Embedding Pragmatic Trials Within Emergency and Critical Care

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Overview

- **Part 1 – Me convincing you to do pragmatic trials**
  - What qualifies me to talk about pragmatic trials?
  - What does “pragmatic trial” even mean, really?
  - Why do a pragmatic trial?

- **Part 2 – Now convinced, key aspects of conducting a pragmatic trial**
  - What questions are a good fit for a pragmatic trial?
  - What are the key tools for pragmatic trials in emergency and critical care?
  - How to deal with grant reviewer #2

What qualifies me to talk about pragmatic trials?

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PREVENTION | TREATMENT | RECOVERY

NECTAR
Novel Experimental COVID Therapies Affecting Host Response

Insight
STRIVE
ACTIV INSIGHT018

JAMA | Original Investigation
Renin-Angiotensin System Modulation With Synthetic Angiotensin (1-7) and Angiotensin II Type 1 Receptor–Biased Ligand in Adults With COVID-19
Two Randomized Clinical Trials

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT
Effect of Vitamin C, Thiamine, and Hydrocortisone on Ventilator- and Vasopressor-Free Days in Patients With Sepsis
The VICTAS Randomized Clinical Trial

NHLBI ARDS Network

PETAL NETWORK
Prevention & Early Treatment of Acute Lung Injury

ORIGINAL ARTICLE
Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension
The National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network*

ORIGINAL ARTICLE
Early High-Dose Vitamin D_3 for Critically Ill, Vitamin D–Deficient Patients

ORIGINAL ARTICLE
Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome
The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network*

JAMA | Original Investigation
Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19
A Randomized Clinical Trial

PRAGMATIC CRITICAL CARE RESEARCH GROUP

ORIGINAL ARTICLE
Balanced Crystalloids versus Saline in Noncritically Ill Adults

ORIGINAL ARTICLE
Oxygen-Saturation Targets for Critically Ill Adults Receiving Mechanical Ventilation

ORIGINAL ARTICLE
Video versus Direct Laryngoscopy for Tracheal Intubation of Critically Ill Adults

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT
Individualized Treatment Effects of Oxygen Targets in Mechanically Ventilated Critically Ill Adults

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT
Effect of Use of a Bougie vs Endotracheal Tube With Stylet on Successful Intubation on the First Attempt Among Critically Ill Patients Undergoing Tracheal Intubation
A Randomized Clinical Trial

ORIGINAL ARTICLE
Balanced Crystalloids versus Saline in Critically Ill Adults

ORIGINAL ARTICLE
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Bag-Mask Ventilation during Tracheal Intubation of Critically Ill Adults

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Cefepime vs Piperacillin-Tazobactam in Adults Hospitalized With Acute Infection
The ACORN Randomized Clinical Trial

JAMA | Original Investigation
Effect of Fluid Bolus Administration on Cardiovascular Collapse Among Critically Ill Patients Undergoing Tracheal Intubation
A Randomized Clinical Trial

EXPLANATORY ⟷ **PRAGMATIC**

What does a “pragmatic trial” even mean, really?

- Is pragmatic a dirty word?
- What is does NOT mean:
  - Less rigorous
  - Making design choices because they make life easier *for the trialist*
  - Evaluating only nudges, decision support, or other implementation interventions
  - Poor separation between groups
  - Poor data on the delivery of the intervention
  - Lack of granularity in the outcome
  - Loss to follow up in outcome assessment
  - Analysis using methods that don’t account for biases
  - Imbalance in importance covariates or cointerventions

Password to the PCCRG website since 2014 = “Pragmatic_does_not_mean_crappy”

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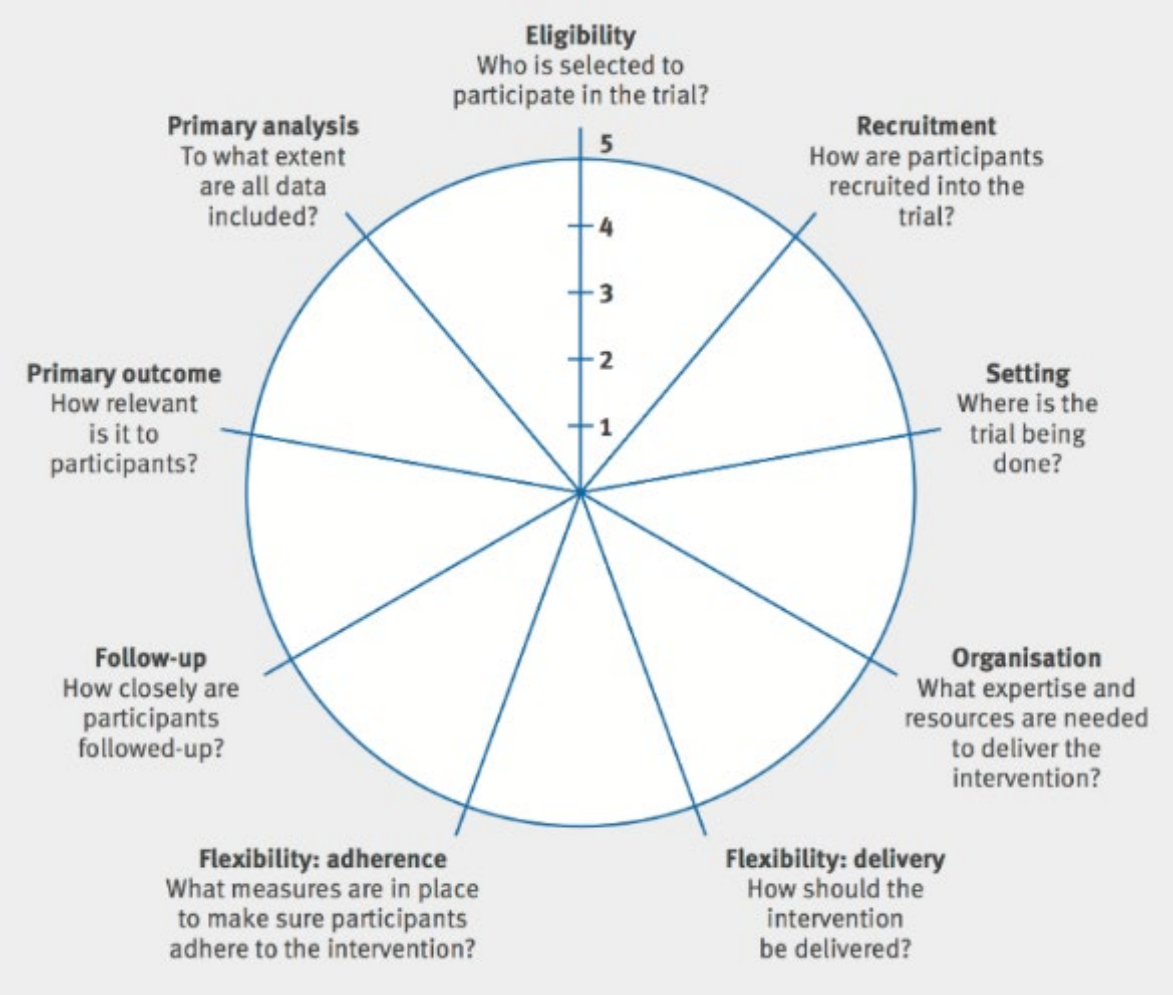
What does “pragmatic trial” even mean, really?

NIH Collaboratory defines a pragmatic clinical trial as a study that takes place in real-world healthcare settings to evaluate the benefits and risks of treatment options. The goal of a PCT is to provide evidence that can be applied to real-world practice and inform policy.

	What is the purpose?	What question does it answer?	Who is enrolled?	Who collects data?	What is studied?	What is compared?	What is the setting?	Adherence to the intervention	Outcomes
Explanatory Trial	Create generalizable knowledge; determine causes and effects	Can this intervention work under ideal conditions?	Selected patients who meet strict inclusion and exclusion criteria	Researchers; data collection occurs outside of clinical care	A biological or mechanistic hypotheses	Treatment vs placebo or non-treatment	Medical centers designated as research sites	Strictly enforced	May be surrogates or process measures
Pragmatic Trial	Create generalizable knowledge, improve care locally, and inform clinical and policy decisions	Does this intervention work under usual conditions?	Diverse, representative populations who meet broad eligibility criteria	Clinicians at the point of care; EHRs; registries	The comparative balance of benefits, burdens and risks of an intervention	The comparative effectiveness of real-world alternatives	Multiple, heterogeneous settings	Flexible (as it would be in usual care)	Directly relevant to participants, funders, communities, and healthcare practitioners

What does a “pragmatic trial” even mean, really?

No trial is “pragmatic” or “explanatory” –
In every trial, investigators must choose where each trial procedure should lie on the spectrum.



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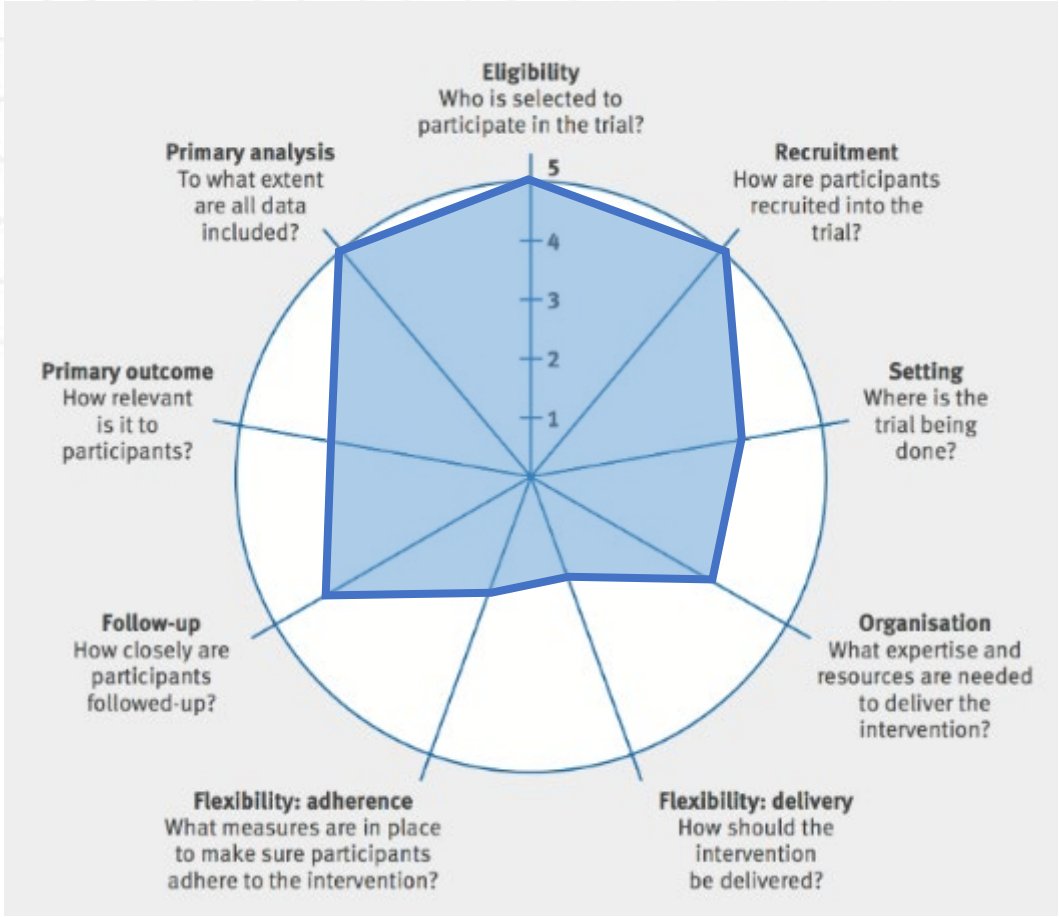
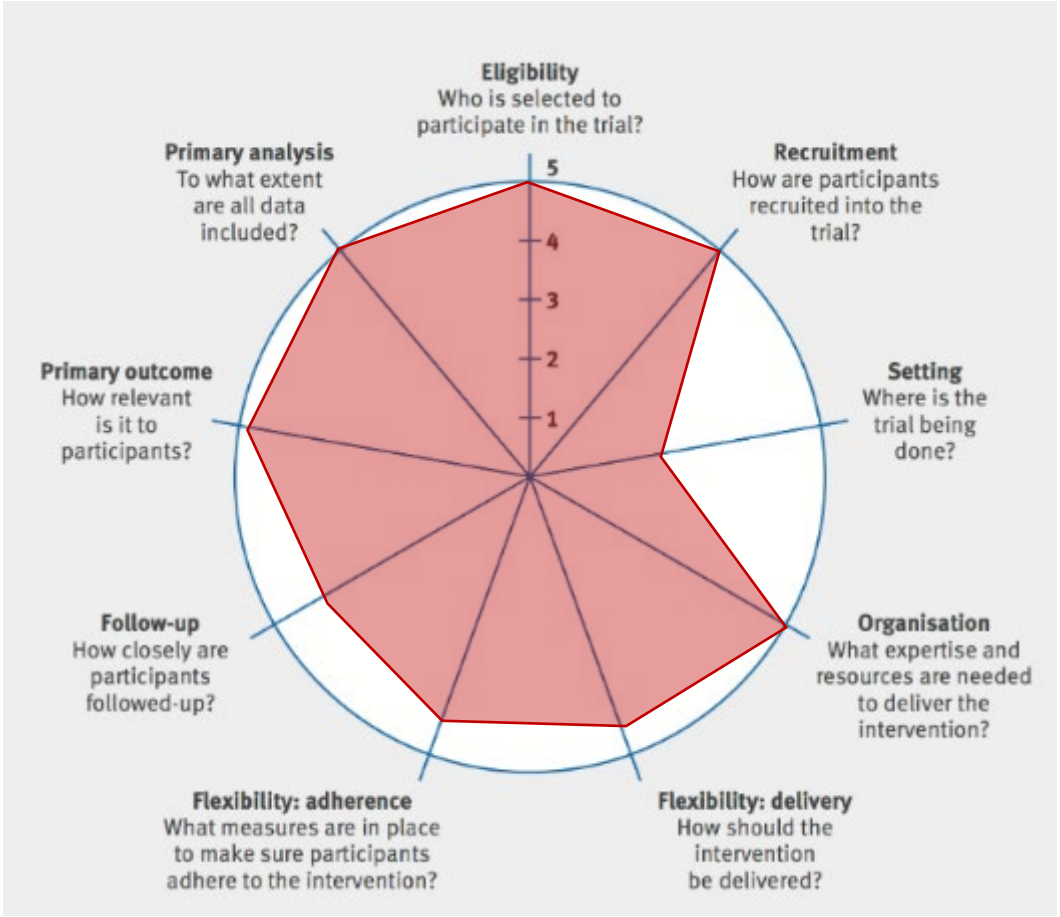
https://www.precis-2.org/

What does a “pragmatic trial” even mean, really?

PREOXI Trial



SMART Trial



https://www.precis-2.org/

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Why do a pragmatic trial?

Sometimes a pragmatic trial may be:

- “Better”
- “More efficient”

"**Better**" – Patients represent full diversity of clinical care

ORIGINAL ARTICLE

Comparison of Two Fluid-Man
Strategies in Acute Lung In

11,512 Patients screened

91%

10,511 Excluded
21% Had a pulm
artery cathe
16% Had their p
refuse
14% Had chroni
disease
11% Had high ri
within 6 mo
9% Required di
8% Exceeded ti
8% Had chroni
disease
6% Had acute
infarction
6% Were unabl
consent
4% Declined to
consent
4% Were not c
to full supp
3% Had neuro
disease

1001 Underwent randomization

9% included

Study	Trial Demographics Black	Trial Demographics Non-Black	City Demographics Black	City Demographics Non-Black	RD with 95% CI	Weight (%)
Billings 2016	26	589	166,549	436,889	-0.23 [-0.25, -0.22]	4.89
Casey 2019	108	290	1,048,575	2,782,077	-0.00 [-0.05, 0.04]	4.75
Curtis 2016	12	217	105,749	1,342,861	-0.02 [-0.05, 0.01]	4.84
Delorme 2017	0	12	14,102	691,001	-0.02 [-0.02, -0.02]	4.91
Festic 2017	3	79	515,488	1,771,974	-0.19 [-0.23, -0.15]	4.77
Girard 2019	76	491	4,285,875	9,026,116	-0.19 [-0.22, -0.16]	4.84
Heyland 2020	2	153	1,259,367	17,925,156	-0.05 [-0.07, -0.03]	4.88
Jaiswal 2019	11	109	91,739	1,332,112	0.03 [-0.02, 0.08]	4.69
Janz 2016	19	130	166,549	436,889	-0.15 [-0.20, -0.09]	4.67
Janz 2018	72	219	901,808	2,204,539	-0.04 [-0.09, 0.01]	4.70
Janz 2019	75	259	2,255,348	9,913,752	0.04 [-0.01, 0.08]	4.74
Limaye 2017	17	143	1,496,934	4,544,802	-0.14 [-0.19, -0.09]	4.72
Moss 2016	9	111	195,188	1,483,453	-0.04 [-0.09, 0.01]	4.72
Schell-Chaple 2017	2	39	49,367	832,182	-0.01 [-0.07, 0.06]	4.56
Semler 2016	19	130	166,549	436,889	-0.15 [-0.20, -0.09]	4.67
Semler 2017	72	219	908,047	2,264,110	-0.04 [-0.09, 0.01]	4.70
Semler 2018	2,165	13,637	183,195	480,555	-0.14 [-0.14, -0.13]	4.91
Sims 2019	82	18	694,454	889,610	0.38 [0.31, 0.46]	4.46
Skrobik 2018	1	99	355,804	2,108,575	-0.13 [-0.15, -0.11]	4.88
STARRT-AKI 2020	27	967	1,410,655	19,921,926	-0.04 [-0.05, -0.03]	4.90
Swan 2016	42	283	524,381	1,795,887	-0.10 [-0.13, -0.06]	4.80
Overall					-0.06 [-0.11, -0.01]	

Heterogeneity: $\tau^2 = 0.01$, $I^2 = 99.71\%$, $H^2 = 339.77$
Test of $\theta_i = \theta_j$: Q(20) = 3066.49, p = 0.00
Test of $\theta = 0$: z = -2.27, p = 0.02

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Youmbi, CJA 2023

oscopy for
lly Ill Adults

criteria
routinely perform intubation in the

was not orotracheal intubation
as not video or direct laryngoscope

27% excluded

exclusion criterion
intubation too urgently to complete trial
es
ngoscope or direct laryngoscope required
leo laryngoscope required*
ect laryngoscope required†
oners
than 18 years old
nant
not enrolled
ng clinician decline enrollment
sonnel error
fied
udy personnel available
udy materials available
surrogates declined enrollment

NIH

1,420 Patients underwent randomization

73% included

"**Better**" – Delivery of intervention mirrors clinical care

Video laryngoscopy vs. direct laryngoscopy: Which should be chosen for endotracheal intubation during cardiopulmonary resuscitation? A prospective randomized controlled study of experienced intubators

Randomized trial of 140 patients at 1 ED
Unit of randomization: intubating clinician
Total of **7 expert clinicians in each group**

VS

ORIGINAL ARTICLE

Video versus Direct Laryngoscopy for Tracheal Intubation of Critically Ill Adults

Randomized trial of 1,417 patients in 17 ED/ICU
Unit of randomization: patient
Total of **~400 unique clinicians**

Characteristic	Video Laryngoscope (N=705)	Direct Laryngoscope (N=712)
Operator*		
Clinical specialty — no. (%)		
Emergency medicine	496 (70.4)	497 (69.8)
Critical care medicine	177 (25.1)	182 (25.6)
Anesthesiology	18 (2.6)	25 (3.5)
Other†	14 (2.0)	8 (1.1)
Level of training — no. (%)		
Resident physician	513 (72.8)	502 (70.5)
Fellow physician	164 (23.3)	173 (24.3)
Attending physician	9 (1.3)	18 (2.5)
Other clinician‡	19 (2.7)	19 (2.7)
Median no. of previous intubations performed (IQR)	50 (25–90)	50 (26–99)

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“More efficient”

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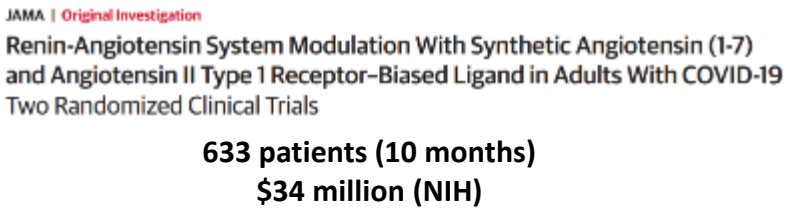
NECTAR
Novel Experimental COVID Therapies Affecting Host Response

1 RCT enrolled 633 patients at direct cost of $34 million


JAMA | Original Investigation

Renin-Angiotensin System Modulation With Synthetic Angiotensin (1-7) and Angiotensin II Type 1 Receptor–Biased Ligand in Adults With COVID-19
Two Randomized Clinical Trials

633 patients (10 months)
$34 million (NIH)

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9 RCTs enrolled ~40,000 patients at total cost of $3.7 million


ORIGINAL ARTICLE

Video versus Direct Laryngoscopy for Tracheal Intubation of Critically Ill Adults

1,417 patients (8 months)
$1.8 million (DoD)


ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Critically Ill Adults

15,802 patients (22 months)
UNFUNDED


ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Noncritically Ill Adults

13,347 patients (16 months)
UNFUNDED


ORIGINAL ARTICLE

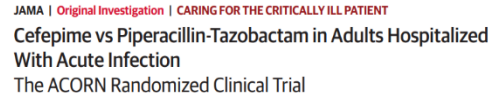
Noninvasive Ventilation for Preoxygenation during Emergency Intubation

1,301 patients (19 months)
$1.6 million (DoD)


ORIGINAL ARTICLE

Bag-Mask Ventilation during Tracheal Intubation of Critically Ill Adults

401 patients (14 months)
UNFUNDED


JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Cefepime vs Piperacillin-Tazobactam in Adults Hospitalized With Acute Infection
The ACORN Randomized Clinical Trial

2,511 patients (11 months)
UNFUNDED


ORIGINAL ARTICLE

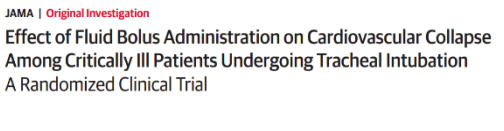
Oxygen-Saturation Targets for Critically Ill Adults Receiving Mechanical Ventilation

2,541 patients (36 months)
$50,000 per year (NIH K23)


JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Use of a Bougie vs Endotracheal Tube With Stylet on Successful Intubation on the First Attempt Among Critically Ill Patients Undergoing Tracheal Intubation
A Randomized Clinical Trial

1,106 patients (21 months)
UNFUNDED


JAMA | Original Investigation

Effect of Fluid Bolus Administration on Cardiovascular Collapse Among Critically Ill Patients Undergoing Tracheal Intubation
A Randomized Clinical Trial

1,067 patients (25 months)
UNFUNDED

EXPLANATORY ⟷ **PRAGMATIC**

"More efficient" – why is it important for patients that our trials be more efficient?

Treatments administered to millions of critically ill patients each year in routine clinical care that would never have been examined in an explanatory randomized trial.

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

bougie vs stylet

vasopressor vs none

ramped vs sniffing position

Traditional explanatory trials focus on new drugs and devices and neglect the comparison of existing therapies that patients are exposed to in care – "a profound moral problem"

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Part 2

Now that you're completely convinced to do pragmatic trials, what are some key aspects of designing and conducting a pragmatic trial?

#1 What questions are a good fit for pragmatic trials?

- **Trials comparing the effectiveness of existing treatment alternatives (A vs B designs)**
- **Trials evaluating a new approach to care delivery (A vs A+ design)**
- **NOT trials evaluating a new drug or device (A vs placebo design)**

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

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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

bougie vs stylet

vasopressor vs none

ramped vs sniffing position

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#2 What are some key tools for a pragmatic trial?

Characteristic of Emergency & Critical Care Environment	RCT Procedure	Tool for Pragmatic Trial
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’

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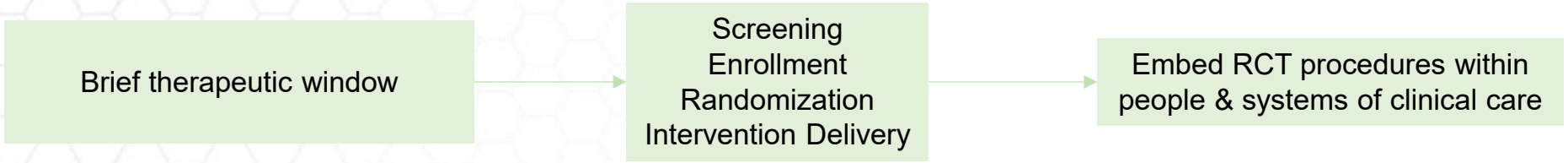

Embedding Screening, Enrollment, Randomization, and Delivery of the Intervention in an RCT within the People and Systems of Clinical Care

Or ‘how to do trials when trial personnel cannot be present’

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
- Median **5 min** from decision-to-intubate to procedure

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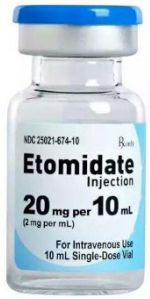
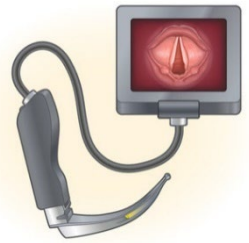
Decisions a clinician must make during every emergency tracheal intubation

or



or

or



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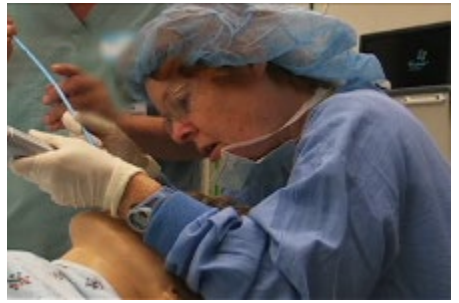

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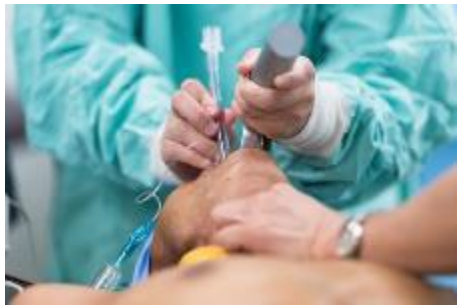

5 million emergency tracheal intubations each year in US.

0 randomized trials to inform best approach to emergency tracheal intubation.

PREO2XI

PRagmatic trial Examining OXygenation prior to Intubation

- Multicenter, parallel-group, randomized trial
- 24 EDs and ICUs across the US
- Eligibility Criteria
  - Inclusion
    1. Undergoing tracheal intubation in a participating unit using a laryngoscope and sedation
  - Exclusion
    1. Patient is <18 years old, pregnant, or a prisoner
    2. Patients is already receiving positive pressure ventilation
    3. Immediate need for tracheal intubation precludes safe performance of study procedures
    4. Clinician has determined that preoxygenation with non-invasive positive pressure ventilation or preoxygenation with a facemask is required or contraindicated for optimal care of the patient

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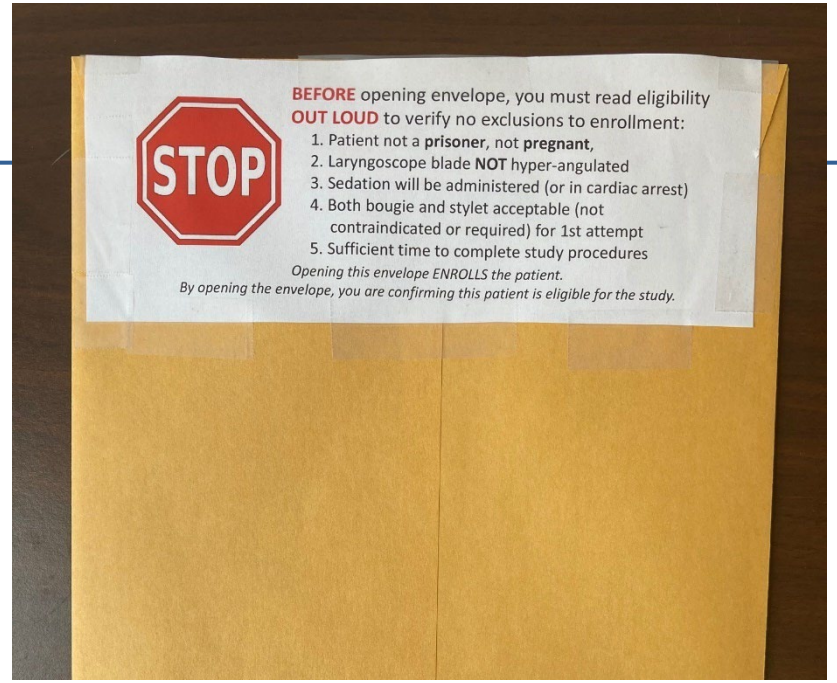
BOUGIE Trial
VS
Before opening this envelope to enroll, record the device you plan to use:
Direct laryngoscope
Video laryngoscope
TRAUMA BAY 3
1453
CLEAN/STOCK
ECOLAB

STOP

BEFORE opening envelope, read OUT LOUD these criteria.
All must be met to open envelope and enroll:

1. Patient **NOT a child (age <18), pregnant, a prisoner, or in custody of law enforcement**
2. Primary presenting diagnosis to ED is **NOT "trauma"**
3. Patient not wearing an "RSI Opt-Out" bracelet
4. Either ketamine or etomidate would be acceptable

Opening this envelope ENROLLS the patient. By writing name/date on collection sheet, operator certifies patient eligibility



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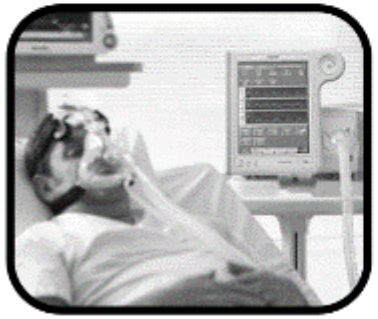
PREO_2XI

PRagmatic trial Examining OXygenation prior to Intubation

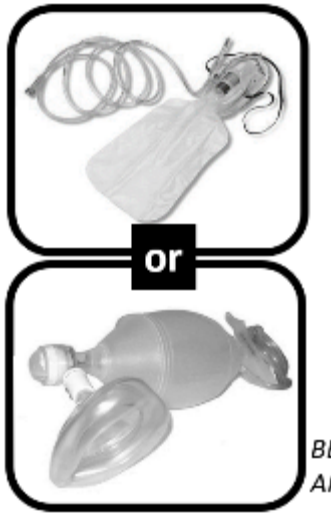
- Clinician perform , Criteria)
- Clinician opens envelope (Trial Enrollment)
- Envelope contains trial group assignment (Randomization)
- Clinician delivers assigned intervention (Delivery of the Intervention)

Non-Invasive Positive Pressure Ventilation



1. Apply BiPAP or ventilator via mask
2. Set
   - FiO2 = 100%
   - Expiratory pressure ≥ 5
   - Inspiratory pressure ≥ 10
   - Respiratory rate ≥ 10
3. Preoxygenate ≥ 3 min (if feasible)
4. Remove mask only as the laryngoscope blade enters mouth

Facemask Oxygen

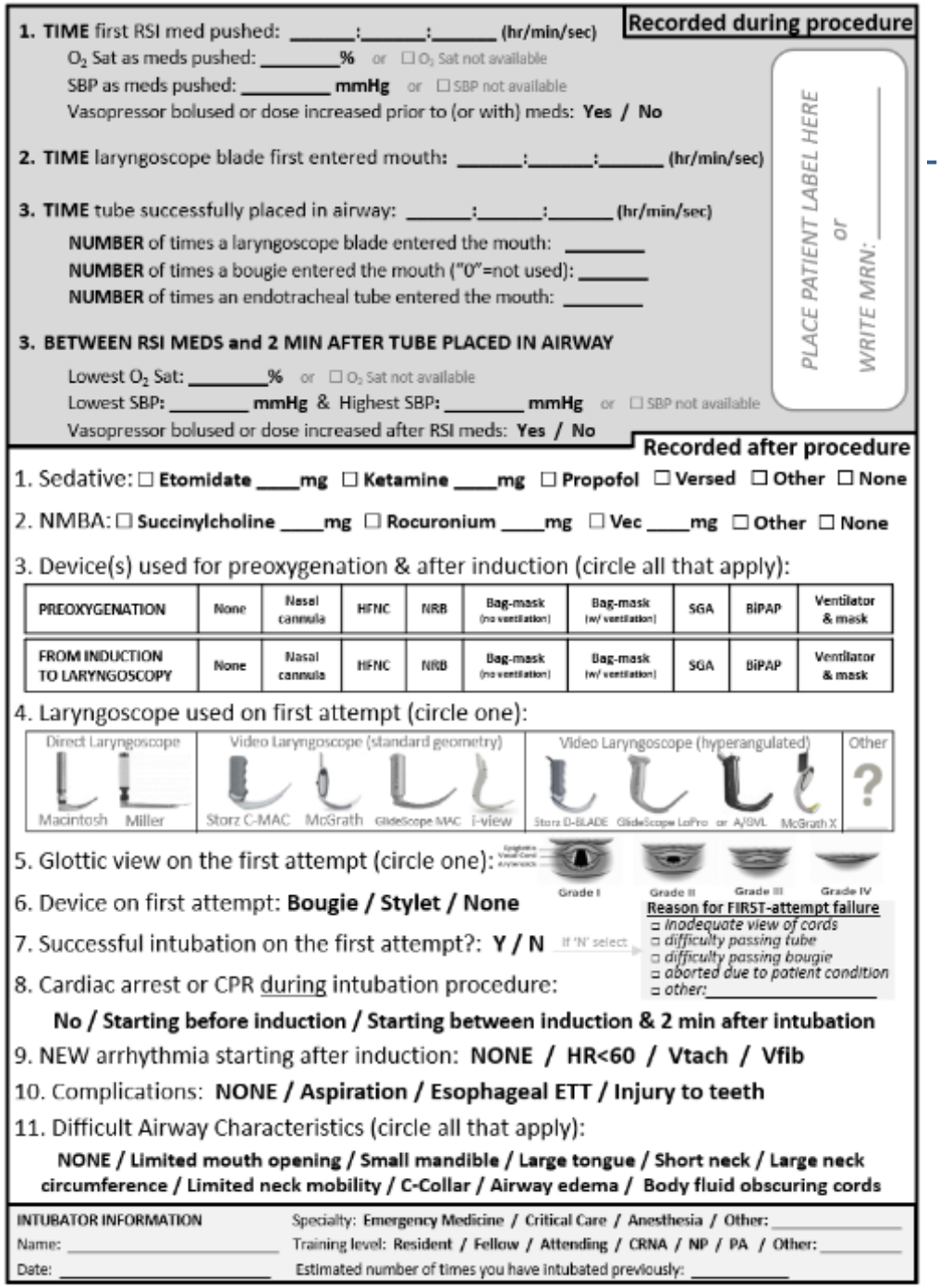


1. Apply non-rebreather or bag-mask
2. Set O_2 flow rate to max (≥ 15 LPM)
3. Preoxygenate ≥ 3 min (if feasible)
4. Remove mask only as the laryngoscope blade enters mouth

BEFORE INDUCTION – do NOT ventilate (squeeze bag)
AFTER INDUCTION – OK to ventilate (squeeze bag)

Data Collection

A second clinician not involved with the performance of the procedure collects data



Recorded during procedure

1. **TIME** first RSI med pushed: _____:_____:_____ (hr/min/sec)
   - O_2 Sat as meds pushed: _____% or ☐ O_2 Sat not available
   - SBP as meds pushed: _____ mmHg or ☐ SBP not available
   - Vasopressor bolused or dose increased prior to (or with) meds: **Yes / No**
2. **TIME** laryngoscope blade first entered mouth: _____:_____:_____ (hr/min/sec)
3. **TIME** tube successfully placed in airway: _____:_____:_____ (hr/min/sec)
   - **NUMBER** of times a laryngoscope blade entered the mouth: _____
   - **NUMBER** of times a bougie entered the mouth ("0"=not used): _____
   - **NUMBER** of times an endotracheal tube entered the mouth: _____
3. **BETWEEN RSI MEDS and 2 MIN AFTER TUBE PLACED IN AIRWAY**
   - Lowest O_2 Sat: _____% or ☐ O_2 Sat not available
   - Lowest SBP: _____ mmHg & Highest SBP: _____ mmHg or ☐ SBP not available
   - Vasopressor bolused or dose increased after RSI meds: **Yes / No**

PLACE PATIENT LABEL HERE or WRITE MRN: _____

Recorded after procedure

1. Sedative: ☐ **Etomidate** ____mg ☐ **Ketamine** ____mg ☐ **Propofol** ☐ **Versed** ☐ **Other** ☐ **None**
2. NMBA: ☐ **Succinylcholine** ____mg ☐ **Rocuronium** ____mg ☐ **Vec** ____mg ☐ **Other** ☐ **None**
3. Device(s) used for preoxygenation & after induction (circle all that apply):

PREOXYGENATION	None	Nasal cannula	HFNC	NRB	Bag-mask (no ventilation)	Bag-mask (w/ ventilation)	SGA	BiPAP	Ventilator & mask
FROM INDUCTION TO LARYNGOSCOPY	None	Nasal cannula	HFNC	NRB	Bag-mask (no ventilation)	Bag-mask (w/ ventilation)	SGA	BiPAP	Ventilator & mask

4. Laryngoscope used on first attempt (circle one):

Direct Laryngoscope		Video Laryngoscope (standard geometry)				Video Laryngoscope (hyperangulated)				Other
Macintosh	Miller	Storz C-MAC	McGrath	GlideScope MAC	i-view	Storz D-BLADE	GlideScope LoPro	or A/GVL	McGrath X	?

5. Glottic view on the first attempt (circle one): Grade I / Grade II / Grade III / Grade IV
6. Device on first attempt: **Bougie / Stylet / None**
7. Successful intubation on the first attempt?: **Y / N** (If 'N' select)
8. Cardiac arrest or CPR during intubation procedure:

Reason for FIRST-attempt failure
- ☐ *inadequate view of cords*
- ☐ *difficulty passing tube*
- ☐ *difficulty passing bougie*
- ☐ *aborted due to patient condition*
- ☐ *other:* _____

No / Starting before induction / Starting between induction & 2 min after intubation

9. NEW arrhythmia starting after induction: **NONE / HR<60 / Vtach / Vfib**
10. Complications: **NONE / Aspiration / Esophageal ETT / Injury to teeth**
11. Difficult Airway Characteristics (circle all that apply):

NONE / Limited mouth opening / Small mandible / Large tongue / Short neck / Large neck circumference / Limited neck mobility / C-Collar / Airway edema / Body fluid obscuring cords

INTUBATOR INFORMATION
Name: _____
Date: _____
Specialty: **Emergency Medicine / Critical Care / Anesthesia / Other:** _____
Training level: **Resident / Fellow / Attending / CRNA / NP / PA / Other:** _____
Estimated number of times you have intubated previously: _____

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PREVENTION | TREATMENT | RECOVERY

Patient Characteristics	Noninvasive Ventilation (N= 645)		Oxygen Mask (N= 656)	
Age, years	61	[47-71]	61	[47-70]
Female sex	255	(39.5%)	260	(39.6%)
Body mass index, kg/m²	27.6	[23.2-32.9]	26.6	[22.5-32.4]
Active conditions				
Altered mental status	402	(62.3%)	390	(59.5%)
Sepsis or Septic Shock	301	(46.7%)	312	(47.6%)
Gastrointestinal bleeding	107	(16.6%)	102	(15.5%)
Location: Intensive Care Unit	476	(73.8%)	476	(72.6%)
In the hour prior to enrollment				
Receipt of vasopressors	178	(27.6%)	178	(27.1%)
Receipt of high-flow nasal cannula	150	(23.3%)	165	(25.2%)
Lowest oxygen saturation	95	[92-98]	95	[92-98]
Highest fraction of inspired oxygen	0.33	[0.21-0.66]	0.36	[0.21-0.70]

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

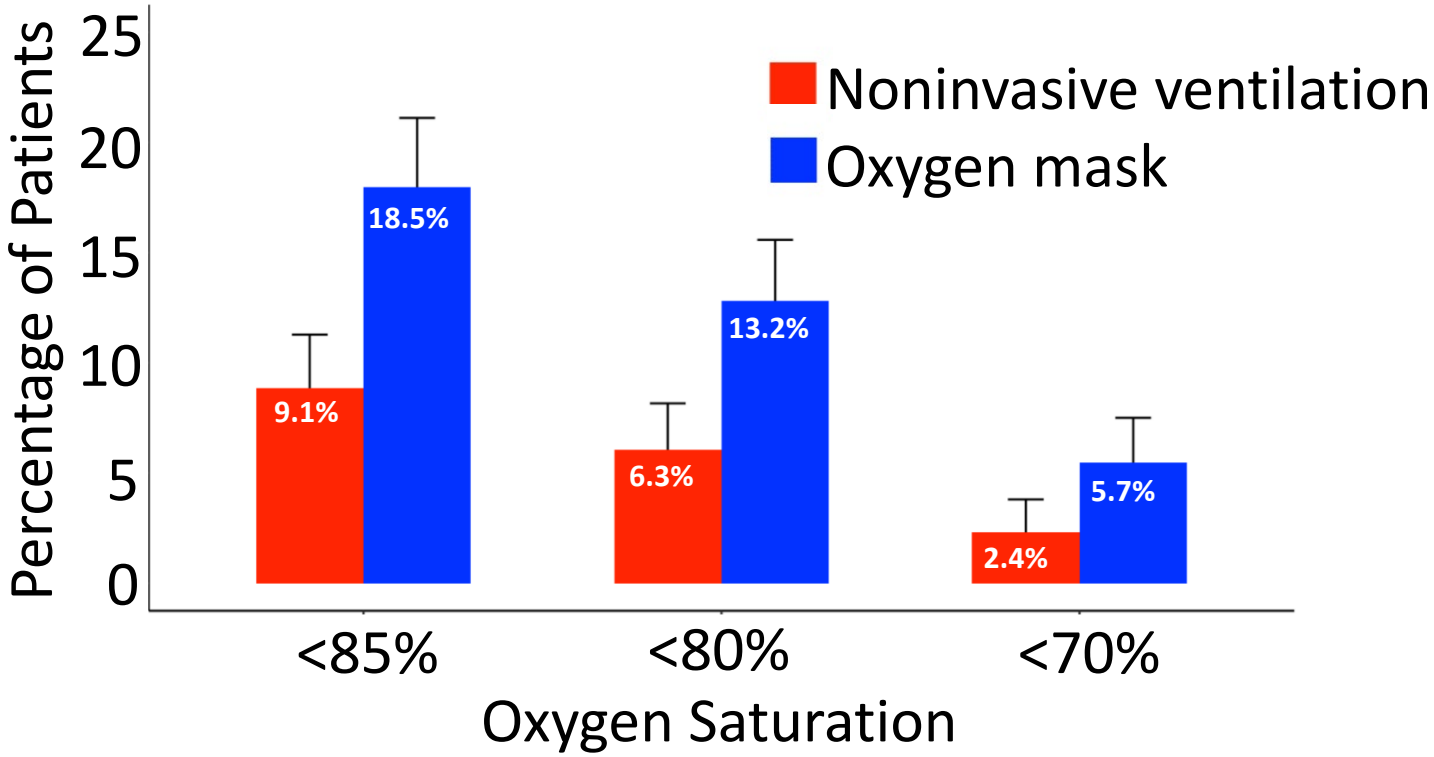
Separation between Trial Groups

	Noninvasive Ventilation (N= 645)		Oxygen Mask (N= 656)	
Noninvasive Ventilation	**616**	**(95.5%)**	4	(0.6%)
Oxygen Mask	22	(3.4%)	**648**	**(98.8%)**
Other	7	(1.1%)	4	(0.6%)

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

Data given as no. (%)

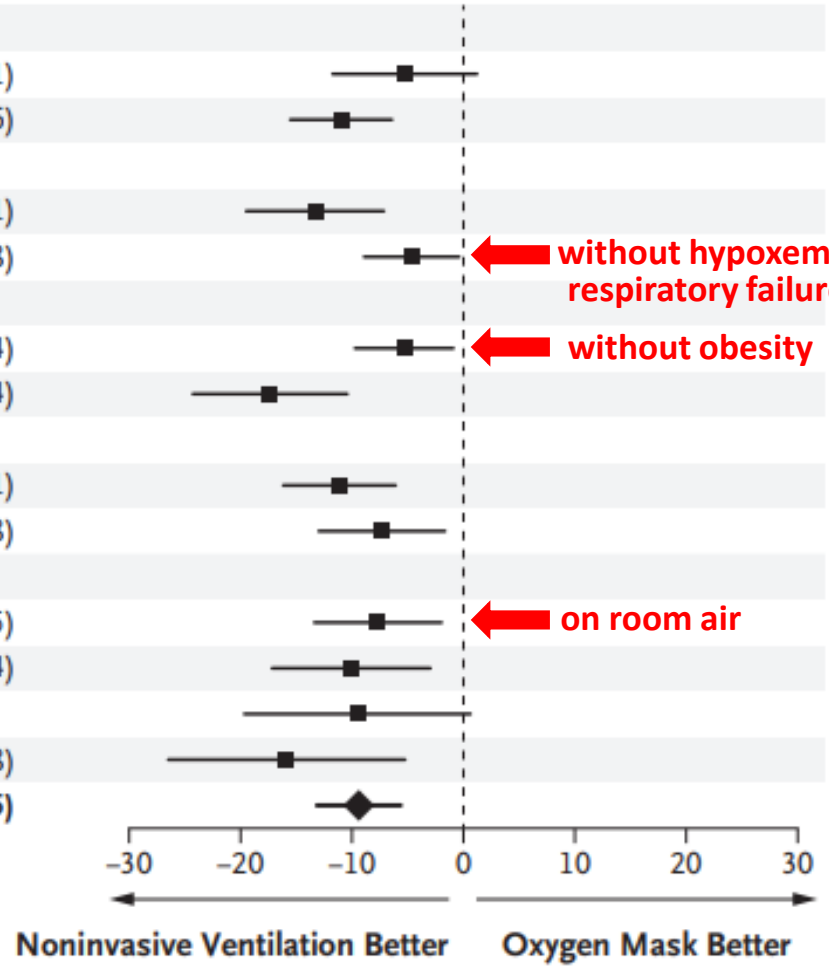
	Noninvasive Ventilation (N= 645)	Oxygen Mask (N= 656)	Absolute risk difference (95% CI)	P value
Primary outcome: Incidence of Hypoxemia (SpO2<85%)	57 (9.1%)	118 (18.5%)	**-9.4%** (-13.2% to -5.6%)	<0.001



Noninvasive ventilation cut in <u>half</u> the risk of hypoxemia during intubation (no matter how hypoxemia was defined)

NIV improved outcomes in all subgroups

Subgroup	Noninvasive Ventilation	Oxygen Mask
	no. of patients with event/total no. of patients (%)	
Location		
Emergency department	13/165 (7.9)	23/175 (13.1)
Intensive care unit	44/459 (9.6)	95/462 (20.6)
Acute hypoxemic respiratory failure		
Yes	36/282 (12.8)	84/322 (26.1)
No	21/342 (6.1)	34/315 (10.8)
Body-mass index		
<30	36/397 (9.1)	59/410 (14.4)
≥30	20/222 (9.0)	58/220 (26.4)
APACHE II score		
<17	27/337 (8.0)	67/350 (19.1)
≥17	30/287 (10.5)	51/287 (17.8)
FIO_2 in previous 1 hr		
0.21	4/142 (2.8)	15/143 (10.5)
0.22–0.40	18/192 (9.4)	35/180 (19.4)
0.41–0.70	9/100 (9.0)	15/81 (18.5)
>0.70	18/106 (17.0)	45/137 (32.8)
Overall	**57/624 (9.1)**	**118/637 (18.5)**



Exploratory Procedural Outcomes	Noninvasive Ventilation (N= 645)	Oxygen Mask (N=656)	Absolute Difference or Median Difference (95% CI)
Successful intubation on the first attempt	534 (82.8)	535 (81.6)	1.2 (-2.9 to 5.4)
Cardiovascular collapse	113 (17.5)	127 (19.4)	-1.8 (-6.1 to 2.4)
SBP <65 mm Hg	18/621 (2.9)	28/633 (4.4)	-1.5 (-3.6 to 0.6)
New or increased use of vasopressors	111 (17.2)	117 (17.8)	-0.6 (-4.8 to 3.5)
Cardiac arrest	**1 (0.2)**	**7 (1.1)**	**-0.9 (-1.8 to -0.1)**

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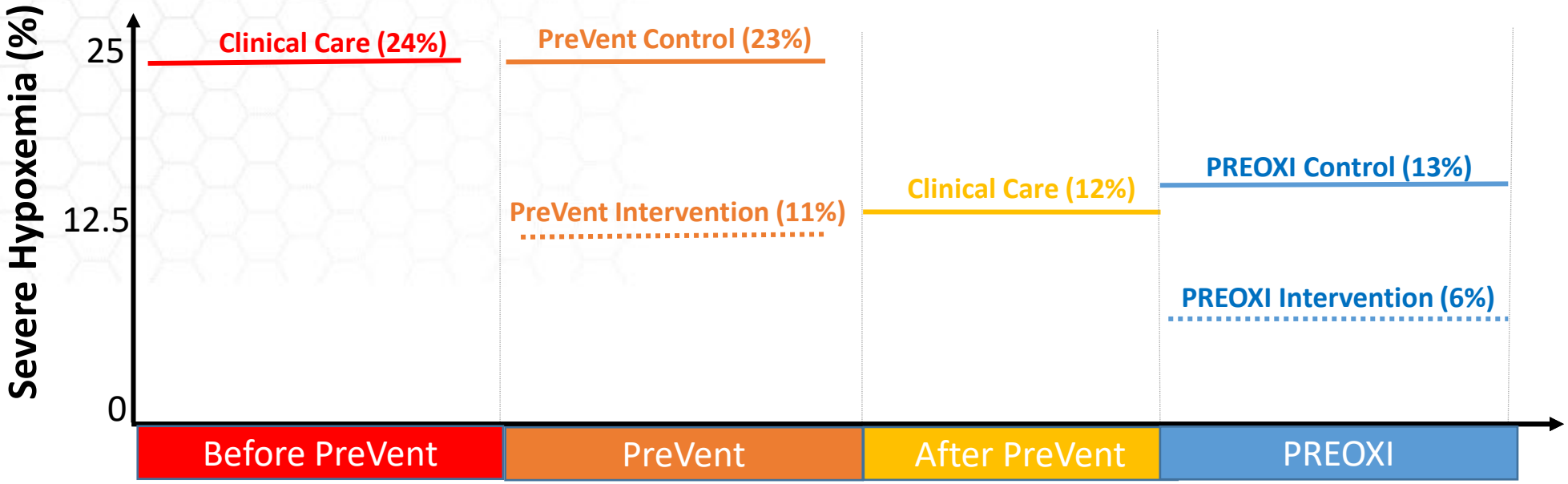
Data given as no. (%) or median [IQR]

Hypoxemia and Cardiac Arrest in Clinical Care



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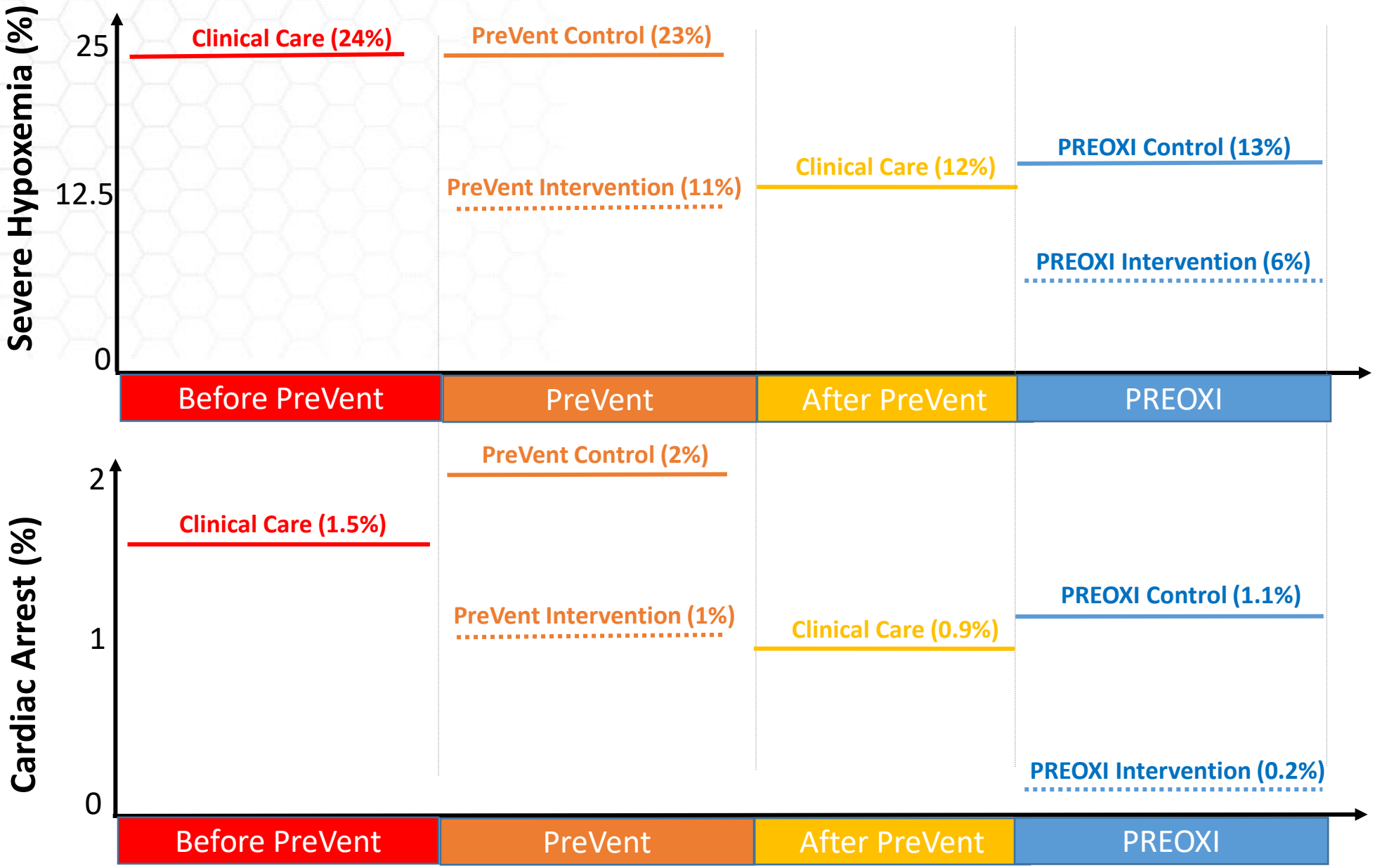
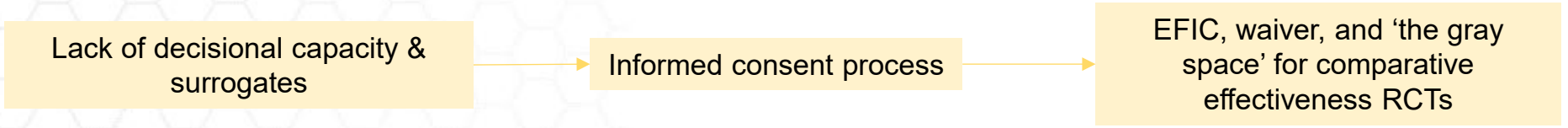
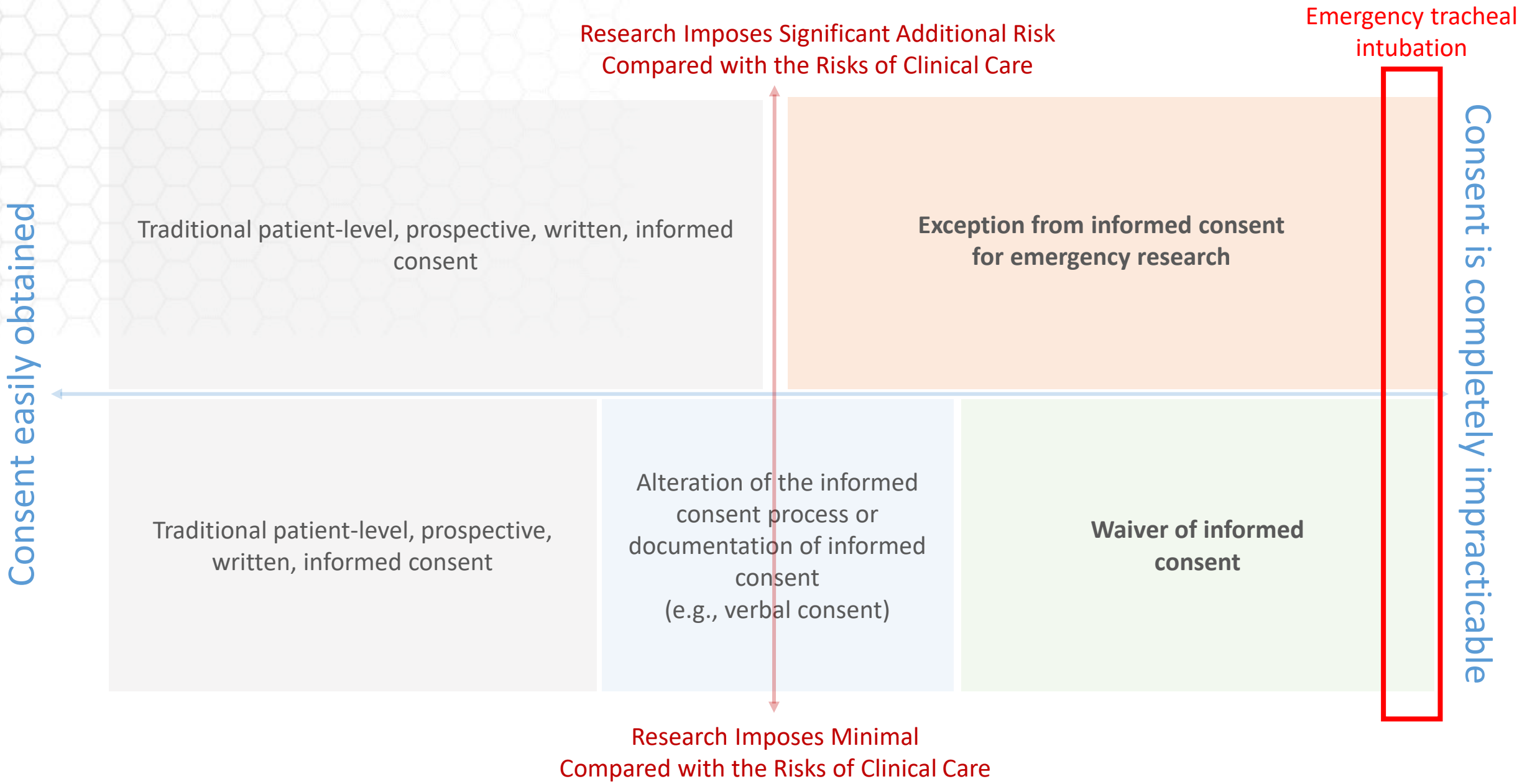
Hypoxemia and Cardiac Arrest in Clinical Care





EFIC, alteration, and waiver of informed consent in pragmatic trials in emergency medicine and critical care

Current Regulations for Informed Consent



Waiver of Informed Consent

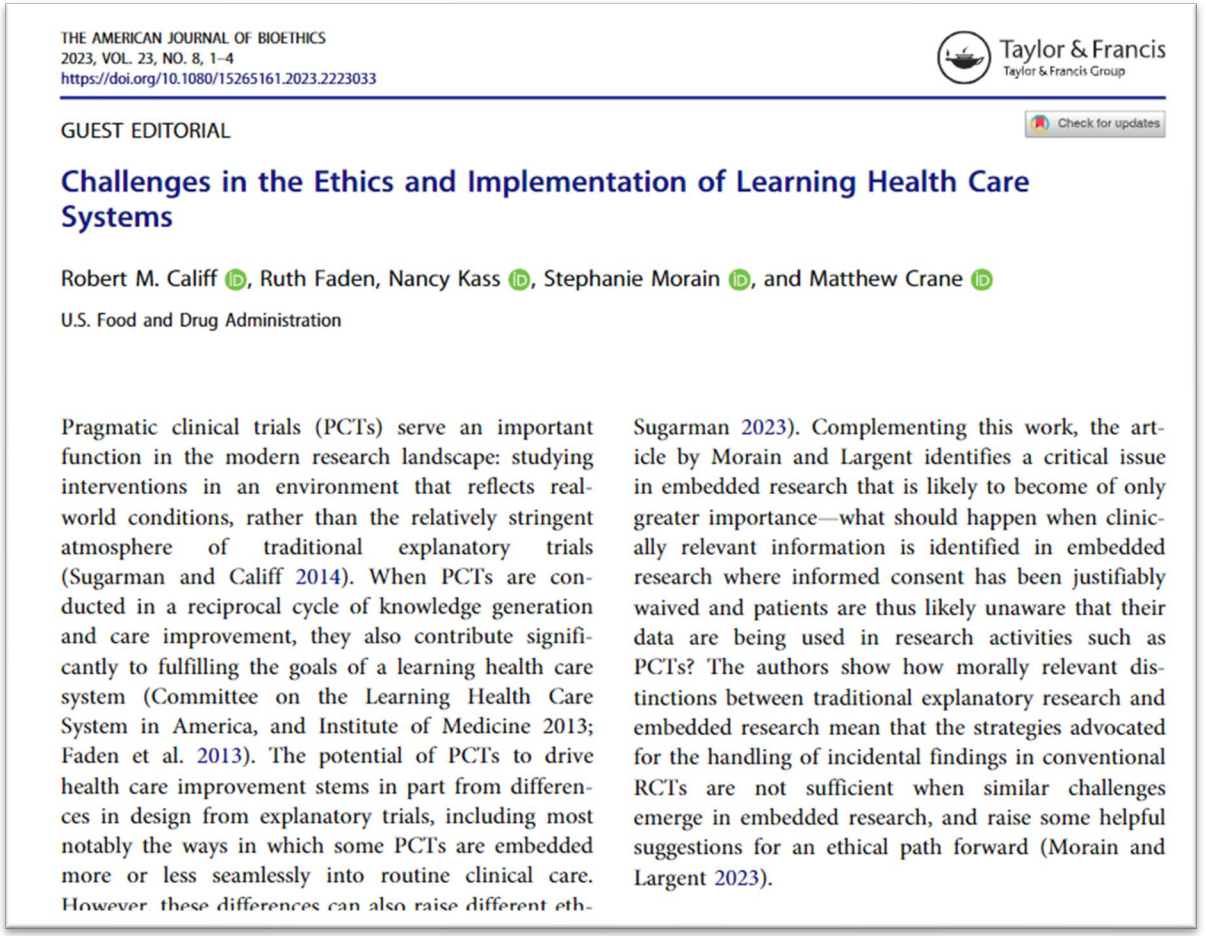
Criteria for waiver of informed consent (45 CFR 46.116(f))

1. **No more than minimal risk to patients**
2. Could not be carried out without the waiver;
3. Only uses identifiable private health information if such information is required to conduct the study
4. Does not adversely affect patients' rights or welfare
5. Whenever appropriate, additional pertinent information is provided after participation.

Why is there controversy on the role of EFIC and waiver in comparative effectiveness research?

FDA Commissioner:

"***Neither HHS nor FDA regulations currently have guidance on whether or when [pragmatic trials] might be categorized as minimal risk . . . These issues need the joint attention of federal agencies, the research community, the health care delivery ecosystem, and patient advocates***"



THE AMERICAN JOURNAL OF BIOETHICS
2023, VOL. 23, NO. 8, 1–4
https://doi.org/10.1080/15265161.2023.2223033

GUEST EDITORIAL

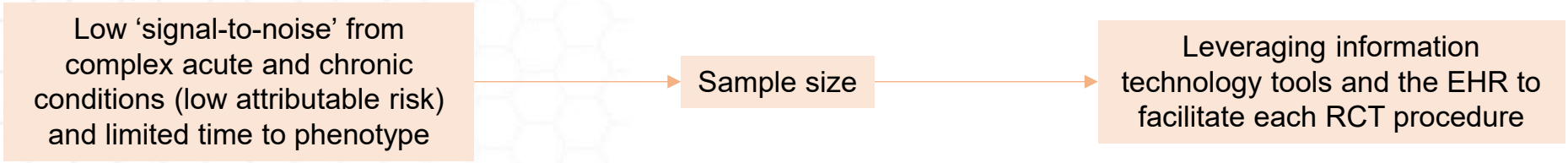
Challenges in the Ethics and Implementation of Learning Health Care Systems

Robert M. Califf, Ruth Faden, Nancy Kass, Stephanie Morain, and Matthew Crane

U.S. Food and Drug Administration

Pragmatic clinical trials (PCTs) serve an important function in the modern research landscape: studying interventions in an environment that reflects real-world conditions, rather than the relatively stringent atmosphere of traditional explanatory trials (Sugarman and Califf 2014). When PCTs are conducted in a reciprocal cycle of knowledge generation and care improvement, they also contribute significantly to fulfilling the goals of a learning health care system (Committee on the Learning Health Care System in America, and Institute of Medicine 2013; Faden et al. 2013). The potential of PCTs to drive health care improvement stems in part from differences in design from explanatory trials, including most notably the ways in which some PCTs are embedded more or less seamlessly into routine clinical care. However, these differences can also raise different eth-

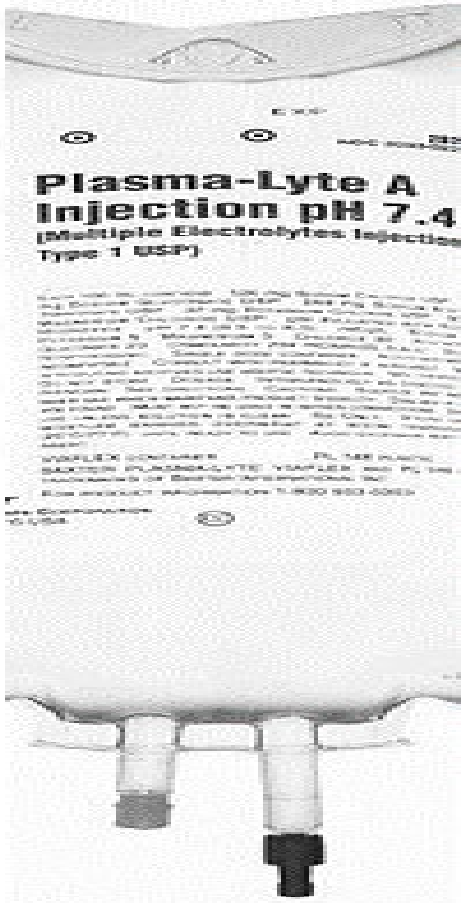
Sugarman 2023). Complementing this work, the article by Morain and Largent identifies a critical issue in embedded research that is likely to become of only greater importance—what should happen when clinically relevant information is identified in embedded research where informed consent has been justifiably waived and patients are thus likely unaware that their data are being used in research activities such as PCTs? The authors show how morally relevant distinctions between traditional explanatory research and embedded research mean that the strategies advocated for the handling of incidental findings in conventional RCTs are not sufficient when similar challenges emerge in embedded research, and raise some helpful suggestions for an ethical path forward (Morain and Largent 2023).



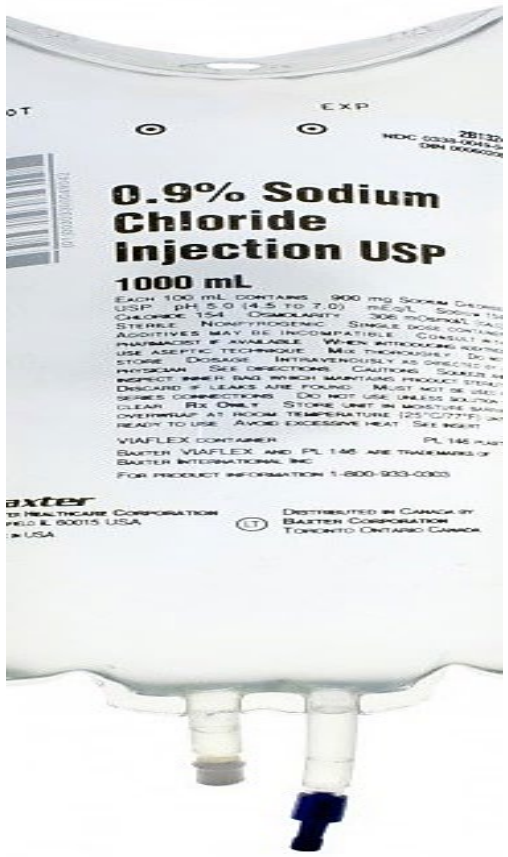
Leveraging the EHR to facilitate trial procedures

Using EHR to efficiently conduct trials large enough to detect small differences in patient-centered outcomes between existing treatments

Balanced Crystalloids



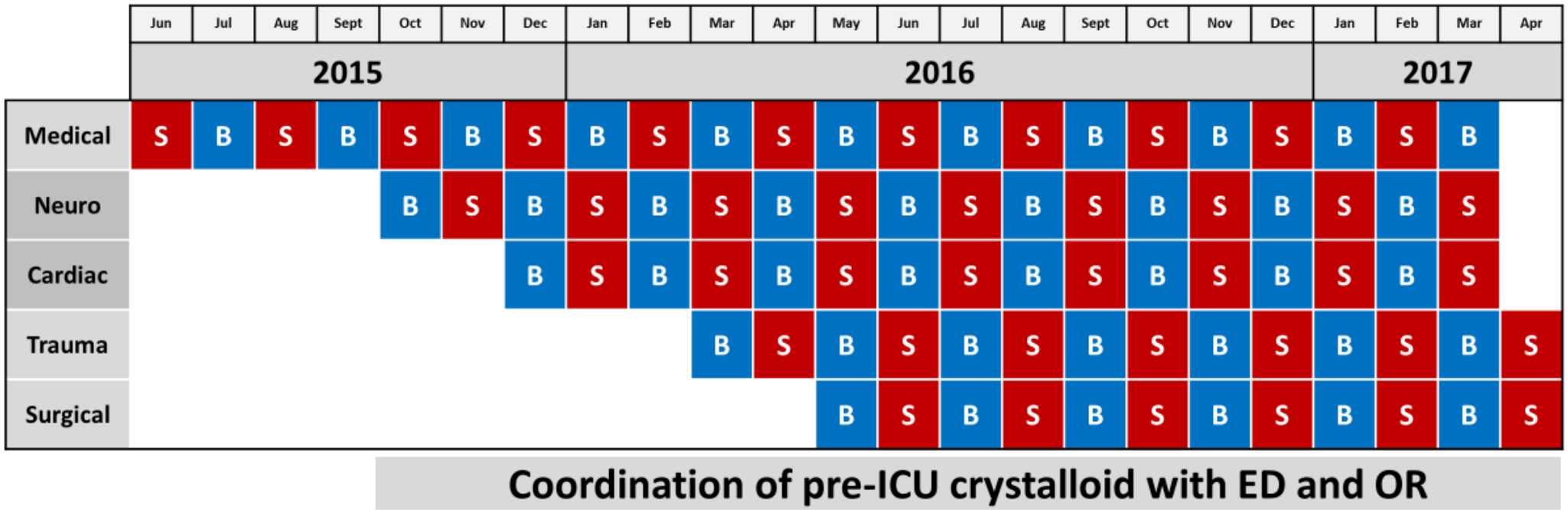
Saline



	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

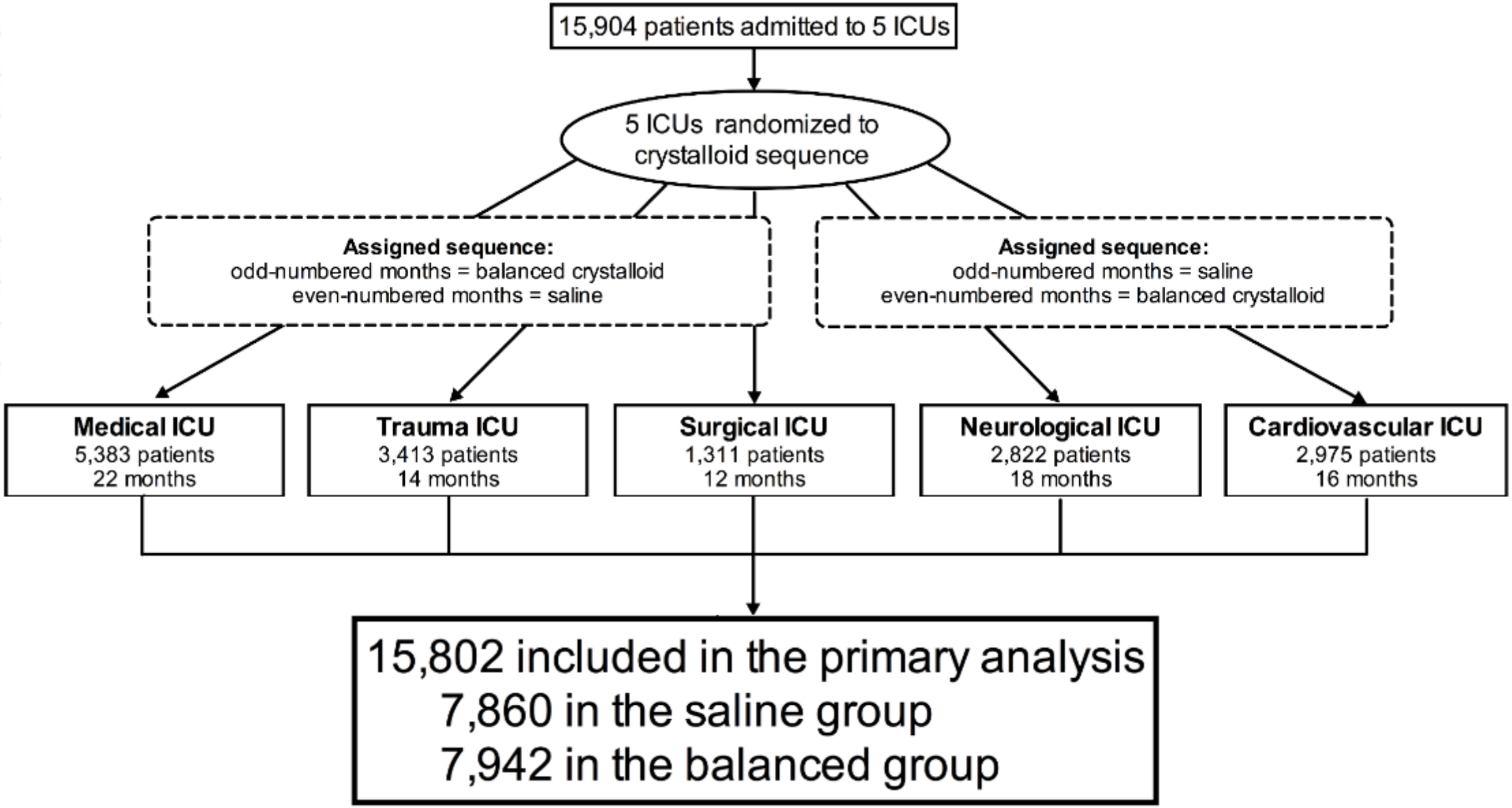
Step 2

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



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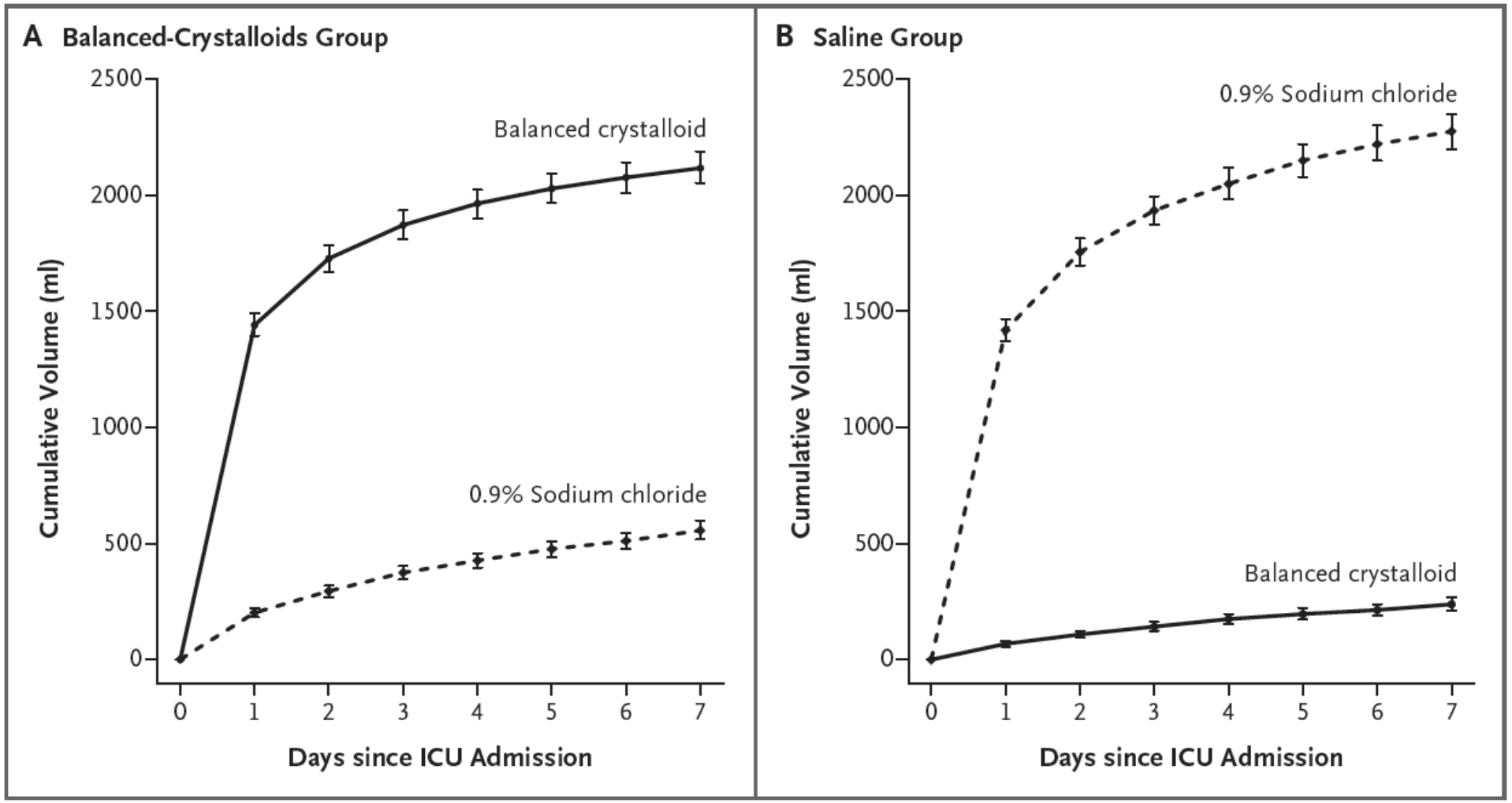
Patient Characteristics	Balanced (n = 7942)	Saline (n = 7860)
Age – years	58 [44 – 69]	58 [44 – 69]
Men	4540 (57.2)	4557 (58.0)
Admitted from ED	3975 (50.1)	3997 (50.9)
Study ICU		
Medical	2735 (34.4)	2646 (33.7)
Trauma	1640 (20.6)	1688 (21.5)
Cardiac	1470 (18.5)	1501 (19.1)
Neurological	1440 (18.1)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

Separation between trial groups



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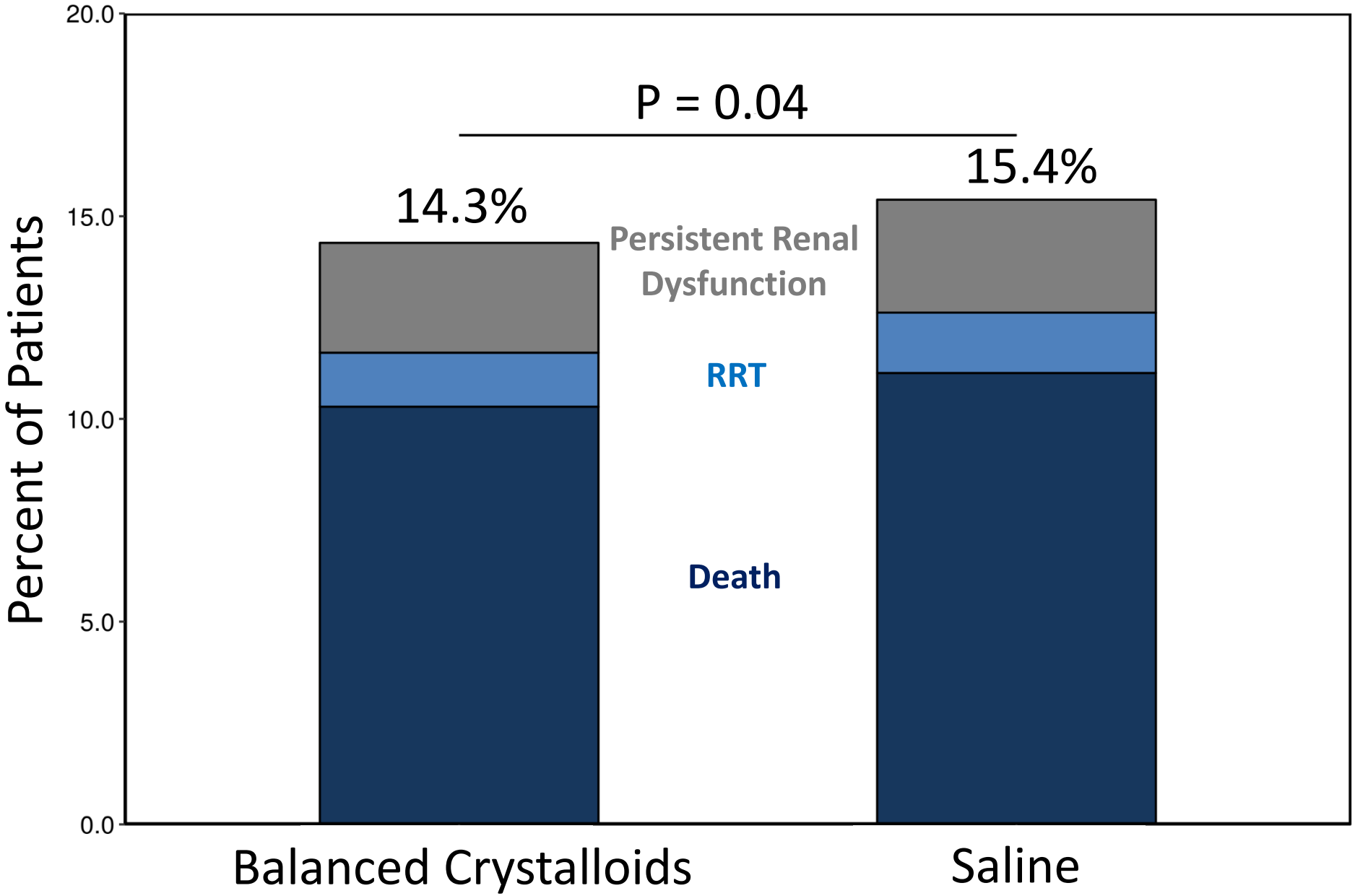
Balanced crystalloids prevented Major Adverse Kidney Events

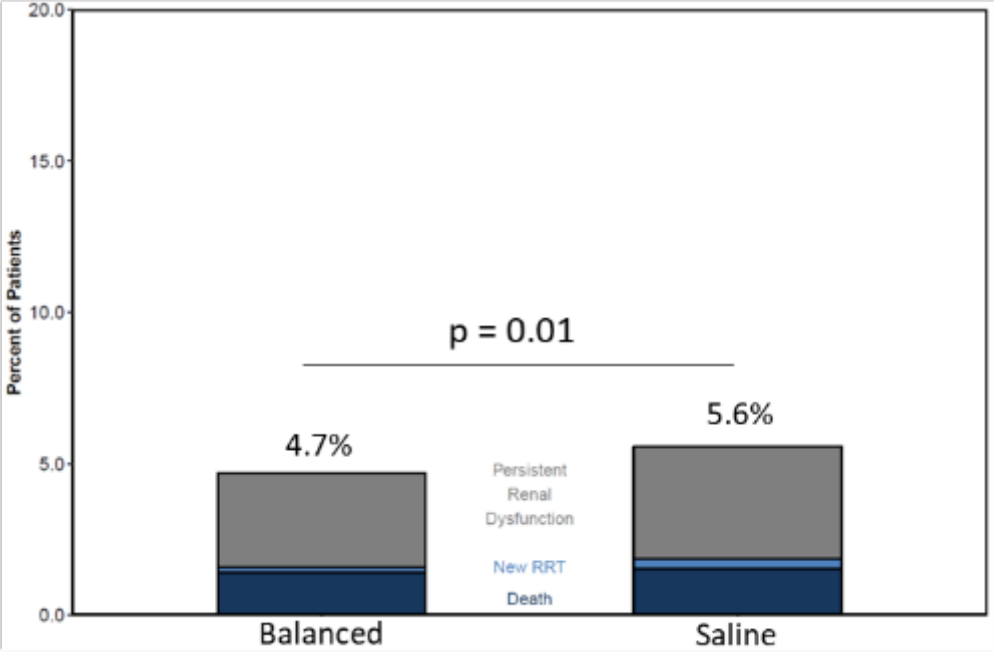


Results similar in second trial

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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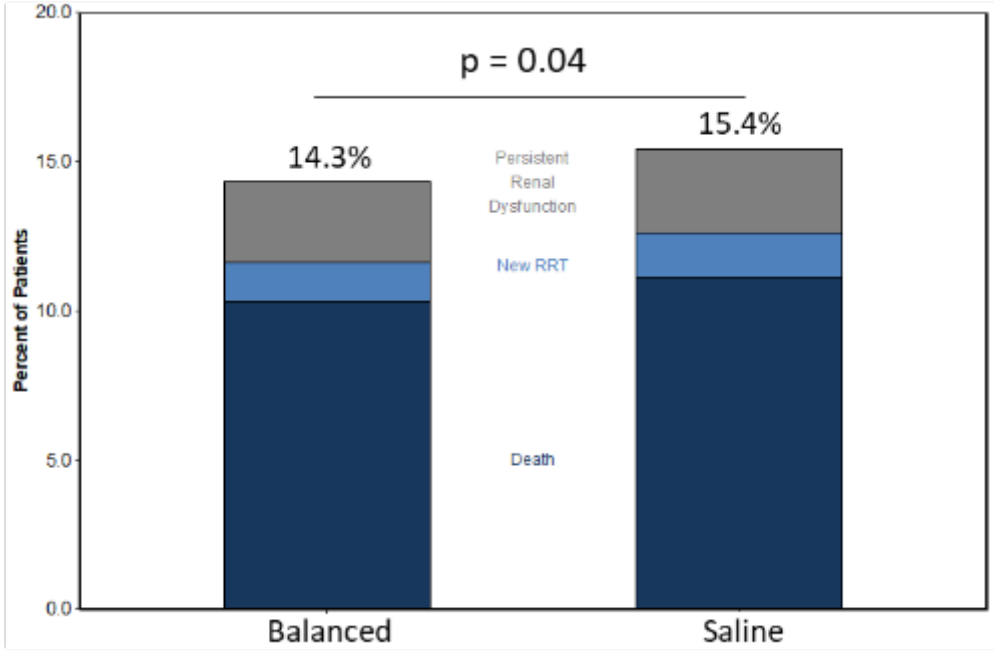

What do trial personnel do in pragmatic trial?

PREOXI Trial

- Train clinicians in trial procedures
- Monitor exclusion vs enrollment
- Verify eligibility after enrollment
- Monitor receipt of intervention
- Provide feedback to clinicians
- Collect data on baseline characteristics and hospital outcomes
- Monitor for AEs
- Communicate with patients and families after enrollment
- Address queries

#3 How to deal with grant reviewer #2

- The scientific and regulatory infrastructure for randomized trials in the US was built for the development of new drugs and devices
- For decades, the NIH and the scientific community have largely conceived of “randomized trials” as explanatory, mechanistic trials
- Peer reviewers may not understand or like trials with pragmatic features

- Our approach:
  - Early on, invest in executing pragmatic trials even without much funding
  - Develop a track record of execution and demonstrate value
  - Seek funders and RFAs that have shown openness to pragmatic trials
  - Jon NIH Collaboratory and other organizations advancing message
  - In grants, describe rigorous trial features without saying “pragmatic”
  - Await turnover in prior generation of scientists and peer reviewers

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PREVENTION | TREATMENT | RECOVERY

Summary

- In every RCT, investigators determine the level of pragmatism for each trial procedure
- Trials with more pragmatic features can sometimes be “better” (more representative) or “more efficient” (shorter enrollment, lower cost)
- The efficiency of pragmatic trials may allow us to answer comparative effectiveness questions that are currently ignored (a moral imperative)
- Pragmatic trials are better suited to comparative effectiveness questions than to the development of new drugs and devices
- Key tools for pragmatic trials are:
  - Embedding trial procedures within clinical care
  - Leveraging the electronic health record to facilitate trial procedures
  - Understanding and appropriately applying EFIC, alteration, and waiver for informed consent
- Barriers to pragmatic trials today are as much cultural or dogmatic as they are scientific or logistical