Clinical Trials for Improving Precision Medicine in ICU Patients

Enhancing Individualized Care through Evidence-Based Approaches

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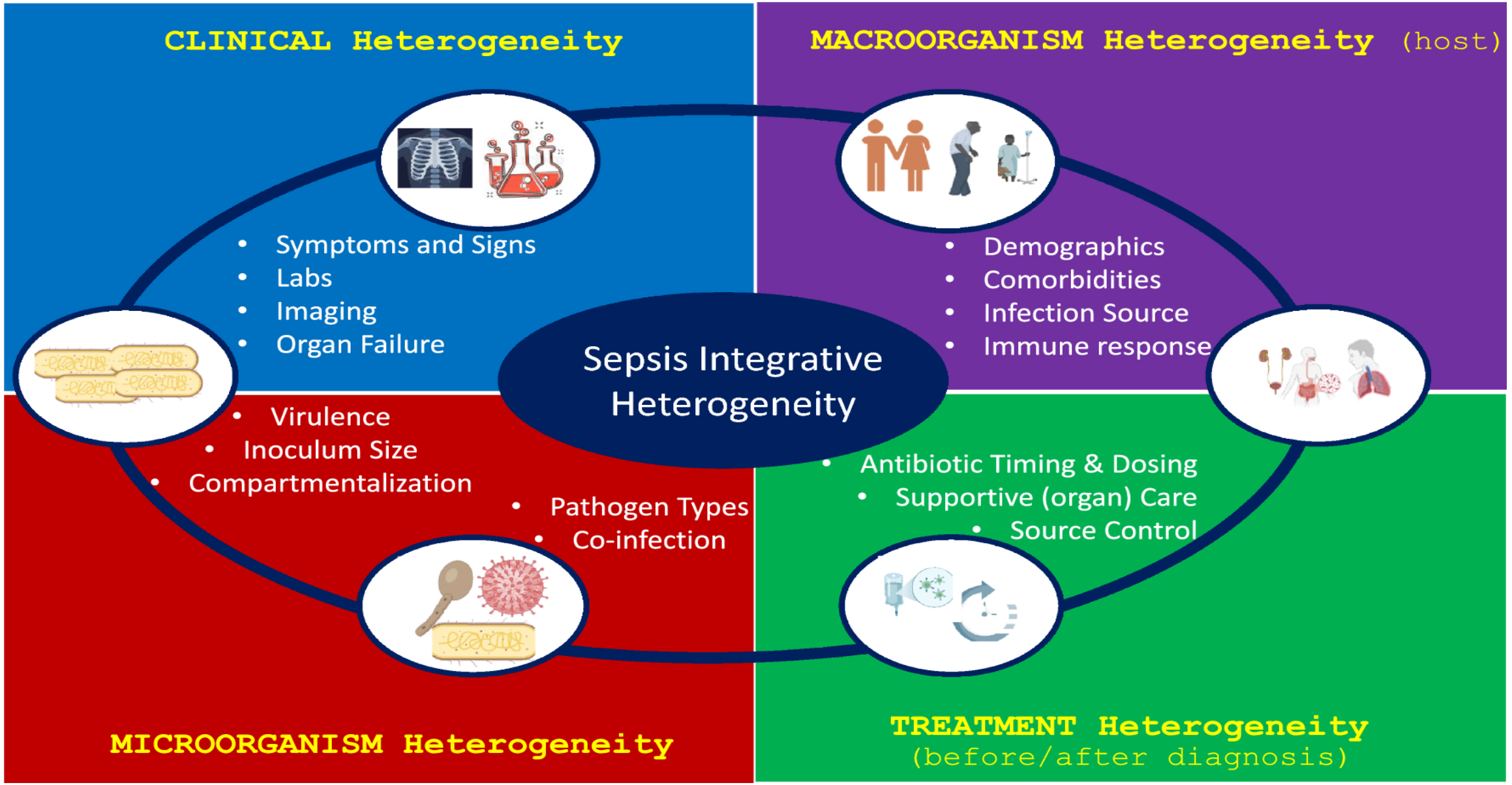
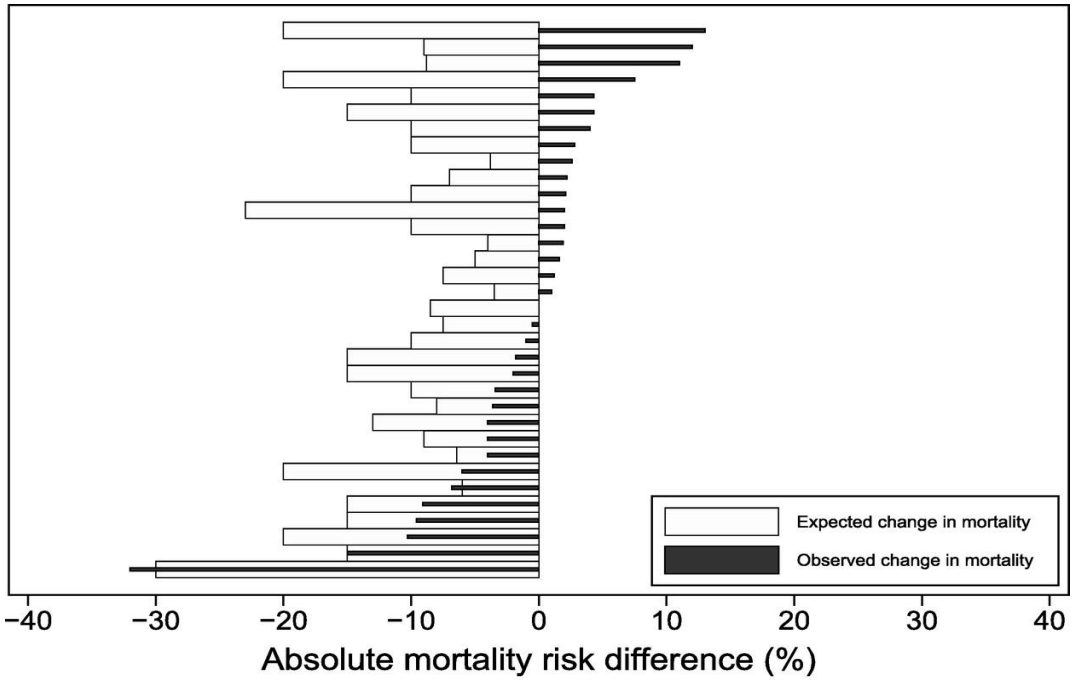
Heterogeneity of Sepsis

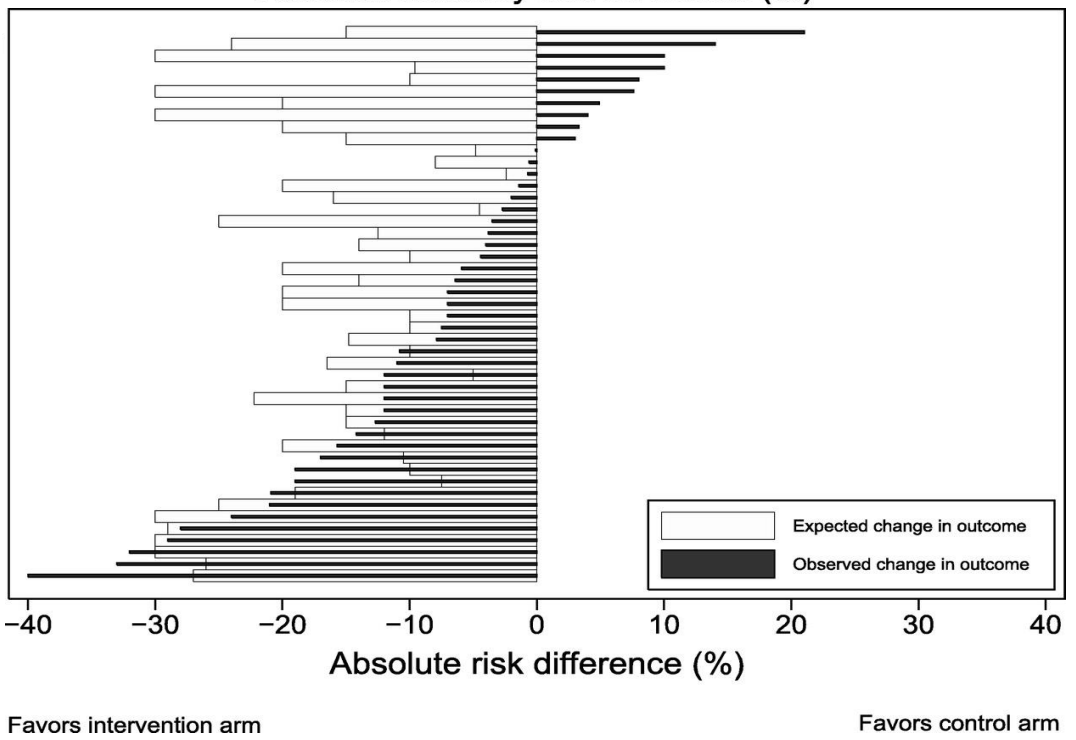


Intensive Care Med. 2025;51:582-584.

The Problems of Clinical Trials in the ICU

- Control group event rates
- Treatment effect
- Optimal dose
- Optimal duration
- Optimal timing
- Target population





Am J Respir Crit Care Med. 2014;189:1469-78.

Randomized ARDS Trials

Therapies	Novel Trial Findings
Lung protective ventilation (LPV)	**ARMA**: Lower mortality with LPV
Open lung ventilation	**ALVEOLI**: No difference in hospital mortality **ExPress**: No difference in 28-day mortality **LOVS**: No difference in 28-day hospital mortality **ART**: Higher 28-day mortality with open lung ventilation **STAMINA**: No difference in 90-day in hospital or ICU mortality
High-frequency oscillatory ventilation (HFOV)	**OSCILLATE**: Higher hospital mortality with HFOV **OSCAR**: No difference in 30-day mortality
Prone position	**PROSEVA**: Lower 28-day mortality with prone position **ECMOSARS**: May be beneficial in patients support by V-V ECMO **PRONECMO**: No difference in 90-day in hospital or ICU mortality
Neuromuscular blocking agents (NMBA)	**ACURASYS**: Lower adjusted 90-day mortality with NMBA **ROSE**: No difference in 90-day mortality
Fluid therapy	**FACTT**: No difference in mortality; more ventilator free days with conservative fluid strategy
Statins	**HARP-2**: No difference in 28-day mortality with simvastatin **SAILS**: No difference in 60-day or hospital mortality with rosuvastatin
Image-guide ventilation	**LIVE**: Personalisation of mechanical ventilation did not decrease mortality
Extracorporeal membrane oxygenation (ECMO)	**CESAR:** Lower 6-months mortality with ECMO **EOLIA**: No difference in 60-day mortality

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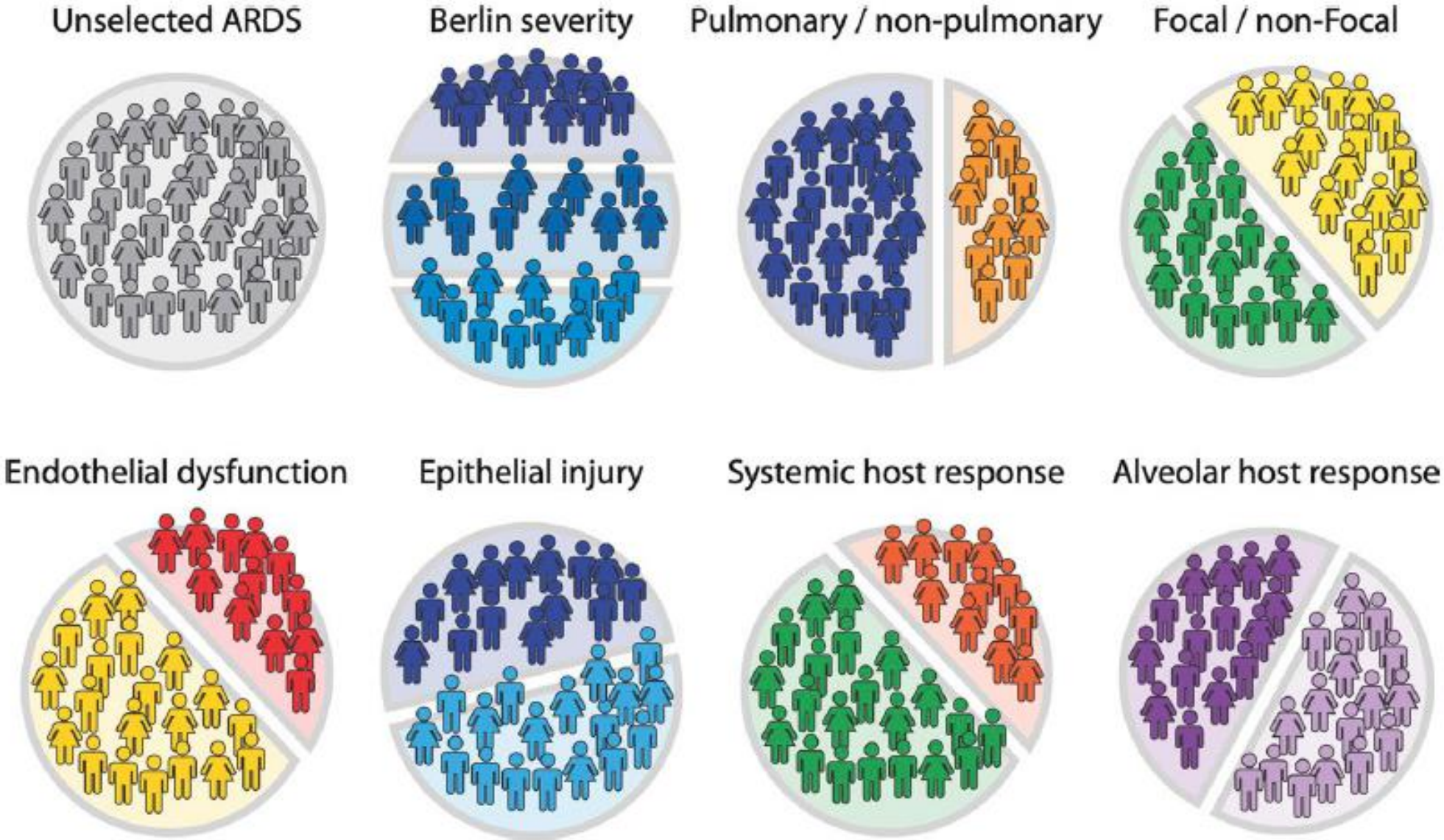
Heterogeneity of ARDS

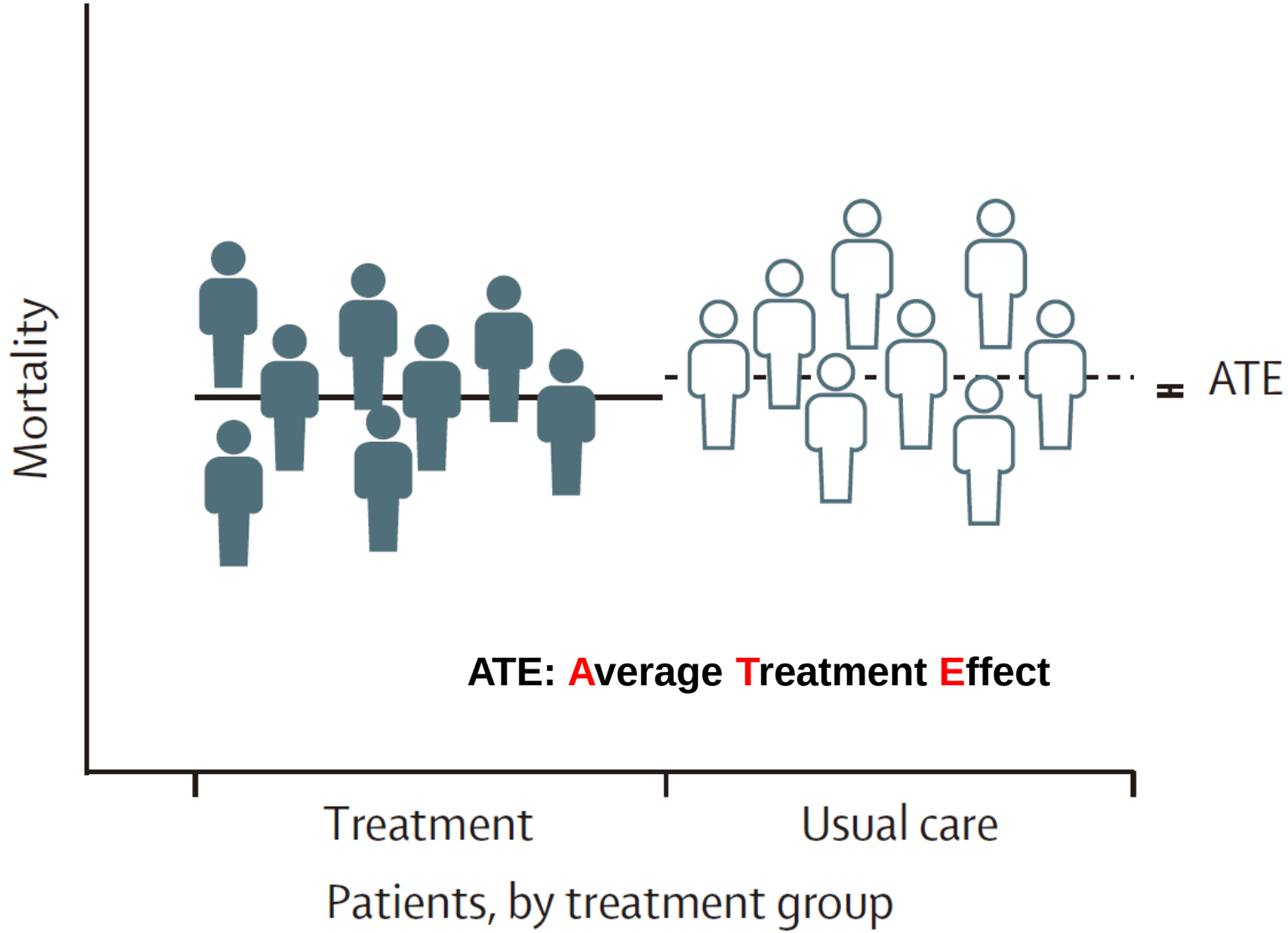


Intensive Care Med Exp. 2022;10:8.

One size doesn't fit all.

One Size Fits One.

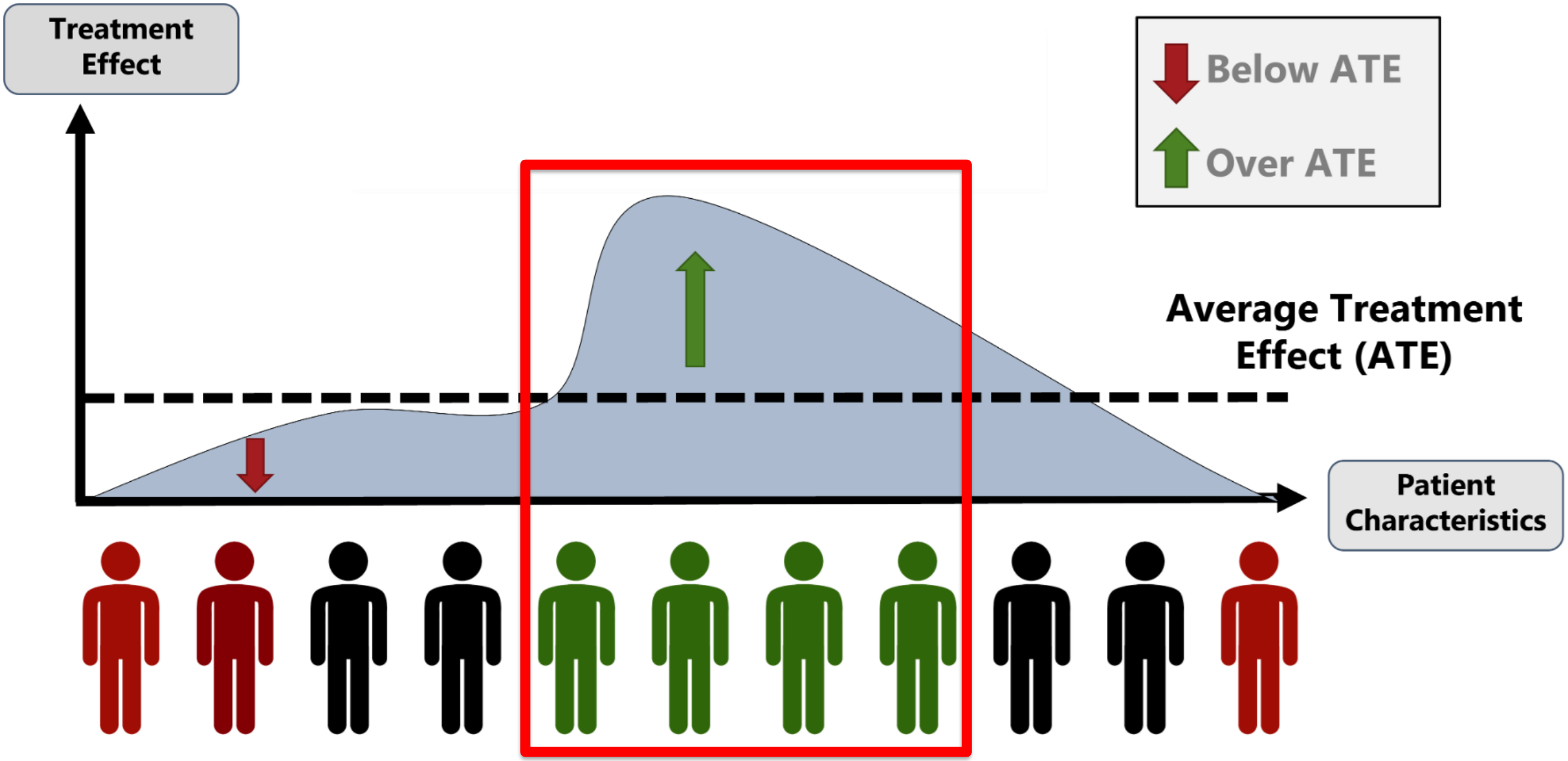
Trials Give Us Average Treatment Effect.



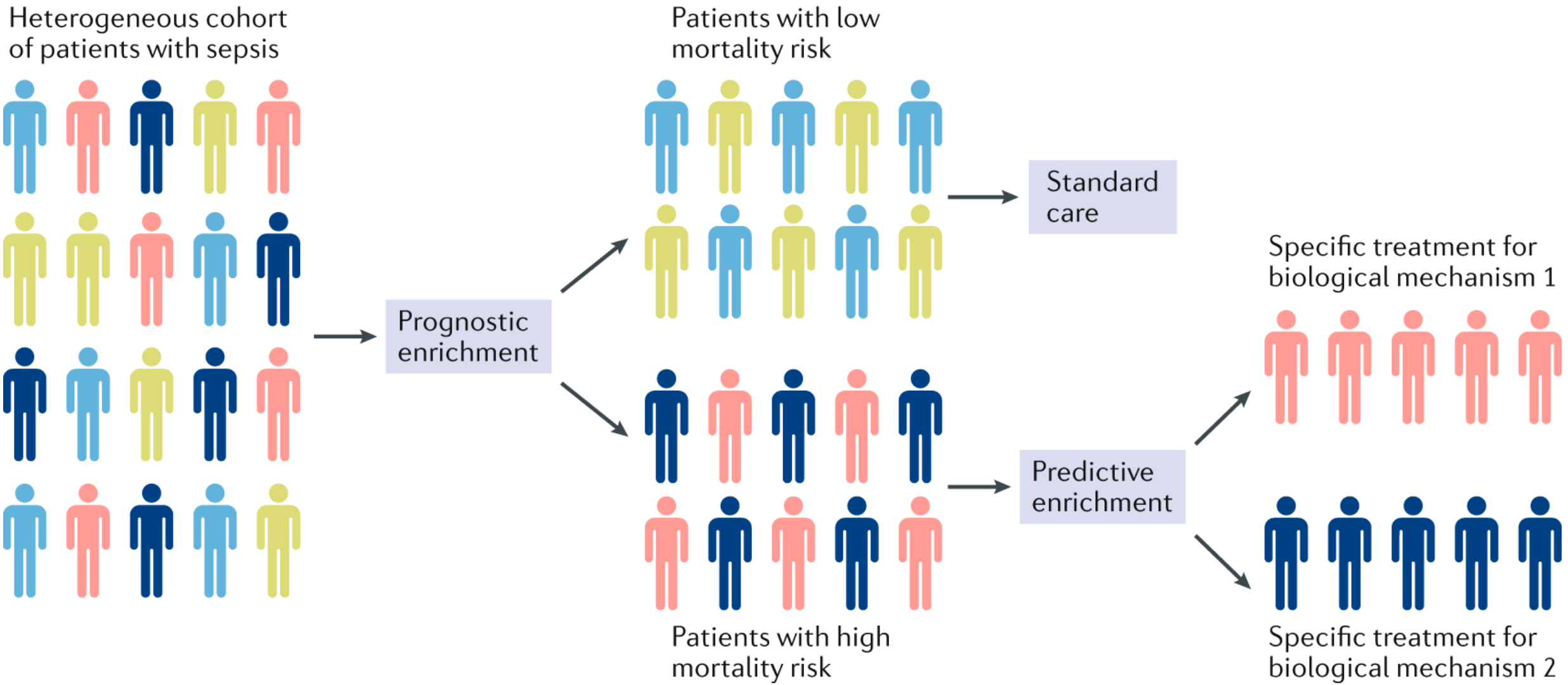
ATE: Average Treatment Effect

Lancet Respir Med. 2025:S2213-2600(25)00054-2.

Individualized Treatment Effect (ITE)



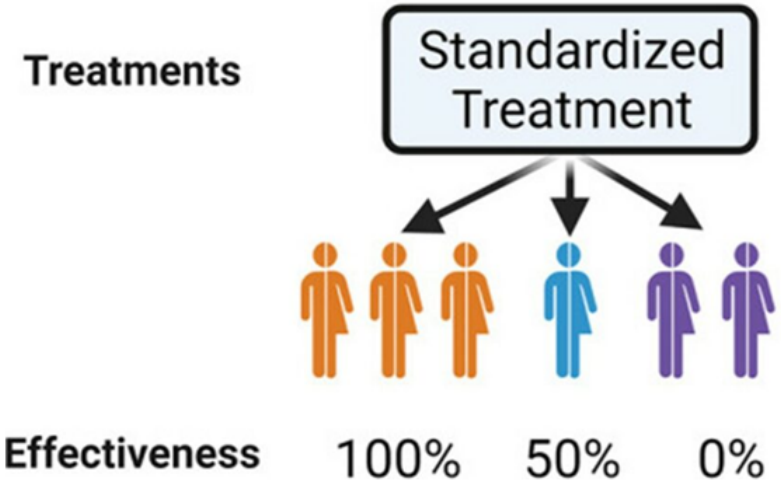
Prognostic and Predictive Enrichment



Nat Rev Nephrol. 2020;16:20–31.

Not One-Size-Fit All, But One-Size-Fit-One

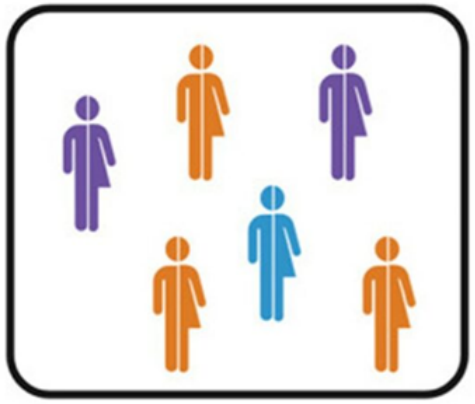
Average Treatment Effect



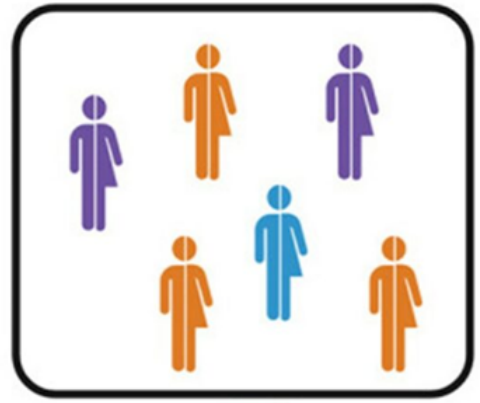
https://nationaleczema.org/blog/personalized-medicine-eczema/

Not One-Size-Fit All, But One-Size-Fit-One

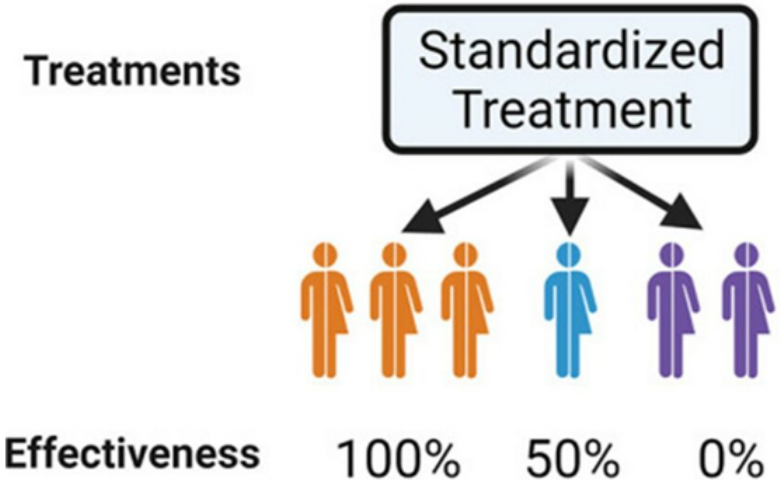
Similar Clinical Presentation



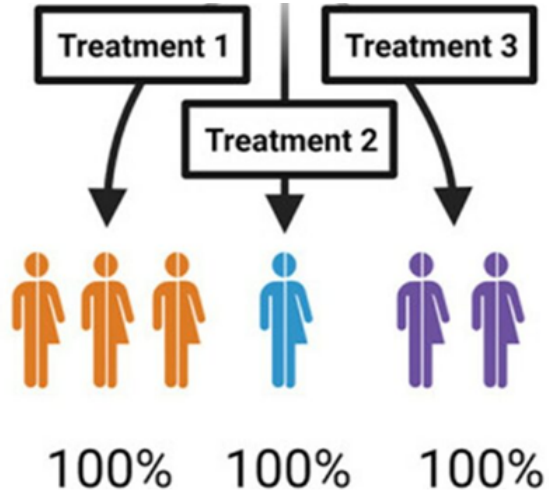
Approaches



Average Treatment Effect



Individualized Treatment Effect



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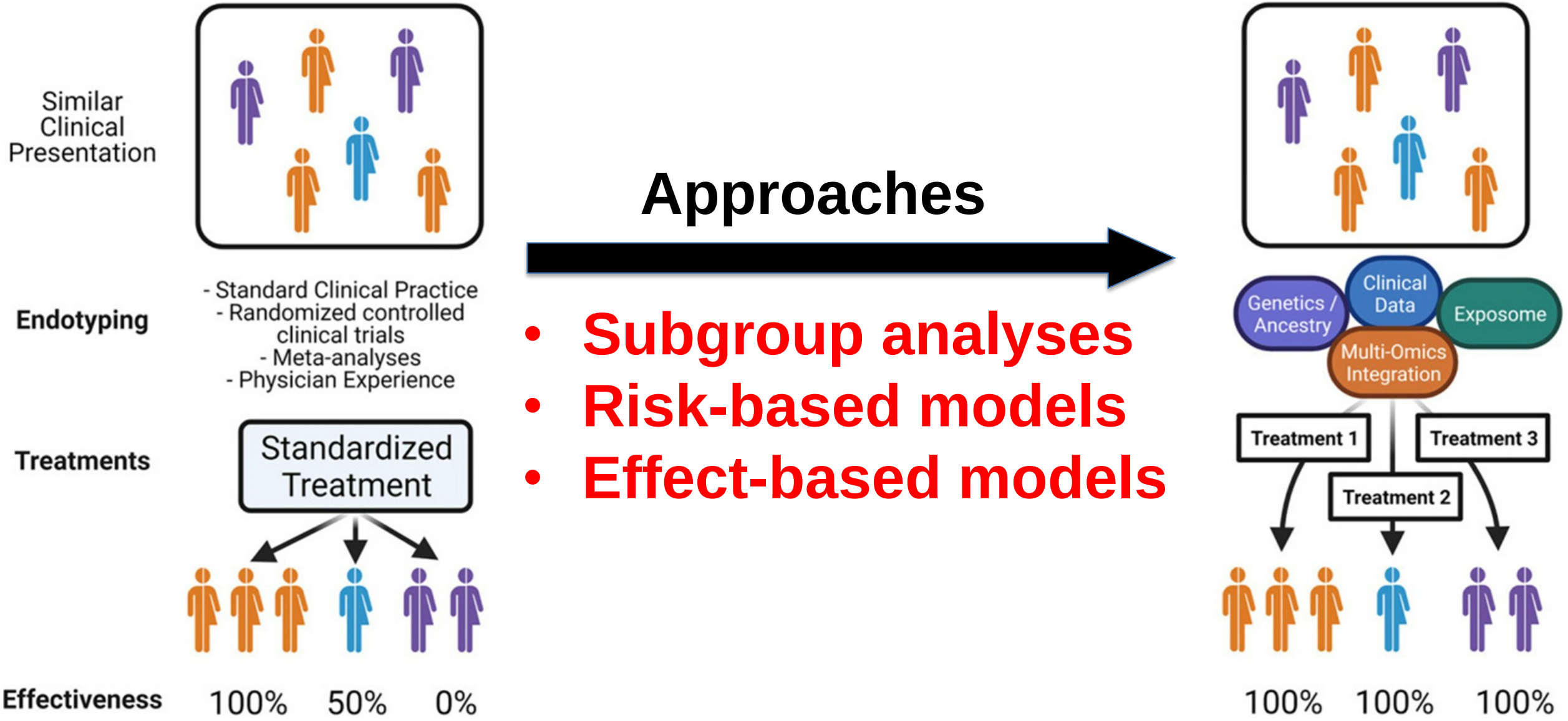

- **Subgroup analyses**
- **Risk-based models**
- **Effect-based models**

https://nationaleczema.org/blog/personalized-medicine-eczema/

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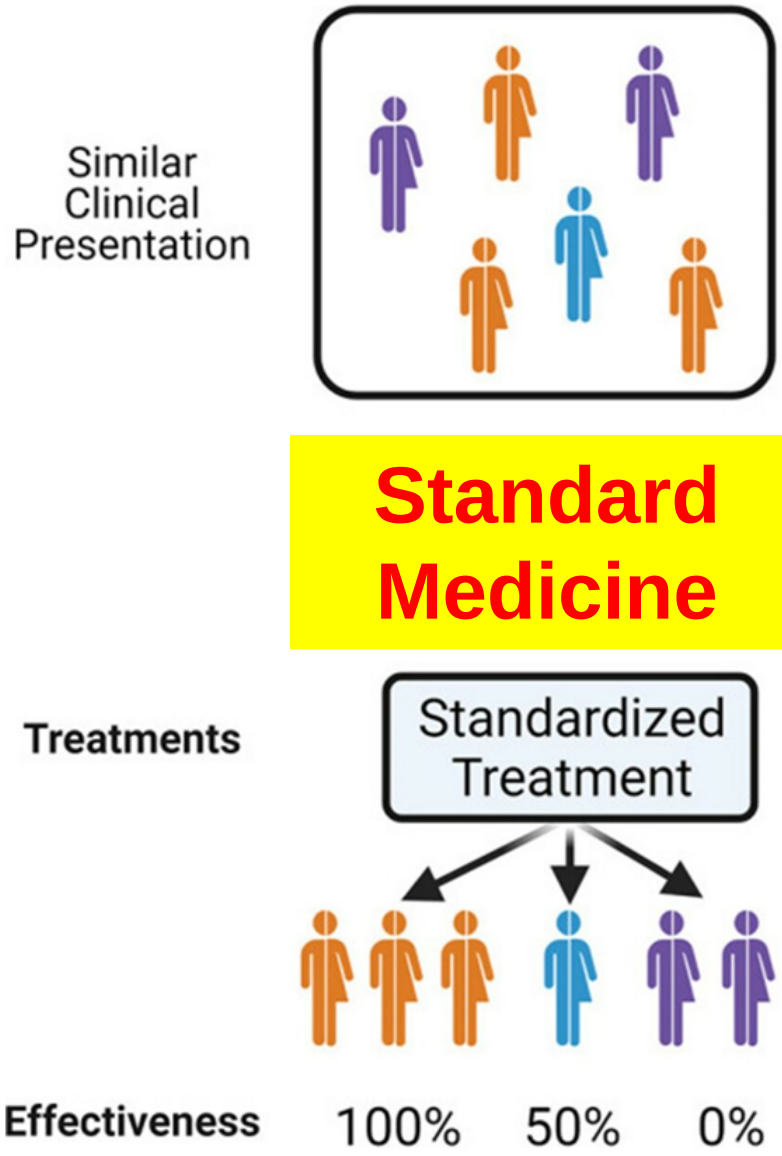

- Subgroup analyses
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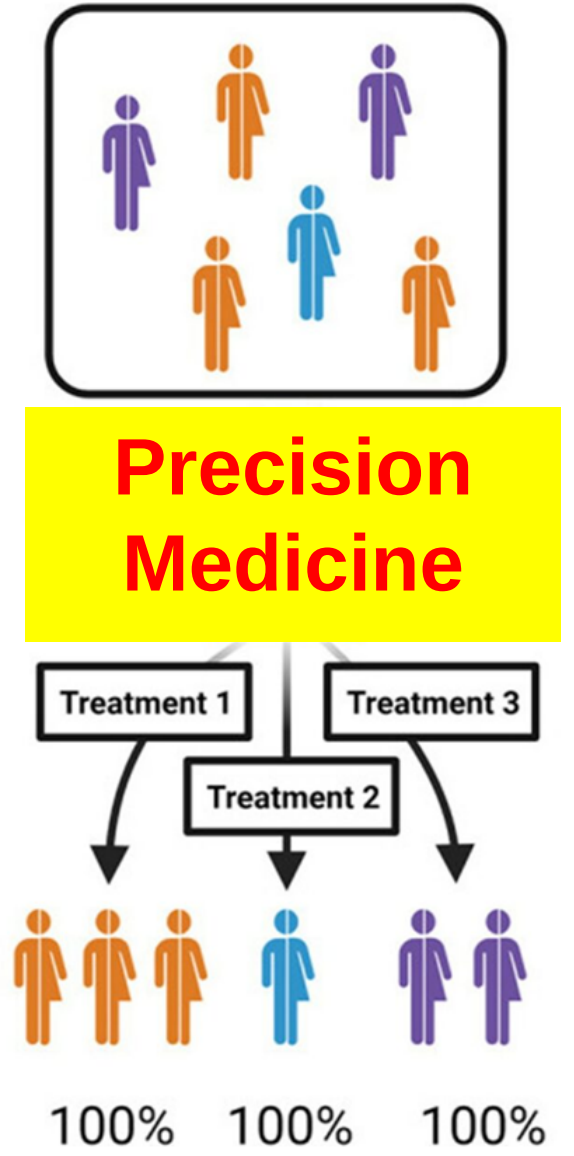

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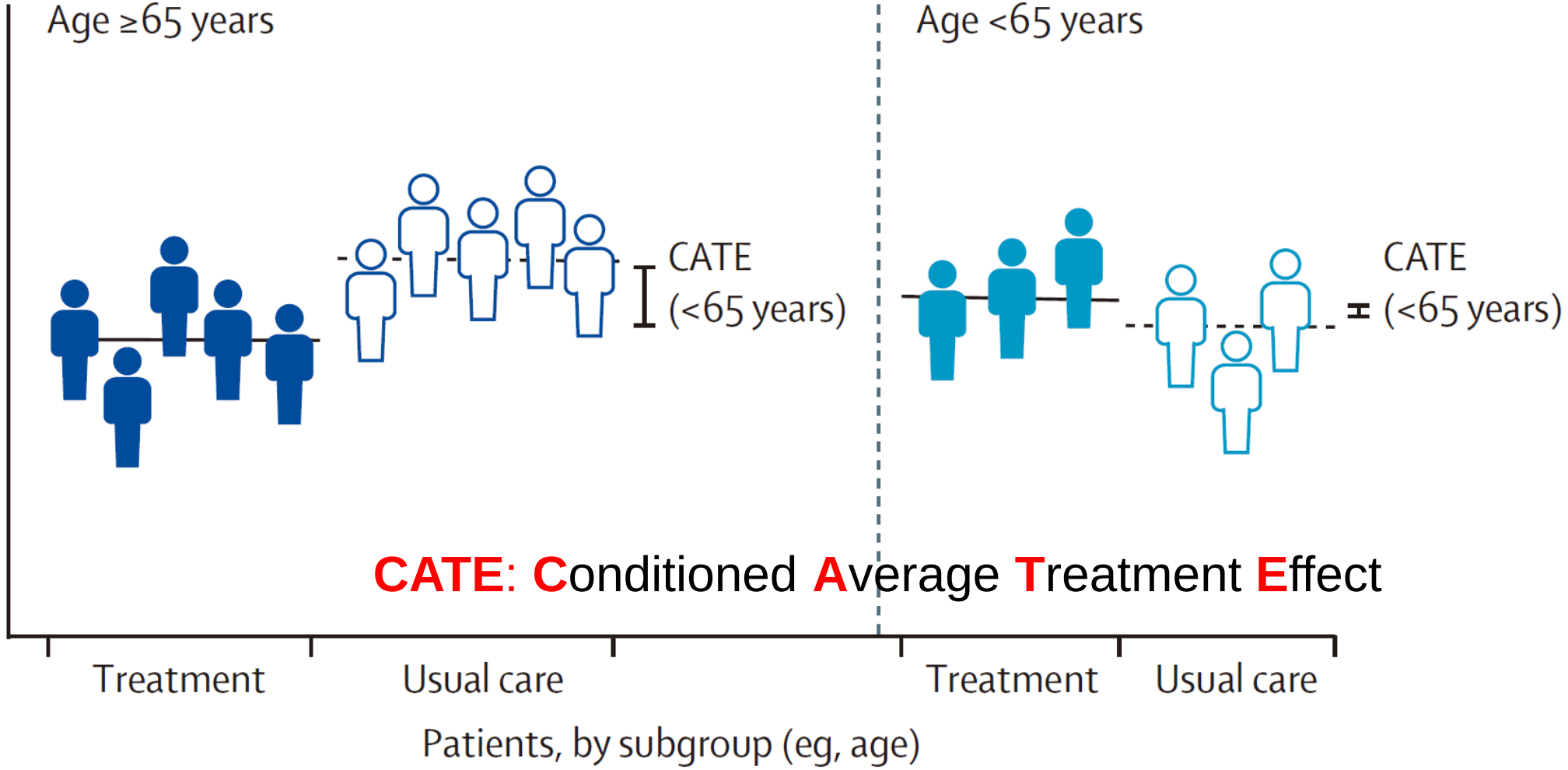
Subgroup Analysis

Average treatment effect for patients with certain characteristics.



Lancet Respir Med. 2025:S2213-2600(25)00054-2.

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

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

DOI: 10.1056/NEJMoa2212663

CLOVER Trial

CLINICAL PROBLEM

Clinicians commonly use intravenous fluids and vasopressor agents in the early care of patients with sepsis-induced hypotension, but there are limited data to guide prioritization of one approach over the other.

CLINICAL TRIAL

Design: A multicenter, randomized, unblinded, superiority trial assessed whether a restrictive fluid strategy that prioritized use of vasopressors during the first 24 hours after resuscitation for sepsis-induced hypotension would improve outcomes as compared with a liberal fluid strategy.

Intervention: 1563 adults with a suspected or confirmed infection and systolic blood pressure <100 mm Hg after receiving ≥1000 ml of intravenous fluid were assigned to a restrictive fluid strategy, in which vasopressors were the primary treatment and "rescue fluids" were allowed as needed, or a liberal fluid strategy, in which an initial 2000-ml infusion of isotonic crystalloid was recommended followed by fluid boluses and "rescue vasopressors" as needed. The primary outcome was death from any cause before discharge home by day 90.

RESULTS

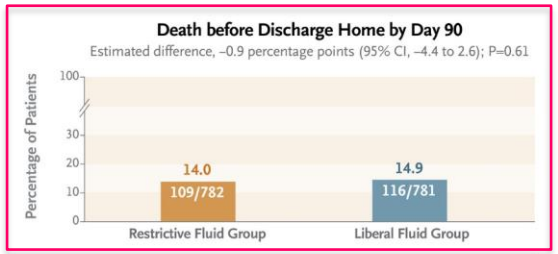
Efficacy: The percentage of patients who died before discharge home by day 90 did not differ significantly between the groups.

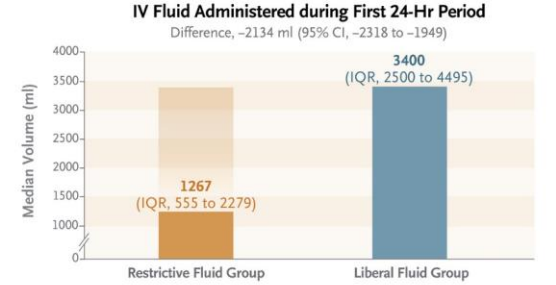
Safety: The number of serious adverse events was similar in the two groups. Serious adverse events involving fluid overload and pulmonary edema occurred in three patients each, all in the liberal fluid group.

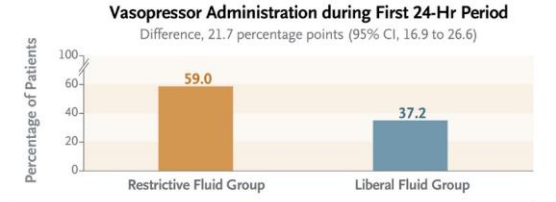
LIMITATIONS AND REMAINING QUESTIONS

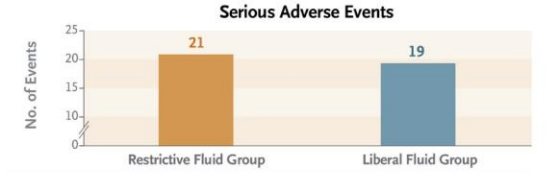
- The results may not be generalizable to patients with extremes of volume overload or depletion.
- Because the trial was unblinded, group assignment may have affected ascertainment and reporting of adverse events.

Links: Full Article | NEJM Quick Take



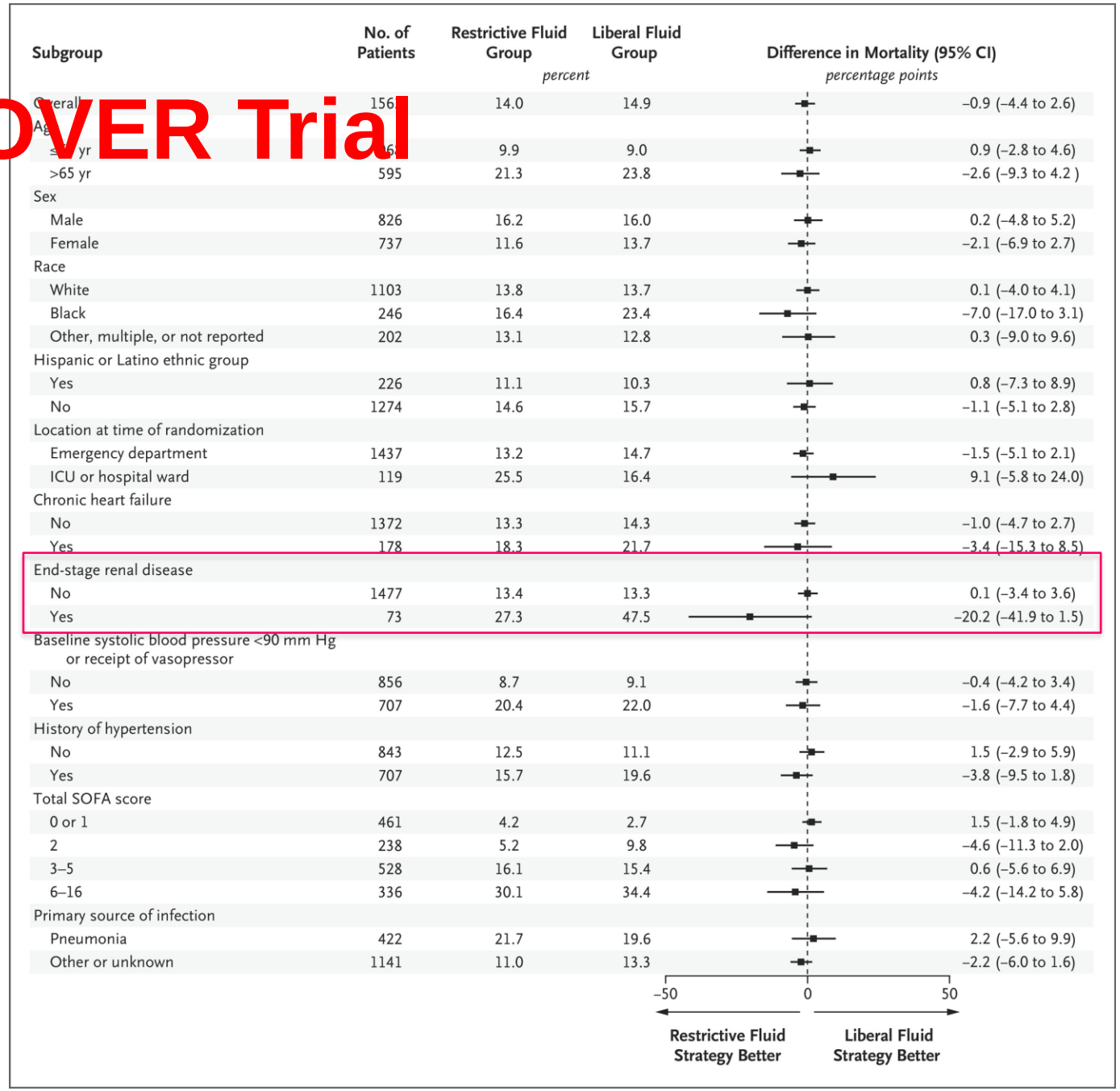






CONCLUSIONS

In patients with sepsis-induced hypotension, a restrictive fluid strategy that prioritized vasopressors in the first 24 hours after resuscitation did not result in significantly lower or higher mortality before discharge home by day 90 than a liberal fluid strategy.



N Engl J Med. 2023;388:499-510.

Subgroup Analysis

- **Limitation**:
  - Evaluate patient s based on **one** characteristic at a time
  - Patients often fall into **multiple** subgroups

Newer Approach

Data-Driven Subgroup Analysis

- Use clustering methods to group patient who are similar based on **multiple** baseline characteristics and biomarkers
- Treat these **clusters** as subgroups
- Evaluate treatment effect by **cluster**

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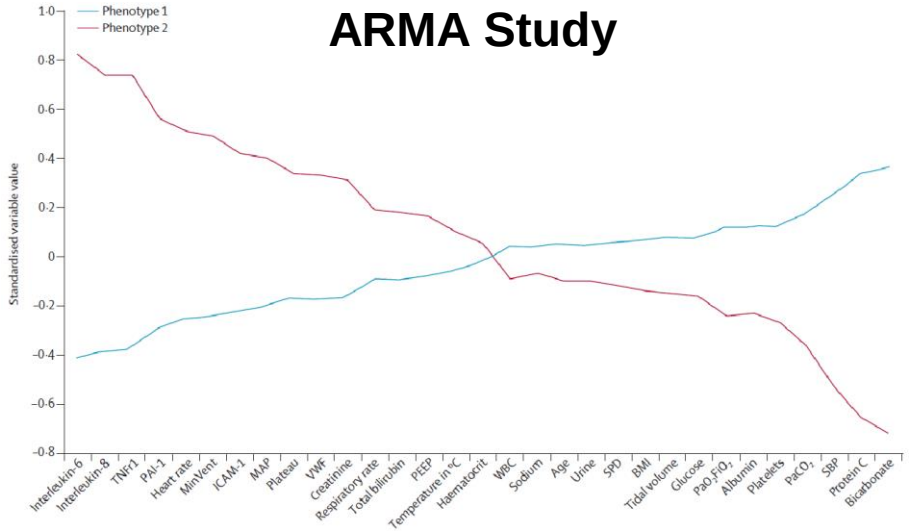
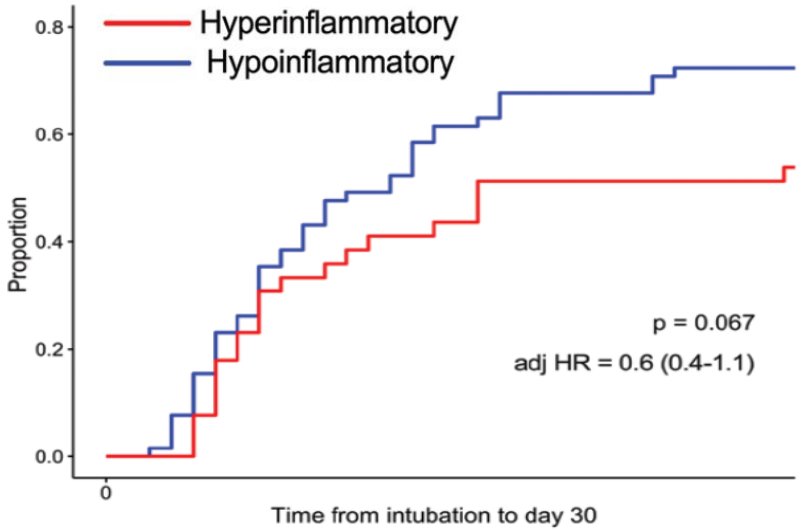
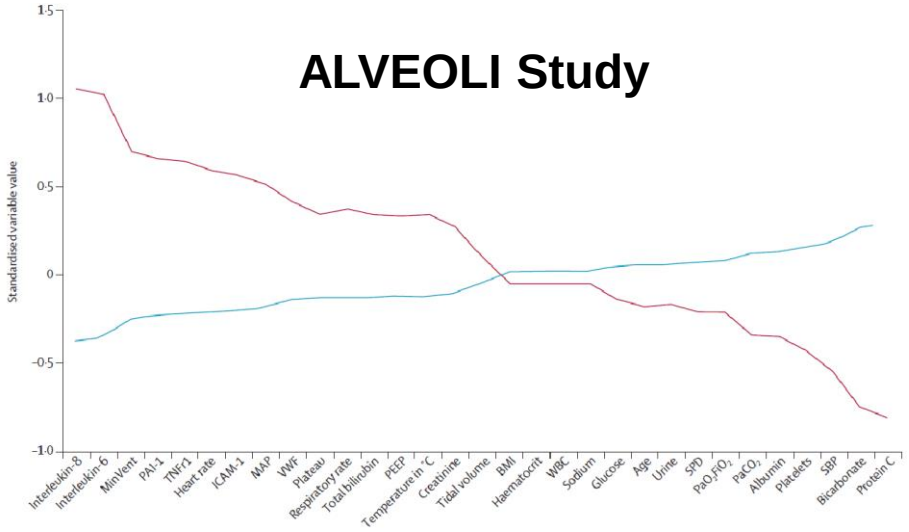
Lancet Respir Med. 2025:S2213-2600(25)00054-2.

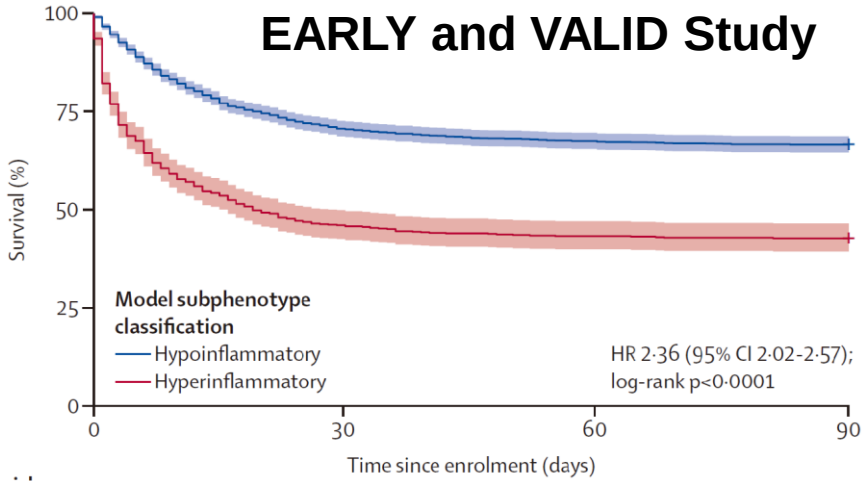
Latent Class Analysis of ARDS

Hypoinflammatory/Hyperinflammatory phenotypes









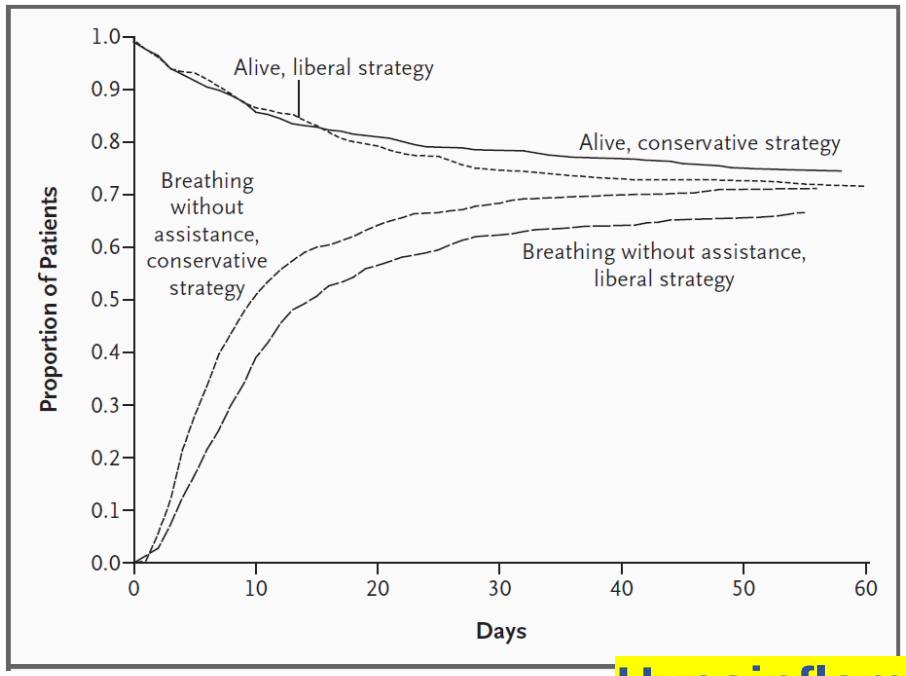
Lancet Respir Med.2014;2:611-620 and 2022;10:367-377. Thorax.2018;73:439-445. Crit Care Med.2019;47:1724-1734.

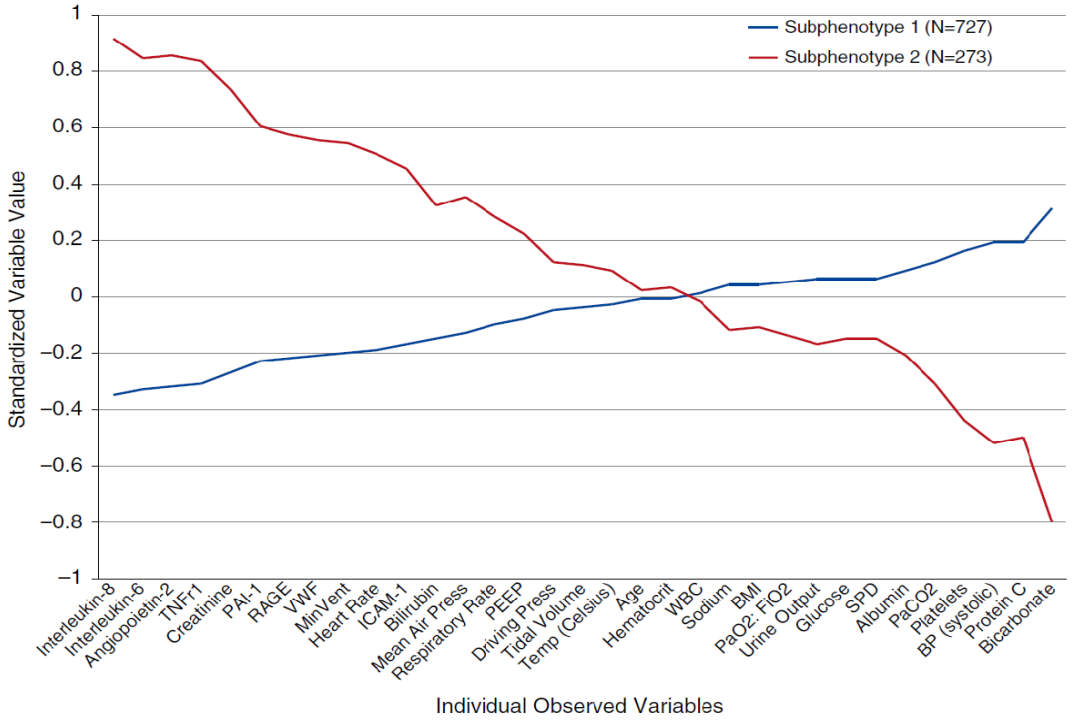
ORIGINAL ARTICLE

Comparison of Two Fluid-Management Strategies in Acute Lung Injury

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*

FACTT trial





	Subphenotype 1 (*n* = 727)	Subphenotype 2 (*n* = 273)	*P* Value
60-d mortality, %	21	44	<0.0001
90-d mortality, %	22	45	<0.0001
Ventilator-free days, median	19	3	<0.0001

Hypoinflammatory **Hyperinflammatory**

	Subphenotype 1		Subphenotype 2		
Fluid-management strategy	Liberal (*n* = 355)	Conservative (*n* = 372)	Liberal (*n* = 142)	Conservative (*n* = 131)	*P* Value
60-d mortality, %	24	17	39	49	0.0093
90-d mortality, %	26	18	40	50	0.0039
Ventilator-free days, median	17	21	5	0	0.35

N Engl J Med. 2006;354:2564-2575. Am J Respir Crit Care Med. 2017;195:331-338.

PEEP in ARDS

EARLI and VALID Study

ARDS Severity by PaO_2/FiO_2	Mortality in Low PEEP	Mortality in High PEEP	P value
Mild (PaO_2/FiO_2 200 – 300) n=828	35% (133/384)	34% (59/173)	0·96
Moderate (PaO_2/FiO_2 100 – < 200) n=1341	39% (172/441)	39% (174/449)	
Severe ($PaO_2/FiO_2 \leq 100$) n=644	48% (55/114)	46% (167/366)	

SOFA subgroups based on mean SOFA score			
ARDS Severity by SOFA score	**Mortality in Low PEEP**	**Mortality in High PEEP**	**P value**
Low SOFA (≤ 10) n=1314	30% (139/457)	30% (132/441)	0·51
High SOFA (> 10) n=1063	54% (165/308)	50% (230/464)	

Lancet Respir Med. 2014;2:611-620 and 2022;10:367-377.

PEEP in ARDS

ARMA and ALVEOLI Study

	Phenotype 1 (n=404)		Phenotype 2 (n=145)		
	Low PEEP (n=202)	High PEEP (n=202)	Low PEEP (n=71)	High PEEP (n=74)	p value*
Mortality at 90 days	33 (16%)	48 (24%)	36 (51%)	31 (42%)	0·049
Ventilator-free days	20 (10–25)	21 (3–24)	2 (0–21)	4·5 (0–20)	0·018
Organ failure free-days	22 (11–26)	22 (9–26)	4 (0–18)	6·5 (0–21)	0·003

Data are n (%) or median (IQR). *p value for interaction between positive end-expiratory pressure (PEEP) assignment and phenotype.

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 31, 2012 VOL. 366 NO. 22

Drotrecogin Alfa (Activated) in Adults with Septic Shock

PROWESS Study

V. Marco Ranieri, M.D., B. Taylor Thompson, M.D., Philip S. Barie, M.D., M.B.A., Jean-François Dhainaut, M.D., Ivor S. Douglas, M.D., Simon Finfer, F.R.C.P., Bengt Gårdlund, M.D., John C. Marshall, M.D., Andrew Rhodes, M.D., Antonio Artigas, M.D., Ph.D., Didier Payen, M.D., Ph.D., Jozsef Tenhunen, M.D., Ph.D., Jason Hussein R. Al-Khalidi, Ph.D., Vivian Thompson, M.P.H., Jonathan Janes, M.B., B.Ch., William L. Macias, M.D., Ph.D., Burkhard Vangerow, M.D., and Mark D. Williams, M.D., for the PROWESS-SHOCK Study Group*

ABSTRACT

BACKGROUND

There have been conflicting reports on the efficacy of recombinant human activated protein C, or drotrecogin alfa (activated) (DrotAA), for the treatment of patients with septic shock.

METHODS

In this randomized, double-blind, placebo-controlled, multicenter trial, we assigned 1697 patients with infection, systemic inflammation, and shock who were receiving fluids and vasopressors above a threshold dose for 4 hours to receive either DrotAA (at a dose of 24 μg per kilogram of body weight per hour) or placebo for 96 hours. The primary outcome was death from any cause 28 days after randomization.

RESULTS

At 28 days, 223 of 846 patients (26.4%) in the DrotAA group and 202 of 834 (24.2%) in the placebo group had died (relative risk in the DrotAA group, 1.09; 95% confidence interval [CI], 0.92 to 1.28; P=0.31). At 90 days, 287 of 842 patients (34.1%) in the DrotAA group and 269 of 822 (32.7%) in the placebo group had died (relative risk, 1.04; 95% CI, 0.90 to 1.19; P=0.56). Among patients with severe protein C deficiency at baseline, 98 of 342 (28.7%) in the DrotAA group had died at 28 days, as compared with 102 of 331 (30.8%) in the placebo group (risk ratio, 0.93; 95% CI, 0.74 to 1.17; P=0.54). Similarly, rates of death at 28 and 90 days were not significantly different in other predefined subgroups, including patients at increased risk for death. Serious bleeding during the treatment period occurred in 10 patients in the DrotAA group and 8 in the placebo group (P=0.81).

CONCLUSIONS

DrotAA did not significantly reduce mortality at 28 or 90 days, as compared with placebo, in patients with septic shock. (Funded by Eli Lilly; PROWESS-SHOCK ClinicalTrials.gov number, NCT00604214.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Thompson at the Pulmonary and Critical Care Unit, Bullfinch Bldg., Rm. 148, Massachusetts General Hospital, 55 Fruit St., Boston, MA 02114, or at tthompson1@partners.org.

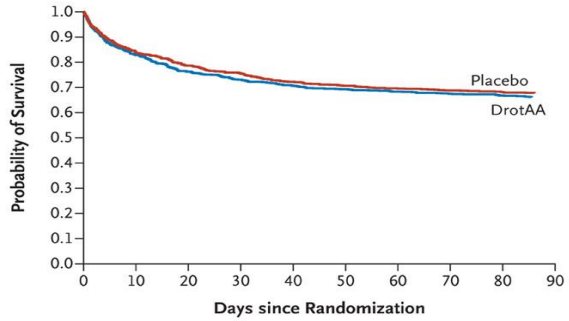
Drs. Ranieri and Thompson contributed equally to this article.

*Investigators in the Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis and Septic Shock (PROWESS-SHOCK) study group are listed in the Supplementary Appendix, available at NEJM.org.

This article (10.1056/NEJMoa1202290) was published on May 22, 2012, at NEJM.org.

N Engl J Med 2012;366:2055-64.

A Probability of Survival

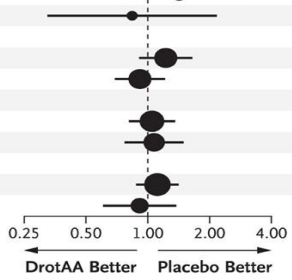


No. at Risk

Placebo	845	703	656	622	593	579	569	563	557	553
DrotAA	851	701	645	616	596	584	576	567	561	555

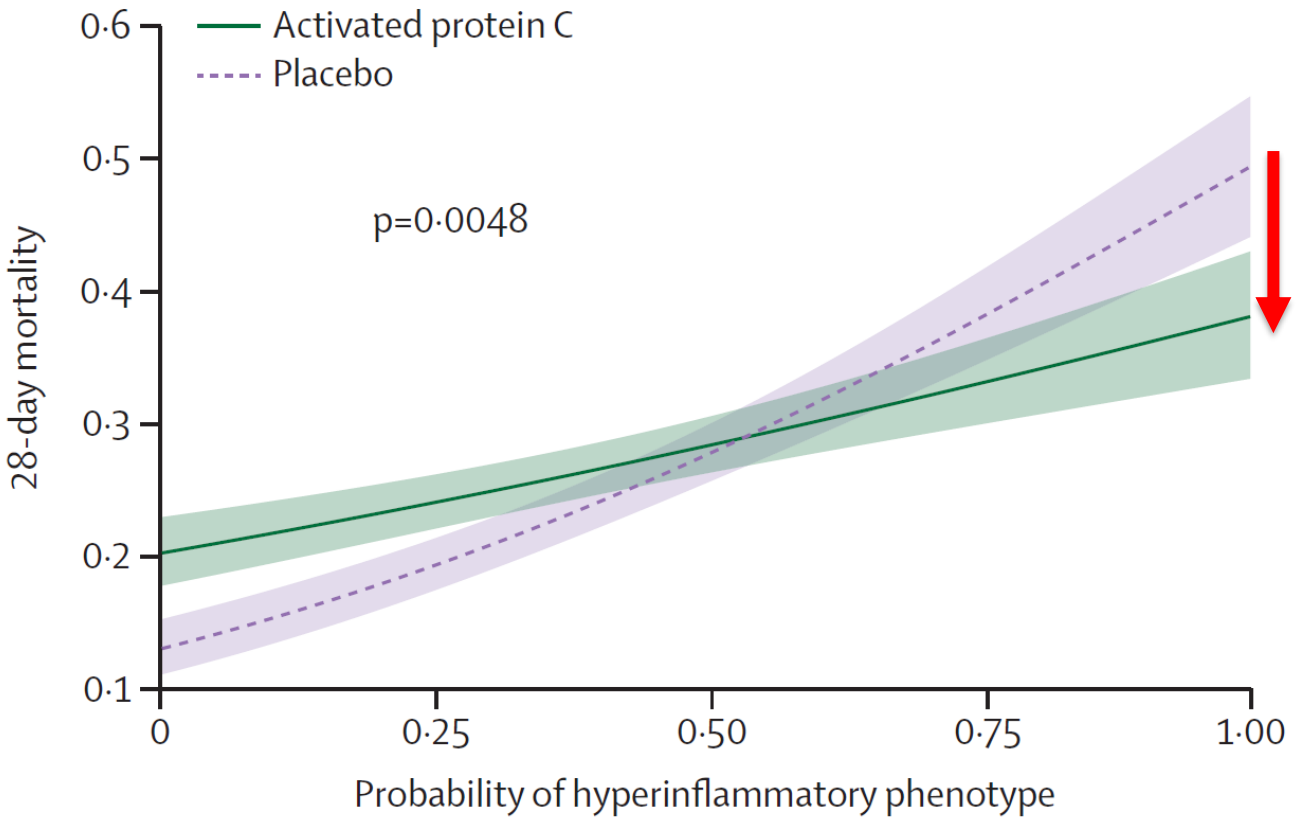
B Odds Ratio for Death

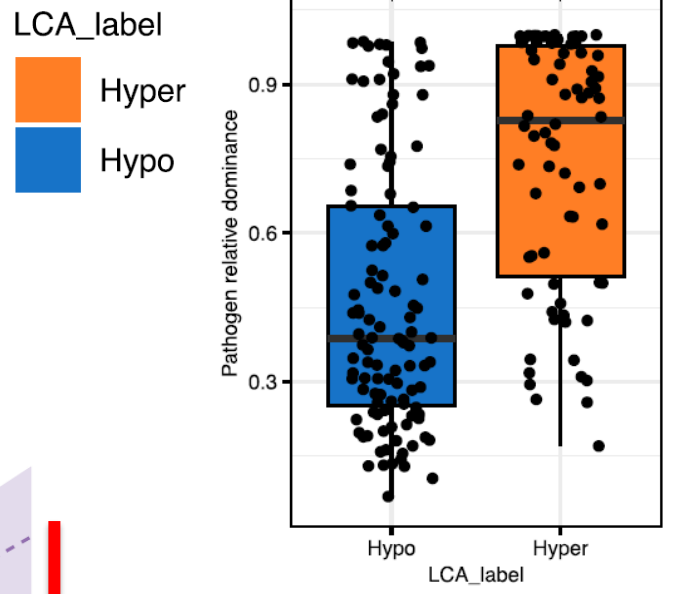
Subgroup	No. of Patients	DrotAA	Placebo	P Value for Heterogeneity
		no. of deaths (%)		
All patients	1664	287 (34.1)	269 (32.7)	
APACHE II class				0.51
<25	827	108 (25.7)	93 (22.9)	
≥25	832	178 (42.6)	175 (42.3)	
No. of baseline organ failures				0.35
1 or 2	260	36 (27.5)	30 (23.3)	
3	560	88 (32.1)	78 (27.3)	
4	633	120 (37.0)	116 (37.5)	
5	211	43 (38.1)	45 (45.9)	
Recent surgery				0.18
No	1048	188 (35.5)	165 (31.8)	
Yes	616	99 (31.6)	104 (34.3)	
Baseline ARDS status				0.29
No	1209	205 (33.1)	178 (30.2)	
Yes	455	82 (36.8)	91 (39.2)	
Quartile of time from start of vasopressor to start of infusion				0.48
First	412	62 (31.8)	64 (29.5)	
Second	413	66 (29.3)	64 (34.0)	
Third	407	72 (36.4)	66 (31.6)	
Fourth	407	79 (38.0)	69 (34.7)	
Protein C class				0.63
≤40%	668	125 (36.5)	130 (39.9)	
41–60%	371	54 (28.7)	52 (28.4)	
61–80%	188	22 (23.7)	17 (17.9)	
>80%	92	10 (23.3)	13 (2.65)	
Baseline glucocorticoid exposure				0.17
No	836	127 (31.2)	116 (27.0)	
Yes	827	160 (36.9)	153 (38.9)	
Baseline prophylactic heparin exposure				0.91
No	1003	185 (35.7)	168 (34.6)	
Yes	661	102 (31.5)	101 (30.0)	
Baseline coagulation SOFA				0.41
0–1	1248	207 (33.2)	193 (30.9)	
2–4	389	76 (36.5)	70 (38.7)	

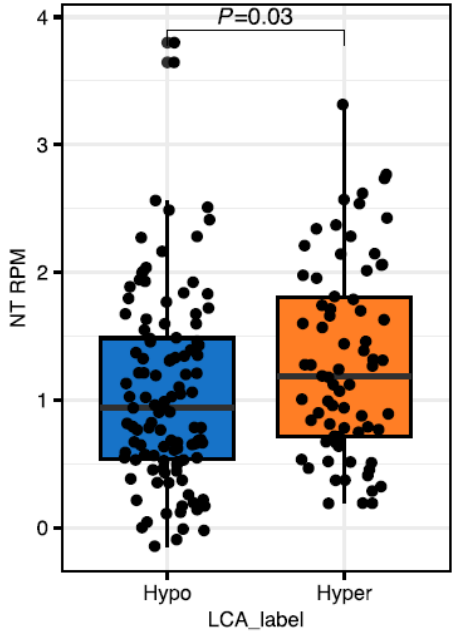


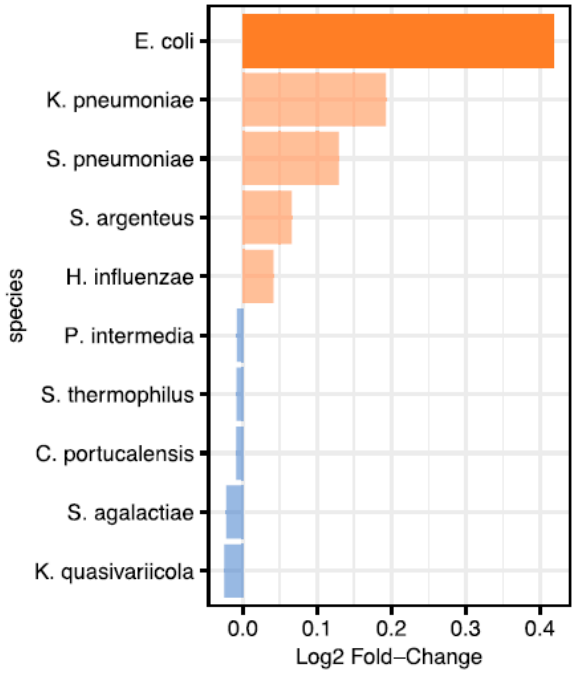
N Engl J Med 2012;366:2055-64.

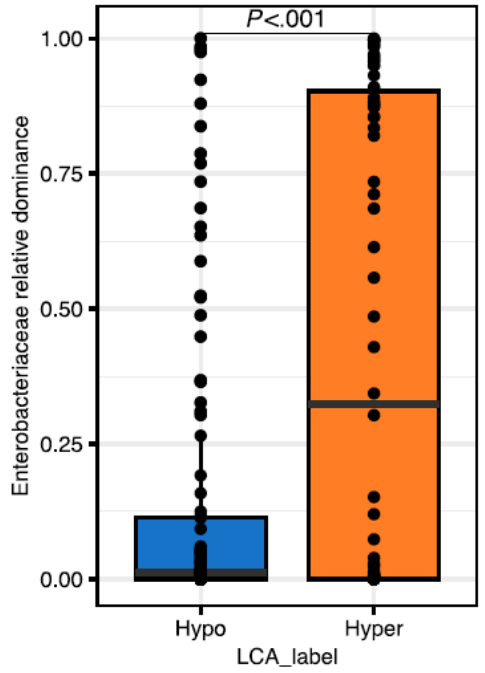
Hyper-inflammatory
Hypo-inflammatory







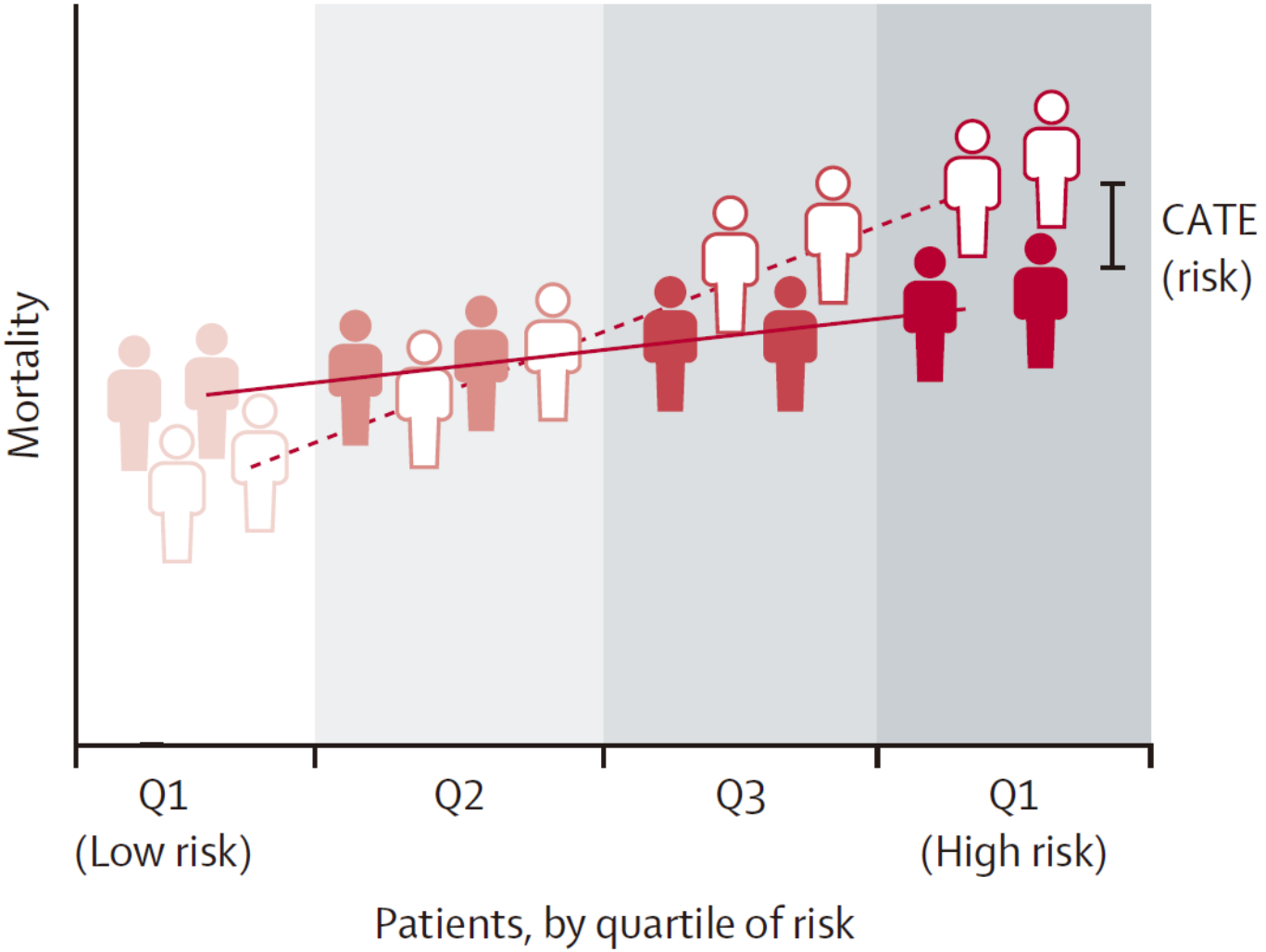




Lancet Respir Med. 2023;11:965-974.
Am J Respir Crit Care Med. 2024;209:805-815.

Risk-Based Models

Treatment effect conditional on baselines risk of mortality.



Lancet Respir Med. 2025:S2213-2600(25)00054-2.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Critically Ill Adults

ABSTRACT

BACKGROUND

Both balanced crystalloids and saline are used for intravenous fluid administration in critically ill adults, but it is not known which results in better clinical outcomes.

METHODS

In a pragmatic, cluster-randomized, multiple-crossover trial conducted in five intensive care units at an academic center, we assigned 15,802 adults to receive saline (0.9% sodium chloride) or balanced crystalloids (lactated Ringer's solution or Plasma-Lyte A) according to the randomization of the unit to which they were admitted. The primary outcome was a major adverse kidney event within 30 days — a composite of death from any cause, new renal-replacement therapy, or persistent renal dysfunction (defined as an elevation of the creatinine level to ≥200% of baseline) — all censored at hospital discharge or 30 days, whichever occurred first.

RESULTS

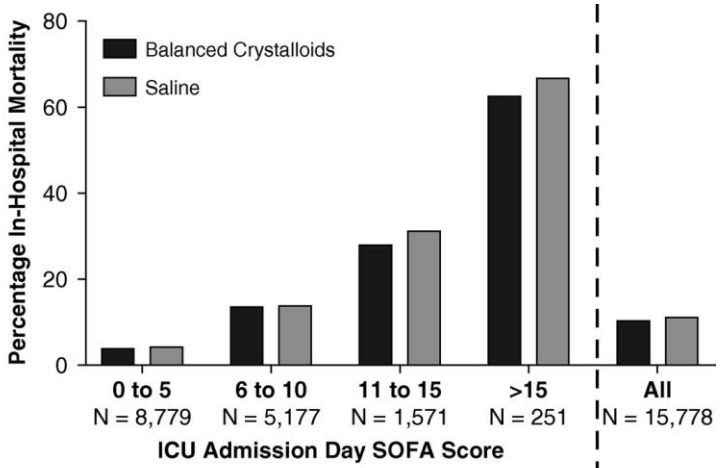
Among the 7942 patients in the balanced-crystalloids group, 1139 (14.3%) had a major adverse kidney event, as compared with 1211 of 7860 patients (15.4%) in the saline group (marginal odds ratio, 0.91; 95% confidence interval [CI], 0.84 to 0.99; conditional odds ratio, 0.90; 95% CI, 0.82 to 0.99; P=0.04). In-hospital mortality at 30 days was 10.3% in the balanced-crystalloids group and 11.1% in the saline group (P=0.06). The incidence of new renal-replacement therapy was 2.5% and 2.9%, respectively (P=0.08), and the incidence of persistent renal dysfunction was 6.4% and 6.6%, respectively (P=0.60).

CONCLUSIONS

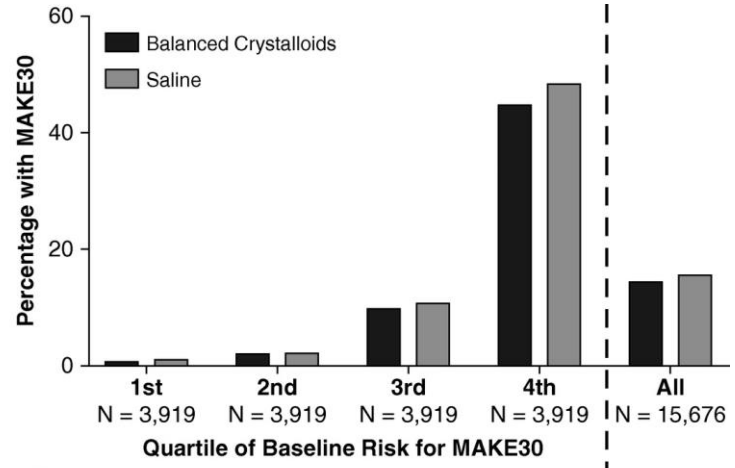
Among critically ill adults, the use of balanced crystalloids for intravenous fluid administration resulted in a lower rate of the composite outcome of death from any cause, new renal-replacement therapy, or persistent renal dysfunction than the use of saline. (Funded by the Vanderbilt Institute for Clinical and Translational Research and others; SMART-MED and SMART-SURG ClinicalTrials.gov numbers, NCT02444988 and NCT02547779.)

Risk-Based Models

SMART (Isotonic Solutions and Major Adverse Renal Events Trial)



	0 to 5	6 to 10	11 to 15	>15	All
Absolute Risk Difference	−0.4%	−0.2%	−3.2%	−4.2%	−0.8%
Risk Ratio	0.92	0.99	0.90	0.94	0.93
Odds Ratio	0.91	0.98	0.86	0.83	0.92



	1st	2nd	3rd	4th	All
Absolute Risk Difference	−0.3%	−0.1%	−0.9%	−3.7%	−1.2%
Risk Ratio	0.67	0.96	0.91	0.92	0.92
Odds Ratio	0.67	0.96	0.90	0.86	0.91

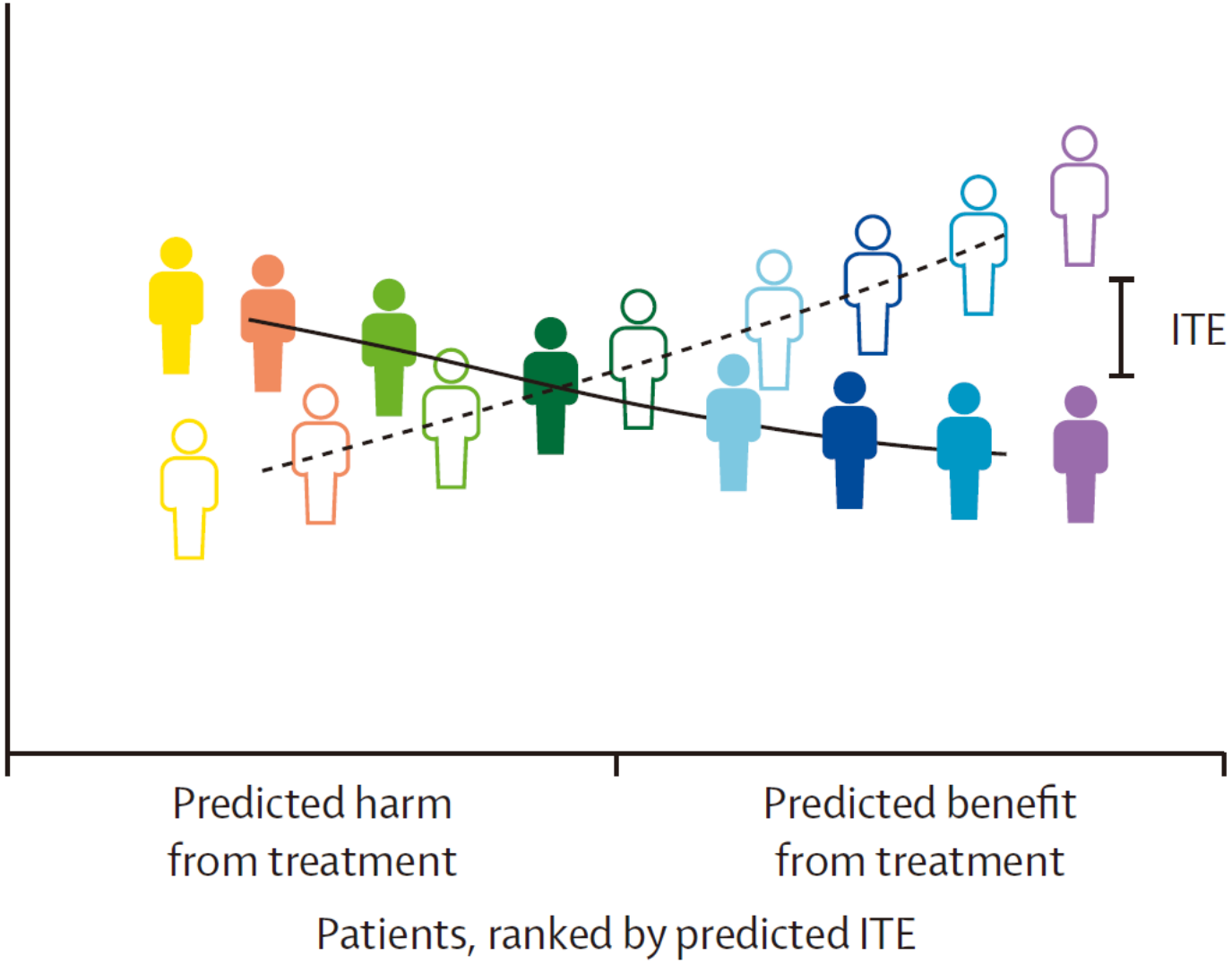
Major Adverse Kidney Events within 30 days (MAKE30)

A composite of in-hospital death, new receipt of renal-replacement therapy, and persistent renal dysfunction (defined as a final inpatient creatinine value ≥200% of the baseline value)

Am J Respir Crit Care Med. 2018;198:810-813.
N Engl J Med. 2018;378:829-839.

Effect-Based Models

Predict individualized treatment effect (ITE) based on each patients baseline characteristics



Lancet Respir Med. 2025:S2213-2600(25)00054-2.

Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill Patients

JAMA Network™

The BaSICS Randomized Clinical Trial

QUESTION Among patients in the ICU requiring intravenous fluid challenges, does the use of a balanced solution compared with saline solution (0.9% sodium chloride) improve 90-day survival?

CONCLUSION Among critically ill patients requiring fluid challenges, treatment with a balanced solution compared with saline solution did not significantly reduce 90-day mortality.

POPULATION

5865 Men **4655** Women

ICU patients with ≥1 risk factor for worse outcomes who required fluid expansion and were expected to stay >24 hours

Mean age: **61** years

LOCATIONS

75
ICUs in Brazil

INTERVENTION

11 052 Patients randomized
10 520 Patients analyzed

5230

Balanced solution
Isotonic solution of pH 7.4 (infusion rate also randomized and analyzed separately)

5290

Saline solution
0.9% sodium chloride (infusion rate also randomized and analyzed separately)

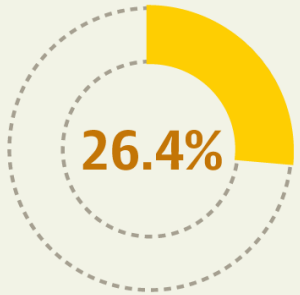
PRIMARY OUTCOME

90-day survival

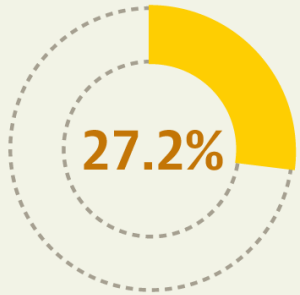
FINDINGS

Deaths within 90 days

Balanced solution
1381 of 5230 patients died



Saline solution
1439 of 5290 patients died

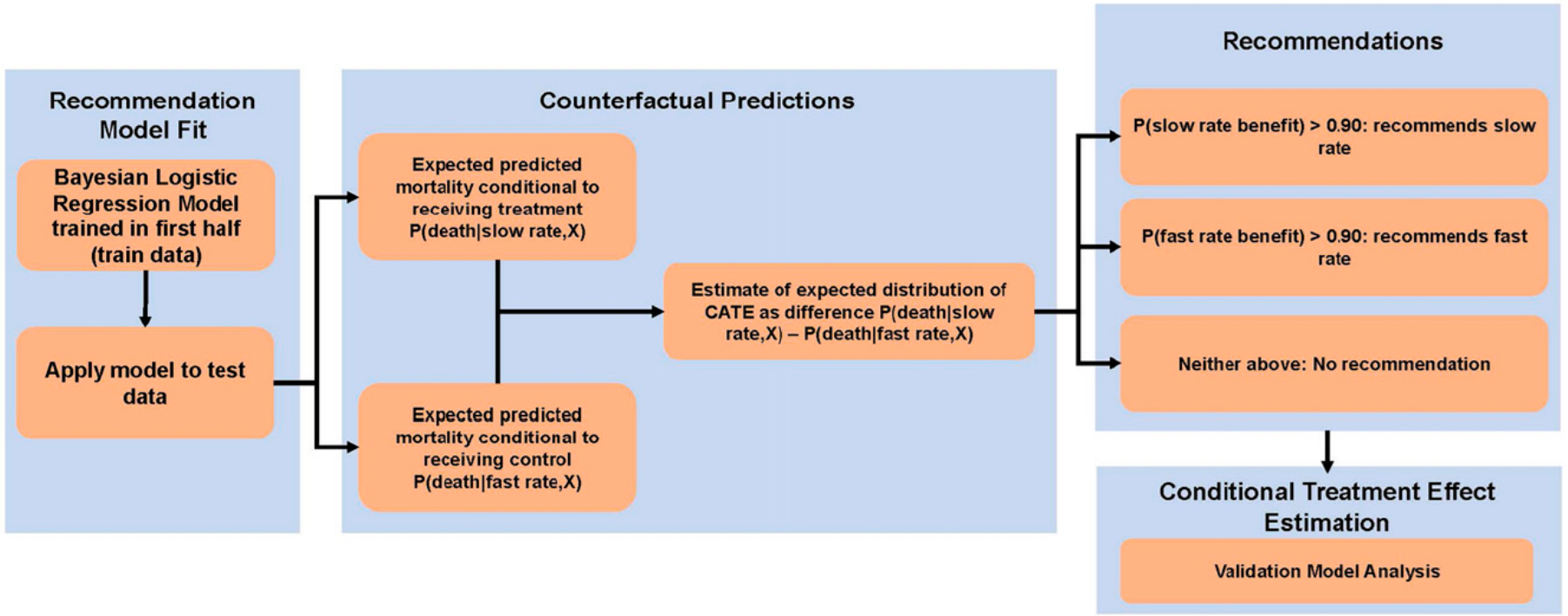


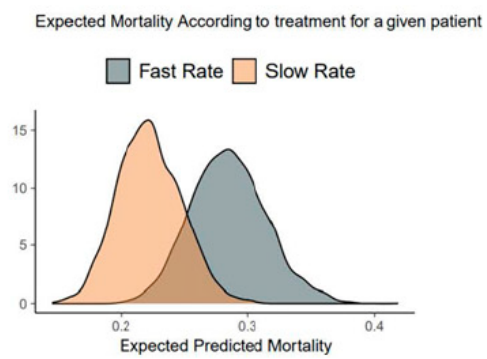
Findings were not statistically significant:
Adjusted HR, **0.97** (95% CI, 0.90 to 1.05)

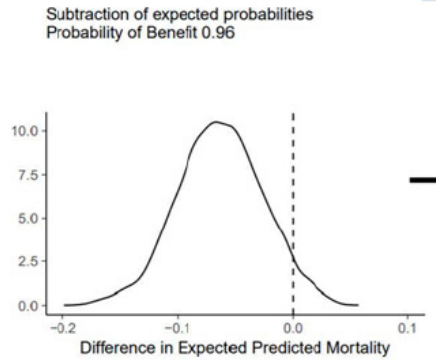
JAMA. 2021;326:818-829.

Conditional Treatment Effect Analysis of Two Infusion Rates for Fluid Challenges in Critically Ill Patients

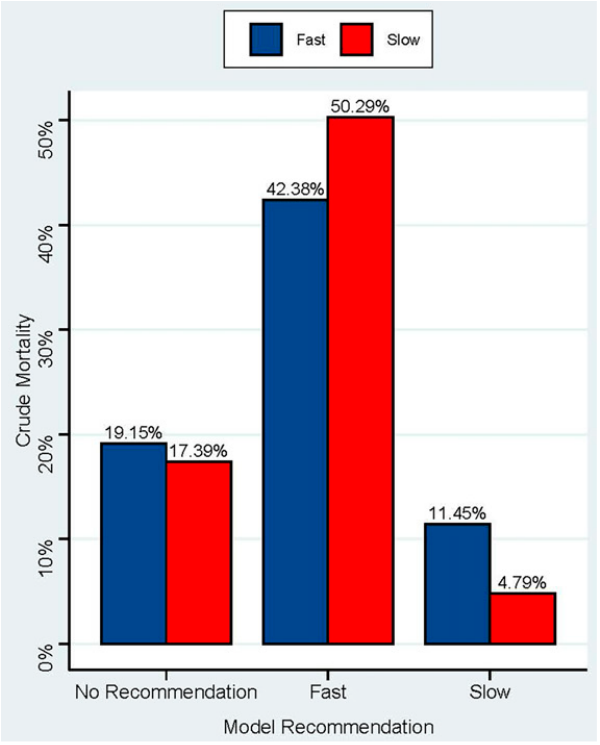
A Secondary Analysis of Balanced Solution versus Saline in Intensive Care Study (BaSICS) Trial

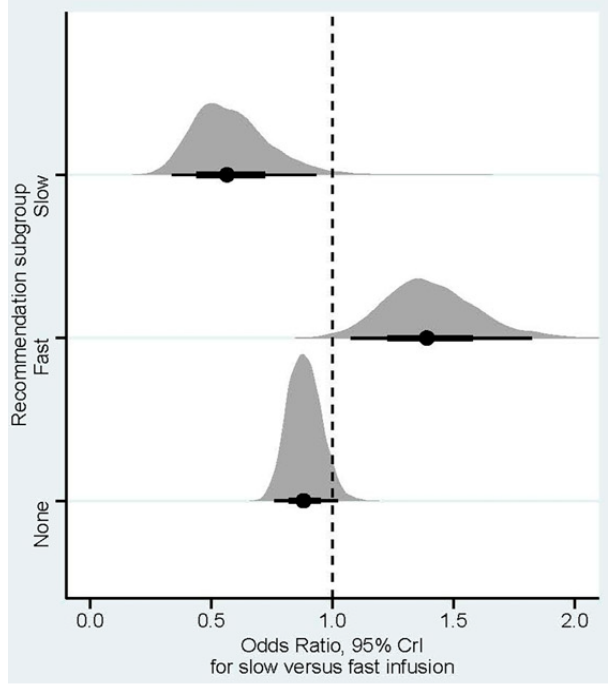






Recommendation Model suggests slow rate for this patient





Ann Am Thorac Soc. 2023;20:872-879.

Conditional Treatment Effect Analysis of Two Infusion Rates for Fluid Challenges in Critically Ill Patients

A Secondary Analysis of Balanced Solution versus Saline in Intensive Care Study (BaSICS) Trial

Overall patient features according to model suggestion in the test set

Characteristic	No Suggestion (*n* = 4,223)	Fast Infusion (*n* = 735)	Slow Infusion (*n* = 277)
Age	62 (50–72)	79 (69–86)	36 (28–43)
Female sex	1,771 (42%)	355 (48%)	136 (49%)
APACHE II score	11 (8–15)	17 (13–23)	7 (5–10)
SOFA score	4.0 (2.0–6.0)	5.0 (3.0–8.0)	4.0 (2.0–6.0)
Mean arterial pressure, mm Hg	74 (63–87)	70 (60–84)	73 (64–84)
Heart rate, beats per min	92 (77–109)	96 (81–112)	97 (81–111)
Vasopressor use	1,627 (39%)	190 (26%)	164 (59%)
Acute kidney injury at enrollment	1,222 (29%)	398 (54%)	57 (21%)
Creatinine, mg/dl	0.95 (0.71–1.28)	1.24 (0.90–1.94)	0.80 (0.60–1.07)
Admission type			
Unplanned, not sepsis	1,249 (30%)	264 (36%)	52 (19%)
Planned	2,480 (59%)	23 (3.1%)	225 (81%)
Unplanned, sepsis	494 (12%)	448 (61%)	0
Mechanical ventilation	2,276 (54%)	435 (59%)	48 (17%)
Noninvasive ventilation	31 (0.7%)	0	9 (3.2%)
Intensive care unit length of stay	3 (2–6)	5 (2–11)	3 (2–4)
Hospital length of stay	8 (5–16)	10 (5–21)	8 (6–15)
Need for kidney replacement therapy	283 (6.7%)	86 (12%)	10 (3.6%)
Hospital mortality	771 (18%)	339 (46%)	22 (7.9%)
90-d mortality	897 (21%)	388 (53%)	32 (12%)

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; SOFA = Sequential Organ Failure Assessment.
Values presented as median (interquartile range) where applicable.

Ann Am Thorac Soc. 2023;20:872-879.

Platforms and Consortiums

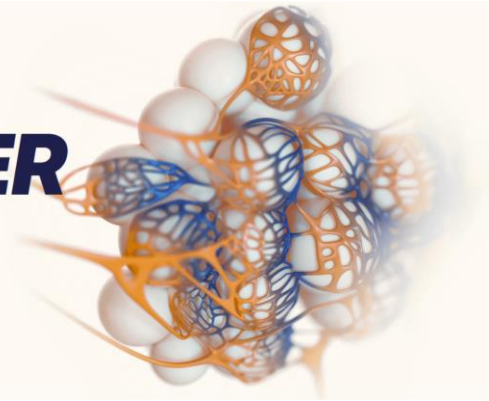
PANTHER

Please note that our website is currently under development, and we are working diligently to bring you more content soon.

PANTHER

TRIAL PLATFORM

PANTHER (Precision medicine Adaptive platform Network Trial in Hypoxaemic acutE respiratory failure) is a Bayesian adaptive platform randomized clinical trial studying novel interventions to improve outcomes for patients with acute hypoxaemic respiratory failure.



PRACTICAL

PLATFORM

PRACTICAL (Platform of Randomized Adaptive Clinical Trials in Critical Illness) is a Bayesian adaptive platform randomized clinical trial studying novel interventions to improve outcomes for patients with acute hypoxemic respiratory failure.

APS Consortium

QL

Quantum Leap Healthcare Collaborative

ISPY COVID/ARDS Trial Sites

INCEPT

The Intensive Care Platform Trial

REMAP-CAP

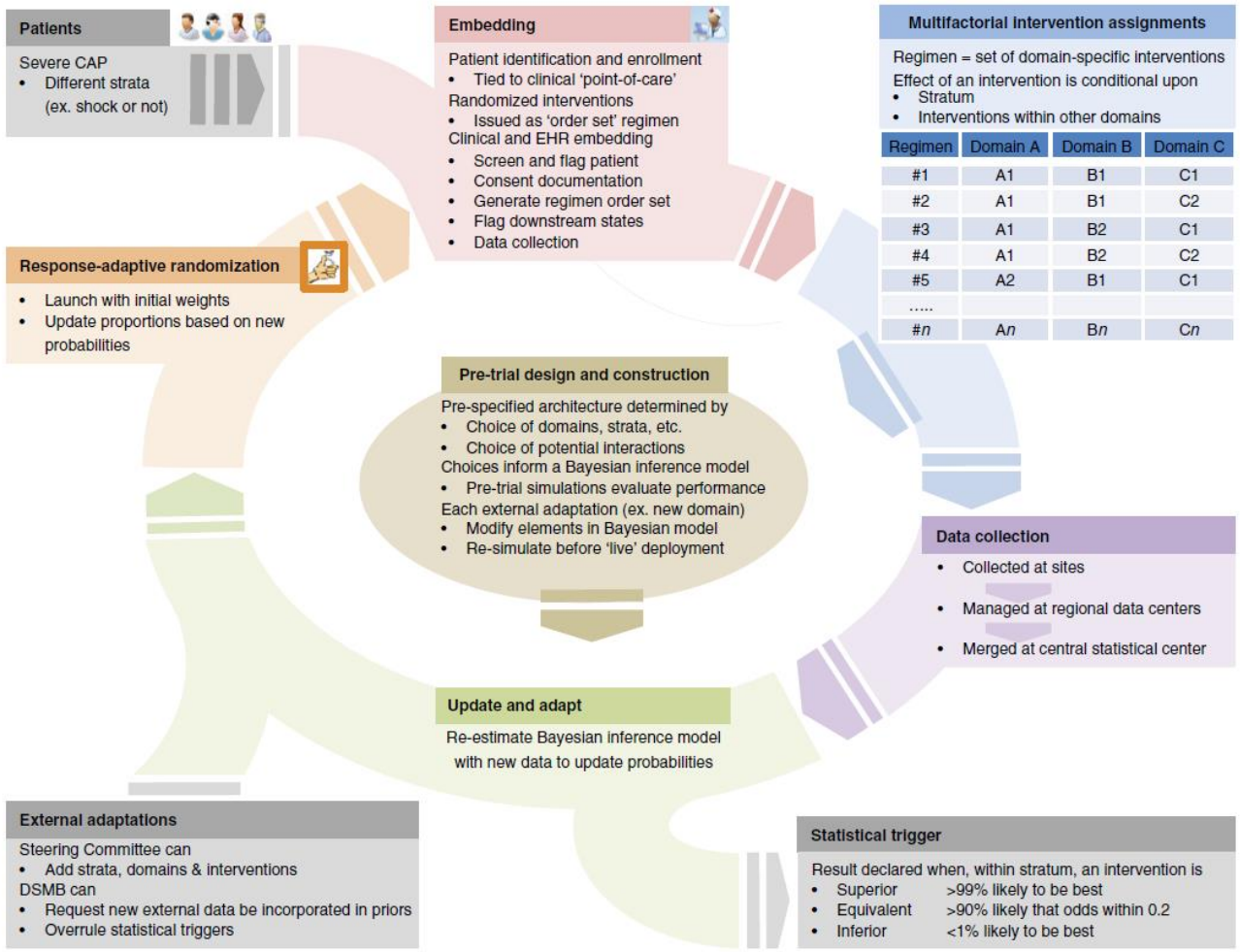
Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

TRAITS

ENABLING PRECISION MEDICINE FOR INTENSIVE CARE

TREATABLE TRAITS | CLINICAL TRIAL | BIOLOGY

REMAP-CAP



R **Randomization.** Once the design is specified, sites are recruited and trained, appropriate oversight and approval is obtained, and all study execution procedures are deployed, the study launches. The trial begins by randomizing patients with fixed allocations to each treatment arm, proportional to the number of arms. Later, randomization weights are adjusted based on updated probabilities from the Bayesian inference model.

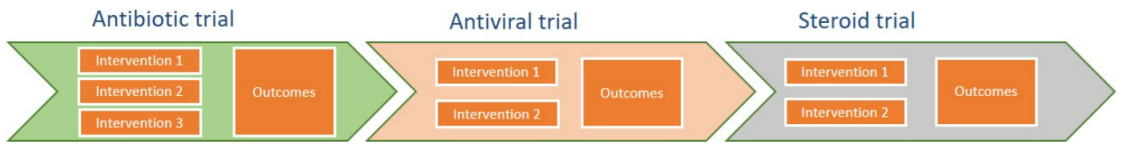
E **Embedding.** A key element of the design is tight integration with clinical operations, including using a clinical 'moment', or 'point-of-care' to flag and enroll patients and to deliver the treatment regimen as an 'order set'. Ideally, embedding will take advantage of electronic health record data, not only to help flag and enroll patients, but to deliver patient order sets and to facilitate on-going monitoring and data collection.

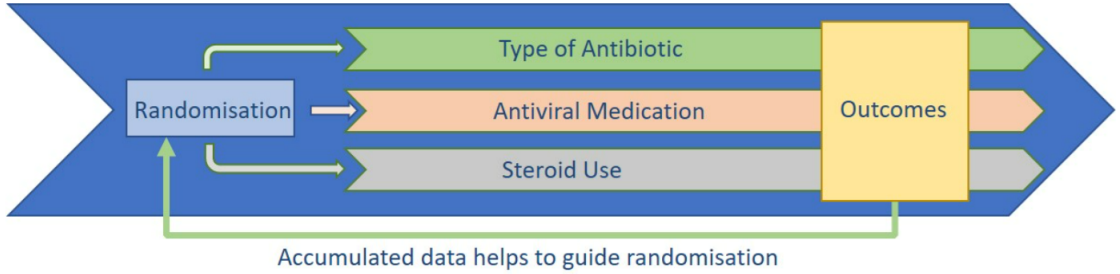
M **Multifactorial intervention assignments.** The treatment regimens themselves are assigned as a regimen, containing each randomized intervention within each domain. In settings with standard ICU order sets, the regimen would ideally be generated automatically, with inclusion of standard non-randomized ICU care elements as well as those randomized items that are part of REMAP-CAP.

A **Adaptation.** The heart of the trial is the monthly update of the Bayesian inference model. Each month, the SAC runs the Bayesian inferencemodel using the updated trial data to generate an updated posterior probability for all trial outcomes. If the model generates a probability that has crossed a predetermined threshold, it triggers a platform conclusion. Otherwise, the probabilities are used to update the randomizationweights.

P **Platform.** The entire trial is envisioned, like all adaptive platform trials, as a learning engine that can test multiple interventions both in parallel and sequentially. Thus, the focus is on the condition, CAP, itself, and not on any particular intervention. This approach allows a standard approach for enrollment and data collection to be built once and then run perpetually, providing numerous efficiencies.

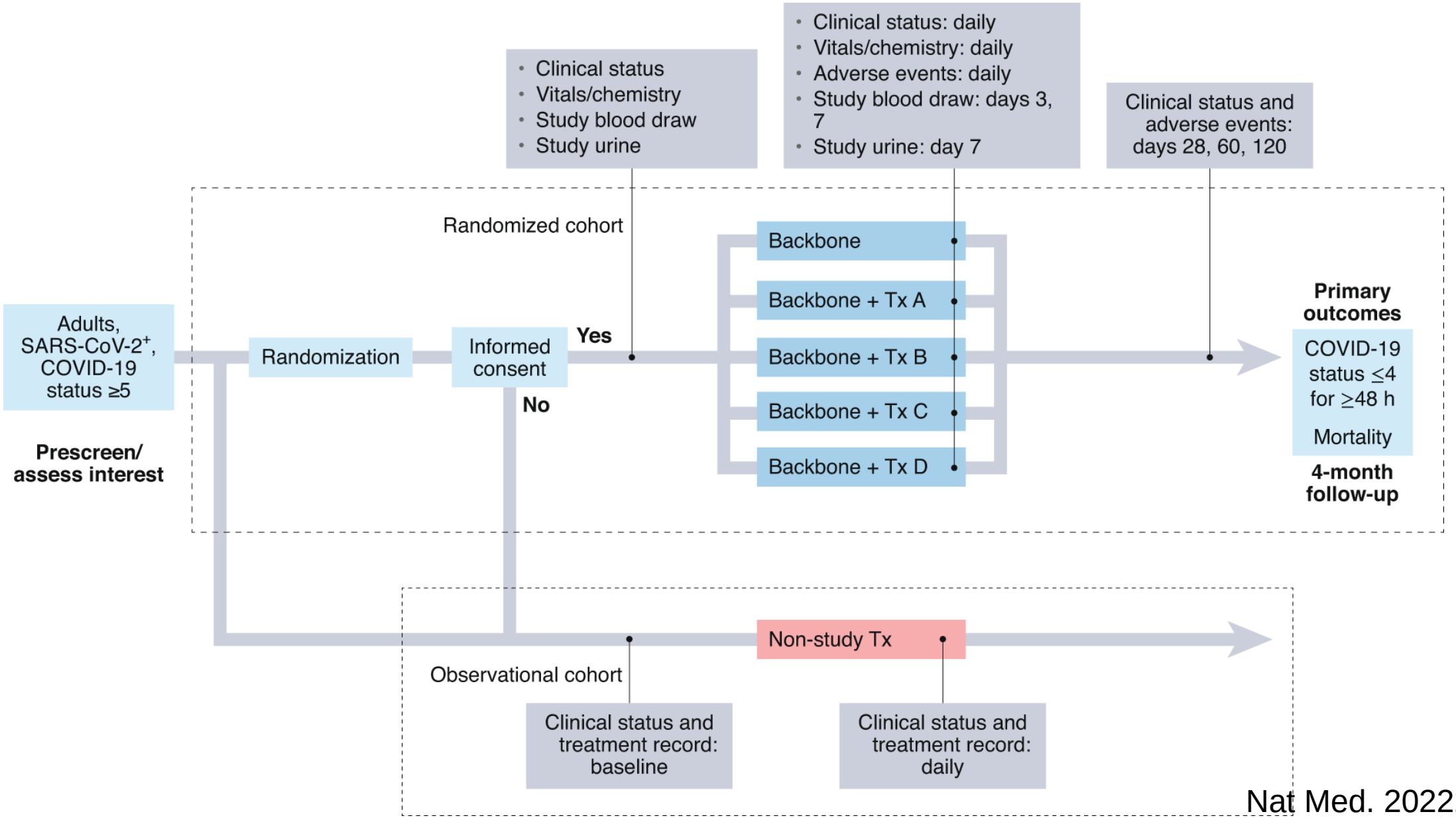
Data collection. Data, ideally via the EHR, is uploaded to regional coordinating centers (RCCs), responsible for local data management and auditand feedback of sites. The RCCs forward data to the statistical analysis committee (SAC).





Ann Am Thorac Soc 2020;17:879-891.

ISPY-COVID/ARDS Trials



Nat Med. 202228:9-11.

PRACTICAL Platforms

Active

CORT-E2

Corticosteroid Early and Extended

The CORT-E2 pilot trial is to examine the role of corticosteroids in 1) early non-COVID acute respiratory failure and 2) non-resolving acute respiratory failure that has already been treated with a 10 day course of corticosteroids.

Active

ULTIMATE

Ultra-Low Tidal Volume Mechanical Ventilation in ARDS through ECMO

The ULTIMATE pilot trial is a multi-centre, randomized, open-label trial, embedded as a domain within the PRACTICAL platform trial.

Active

PROACTIVE

Prevent Reduced Outcomes in ARDS by Transitioning from Invasive Ventilation to ECMO

The PROACTIVE pilot trial is a multi-centre, randomized, open-label trial, embedded as a domain within the PRACTICAL platform trial.

Active

IMV-ECLS

Mechanical Ventilation Strategies in Venovenous Extracorporeal Life Support (IMV-ECLS)

The Invasive Mechanical Ventilation Strategies in Venovenous-Extracorporeal Life Support (PRESSURE) is a pilot trial to identify PEEP strategies that improve lung function in AHRF patients on ECLS.

Active

IMV

Invasive Mechanical Ventilation Strategies

Interventions in this domain will be evaluated at various stages including pilot/feasibility evaluations, phase II, or phase III.

Active

CAPTIVATE

Consent for Adaptive Platform Trlals using abbreViATEd, patient-centered, modular audiovisual methods

CAPTIVATE is a study evaluating novel consent methods that is embedded within PRACTICAL and aims to innovate the conduct of informed consent methods within this trial, and inform the application of novel consent designs to future clinical trials.

Active

FAST-3

Nebulized Furosemide for the Treatment of Pulmonary Inflammation in Patients with Respiratory Failure Secondary to Pulmonary Infection – A Phase 3 study

Nebulized furosemide, in addition to usual care will be evaluated as an adjunctive treatment in patients with hypoxemic respiratory failure requiring either invasive or non-invasive mechanical ventilation as to its efficacy for improvement of patient cente

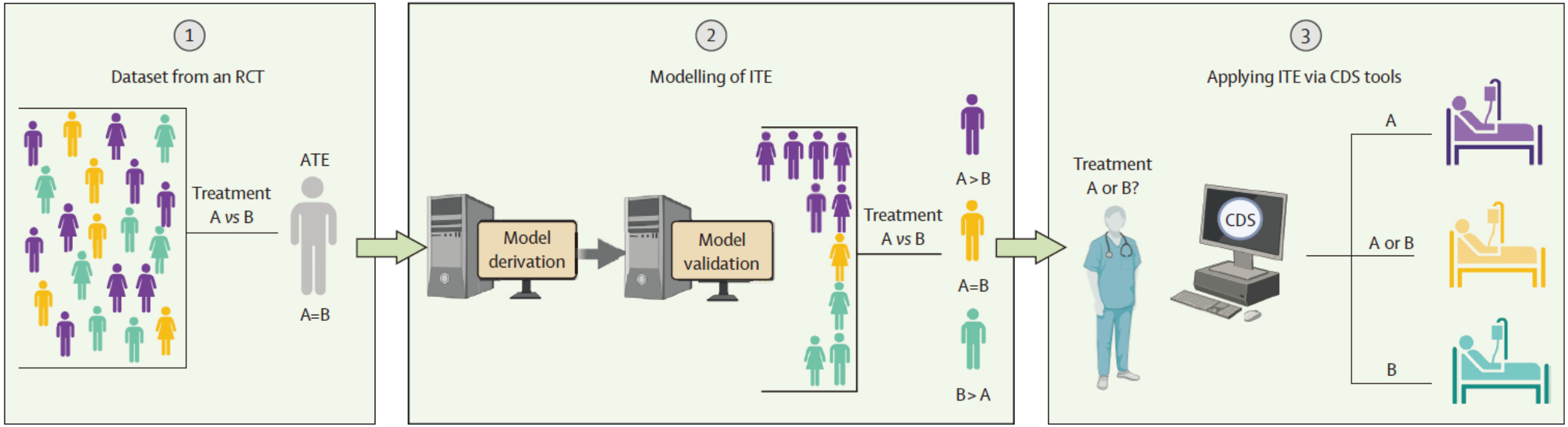
Active

FLUDRO

Fludrocortisone therapy in acute hypoxemic respiratory failure with airspace disease.

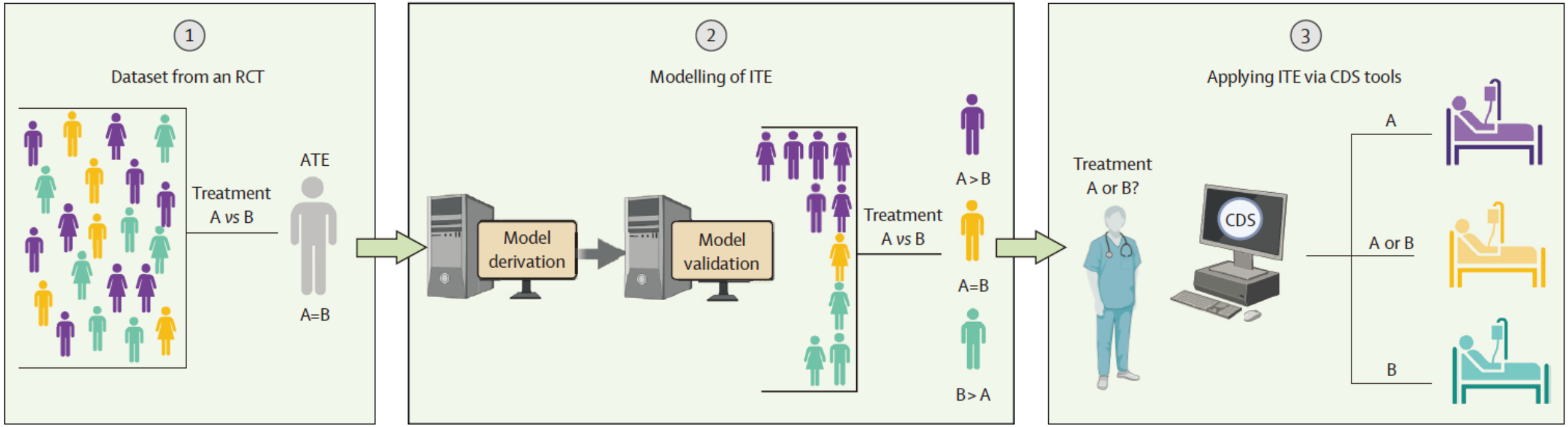
The FLUDRO-1 trial aims to gather direct evidence assessing the potential role of fludrocortisone combination therapy in the treatment acute hypoxemic respiratory failure (AHRF).

Clinical Trials for Improving Precision Medicine in ICU Patients



Lancet Respir Med. 2025:S2213-2600(25)00054-2.

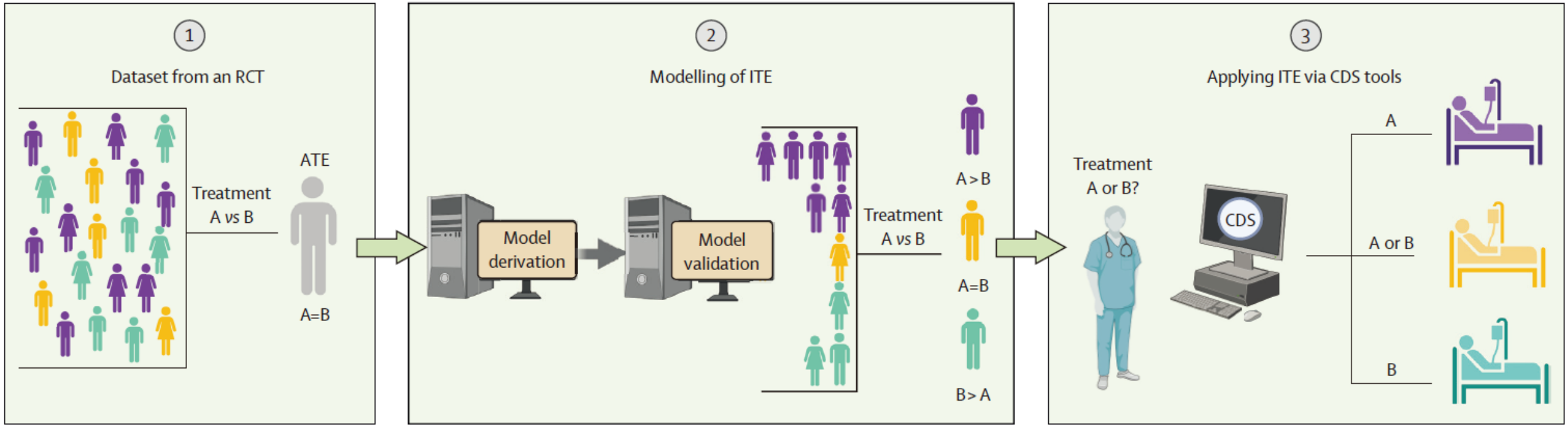
Clinical Trials for Improving Precision Medicine in ICU Patients



Average Treatment Effect → **Individualized Treatment Effect**

Lancet Respir Med. 2025:S2213-2600(25)00054-2.

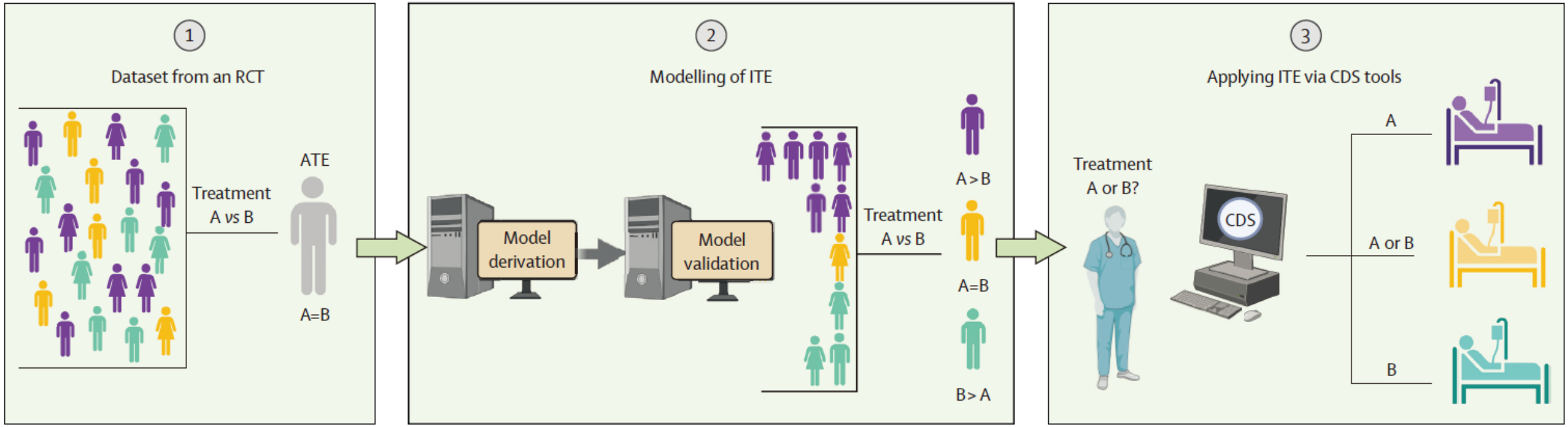
Clinical Trials for Improving Precision Medicine in ICU Patients



Average Treatment Effect → **More …..** → **Individualized Treatment Effect**

Lancet Respir Med. 2025:S2213-2600(25)00054-2.

Clinical Trials for Improving Precision Medicine in ICU Patients



Average Treatment Effect → **Artificial Intelligence** → **Individualized Treatment Effect**

Lancet Respir Med. 2025:S2213-2600(25)00054-2.