

Pragmatic Trials in Critical Care

Integrating comparative effectiveness trials into
clinical care as part of a Learning Healthcare System

Network for Investigation of Delirium

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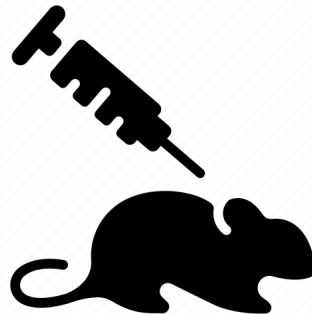
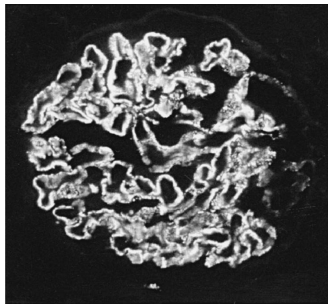
Disclosures

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- Disclosures or Potential Conflicts of Interest:
 - None

Traditional Model

Surfactant for ARDS
Monoclonal antibodies for sepsis
Prostaglandin for ARDS
Statins for ARDS
Fish oil for ARDS
B-agonists for ARDS
Ketoconazole for ARDS

Phase III Explanatory RCTs



T0

T1

T2

T3

T4

Understand biology

Identify treatments

Safety in

Efficacy in

Implementation

Identify treatment targets

surrogate outcomes

Humans

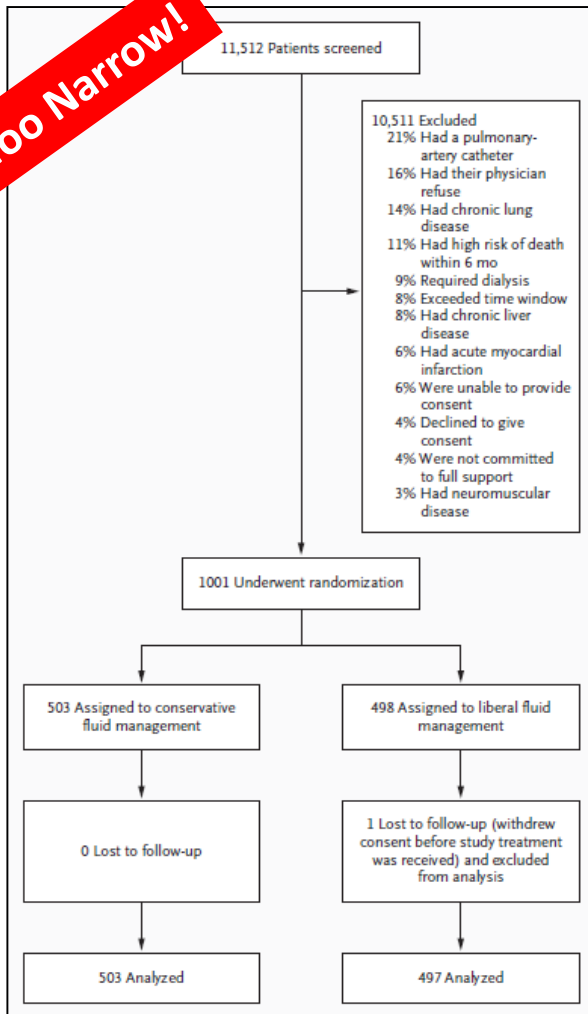
Patients

Into Practice

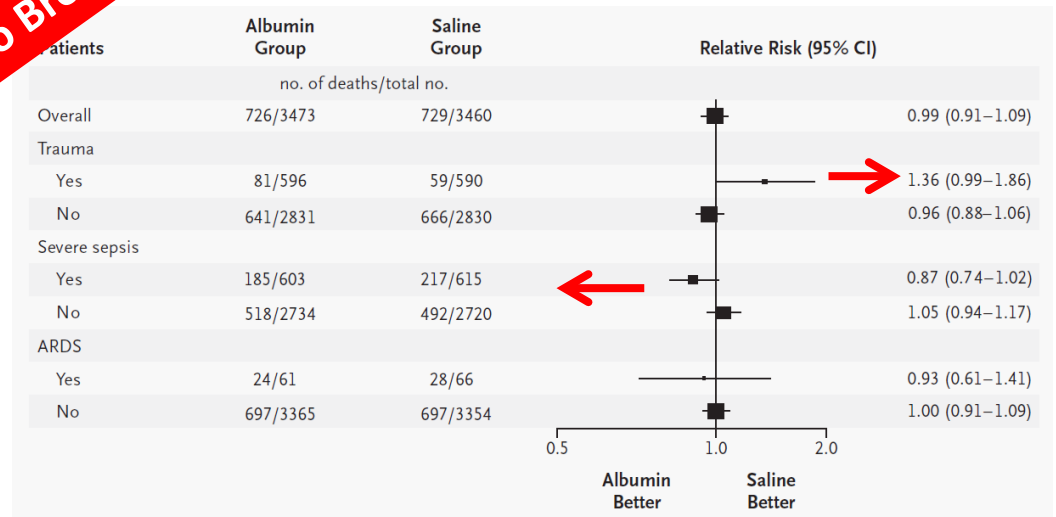
Traditional Randomized Trials



Too Narrow!



Too Broad!



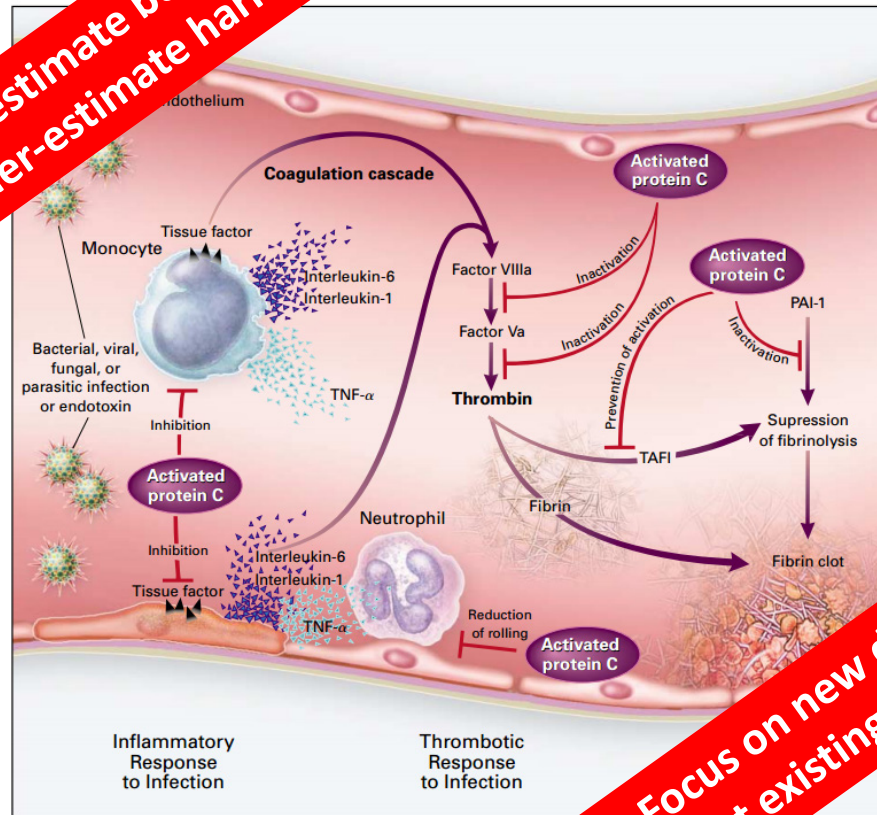
There were 20 records found. Click on the links to view details. T: Agency, IC, Serial No., Year, Support Year/Supplement/Amendment										Show/Hide Search Criteria
				Contact PI/ Project Leader	Organization	FY	Admin IC	Funding IC	FY Total Cost by IC	Similar Projects
					PITTSBURGH					
				MECHANISMS OF ACTION	ANGUS, DEREK C					
				COSTS AND COST EFFECTIVENESS	ANGUS, DEREK C	2009	NIGMS		\$341,282	
				PROTOCOLIZED CARE FOR EARLY SEPTIC SHOCK (PROCESS)	ANGUS, DEREK C	2009	NIGMS		\$221,860	
				CLINICAL EFFICACY	ANGUS, DEREK C	2009	NIGMS	NIGMS	\$1,948,857	
				MECHANISMS OF ACTION	ANGUS, DEREK C	2008	NIGMS		\$953,349	
				COSTS AND COST EFFECTIVENESS	ANGUS, DEREK C	2008	NIGMS		\$296,616	
				PROTOCOLIZED CARE FOR EARLY SEPTIC SHOCK (PROCESS)	ANGUS, DEREK C	2008	NIGMS	NIGMS	\$131,012	
				CLINICAL EFFICACY	ANGUS, DEREK C	2008	NIGMS		\$1,711,416	
				MECHANISMS OF ACTION	ANGUS, DEREK C	2007	NIGMS		\$1,003,370	
				COSTS AND COST EFFECTIVENESS	ANGUS, DEREK C	2007	NIGMS		\$252,708	
				PROTOCOLIZED CARE FOR EARLY SEPTIC SHOCK (PROCESS)	ANGUS, DEREK C	2007	NIGMS	NIGMS	\$61,898	
				CLINICAL EFFICACY	ANGUS, DEREK C	2007	NIGMS		\$1,693,937	
				MECHANISMS OF ACTION	ANGUS, DEREK C	2006	NIGMS		\$885,525	
				COSTS AND COST EFFECTIVENESS	ANGUS, DEREK C	2006	NIGMS		\$253,706	
				PROTOCOLIZED CARE FOR EARLY SEPTIC SHOCK (PROCESS)	ANGUS, DEREK C	2006	NIGMS	NIGMS	\$50,297	
				CLINICAL EFFICACY	ANGUS, DEREK C	2006	NIGMS		\$2,264,684	

use study into care!

Study	Median (x)	Range (Line)
Coomore and Tripps	~28	~10 - 41
Cookburn and Henderson	~6	~1 - 10
Manfield	~11	~1 - 10
Sternfield	~11	~1 - 10
Watschoke	~11	~1 - 10
Balas and Bohan	~16	~1 - 10
Stern and Simes	~11	~1 - 10
Stern and Simes	~11	~1 - 10
Ioannidis	~4	~1 - 10
Miskin and Bro	~3	~1 - 10
Decurtis et al	~6	~1 - 10
DMail(2003)	~6	~1 - 10
Astrman	~6	~1 - 10
DMail(2006)	~4	~1 - 10
Pulido et al (1982)	~4	~1 - 10
Pulido et al (1992)	~1	~1 - 10
Karris	~1	~1 - 10
Ioannidis	~2	~1 - 10
Ioannidis	~2	~1 - 10
Altman	~1	~1 - 10
Grant et al	~16	~1 - 41
Grant et al	~7	~1 - 41
HERG	~11	~1 - 41
HERG	~7	~1 - 41
Contopoulos-Ioannidis	~23	~13 - 41
Contopoulos-Ioannidis	~23	~13 - 41
Contopoulos-Ioannidis	~23	~13 - 41

\$16 million / 7 years
>\$10,000 per patient

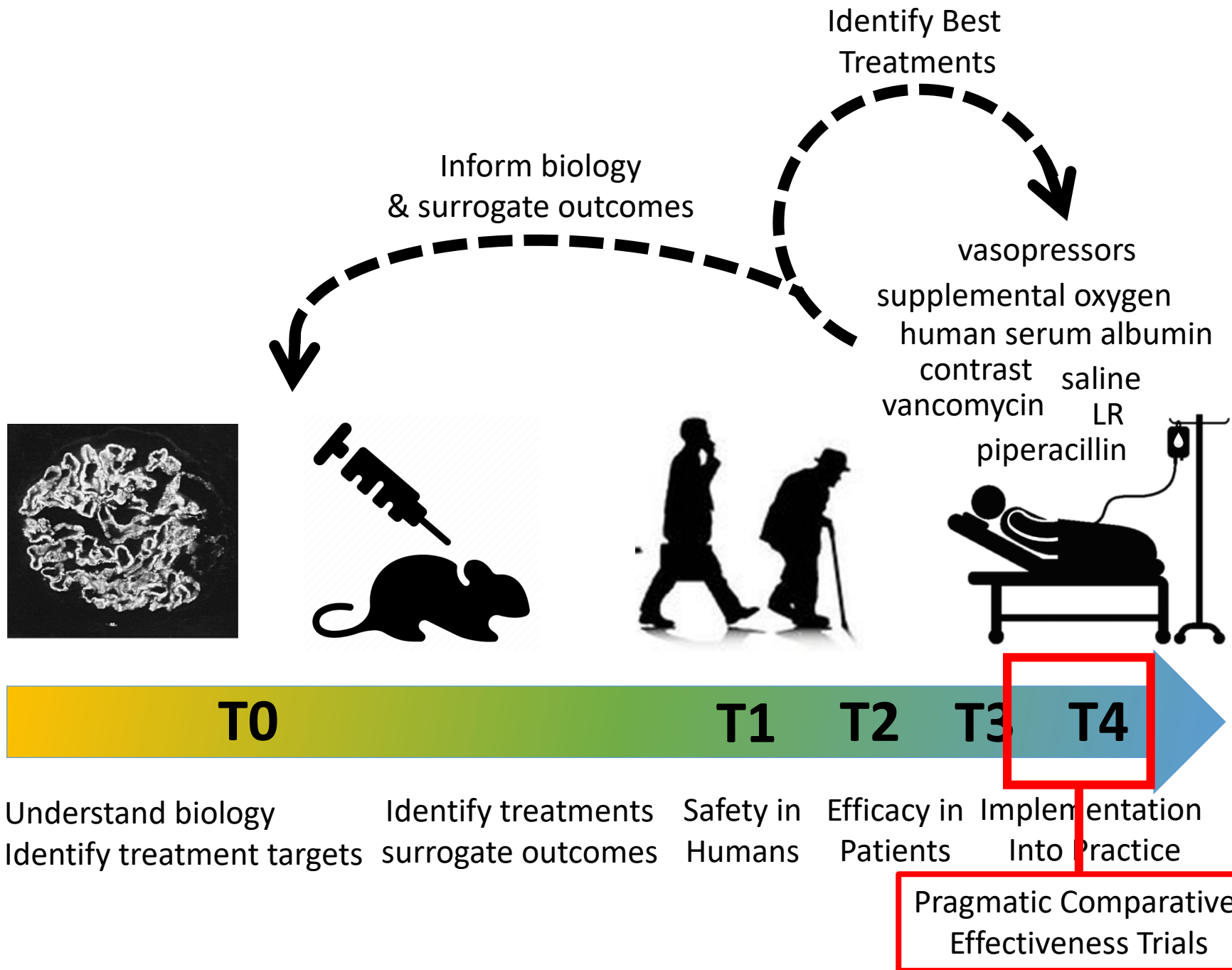
Over-estimate benefit,
Under-estimate harm.



Focus on new drugs
Neglect existing therapies

Traditional Randomized Trials

- Don't apply to patients we care for
 - Too narrow
 - Too broad
- Too expensive & difficult
- Delayed diffusion into care
- Aren't conducted by real clinicians in real settings
 - Over-estimate benefit
 - Under-estimate harm



Pragmatic...

	Explanatory Trial	Pragmatic Trial
Question	“Can the intervention work under ideal conditions?”	“Does the intervention work in practice?”
Setting	Resource-intensive ideal setting	Real-world clinical setting
Population	Highly selected, homogenous	Heterogeneous, limited exclusions
Providers	Highly trained	Representative of usual practice
Intervention	Strictly standardized & enforced	Flexibly applied

...Comparative Effectiveness...

[common ICU therapies for which the effect on patients is unknown]

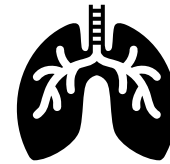


Saline vs balanced crystalloids

albumin vs crystalloids in septic shock

Restrictive vs liberal fluid management in sepsis

fluid responsiveness measures to guide fluid therapy



Higher vs lower SpO2 targets

HFNC vs NIV vs COT in AHRF

Mode of ventilation



etomidate vs ketamine

rocuronium vs succinylcholine

sedative-first vs NMB-first

NIV vs HFNC vs BMV

neuromuscular blocker vs none

fluid bolus vs none

vasopressor vs none

video vs direct laryngoscopy

hyperangulated vs standard geometry

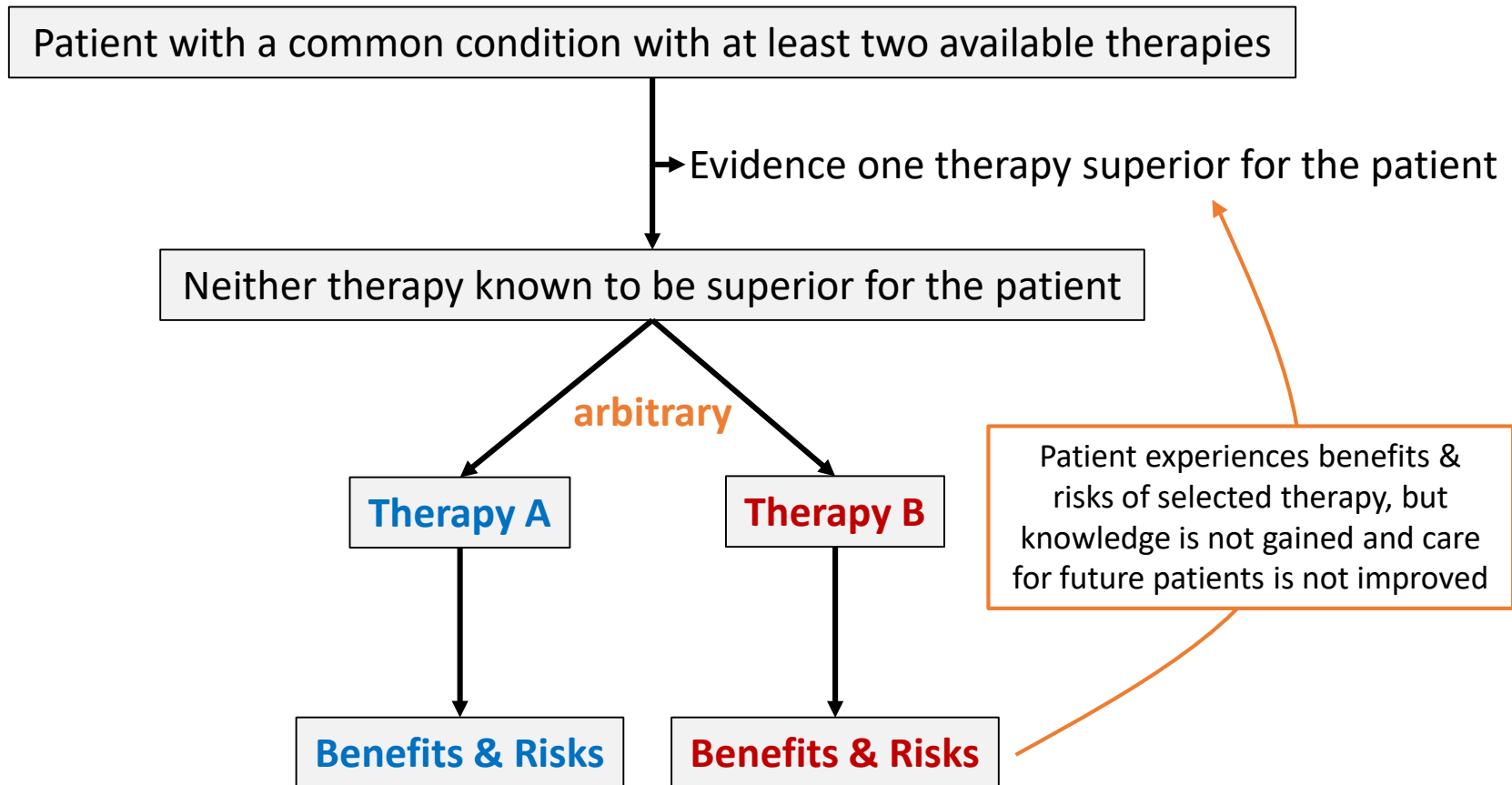
Bag-mask ventilation vs none during intubation

“apneic oxygenation” vs none

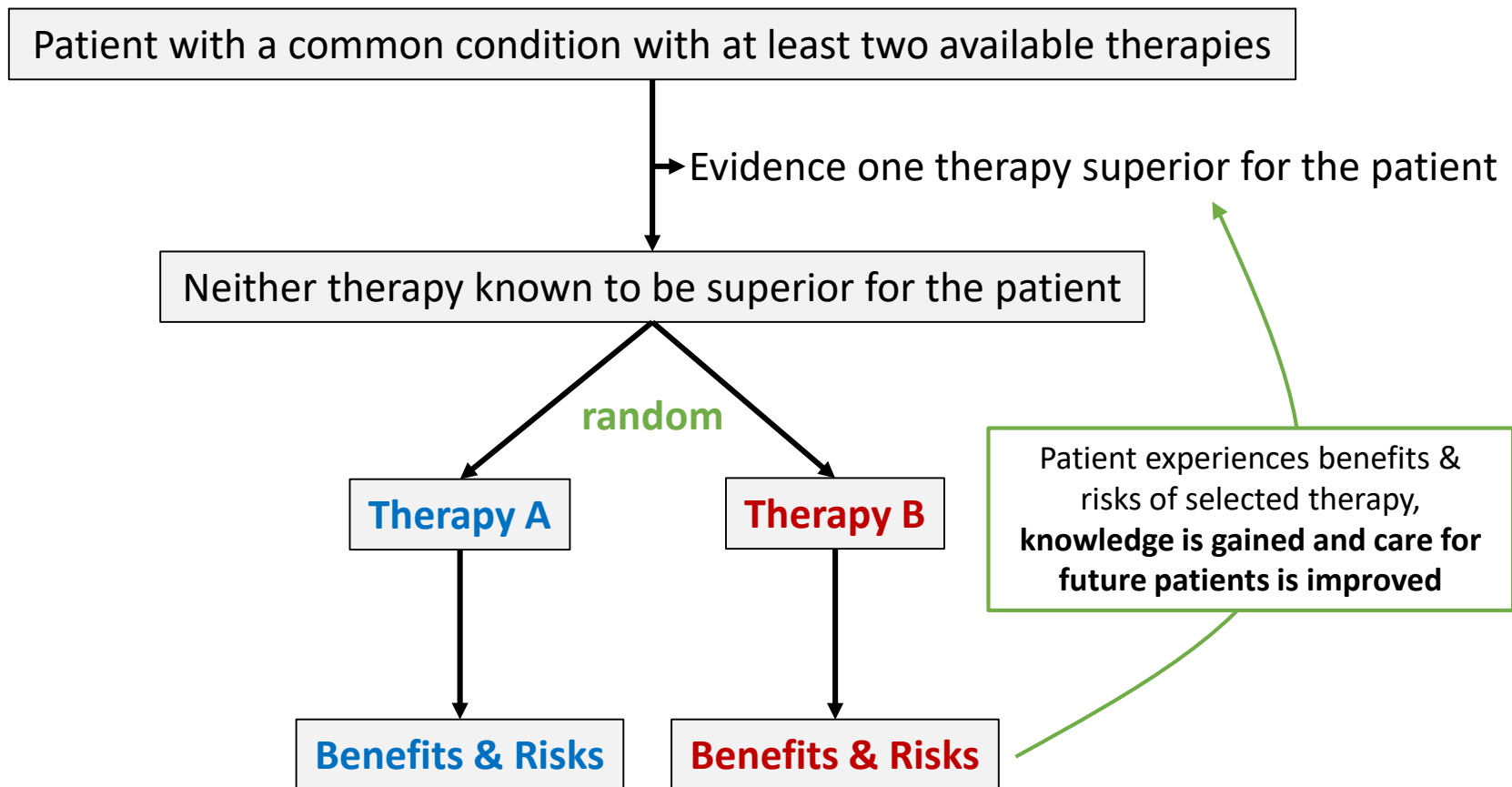
bougie vs stylet

ramped vs sniffing position

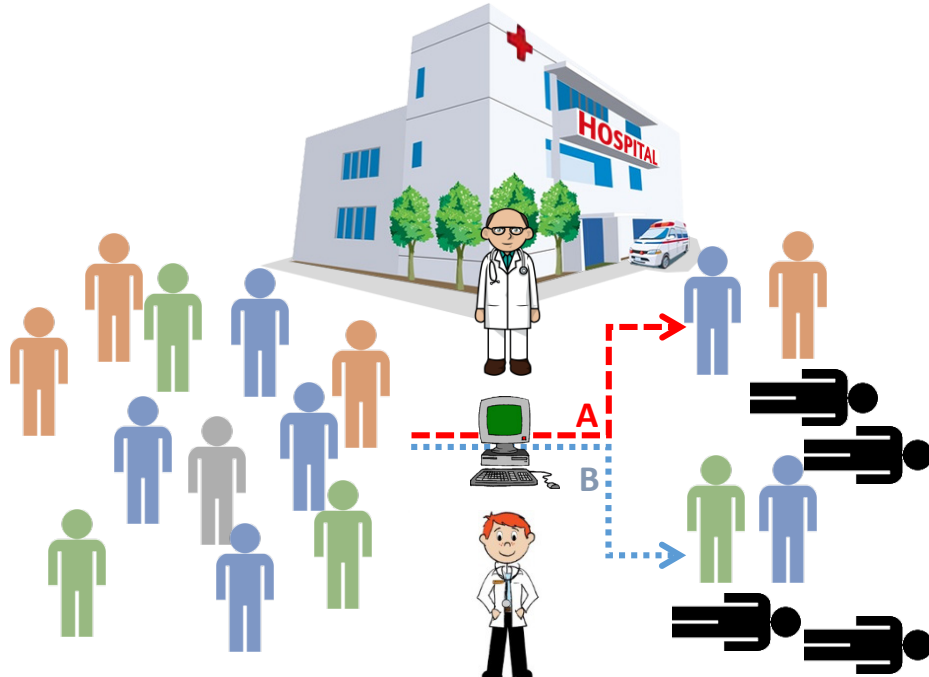
Arbitrary Variation in Clinical Care



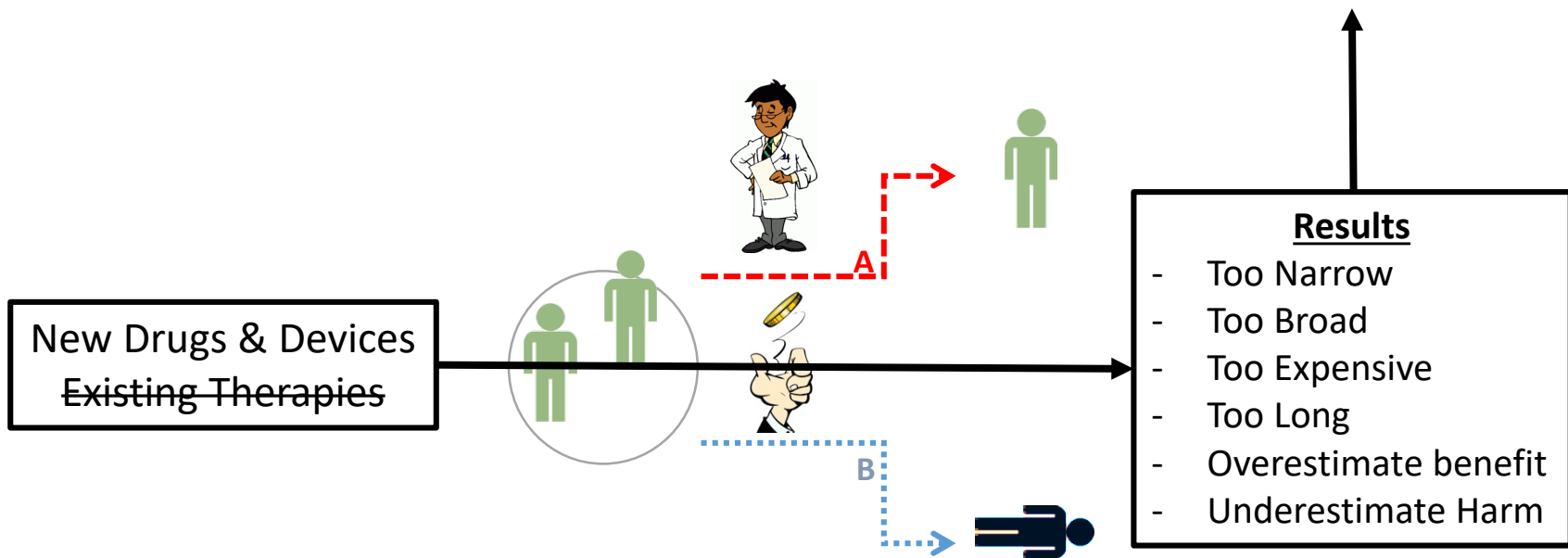
Structured Variation in a Clinical Trial



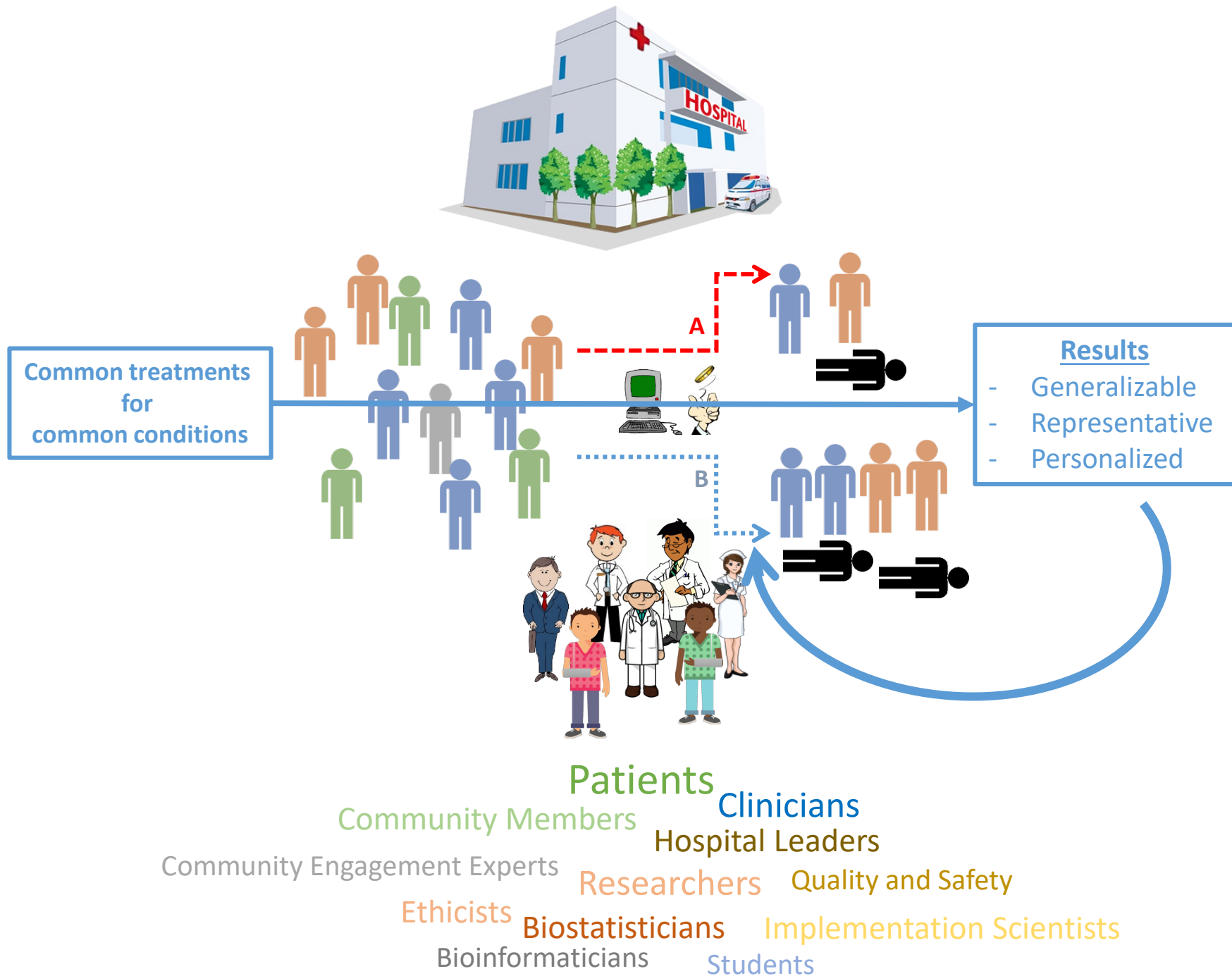
Clinical Care



Research



Learning Healthcare System



Balanced crystalloids vs saline

15,000-patient trial conducted without study
personnel for \$25,000

Balanced Crystalloids

Saline



	Na ⁺	Cl ⁻	K ⁺	Ca ²⁺	Mg ²⁺	Organic anion
0.9% saline	154	154				
Lactated Ringer's	130	109	4.0	2.7		+
Plasma-Lyte A [®]	140	98	5.0		3.0	+

Pragmatic Trial Design

- Isotonic Solutions and Major Adverse Renal Events Trial (SMART)
- Cluster-randomized, multiple-crossover trial
- Adults admitted to five ICUs at Vanderbilt

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

Coordination of pre-ICU crystalloid with ED and OR

Step 1

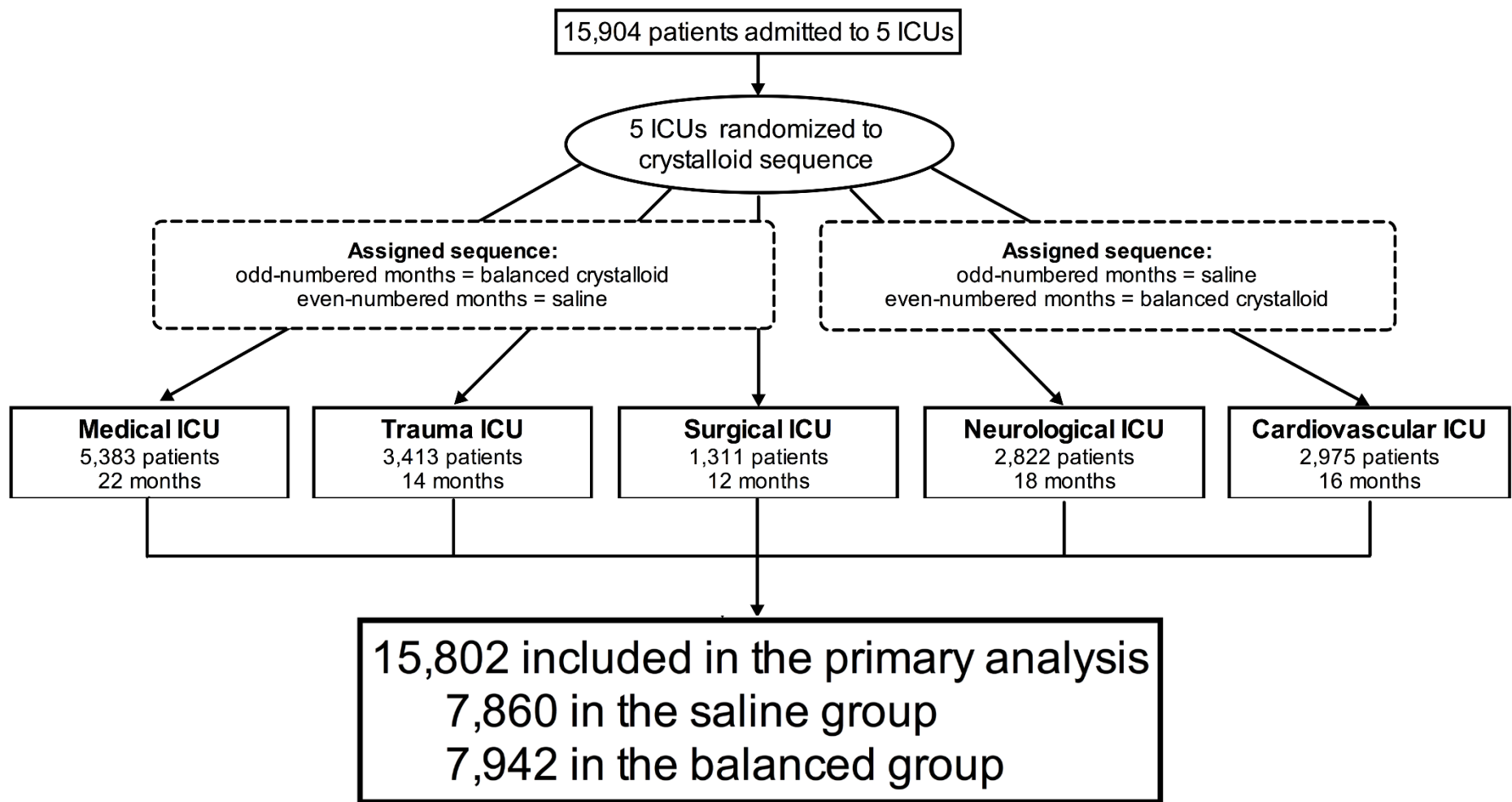


This patient has been assigned to receive LR or PLA for all isotonic fluid orders, unless a contraindication is present.

If a contraindication to LR and PLA is present, please select from the list below to order off-study IV fluid. Otherwise, please select option 1 to order LR or 2 to order PLA.

Select an option:

- 1 Order Lactated Ringer's bolus**
- 2 Order Plasma-lyte bolus**
- 3 Hyperkalemia**
- 4 Brain injury**
- 5 Specific attending request**

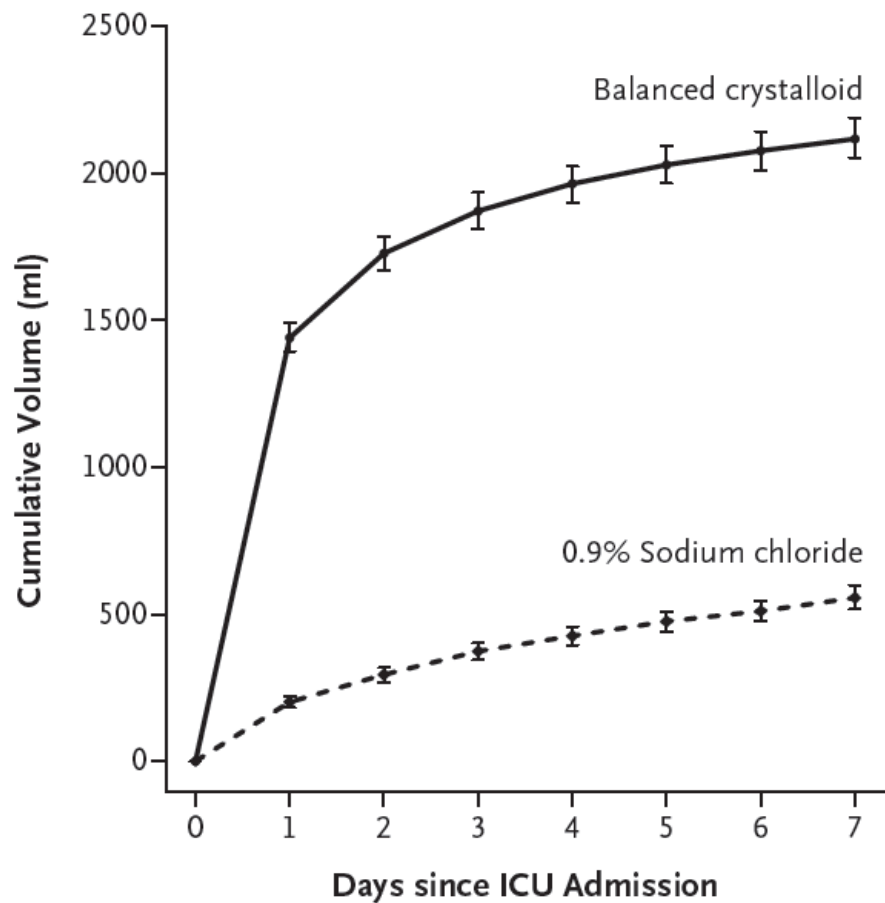


Patient Characteristics	Balanced (n = 7942)	Saline (n = 7860)
Age – years	58 [44 – 69]	58 [44 – 69]
Men	4540 (57.2)	4557 (58.0)
Admitted from ED	3975 (50.1)	3997 (50.9)
Study ICU		
Medical	2735 (34.4)	2646 (33.7)
Trauma	1640 (20.6)	1688 (21.5)
Cardiac	1470 (18.5)	1501 (19.1)
Neurological	1440 (18.1)	1377 (17.5)
Surgical	657 (8.3)	648 (8.2)
Sepsis or septic shock	1167 (14.7)	1169 (14.9)
Vasopressors	2094 (26.4)	2058 (26.2)
Mechanical ventilation	2723 (34.3)	2731 (34.7)
Baseline creatinine – mg/dL	0.89 [0.74 – 1.10]	0.89 [0.74 – 1.10]
Acute kidney injury	681 (8.6)	643 (8.2)

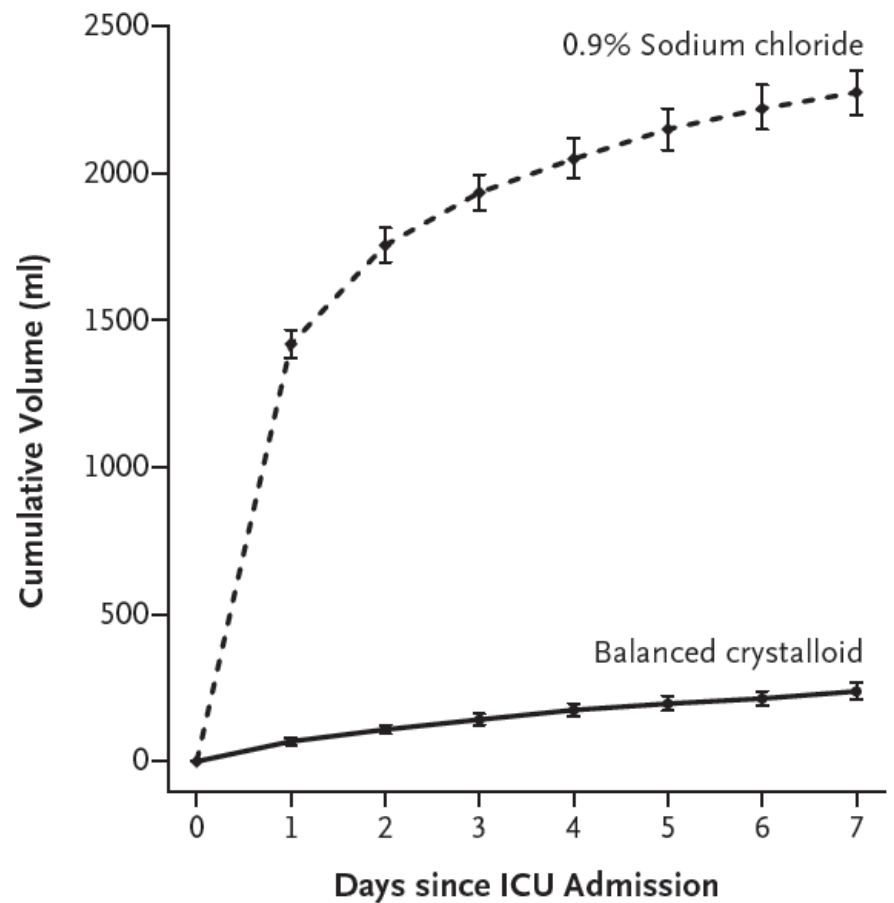
Data given as no. (%) or median [IQR]

Patients received largely the assigned fluid

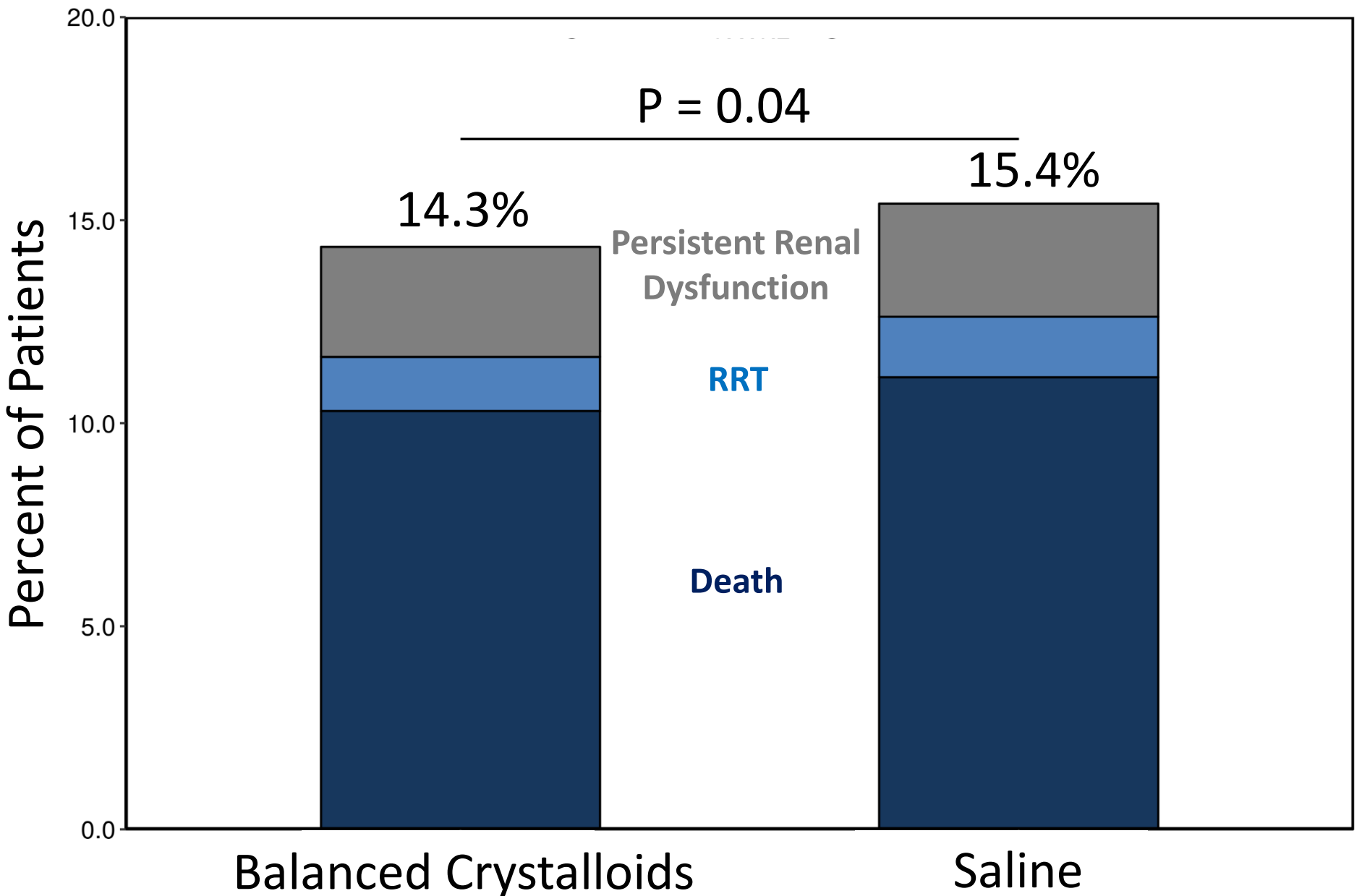
A Balanced-Crystalloids Group



B Saline Group



Balanced crystalloids prevented Major Adverse Kidney Events



Design Efficiencies

1. Cluster-level designs
2. Leveraging the electronic health record

Cluster-randomized trial

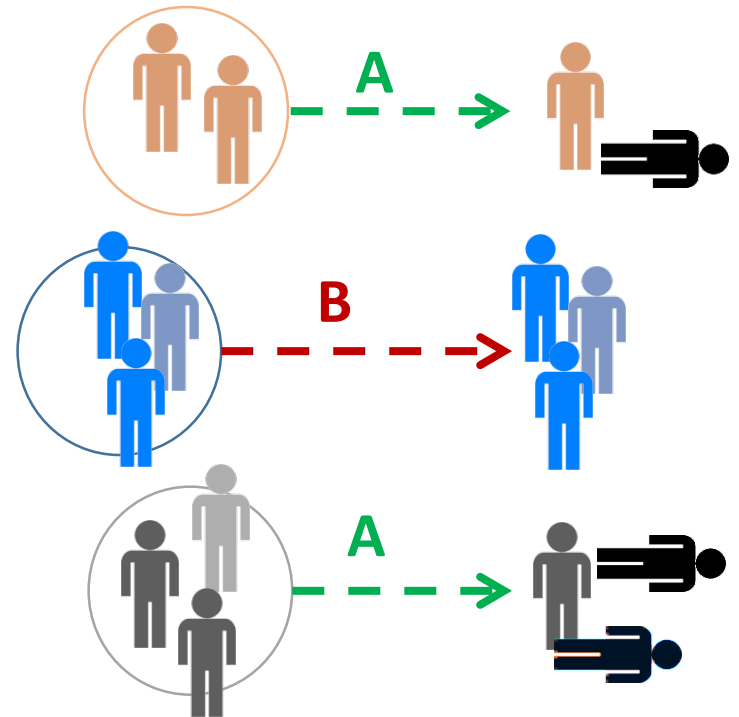
Intra-cluster correlation: *Patients are more similar to other patients in their cluster*

Cluster sample size = RCT sample size $\times 1 + (m-1)\rho$

Patient-level RCT \rightarrow 1,000 patients

Clusters of 4 patients \rightarrow 1,150 patients

Clusters of 200 patients \rightarrow 9,950 patients

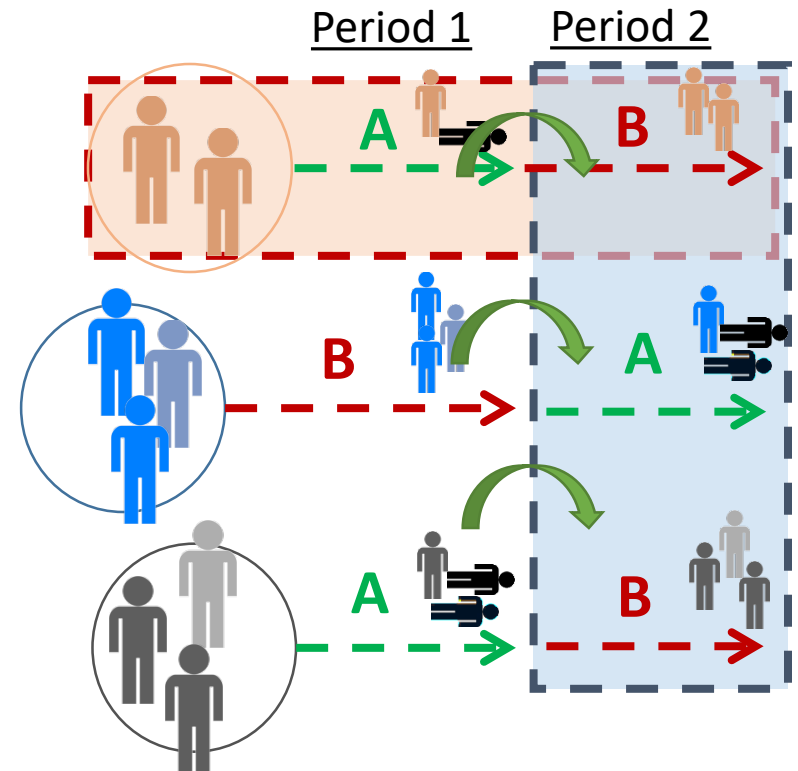


YOU WANT A LOT OF LITTLE CLUSTERS!

3. Cluster-crossover Trial

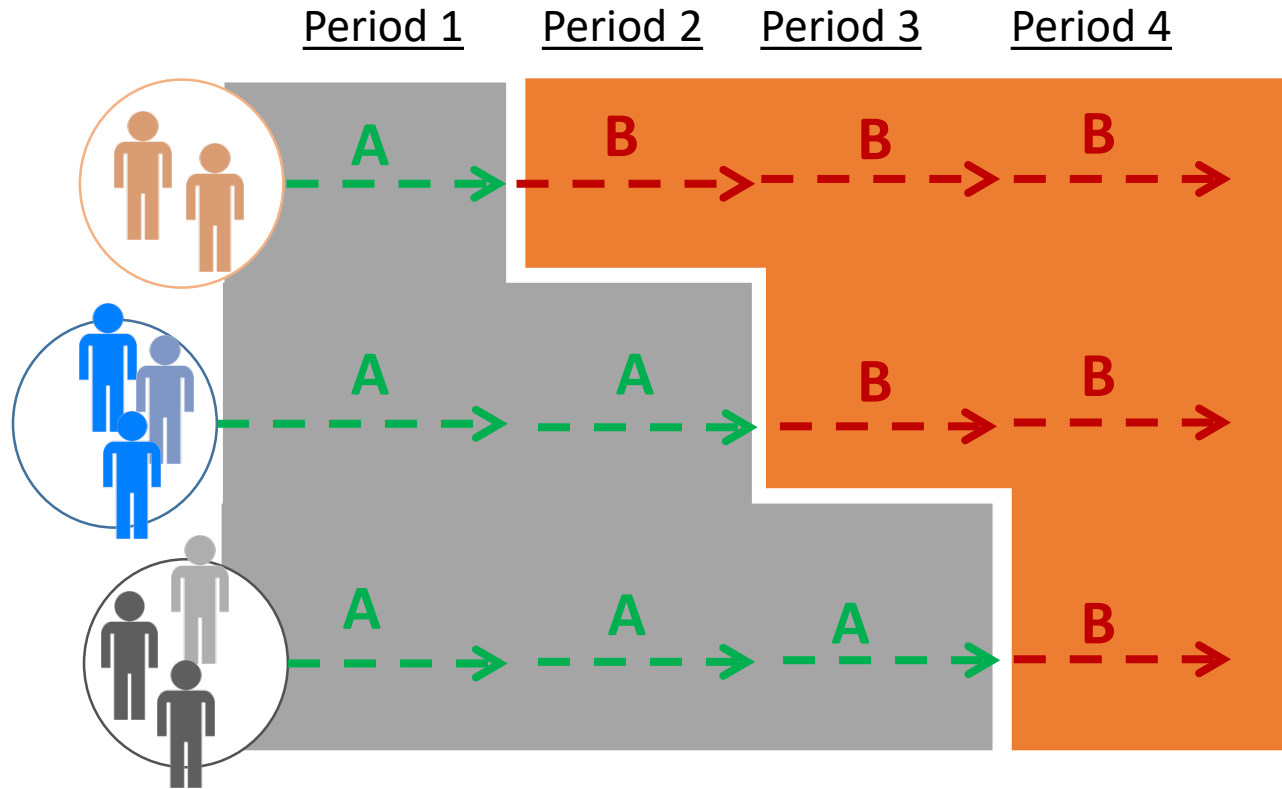
Challenges

- Intra-cluster correlation
- Intra-period correlation
- Temporal changes
- Carry-over (washout)
 - Patient-level
 - Provider-level



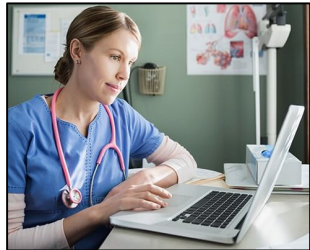
YOU WANT A LOT OF CROSS-OVERS!

Stepped-wedge trial



YOU WANT A LOT OF STEPS!

Leveraging the EHR for RCTs



SCREENING



CONSENT



RANDOMIZATION



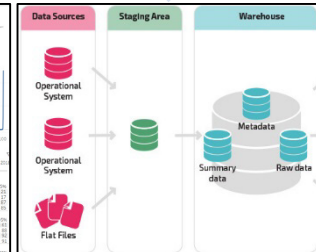
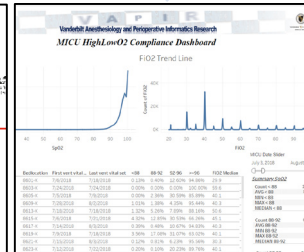
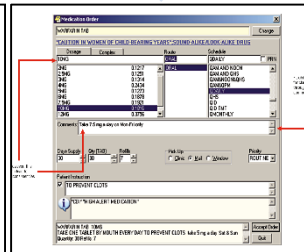
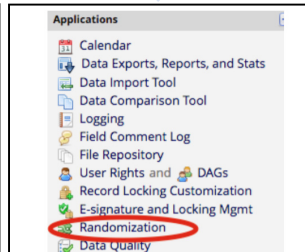
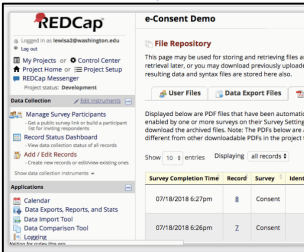
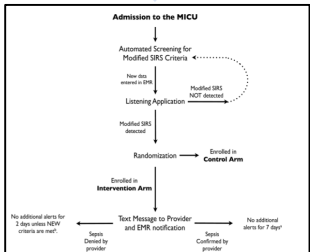
DELIVERY



MONITORING



DATA COLLECTION

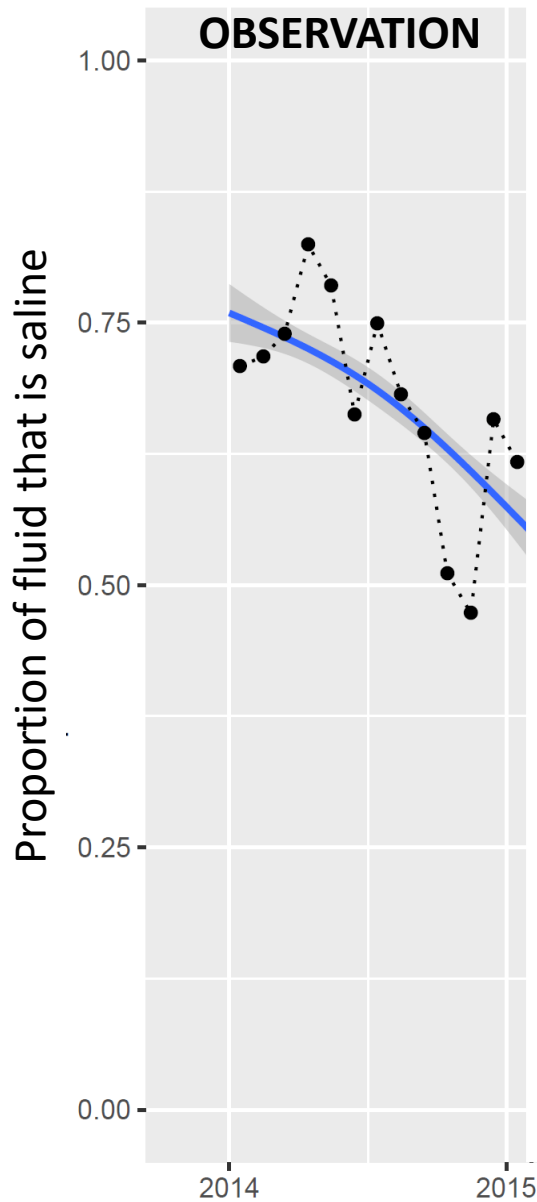


How do we integrate pragmatic comparative effectiveness trials into critical care to create a Learning Healthcare System?

1. Challenge the idea that arbitrary variation in clinical care is safer than structured variation in a clinical trial
2. Develop new approaches for involving patients and community members in research when prospective informed consent is impracticable due to urgency or scale
3. Innovate approaches to embedding each step of a clinical trial within clinical care (e.g., EHR for eligibility, enrollment, randomization, delivery of the intervention, data collection)
4. Develop and apply novel clinical trial designs better suited for pragmatic comparative effectiveness research
5. Aim to understand the effects of common interventions for all patients who would be exposed to an intervention in practice & develop tools to estimate effects of interventions for individual patients rather than average effects

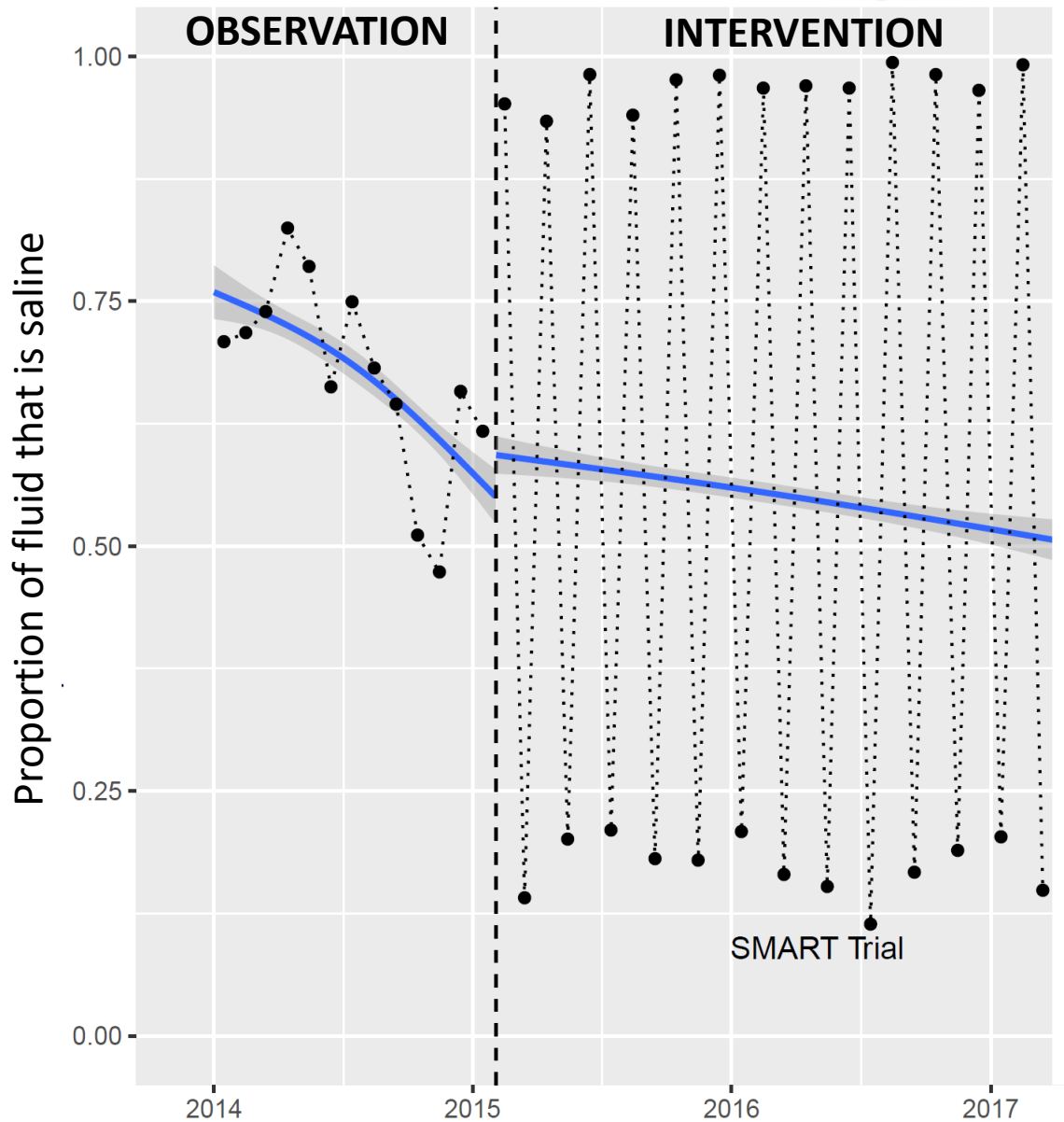
Thank you.

Vanderbilt University Learning Healthcare System



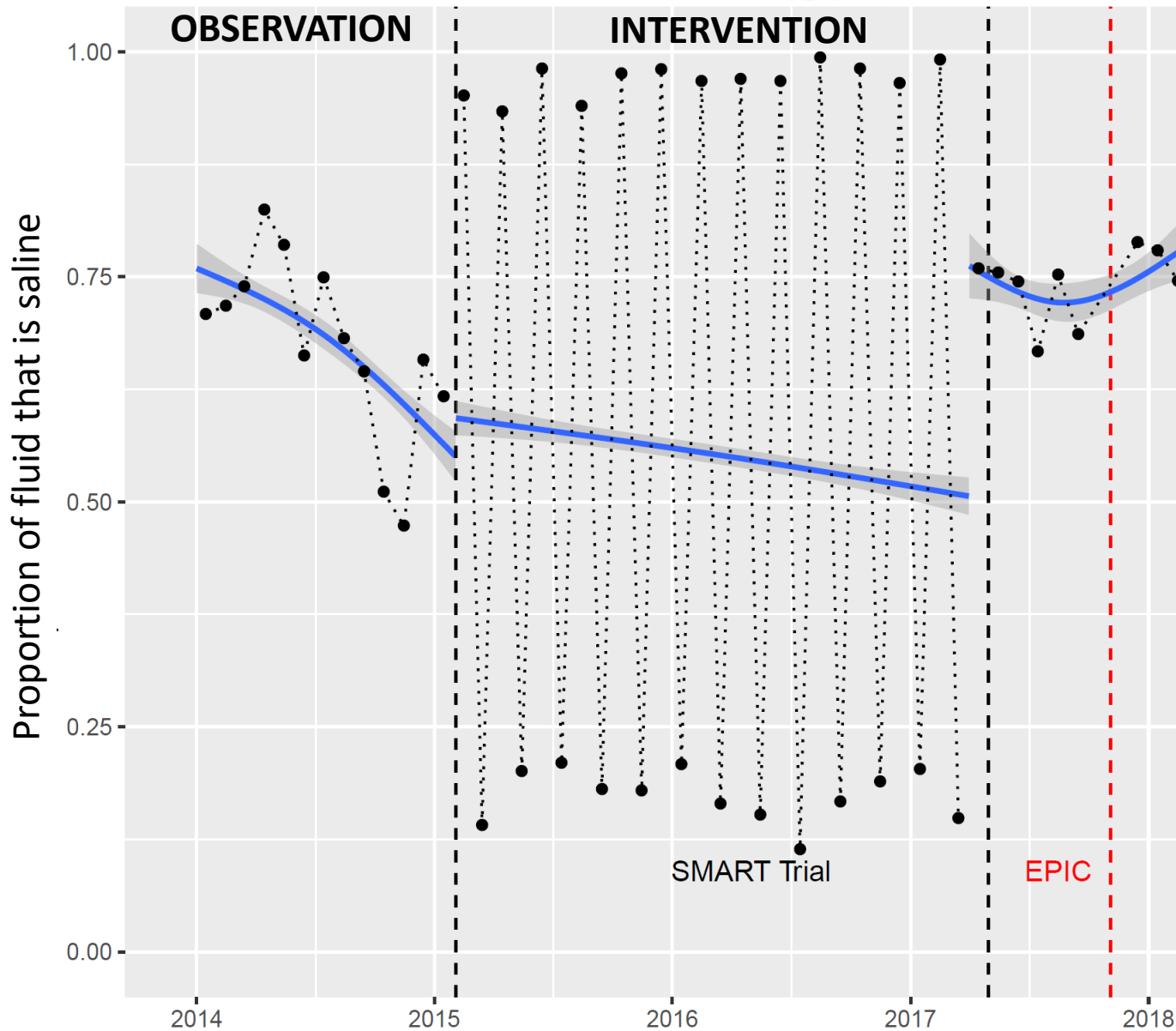
During usual care in the Vanderbilt MICU,
around **60-75%** of IV crystalloid was **saline**

Vanderbilt University Learning Healthcare System



During the SMART trial, around **50%** of IV crystalloid was **saline**

Vanderbilt University Learning Healthcare System



During usual care after the SMART trial, **75%** of IV crystalloid was **saline**

Vanderbilt University Learning Healthcare System

