone				
1. No ICU within 2 days	1635	31.6 (3.9)	31.2 (4.5)	0.98 (-3.73, 5.69)
2. ICU within 2 days	84	28.1 (15.8)	35.2 (26.4)	-3.74 (-31.98, 24.49)
Infection + organ dysfunction				
1. No ICU within 2 days	930	46.8 (7.5)	50.3 (4.2)	-3.73 (-10.52, 3.07)
2. ICU within 2 days	427	54.0 (12.0)	50.5 (7.4)	3.71 (-12.99, 20.42)
Trauma + ISS => 12				
1. No ICU within 2 days	408	20.5 (8.9)	8.5 (6.2)	12.06 (-22.29, 46.40)
2. ICU within 2 days	241	25.4 (18.8)	56.2 (29.5)	-30.21 (-144.24, 83.82)
TBI				
1. No ICU within 2 days	75	49.8 (31.1)	15.6 (13.3)	29.77 (-37.47, 97.00)
2. ICU within 2 days	90	40.9 (20.7)	45.0 (30.8)	-11.84 (-57.65, 33.96)



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Pre-Specified Sensitivity Analyses on the Primary Outcome

Sensitivity Analyses*	Ringers Lactate N = 22,017 (mean, SD) %	Normal Saline N = 21,609 (mean, SD) %	Adjusted Mean Risk Difference (95% CIs)	Adjusted Relative Risk Difference (95% CIs)
Removal of elective surgery (from home) ≤ 1 day from hospital admission	20.4 (3.6)	21.5 (3.3)	-0.62 (-2.03 to 0.79)	0.96 (0.89 to 1.05)
Removal of Mental Health Case Mix Group	20.3 (3.5)	21.4 (3.3)	-0.52 (-1.91 to 0.86)	0.97 (0.90 to 1.05)
Removal of deliveries (vaginal and C-sections)	23.0 (3.3)	24.1 (2.9)	-0.53 (-1.93 to 0.86)	0.97 (0.91 to1.04)
Removal of patients who could have experienced both study fluids	20.0 (3.5)	21.1 (3.2)	-0.64 (-1.88 to 0.60)	0.96 (0.90 to 1.04)

Sensitivity Analyses: to Assess for Potential Seasonal Effect

Models*	Ringers Lactate N = 22,017 (mean, SD) %	Normal Saline N = 21,609 (mean, SD) %	Adjusted Mean Risk Difference (95% CIs)	Adjusted Relative Risk Difference (95% CIs)
Binary period effect	20.3 (3.5)	21.4 (3.3)	- 0.53 (-1.85 to 0.79)	0.97 (0.90 to 1.05)
Linear period effect	20.3 (3.5)	21.4 (3.3)	-0.52 (-1.84 to 0.80)	0.97 (0.90 to 1.05)
Restricted Cubic Spline period effect	20.3 (3.5)	21.4 (3.3)	-0.53 (-2.24 to 1.18)	0.97 (0.88 to 1.07)

Footnotes:

* Estimates obtained from linear regression analyses of cluster-level summary data with period (as a continuous variable representing calendar time), intervention and cluster as independent variables; all estimates have been adjusted for prespecified patient covariates: age, sex, case mix group, Elixhauser comorbidity index and ICU admission within 1 day after hospital admission

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Limitations

- FLUID was stopped early due to the COVID pandemic
- Adherence to Ringer's Lactate arm lower than Normal Saline arm
- Health administrative data may be less accurate as compared to data collection performed by research co-ordinators
  - Misclassifications would be non-differential
- Complex logistics necessitated sequential site enrolment so vulnerable to time confounding seasonal effects
  - Secondary analyses adjusting for calendar time consistent with the trial findings

Discussion/Conclusion

- FLUID findings align with recent meta-analyses of RCTs which suggest small but clinically relevant reduction in death favoring balanced crystalloid fluid

- Although the adjusted absolute difference of 0.5% in favor or Ringer's Lactate was small, differences could have a major effect at the level of the hospital/health care system

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