Embedding Pragmatic Trials into Emergency and Critical Care

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Disclosures

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  - NHLBI K23HL153584 (Casey)
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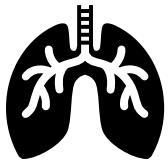
  - PCORI ME-2018C3-14549 (Gobbel)

- Conflicts of Interest:
  - We have no financial relationships with a commercial entity that is relevant to the content of this presentation.
  - We will not reference unlabeled or unapproved uses of drugs or other products.

Common emergency & critical care therapies for which the effect on patient outcomes is unknown



Higher vs lower SpO2 targets

HFNC vs NIV vs COT in AHRF

Mode of ventilation

Saline vs balanced crystalloids

albumin vs crystalloids in septic shock

Restrictive vs liberal fluid management in sepsis

fluid responsiveness measures to guide fluid therapy

etomidate vs ketamine

sedative-first vs NMB-first

video vs direct laryngoscopy

hyperangulated vs standard geometry

Bag-mask ventilation vs none during intubation

NIV vs HFNC vs BMV

neuromuscular blocker vs none

"apneic oxygenation" vs none

fluid bolus vs none

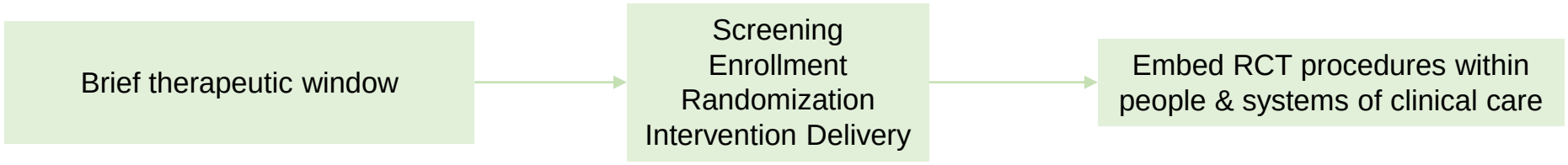
vasopressor vs none

bougie vs stylet

ramped vs sniffing position

Challenges to conducting RCTs in emergency procedures & critical care

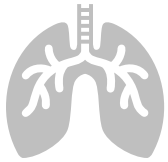
Characteristic of Emergency & Critical Care Environment	RCT Procedure	Potential Solution
Brief therapeutic window	Screening Enrollment Randomization Intervention Delivery	Embed RCT procedures within people & systems of clinical care
Low ‘signal-to-noise’ from complex acute and chronic conditions (low attributable risk) and limited time to phenotype	Sample size	Leveraging information technology tools and the EHR to facilitate each RCT procedure
Lack of decisional capacity & surrogates	Informed consent process	EFIC, waiver, and ‘the gray space’ for comparative effectiveness RCTs
Heterogeneity of patients in response to therapy	Analysis of treatment effect	Large sample size & analysis of ‘heterogeneity of treatment effect’ and ‘individual treatment effect’



Therapeutic Window

Embedding Screening, Enrollment, Randomization, and Intervention Delivery into the People and Systems of Clinical Care

Common emergency & critical care therapies for which the effect on patient outcomes is unknown



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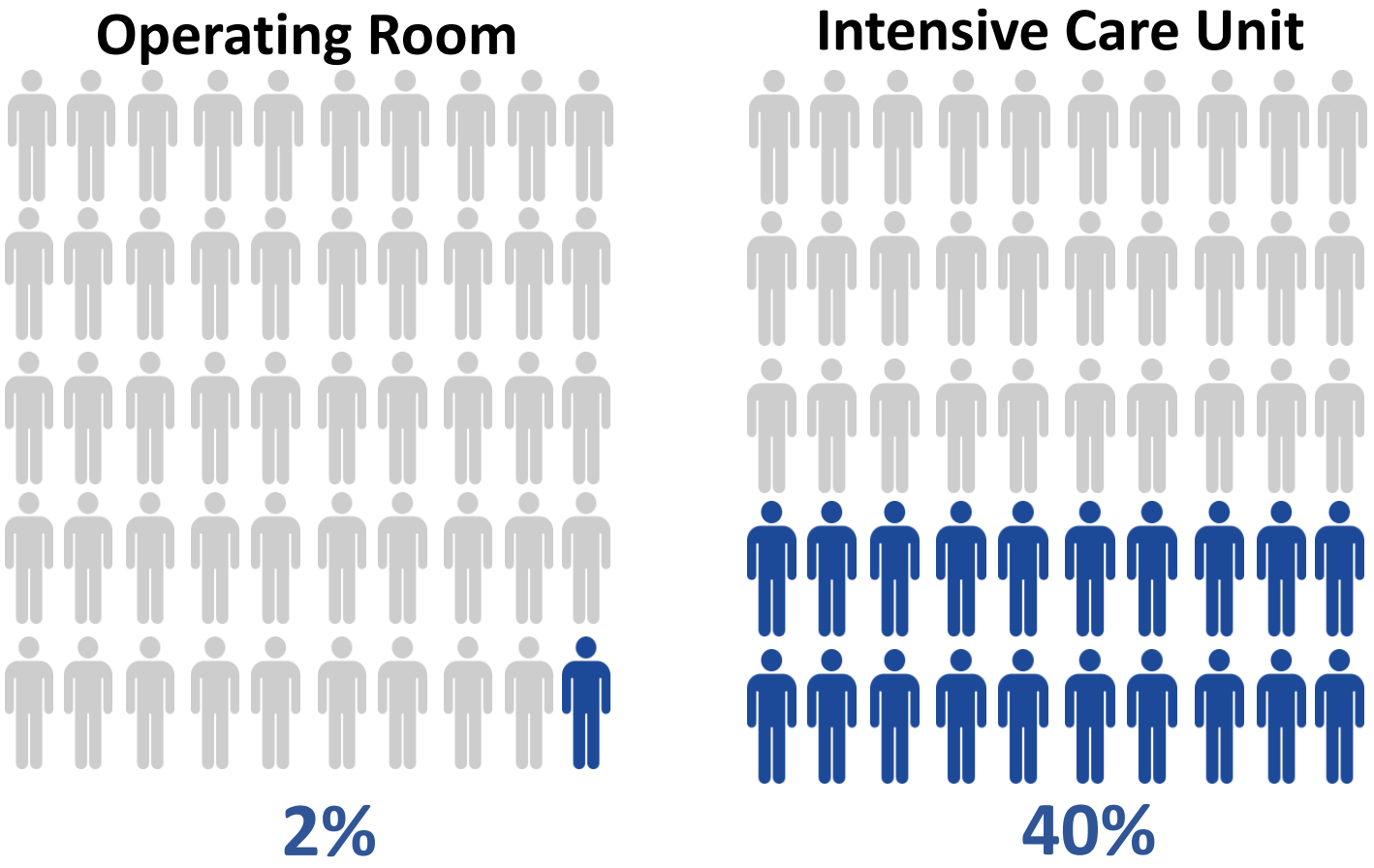
Emergency Tracheal Intubation

- 2-5 million adults intubated in ED and ICU each year
- 75% of patients are comatose or delirious
- 5% of patients are in cardiac arrest
- Surrogates are frequently unavailable
- Median 5 min from decision-to-intubate to procedure

Complications during emergency tracheal intubation are common



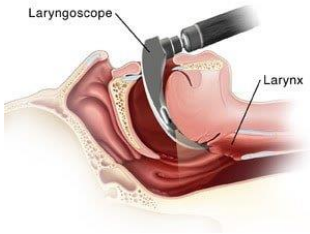
Russotto et al. JAMA 2021

Emergency Tracheal Intubation

or

or

or



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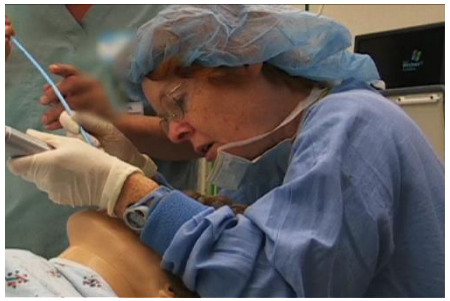

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Emergency Tracheal Intubation

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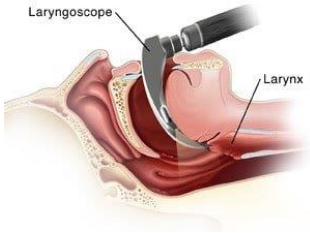

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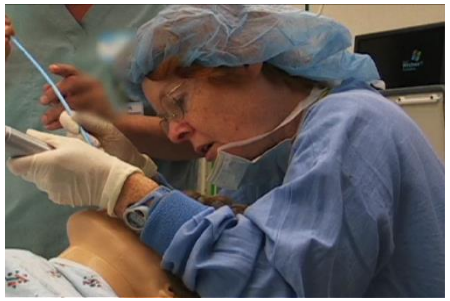
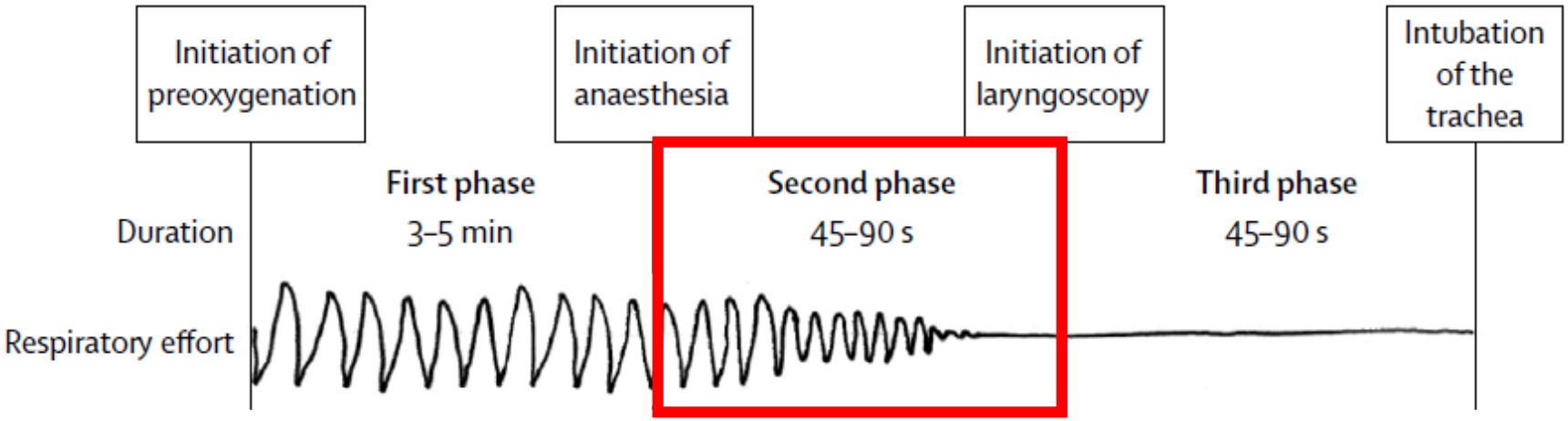


or

To ventilate, or not to ventilate…



- Delay of 45-90 sec from induction until laryngoscopy
- **50 years** of debate as to whether to ventilate during this interval
- Hypotheses:
  - Bag-mask ventilation might prevent hypoxemia
  - Bag-mask ventilation might cause aspiration

The PreVent Trial

Preventing Hypoxemia with Manual Ventilation during Endotracheal Intubation

- **Study locations**
  - 7 intensive care units in the United States
- **Eligibility**
  - Inclusion: Adults undergoing tracheal intubation with sedation
  - Exclusion: Pregnancy, Prisoner, BMV required or contraindicated
- **Randomization**
  - 1:1 to bag-mask ventilation vs no bag-mask ventilation
- **Delivery of the Intervention**
  - Treating clinicians and respiratory therapists
- **Data collection**
  - Independent observer

Efficient Trial Procedures

- Strategically placed randomization envelopes
- Broad eligibility criteria
- Simple intervention instructions
- 1-page data collection sheet
- Site-specific observers
- Daily feedback from research team on data quality

Box 1: Data to be entered by OBSERVER

1. BEFORE MEDS PUSHED …

NEW fluid bolus started prior to meds pushed: **Yes / No**

Vasopressor bolus or dose increase prior to meds pushed: **Yes / No**

2. AS INTUBATION MEDS PUSHED….

Time first med pushed: _____:_____:_____**(hr/min/sec)**

O2 Sat as meds pushed: _____**%**

SBP as meds pushed: _____ **mmHg**

2. TIME laryngoscope blade first entered mouth: _____:_____:_____**(hr/min/sec)**

3. TIME ET tube successfully placed in airway: _____:_____:_____**(hr/min/sec)**

4. AFTER MEDS PUSHED until 2 MIN AFTER TUBE PLACED IN AIRWAY

Lowest O2 Sat**:** _____**%**

Lowest SBP**:** _____ **mmHg**

NEW Fluid bolus started after meds pushed: **Yes / No**

New or increased vasopressor: **None / Neostick / Levophed / Epi / Other**

OBSERVER Name: _____ OBSERVER Signature _____ Date _____

Box 2: Data to be entered by Intubator **Patient MRN:** _____

1. Estimated # of times you've intubated previously: _____
2. Bag-valve-mask ventilation (bag squeezed) starting at induction: **Yes / No**
3. Bag-valve-mask ventilation (bag squeezed) at any point between induction and intubation: **Yes* / No**

   *If yes, why?: **Study assignment / O_2 sat < 90% / after failed attempt / Other:** _____
4. Airway patency maneuvers (circle all): **oral airway / nasal airway / jaw thrust / head-tilt-chin-lift**
5. Continuous cricoid pressure: **Yes / No**
6. O_2 between induction & laryngoscopy: **none / nasal cannula / HFNC / NRB / BiPAP / Other:** _____
7. Laryngoscope used on first attempt: **DL / McGrath / C-MAC / GlideScope / Other**
8. Best glottic view obtained on the first attempt:

9. Number of laryngoscopy attempts for successful intubation: _____
10. Additional items used (circle all): **Bougie / VL / DL / LMA / Bronch / 2nd proceduralist**
11. Do you think the patient experienced **aspiration** between induction and intubation? **Yes / No**
12. Complications (circle all):

    cardiac arrest / HR<40 / esophageal intubation / airway trauma / Other: _____

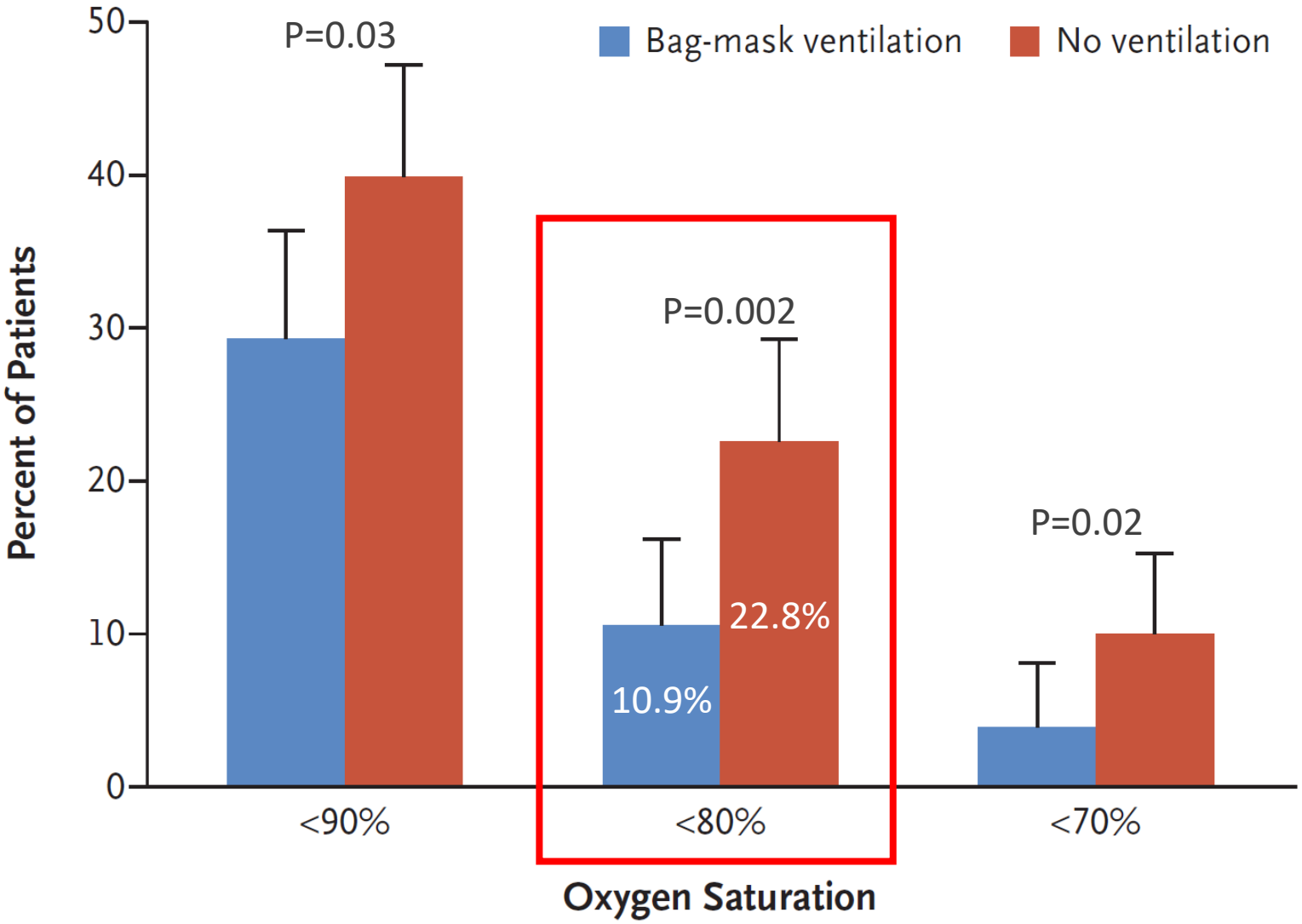
FELLOW Name: _____ FELLOW Signature _____ Date _____

Patient Characteristics	Bag-Mask Ventilation (n=199)	No Ventilation (n=202)
Age (years)	59 [45-67]	60 [48-68]
Male sex	118 (59.3%)	108 (53.5%)
APACHE II score	22 [16-29]	22 [16-28]
Vasopressors	35 (17.6%)	40 (19.8%)
Hypoxemic respiratory failure	117 (58.8%)	116 (57.4%)
One or more risk factor for aspiration	123 (61.8%)	117 (57.9%)

Characteristics of the Procedure	Bag-Mask Ventilation (n=199)	No Ventilation (n=202)	P Value
Bag-mask ventilation to prevent hypoxemia	198 (99.5)	5 (2.5)	<0.001

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

Severe Hypoxemia



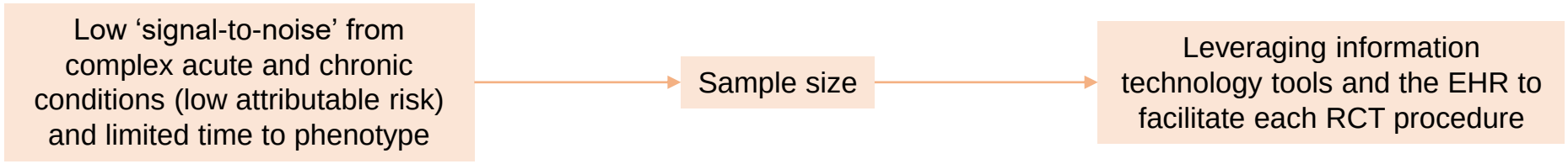
Casey, Semler et al. *N Engl J Med.* 2019

Safety Outcomes	Bag-mask Ventilation (n=199)	No Ventilation (n=202)	P Value
Operator-reported aspiration	5 (2.5%)	8 (4.0%)	0.41
New chest x-ray infiltrate	31/189 (16.4%)	29/196 (14.8%)	0.73
Lowest SpO_2 6-24 hrs post-intubation	94 [91-97]	94 [91-97]	0.90
Highest FiO_2 6-24 hrs post-intubation	0.5 [0.4-0.7]	0.5 [0.4-0.7]	0.30
Highest PEEP 6-24 hrs post-intubation	5 [5-8]	5 [5-8]	0.73

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

Summary of PreVent

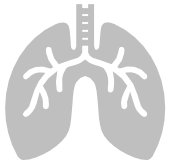
- 50 years of debate about whether to bag-mask ventilate
- 2-5 million patients a year, about half receive bag-mask ventilation
- Pragmatic RCT conducted by treating clinicians at 7 centers
- Bag-mask ventilation *halves* the risk of severe hypoxemia without affecting aspiration



Sample Size

Conducting large RCTs by using information technology tools and the EHR to efficiently facilitate each RCT procedure

Common emergency & critical care therapies for which the effect on patient outcomes is unknown



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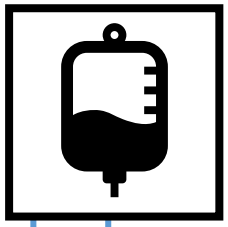

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ramped vs sniffing position

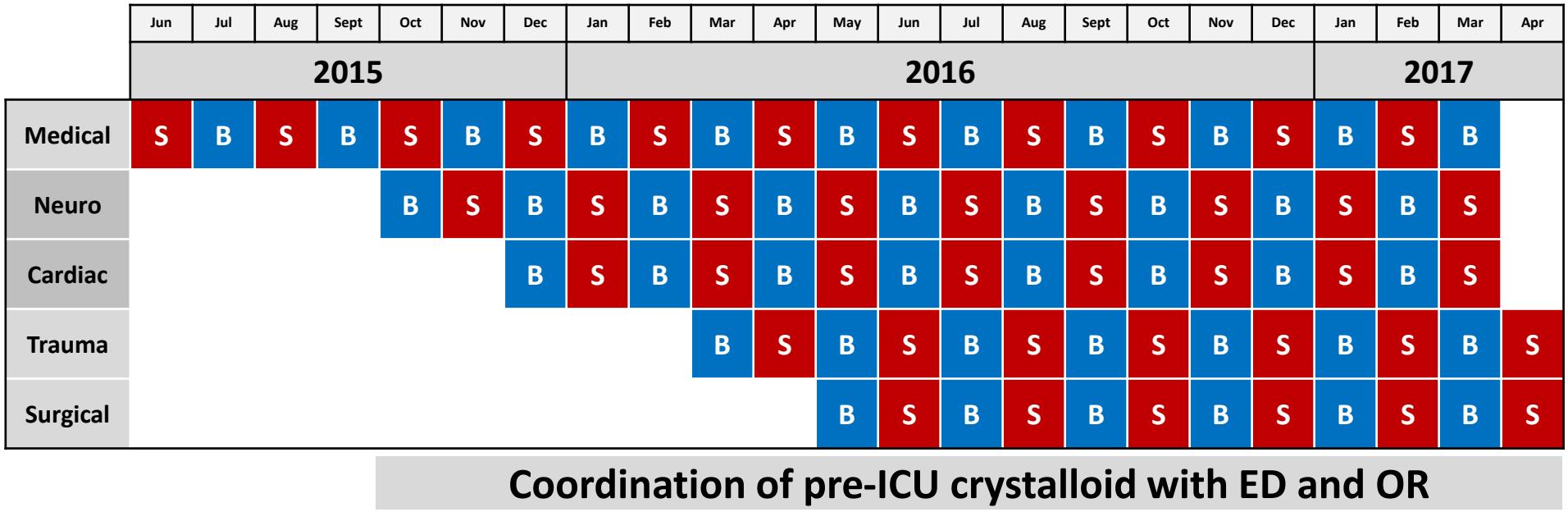
Balanced Crystalloids

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 of fluid management

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



Step 1

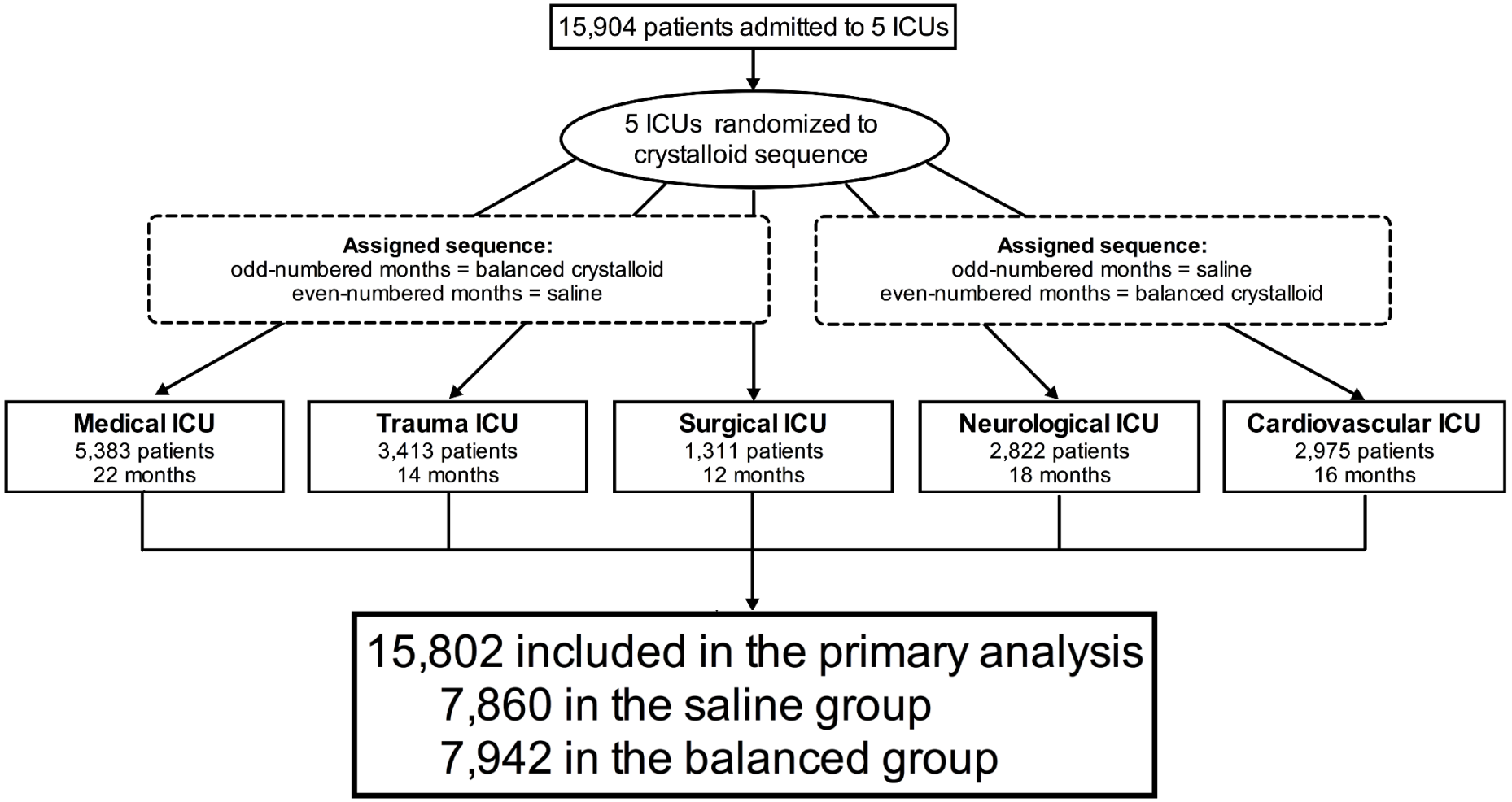
Step 2

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

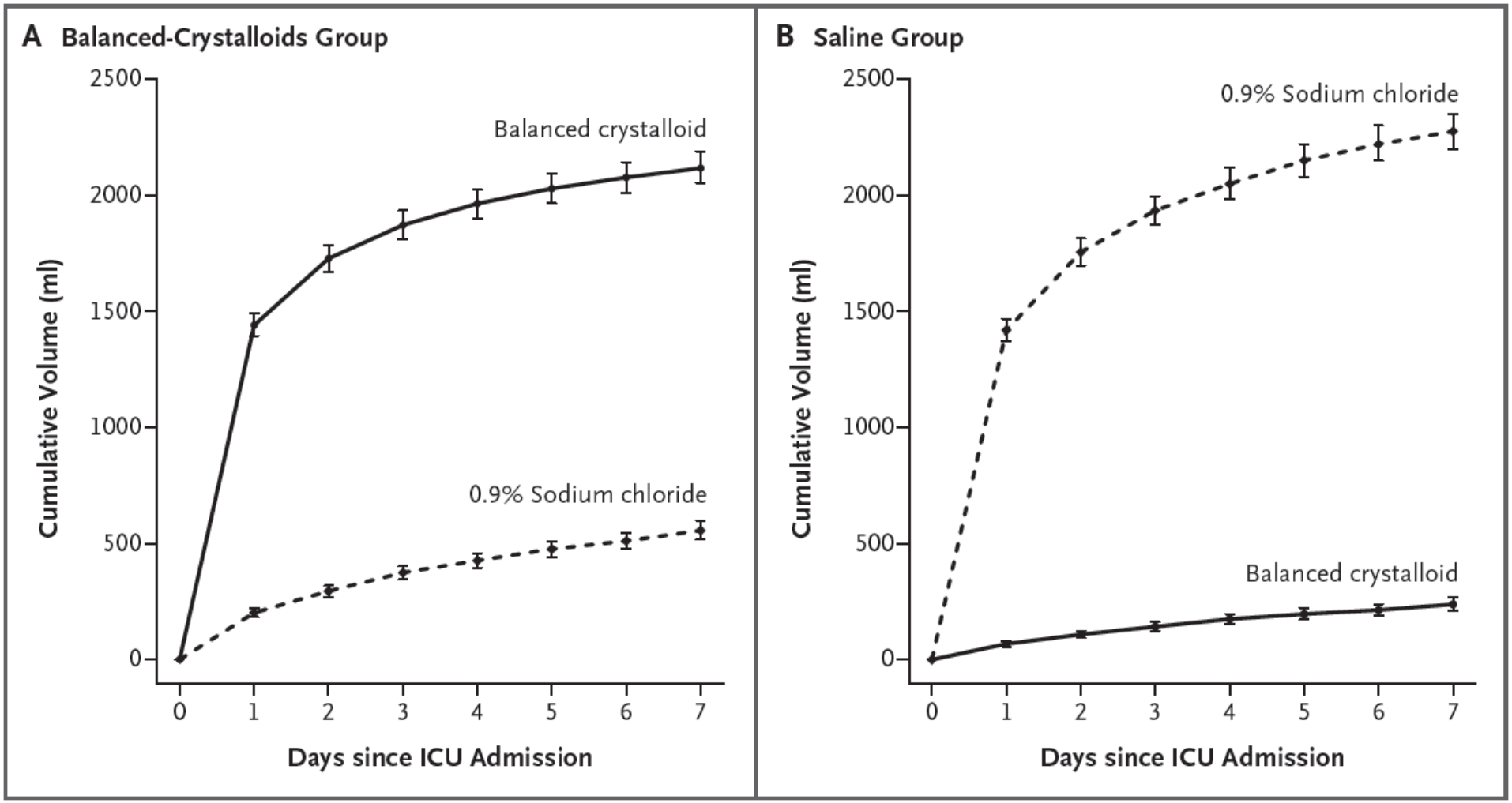


Semler et al. *N Engl J Med.* 2018

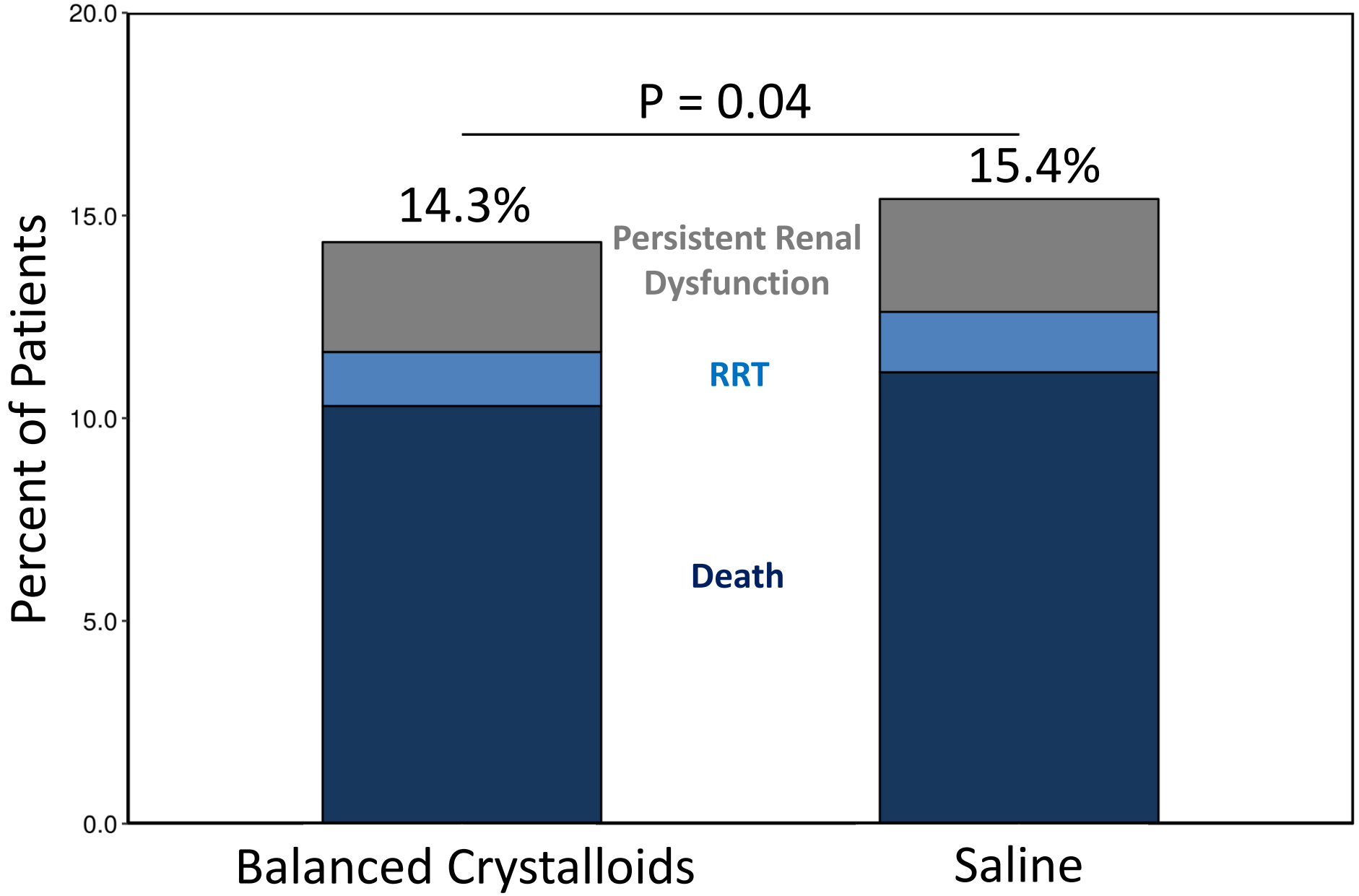
Patient Characteristics	Balanced (n = 7942)	Saline (n = 7860)
Age – years	58 [44 – 69]	58 [44 – 69]
Men	4540 (57.2)	4557 (58.0)
Admitted from ED	3975 (50.1)	3997 (50.9)
Study ICU		
Medical	2735 (34.4)	2646 (33.7)
Trauma	1640 (20.6)	1688 (21.5)
Cardiac	1470 (18.5)	1501 (19.1)
Neurological	1440 (18.1)	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



Balanced crystalloids prevented Major Adverse Kidney Events

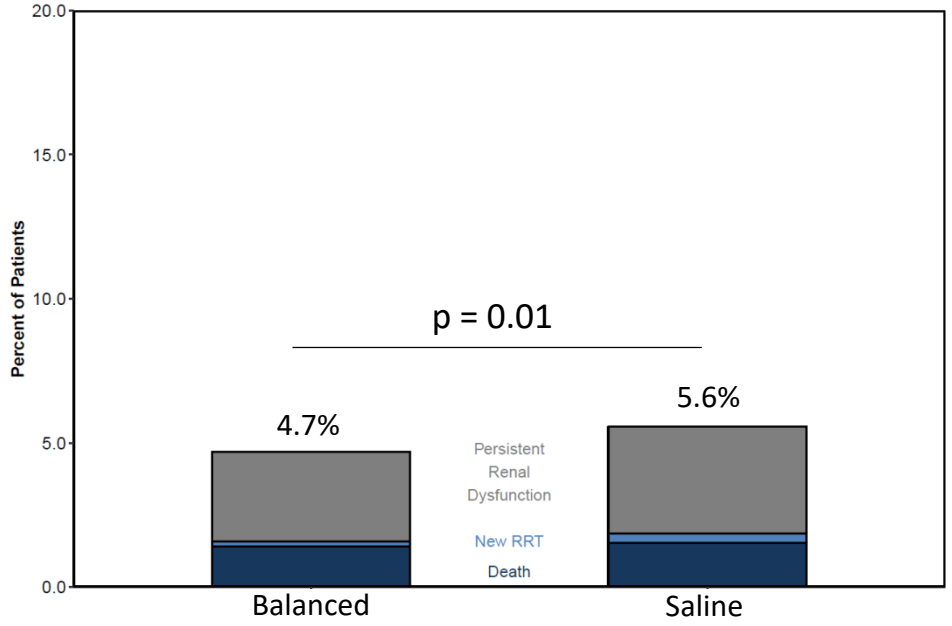


Benefit of balanced crystalloids similar in second trial

The NEW ENGLAND JOURNAL of MEDICINE

Balanced Crystalloids versus Saline in Noncritically Ill Adults

Wesley H. Self, M.D., M.P.H., Matthew W. Semler, M.D., Jonathan P. Wanderer, M.D., Li Wang, M.S., Daniel W. Byrne, M.S., Sean P. Collins, M.D., Corey M. Slovis, M.D., Christopher J. Lindsell, Ph.D., Jesse M. Ehrenfeld, M.D., M.P.H., Edward D. Siew, M.D., Andrew D. Shaw, M.B., Gordon R. Bernard, M.D., and Todd W. Rice, M.D., for the SALT-ED Investigators*



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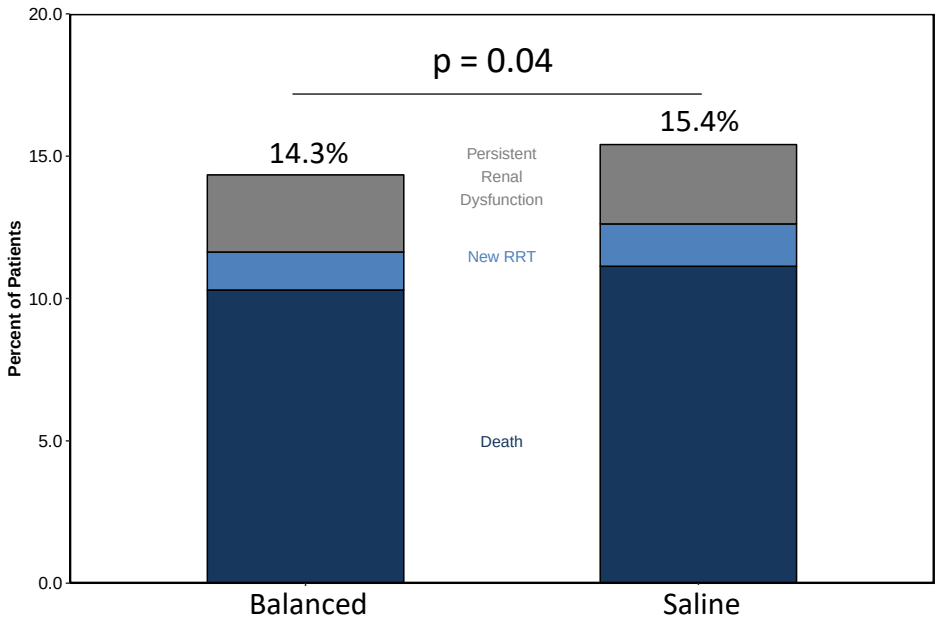
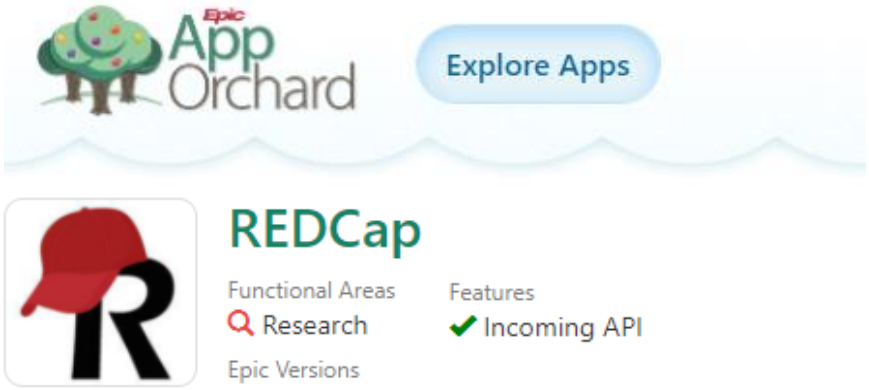


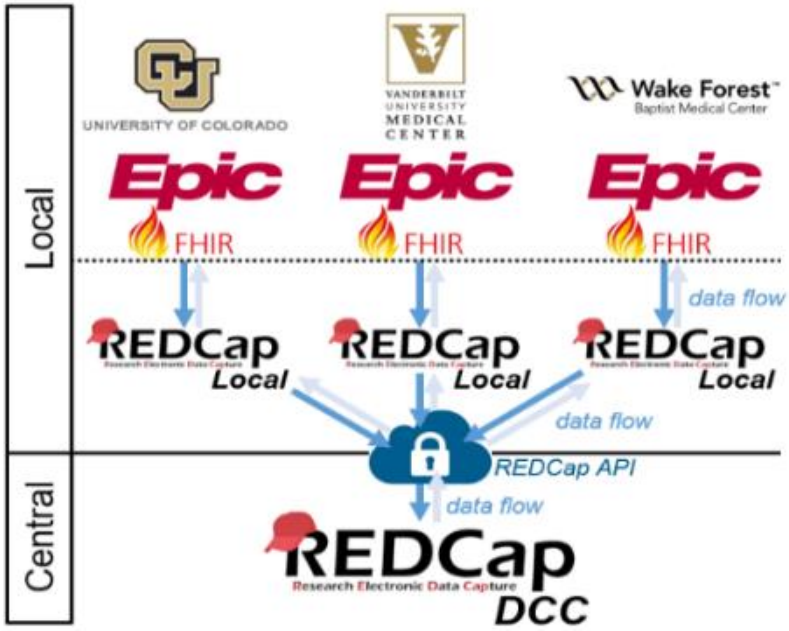
But…

…only at a single center.

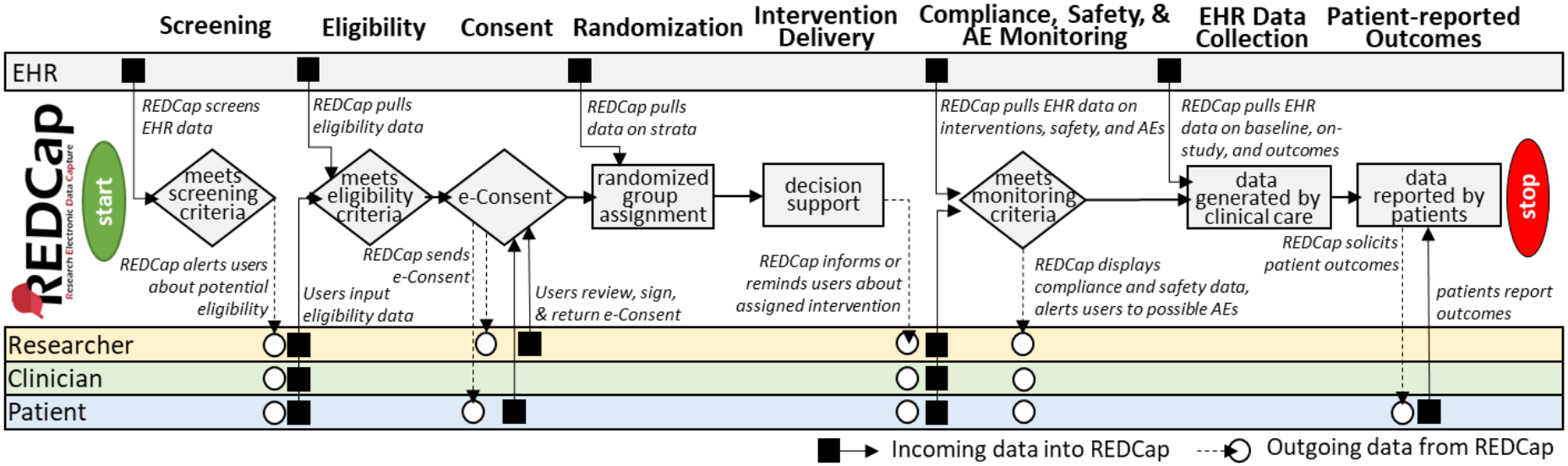
To be transformative, information technology tools must be freely available to [1] connect an EHR directly to a study database and [2] facilitate each step of an RCT, in a single, simple-to-use package, at any center with any EHR.

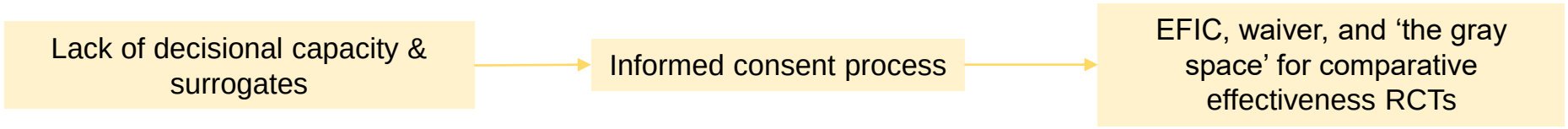
EHR-REDCap Integration





REDCap RCT Toolkit

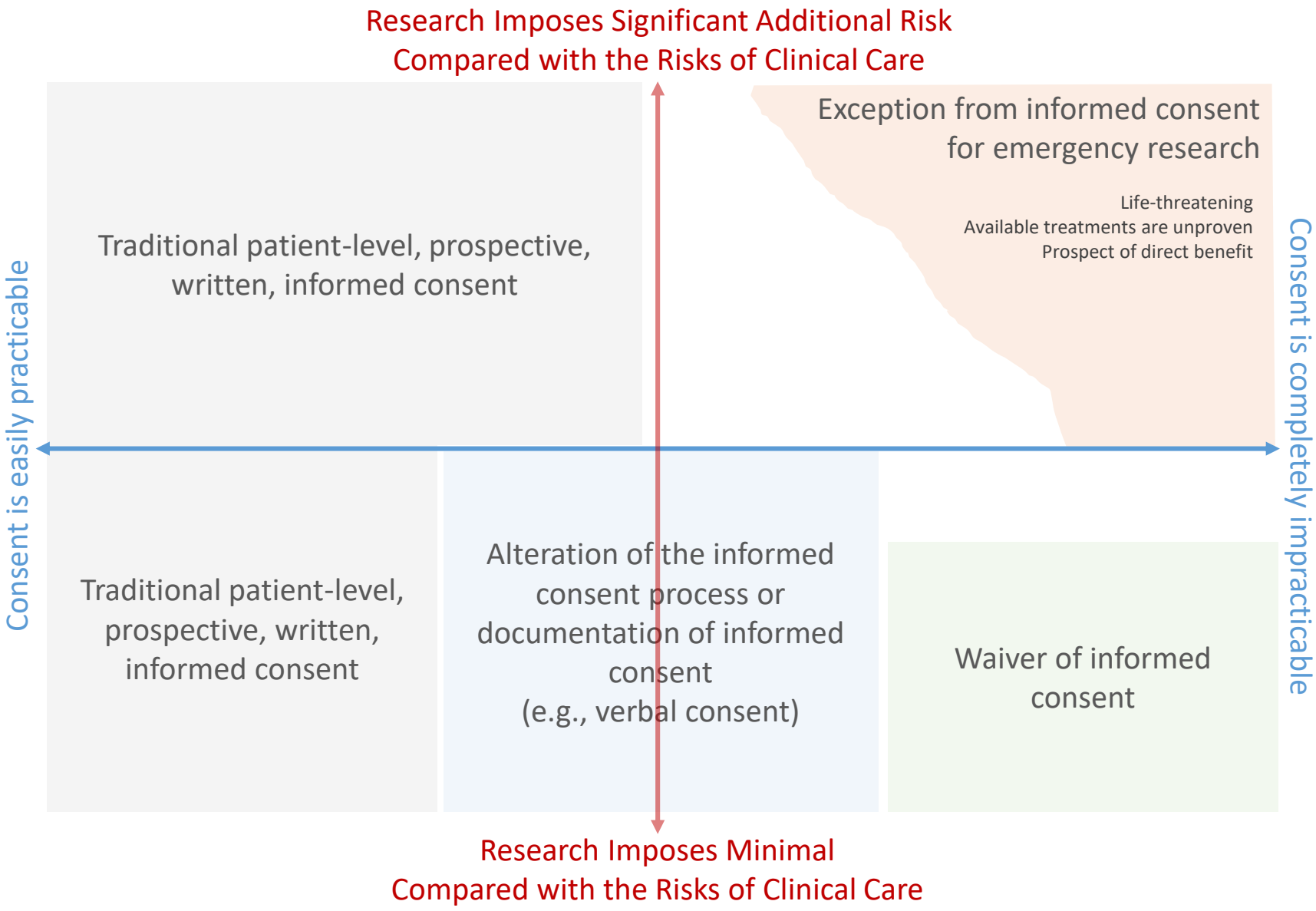




Informed Consent Process

EFIC, Waiver, and the Gray Space for RCTs comparing the effectiveness of emergency procedures when consent is not practicable

Current Regulations for Informed Consent



Exception from Informed Consent (EFIC)

- Implemented in 1996 to allow trials in emergency settings and procedures
- Attempts to demonstrate transparency and "respect for persons" (principle of the *Belmont Report,* 1979) when therapeutic window is too narrow for prospective informed consent

- The condition being studied is **life-threatening**
- Existing treatments are **unproven or unsatisfactory**
- Research involves **more than minimal risk**

Components of EFIC

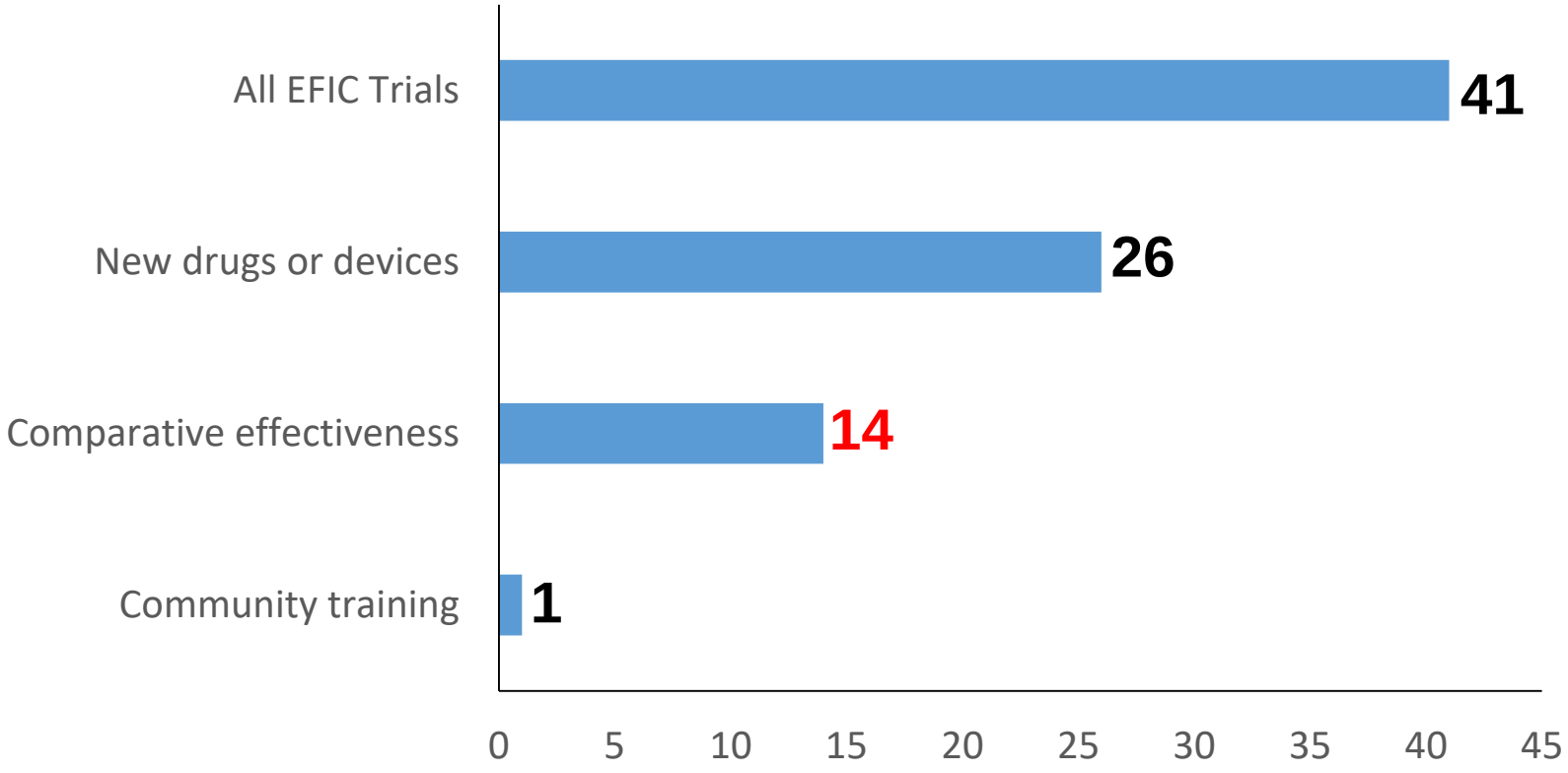
1. Community consultation
    - Two-way communication: town hall meetings, focus groups, one-on-one meetings
    - Provides the opportunity for affected communities to provide meaningful input to the IRB
2. Public disclosure before/after the trial
    - One-way communication: press releases, radio/newspaper/social media advertisements
    - Maximize transparency

Cost and duration of community consultation and public disclosure prior to trial initiation

- 1-3 years
- $50,000 per site

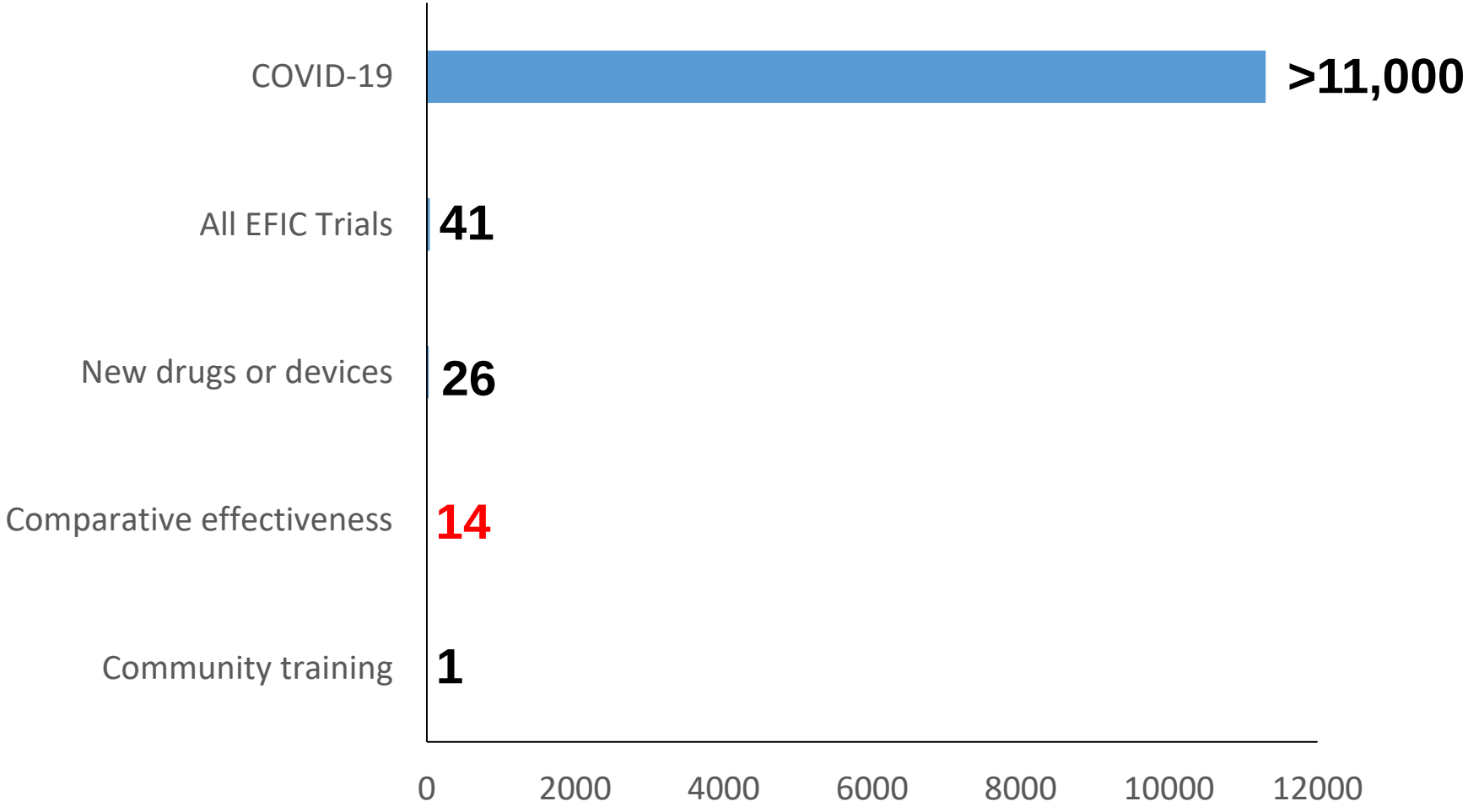
Silbergleit R, et al. Acad Emerg Med. 2012

Total number of RCTs conducted using EFIC over 20 years



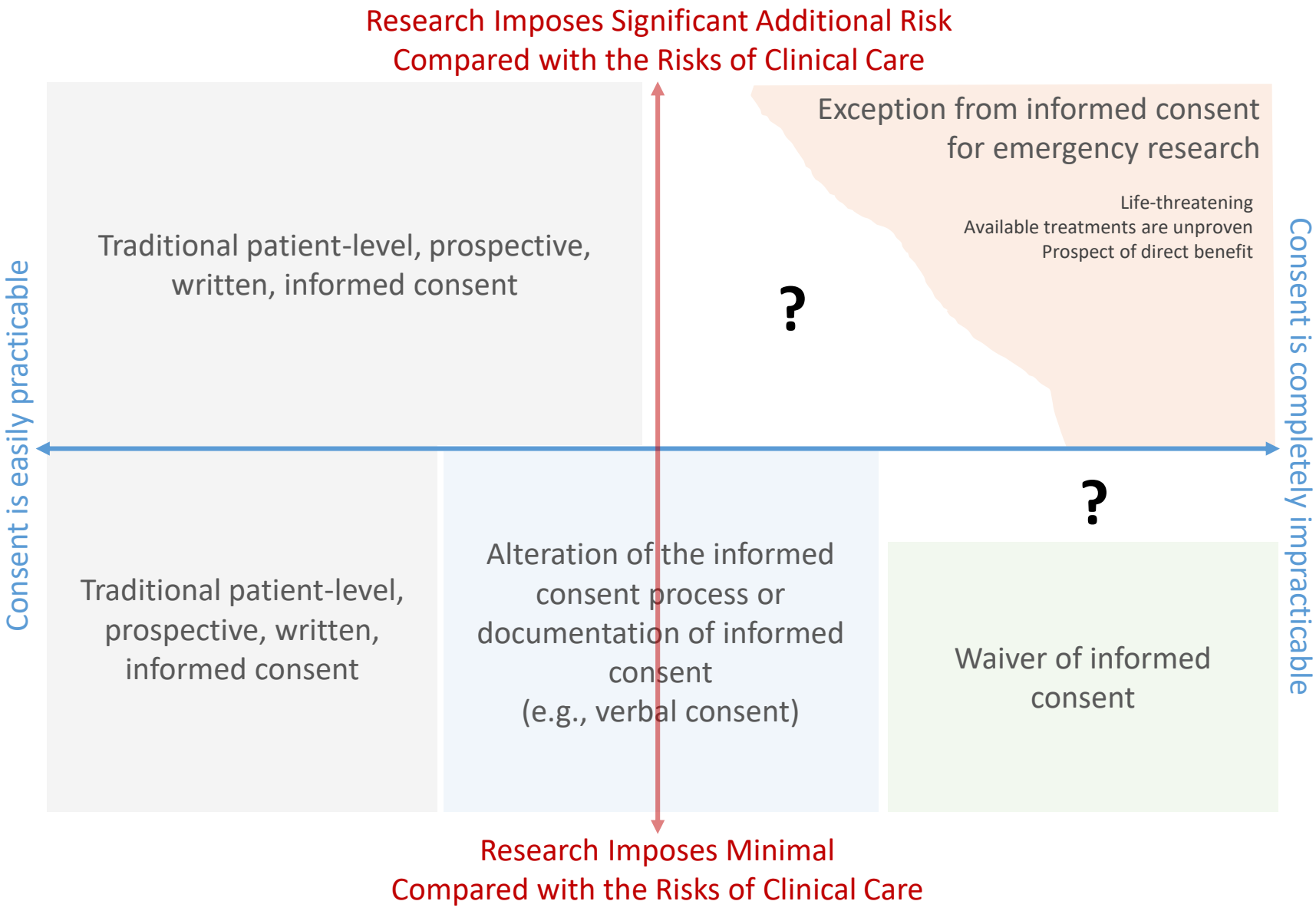
Feldman WB, et al. Health Aff. 2018

Total number of RCTs in COVID-19 over 2 years

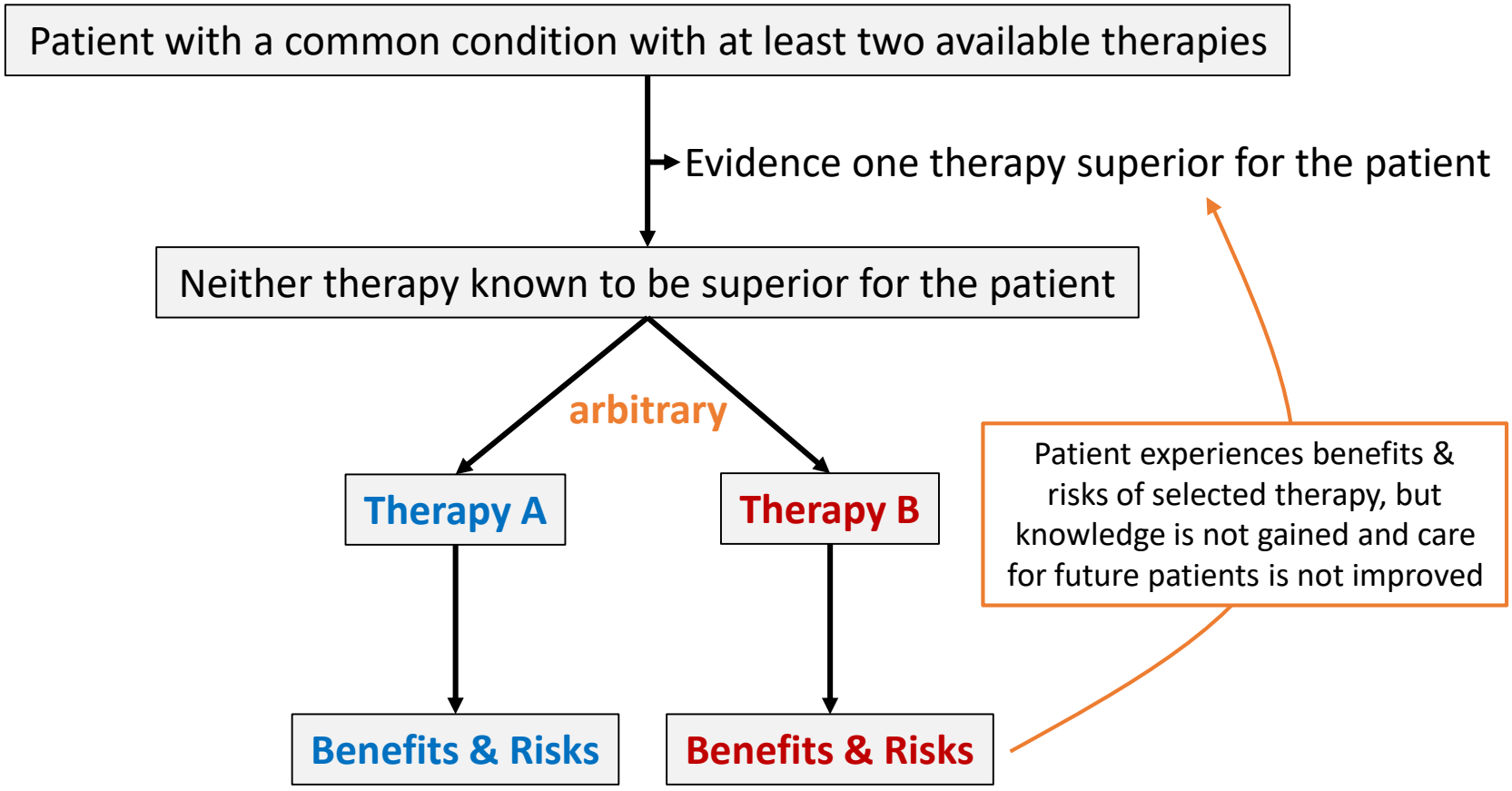


Statistica: Number of COVID-19 clinical trials as of October 25, 2021

Current Regulations for Informed Consent

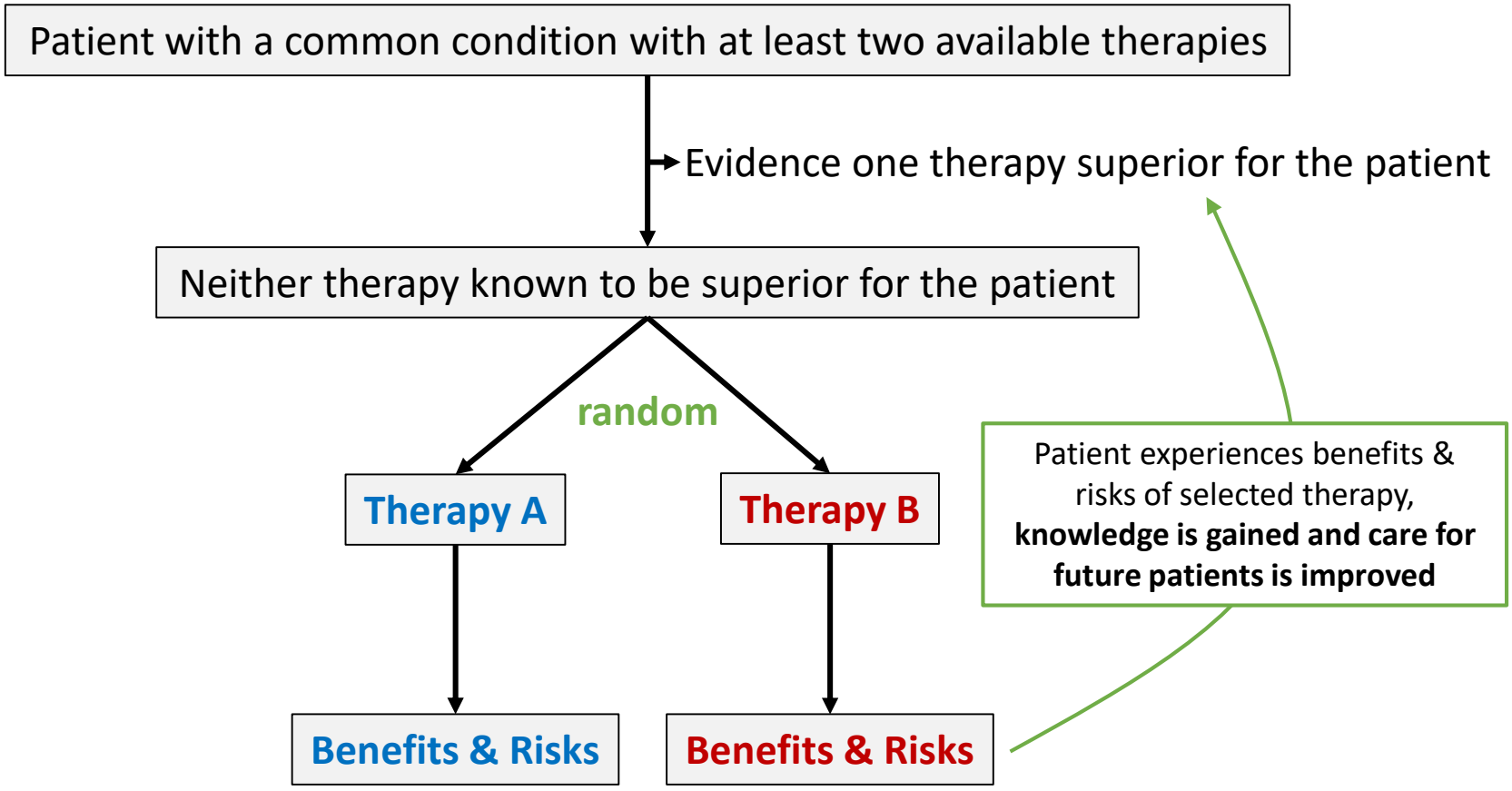


Arbitrary Variation in **Clinical Care**



Arbitrary variation (different clinicians choosing different treatments for the same patient) = Clinical Equipoise

Structured Variation in a **Comparative Effectiveness Trial**



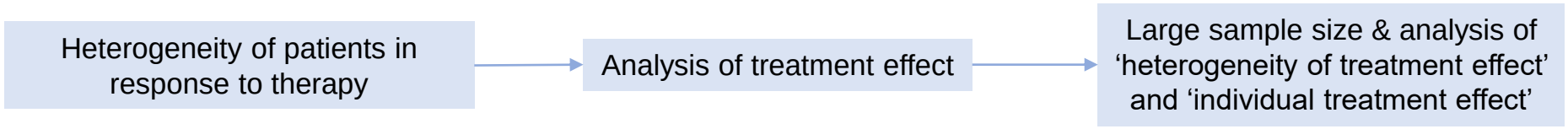
When two interventions are commonly used in clinical care and neither is known to be superior, having the choice between the two made randomly rather than based on the arbitrary preference of the treating clinician may represent **no more than minimal incremental risk**, compared to the risk of routine clinical care

How to conduct RCTs comparing standard-of-care emergency treatments when consent is not practicable?

- **EFIC**
  - No mechanism to conduct RCTs for conditions not immediately life-threatening (e.g., severe agitation, alcohol withdrawal)
  - Better methods to facilitate beneficial, low-risk comparative effectiveness trials while matching the intensity of the Community Consultation and Public Disclosure to the risk of research

- **Waiver of informed consent**
  - How should we define minimal risk?
  - In what circumstances is waiver of consent an appropriate mechanism for comparative effectiveness research?

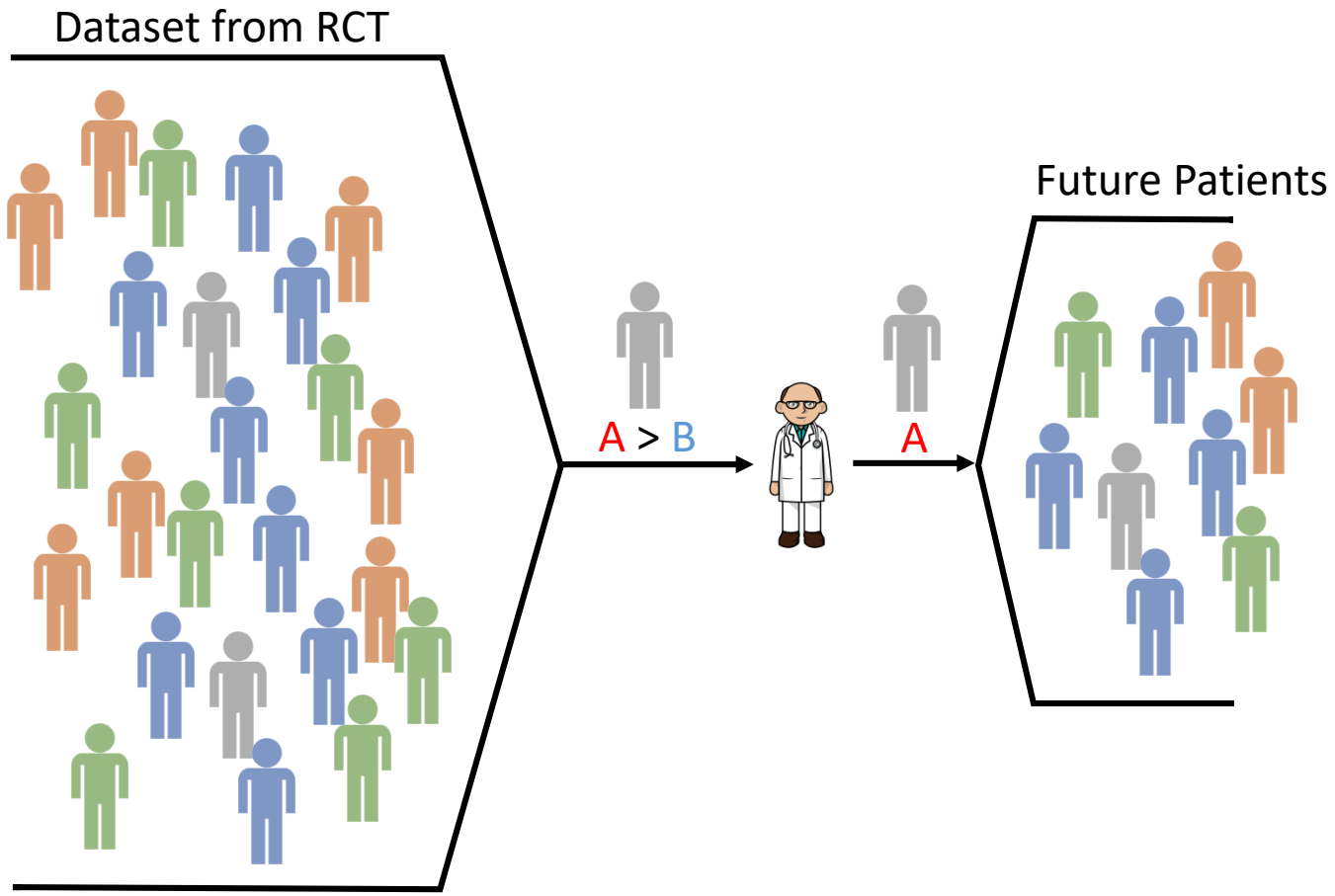
- **Moral imperative to address this barrier**
  - "Insofar as contemporary research ethics and oversight interfere with learning activities that could reduce errors and improve clinical effectiveness, the **overprotection is itself a source of harm to patient's interests**" – Ruth Faden



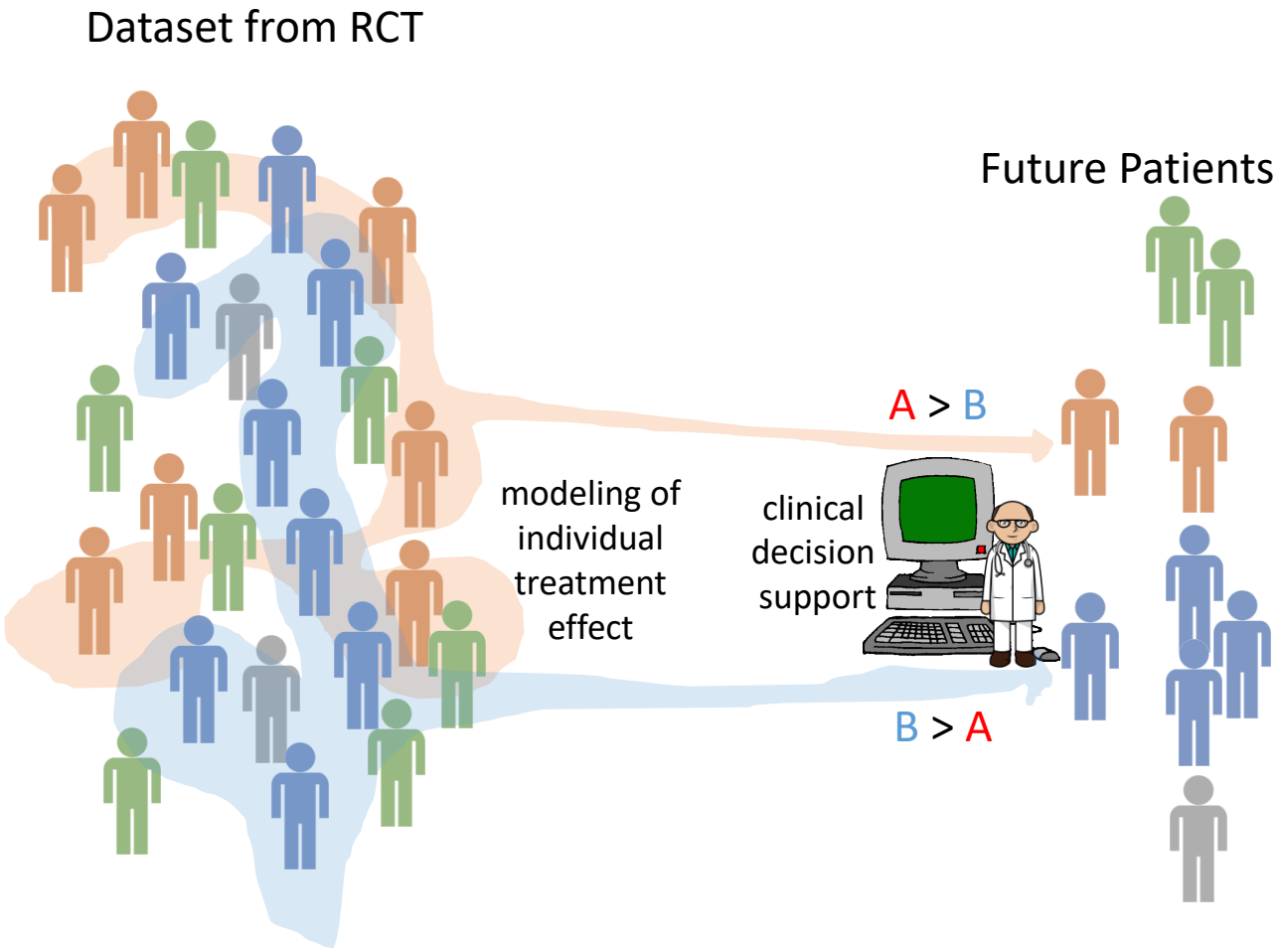
Analysis of Treatment Effect

Analyzing heterogeneity of treatment effect and estimating 'individual treatment effect' in large RCTs

Traditional Implementation of RCT Results



Evidence-based Individual Treatment Effects



Methods for Estimating 'Individual Treatment Effect' in RCTs

Original Investigation | Critical Care Medicine

Assessment of Machine Learning to Estimate the Individual Treatment Effect of Corticosteroids in Septic Shock

Romain Pirracchio, MD, PhD; Alan Hubbard, PhD; Charles L. Sprung, MD; Sylvie Chevret, MD, PhD; Djillali Annane, MD, PhD; for the Rapid Recognition of Corticosteroid Resistant or Sensitive Sepsis (RECORDS) Collaborators

ORIGINAL ARTICLE

Machine Learning Classifier Models Can Identify Acute Respiratory Distress Syndrome Phenotypes Using Readily Available Clinical Data

Pratik Sinha[1,2], Matthew M. Churpek[3], and Carolyn S. Calfee[1,2]

[1]Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, Department of Medicine, and [2]Department of Anesthesia, University of California San Francisco, San Francisco, California; and [3]Department of Medicine, University of Wisconsin, Madison, Madison, Wisconsin

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis

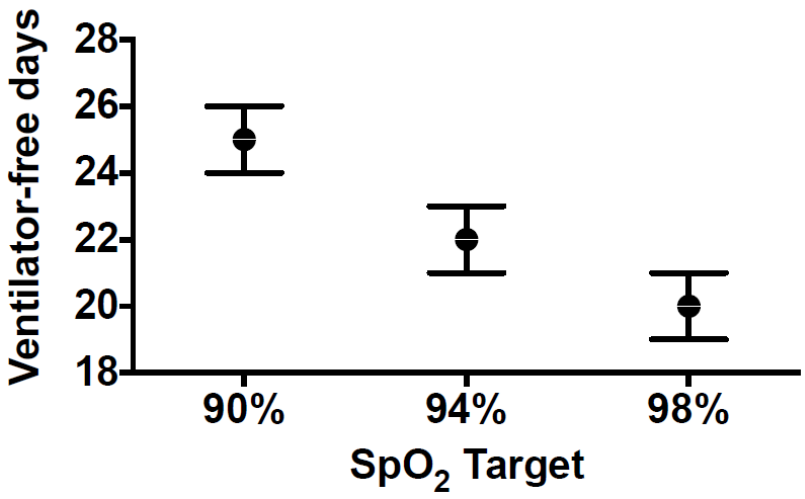
Christopher W. Seymour, MD, MSc; Jason N. Kennedy, MS; Shu Wang, MS; Chung-Chou H. Chang, PhD; Corrine F. Elliott, MS; Zhongying Xu, MS; Scott Berry, PhD; Gilles Clermont, MD, MSc; Gregory Cooper, MD, PhD; Hernando Gomez, MD, MPH; David T. Huang, MD, MPH; John A. Kellum, MD, FACP, MCCM; Qi Mi, PhD; Steven M. Opal, MD; Victor Talisa, MS; Tom van der Poll, MD, PhD; Shyam Visweswaran, MD, PhD; Yoram Vodovotz, PhD; Jeremy C. Weiss, MD, PhD; Donald M. Yealy, MD, FACEP; Sachin Yende, MD, MS; Derek C. Angus, MD, MPH

Clinical decision support tool for estimating individual treatment effects using data form an RCT of SpO_2 targets.

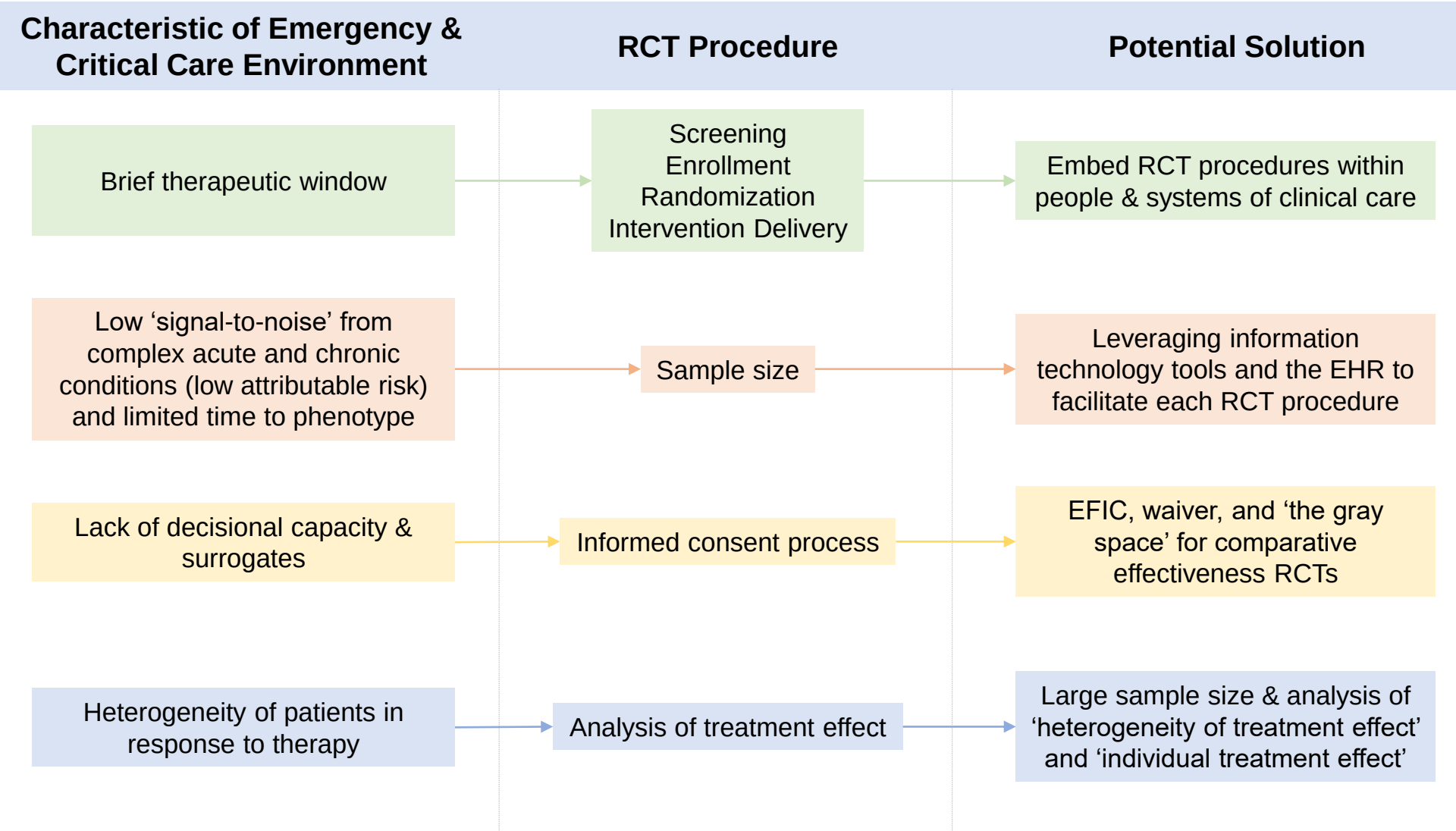
Age (years)	18 — 99 reset
Home supplemental oxygen?	Yes / No reset
COPD	Yes / No reset
NYHA stage of CHF	I / II / III / IV
Coronary artery disease	Yes / No reset
Cardiac arrest	Yes / No reset
Myocardial infarction	Yes / No reset
ARDS	Yes / No reset
Pneumonia	Yes / No reset
Sepsis	Yes / No reset
Ischemic stroke	Yes / No reset
Status epilepticus	Yes / No reset
Acute kidney injury	Yes / No reset
SOFA score	0 — 24
Static compliance (VT/Pplat - PEEPtotal)	0 — 150 reset
PaO2 to FiO2 ratio	0 — 600 reset
Hemoglobin (g/dL)	11
Serum bicarbonate (mmol/L)	17
Serum albumin (g/dL)	2.9

How PILOT Trial results apply to your patient:

For this patient, an SpO_2 target of 90% is predicted to produce more ventilator-free days than an SpO_2 target of 94% or 98%.



Summary


Characteristic of Emergency & Critical Care Environment
RCT Procedure
Potential Solution
Brief therapeutic window
Screening
Enrollment
Randomization
Intervention Delivery
Embed RCT procedures within people & systems of clinical care
Low ‘signal-to-noise’ from complex acute and chronic conditions (low attributable risk) and limited time to phenotype
Sample size
Leveraging information technology tools and the EHR to facilitate each RCT procedure
Lack of decisional capacity & surrogates
Informed consent process
EFIC, waiver, and ‘the gray space’ for comparative effectiveness RCTs
Heterogeneity of patients in response to therapy
Analysis of treatment effect
Large sample size & analysis of ‘heterogeneity of treatment effect’ and ‘individual treatment effect’

Thank you to those supporting our career development and research.

Trial	Topic	N	Status	Funding Support
Chlorhexidine	Infection Control	9,340	Published (JAMA)	--
SMART	IVF	15,802	Published (NEJM)	*NHLBI T32*
SALT-ED	IVF	13,347	Published (NEJM)	*NHLBI T32*
SALT	IVF	974	Published (AJRCCM)	*NHLBI T32*
FELLOW-AO	Intubation	150	Published (AJRCCM)	*NHLBI T32*
FELLOW-VL	Intubation	150	Published (CCM)	*NHLBI T32*
CHECK-UP checklist	Intubation	262	Published (Chest)	*NHLBI T32*
CHECK-UP ramped	Intubation	260	Published (Chest)	*NHLBI T32*
PREPARE	Intubation	337	Published (LRM)	*Trans-NIH K12 Emergency Care*
PreVent	Intubation	401	Published (NEJM)	*NHLBI T32*
PROPER	Post-Extubation	751	Published (AJRCCM)	*NHLBI T32*
BASE	IVF	2,093	Complete	*Trans-NIH K12 Emergency Care*
BOUGIE	Intubation	1,106	Complete	*Trans-NIH K12 Emergency Care*
PREPARE2	Intubation	1,065	Complete	*Trans-NIH K12 Emergency Care*
PILOT	Oxygen Targets	2,541	Complete	**NHLBI K23 (Semler)**
ACORN	Antibiotic choice	2,000	Enrolling	*NHLBI T32*
RSI	Intubation	1,900	In Start-up	**NHLBI K23 (Casey)**
PREOXI	Intubation	1,300	Funded	**Dept. of Defense**
DEVICE	Intubation	2,000	Funded	**Dept. of Defense**
TOTAL - 19 RCTs		**55,779**		

Thank you.

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