REMAP-CAP:

A Pandemic Platform Trial

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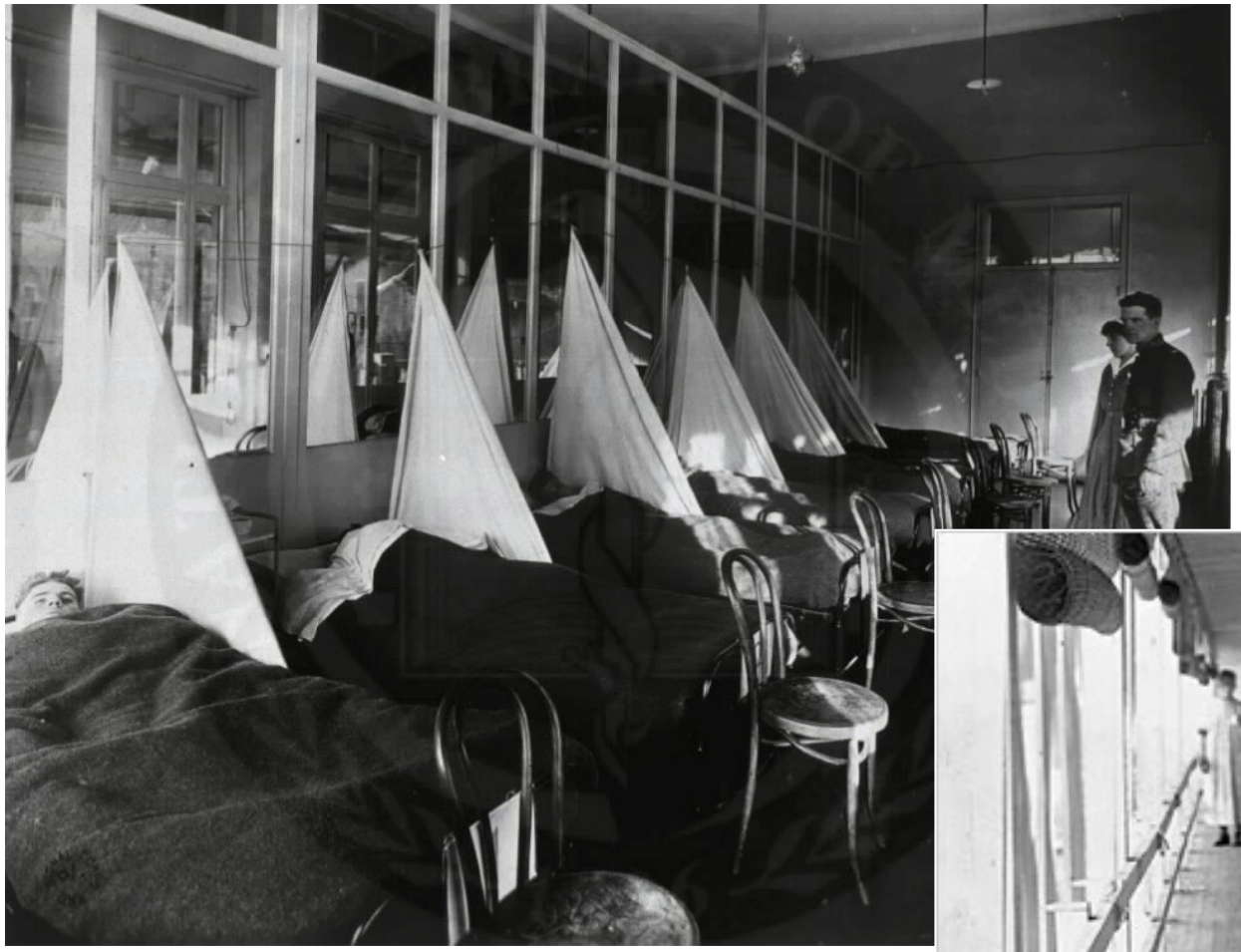
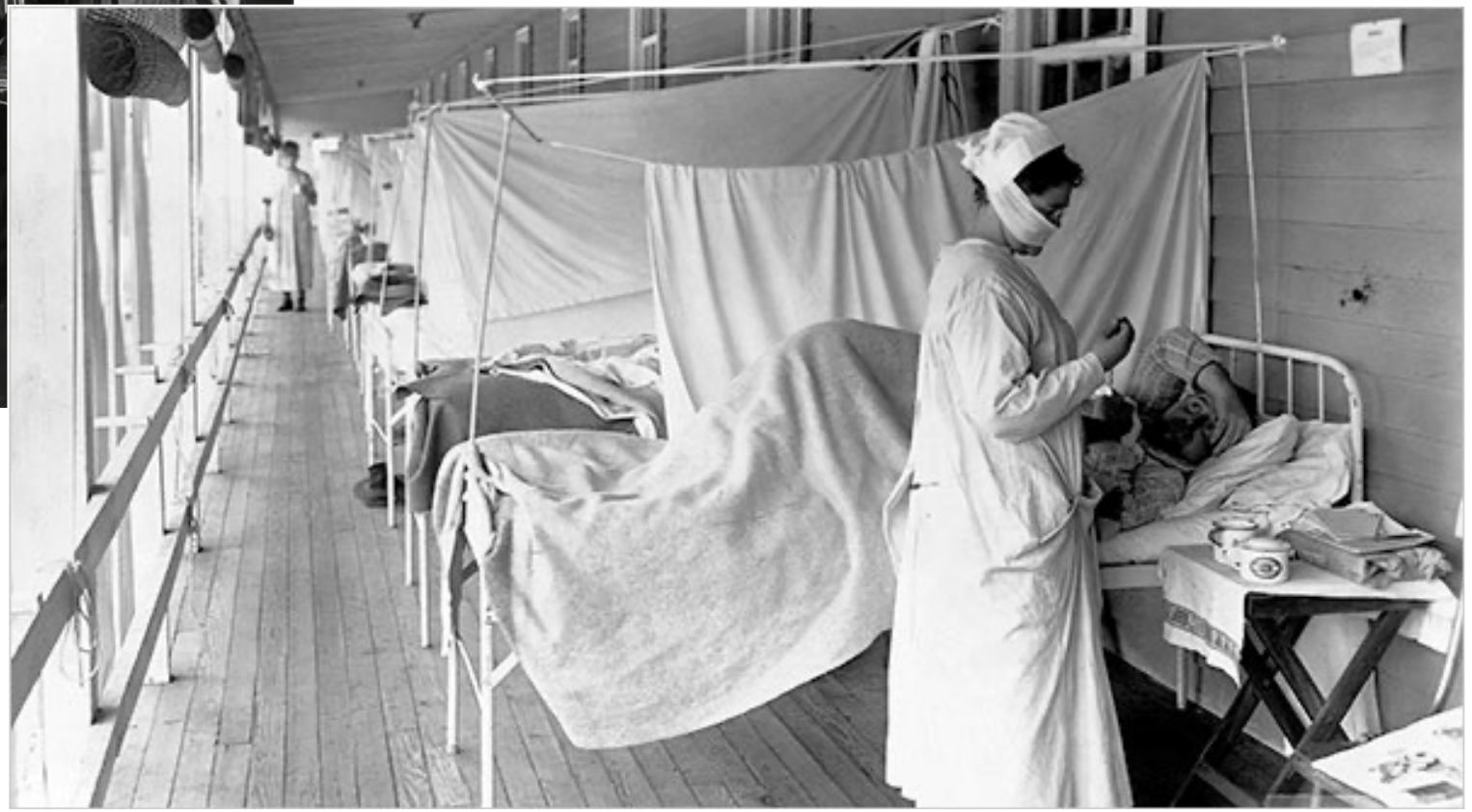
Unity Health Toronto

University of Toronto

September 28, 2023

1918/19 H1N1 Influenza Pandemic





Copenhagen 1952


SARS
The Dangers Ahead
Political Fallout in China
Developing World
Threats
SEE PAGE 10
SWINE FLU SPREADS!
BEATDOWN
LOST WEEKEND AT FENWAY AS SOX SWEEP YANKS
SEE SPORTS
turn deadly in U.S.
NEWS
Coronavirus
coronavirus in U.S.
outbreak
person
officials

Critically Ill Patients With Severe Acute Respiratory Syndrome

Robert A. Fowler, MD, MS
Stephen E. Lapinsky, MB, BCh, MSc
David Hallett, MSc
Allan S. Detsky, MD, PhD
William J. Sibbald, MD
Arthur S. Slutsky, MD
Thomas E. Stewart, MD
for the Toronto SARS Critical Care Group

Context Severe acute respiratory syndrome (SARS) is a ne
disease capable of causing severe respiratory failure.

Objective To determine the epidemiological features, co
tients with SARS-related critical illness.

Design, Setting, and Patients Retrospective case serie
SARS-related critical illness admitted to 13 intensive care u
area between the onset of the outbreak and April 15, 2003
during the first 7 days in the ICUs, and patients were follo

Main Outcome Measures The primary outcome was
ICU admission. Secondary outcomes included rate of SARS-
ber of tertiary care ICUs and staff placed under quarantine,

Acute Respiratory Distress Syndrome in Critically Ill Patients With Severe Acute Respiratory Syndrome

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Shi Loo, MMed, EDIC
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Y. Rubuen Chelliah, MMed
Yeow Choy Lai, MMed
Soon-Keng Goh, FRCPE, EDIC

Context Severe acute respiratory syndrome (SARS) is an emerging infectious disease with a 25% incidence of progression to acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) and mortality exceeding 10%.

Objective To describe the clinical spectrum and outcomes of ALI/ARDS in patients with SARS-related critical illness.

Design, Setting, and Patients Retrospective case series of adult patients with probable SARS admitted to the intensive care unit (ICU) of a hospital in Singapore between March 6 and June 6, 2003.

Main Outcome Measures The primary outcome measure was 28-day mortality after symptom onset.

Results Of 199 patients hospitalized with SARS, 46 (23%) were admitted to the ICU, including 45 who fulfilled criteria for ALI/ARDS. Mortality at 28 days for the entire cohort was 20 (10.1%) of 199 and for ICU patients was 17 (37%) of 46. Intensive care unit mortality at 13 weeks was 24 (52.2%) of 46. Nineteen of 24 ICU deaths occurred late (≥7 days after ICU admission) and were attributed to complications related to severe ARDS, multiorgan failure, thromboembolic complications, or septicemic shock. ARDS was characterized by ease of derecruitment of alveoli and paucity of airway secretion, bronchospasm, or dynamic hyperinflation. Lower Acute Physiology and Chronic Health Evaluation II scores and higher baseline ratios of Pao_2 to fraction of inspired oxygen were associated with earlier recovery

InFACT/ISARIC/LKSKI Colloquium on Pandemic Research Preparedness

June 2011

To successfully conduct research during a pandemic, the necessary infrastructure needs to be in place, and the trial ready to recruit in advance of the pandemic.

VIEWPOINT

The Platform Trial
An Efficient Strategy for Evaluating Multiple Treatments

Scott M. Berry, PhD
Berry Consultants LLC, Austin, Texas; and Department of Biostatistics, University of Kansas Medical Center, Kansas City.

Jason T. Connor, PhD
Berry Consultants LLC, Austin, Texas; and University of Central Florida College of

The drug development enterprise is struggling. The development of new therapies is limited by high costs, slow progress, and a high failure rate, even in the late stages of development. Clinical trials are most commonly based on a "one population, one drug, one disease" strategy, in which the clinical trial infrastructure is created to test a single treatment in a homogeneous population.

This approach has been largely unsuccessful for multiple diseases, including sepsis, dementia, and stroke. Despite promising preclinical and early human trials, there have been numerous negative phase 3 trials of treatbenefits when evaluating potentially synergistic combination treatments (eg, treatment A, treatment B, treatment C, and all combinations) if the starting point is the testing of each treatment in isolation.

What Is a Platform Trial?

A platform trial is defined by the broad goal of finding the best treatment for a disease by simultaneously investigating multiple treatments, using specialized statistical tools for allocating patients and analyzing results. The focus is on the disease rather than any particular experimental therapy.

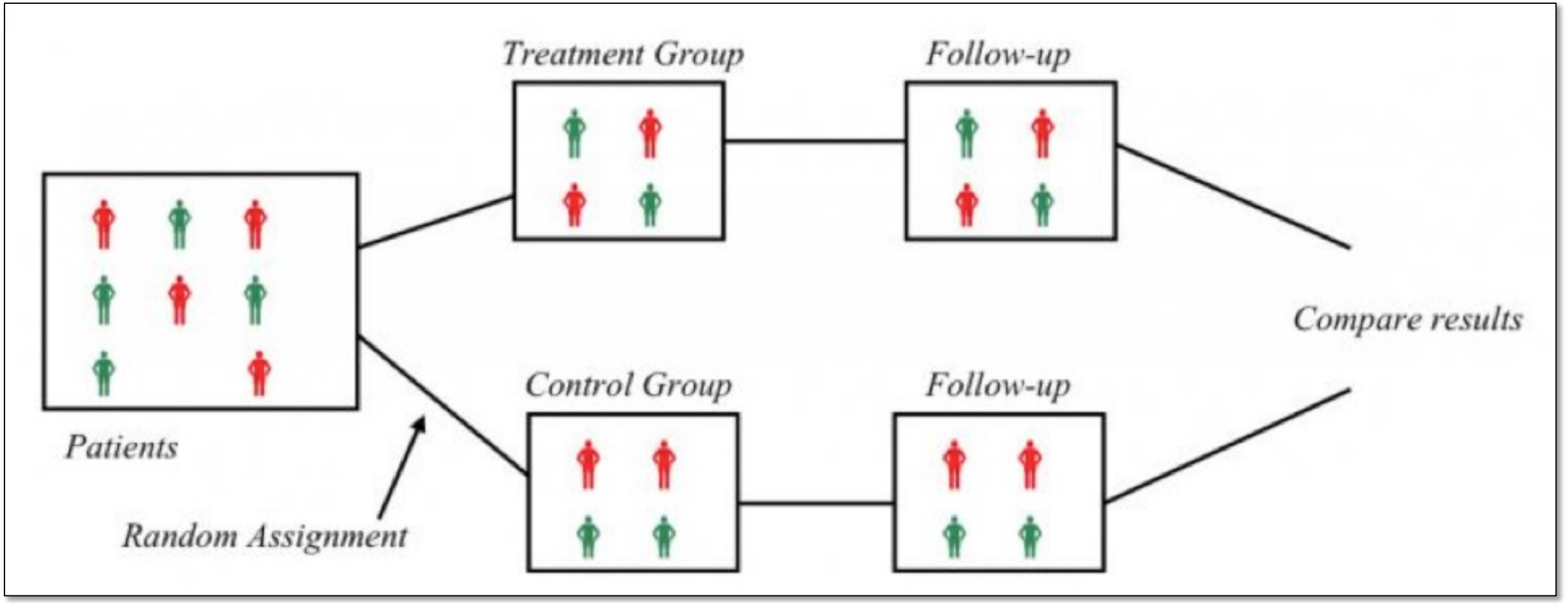
Table. General Characteristics of Traditional and Platform Trials[a]

Characteristic	Traditional Trial	Platform Trial
Scope	Efficacy of a single agent in a homogeneous population	Evaluating efficacy of multiple agents in a heterogeneous population; explicitly assumes treatment effects may be heterogeneous
Duration	Finite, based on time required to answer the single primary question	Potentially long-term, as long as there are suitable treatments requiring evaluation
No. of treatment groups	Prespecified and generally limited	Multiple treatment groups; the number of treatment groups and the specific treatments may change over time
Stopping rules	The entire trial may be stopped early for success or futility or harm, based on the apparent efficacy of the single experimental treatment	Individual treatment groups may be removed from the trial, based on demonstrated efficacy or futility or harm, but the trial continues, perhaps with the addition of new experimental treatment(s)
Allocation strategy	Fixed randomization	Response-adaptive randomization
Sponsor support	Supported by a single federal or industrial sponsor	The trial infrastructure may be supported by multiple federal or industrial sponsors or a combination

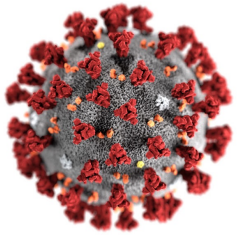
[a] Platform trials and similar trials may also be called basket, bucket, umbrella, or standing trials.

- *JAMA* 313:1619, 2015

Conventional RCTs Study an Intervention



A platform trial studies a disease or a population



COVID-19 with organ dysfunction

IL-6 RA, IFNβ, IL-1ra

Anticoagulants

Corticosteroids

COVID Antivirals

Antibiotics

Domain

Intervention

Time

R Randomized

E Embedded in the electronic health record

M Multifactorial - Multiple domains

A Adaptive

P Platform - Perpetual

Frequentist: **The probability of the data given the hypothesis**

Bayesian: **The probability of the hypothesis given the data**

The frequentist trial estimates …

- **Baseline rate of primary outcome**
- **Anticipated change as a result of intervention**
- **Confidence in the resulting estimate**

… to determine the needed sample size

Interpreting a Frequentist p Value

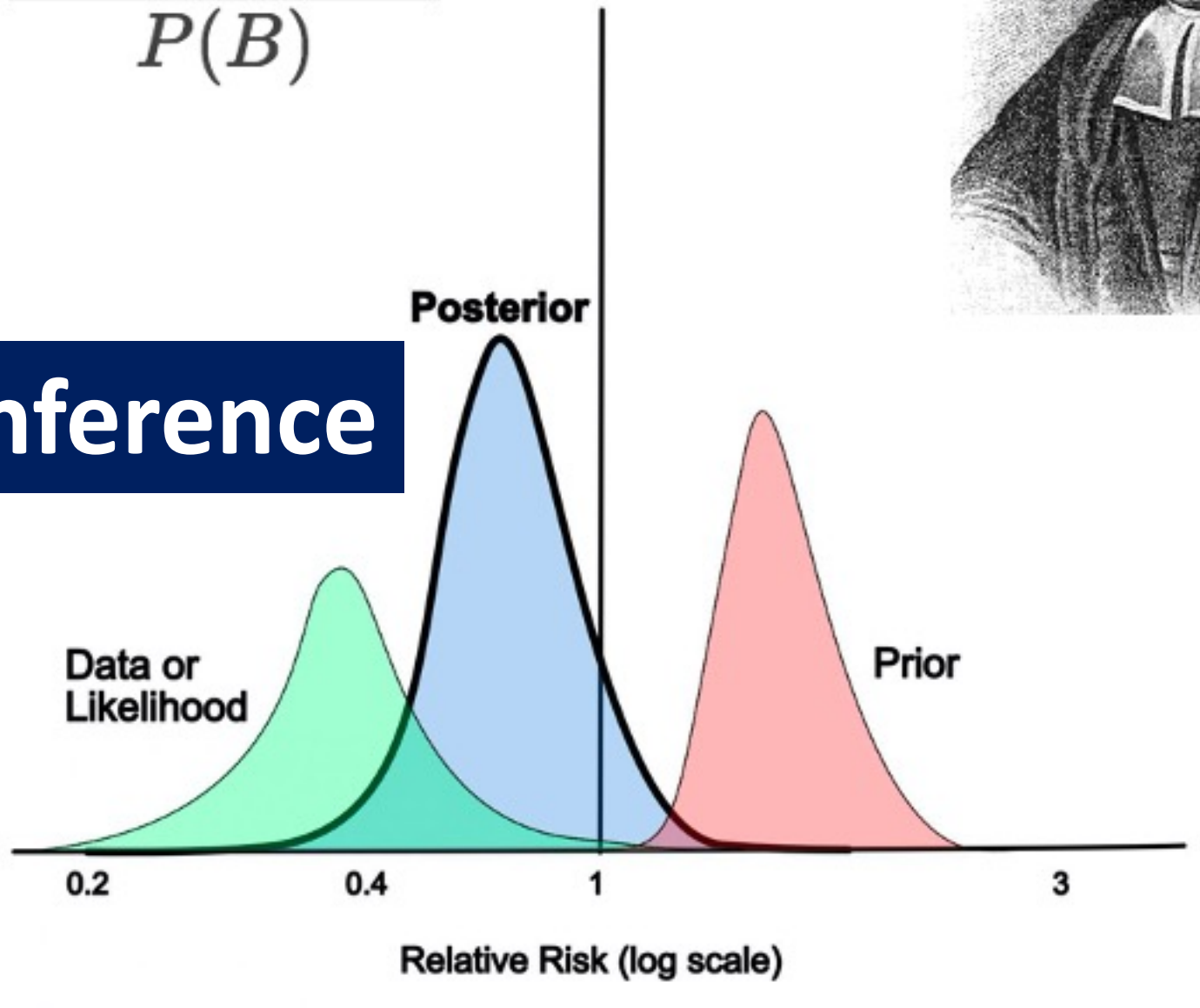
received the study product for a median of 9 days (IQR, 5-15 days). VAP developed among 289 of 1318 patients (21.9%) receiving probiotics vs 284 of 1332 controls (21.3%; hazard ratio [HR], 1.03 (95% CI, 0.87-1.22; *P* = .73, absolute difference, 0.6%, 95% CI, –2.5% to 3.7%).

Frequentist p-value:

"The probability of observing a result as or more extreme than that observed, assuming the treatment is ineffective"

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}$$

Bayesian Inference

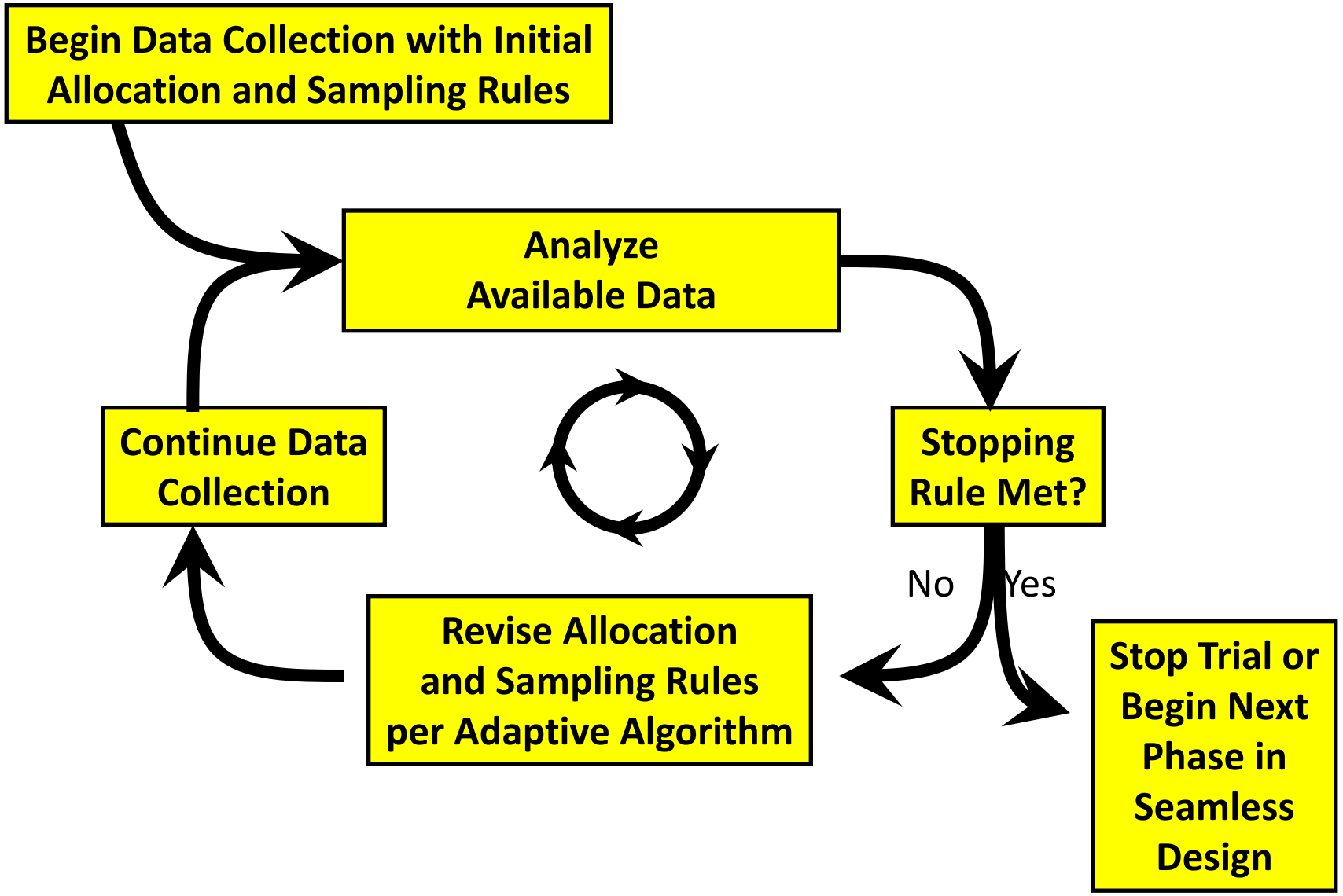


Frequentist versus Bayesian Approaches

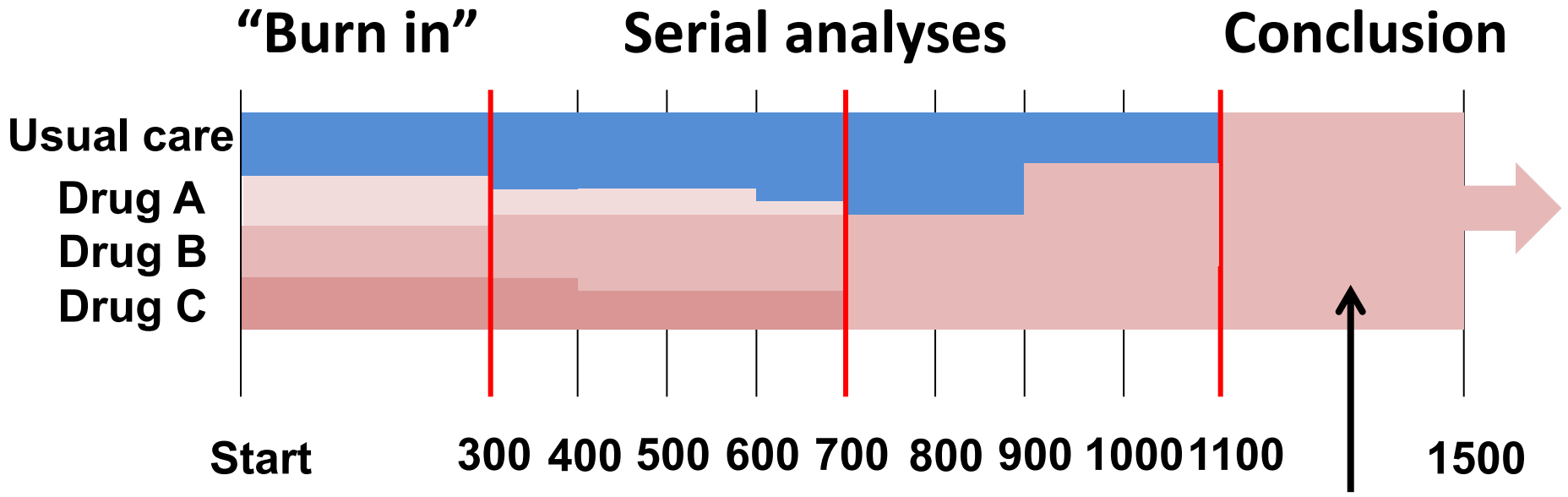
Bayesian posterior probability:

"The probability that the therapy is effective"

The Adaptive Process

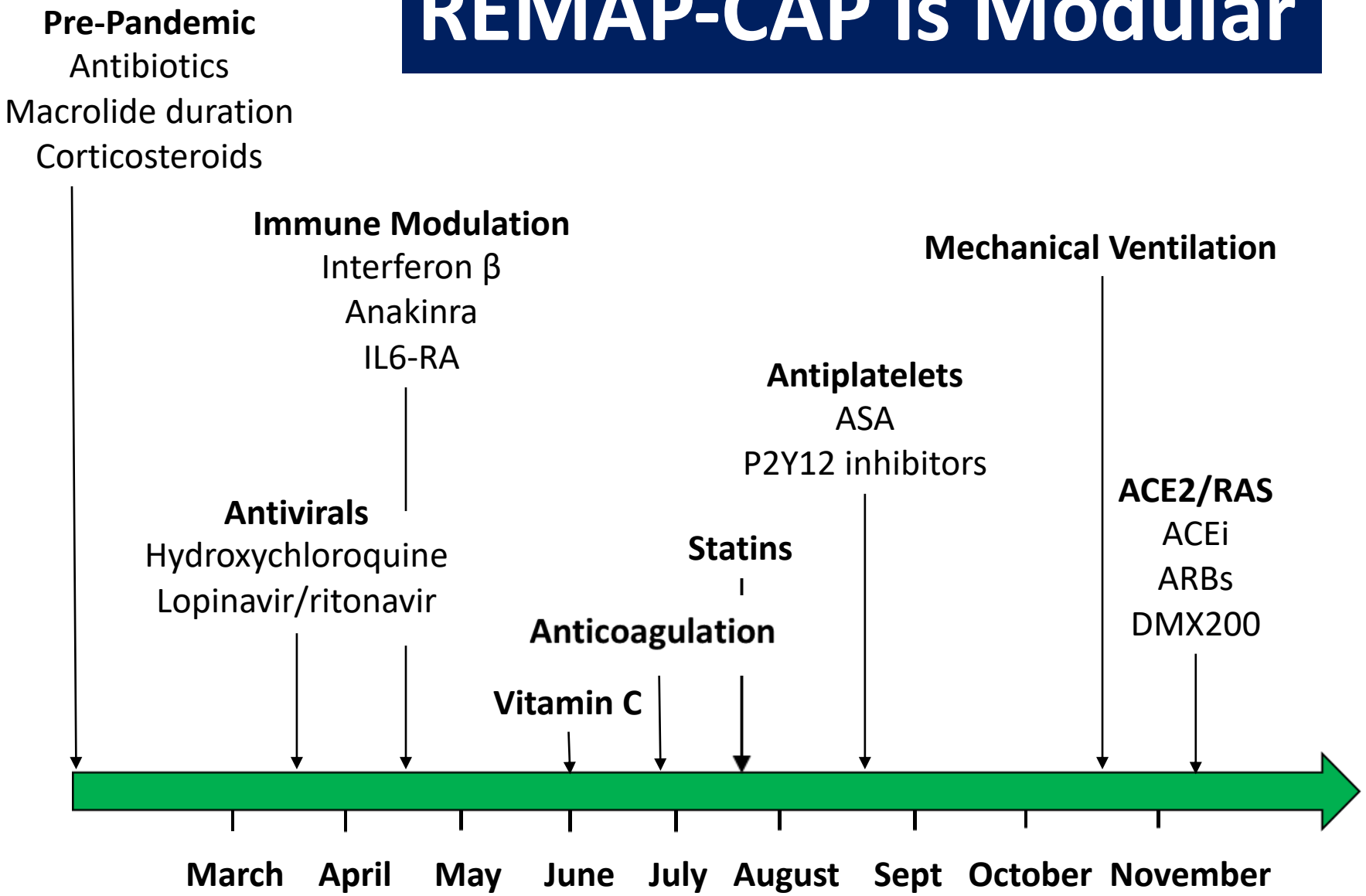


Response Adaptive Randomization



Adaptive trials review accruing data. Patients are preferentially randomized to the arm(s) that are showing better results.

REMAP-CAP is Modular



Terminology

Domain: Set of alternative and competing interventions within a common clinical mode

Intervention: A single treatment option within a domain

Regimen: The unique combination of interventions within multiple domains

Domain Conclusion

- Domains analyzed independently
- Terminate when a priori stopping boundary for benefit, harm, or equivalence met
- Results reported as for a conventional RCT
- Results inform care of future participants (ie RAR = 100%)

Domain Conclusions

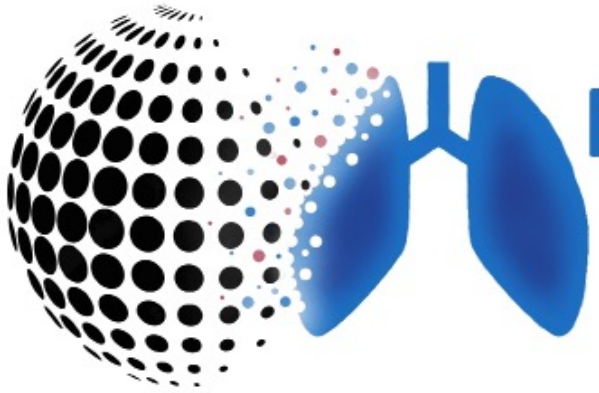
Superiority: Posterior probability of 99% that OR > 1.2

Equivalence: >0.9 probability that OR between 0.8 and 1.2

Inferiority: Posterior probability of 99% that OR <1

Sites are able to choose:

- **Which domains they will participate in**
- **Which interventions within a domain that they will randomize patients to**



REMAP-CAP

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

NCT02735707

Randomized Embedded Multifactorial Adaptive Platform Trial

1. Adult patient admitted to an ICU for severe CAP within 48 hours of hospital admission with
    a. symptoms or signs or both that are consistent with lower respiratory tract infection (for example, acute onset of dyspnea, cough, pleuritic chest pain) AND
    b. Radiological evidence of new onset consolidation (in patients with pre-existing radiological changes, evidence of new infiltrate)
2. Requiring organ support with one or more of:
    a. Non-invasive or invasive ventilatory support;
    b. Receiving infusion of vasopressor or inotropes or both

Primary Outcome: All-cause mortality at 90 days

International Trial Steering Committee

Statistical Analysis Committee

Data Coordinating Centre

Domain Working Groups

Operational Working Groups

Regional Steering Committees

Data Safety Monitoring Board

January, 2020

Two States

Severe: Receiving positive pressure respiratory support or vasoactive agents

Moderate: Hospitalized without organ support

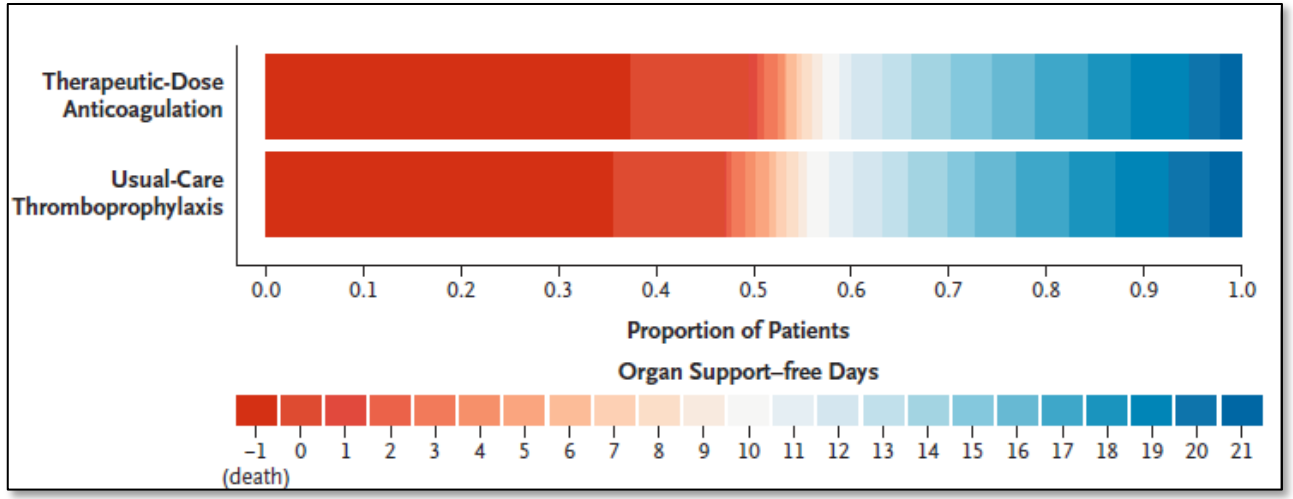
REMAP-CAP
Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP):

PANDEMIC APPENDIX TO THE CORE PROTOCOL

Primary Outcome

Organ support-free days over 21 days, with mortality = -1



REMAP-CAP

A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia

22,485

Patient randomisations

18,471

Patient randomisations with suspected or proven COVID-19

61

Current or completed interventions in 17 Domains

12,826

Total patients

10,254

Patients with suspected or proven COVID-19

325

Active Sites

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

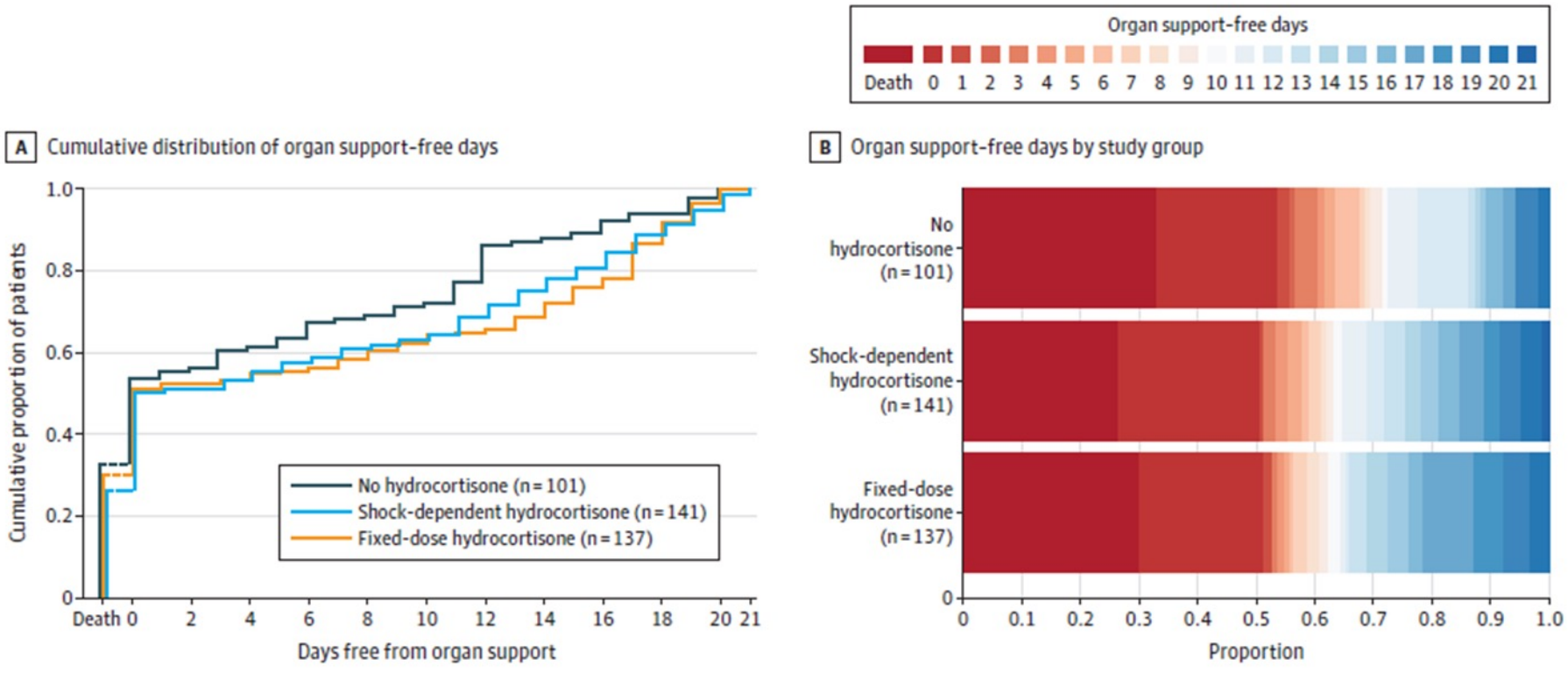
Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19

The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial

The Writing Committee for the REMAP-CAP Investigators

379 Patients

Figure 2. Organ Support-Free Days

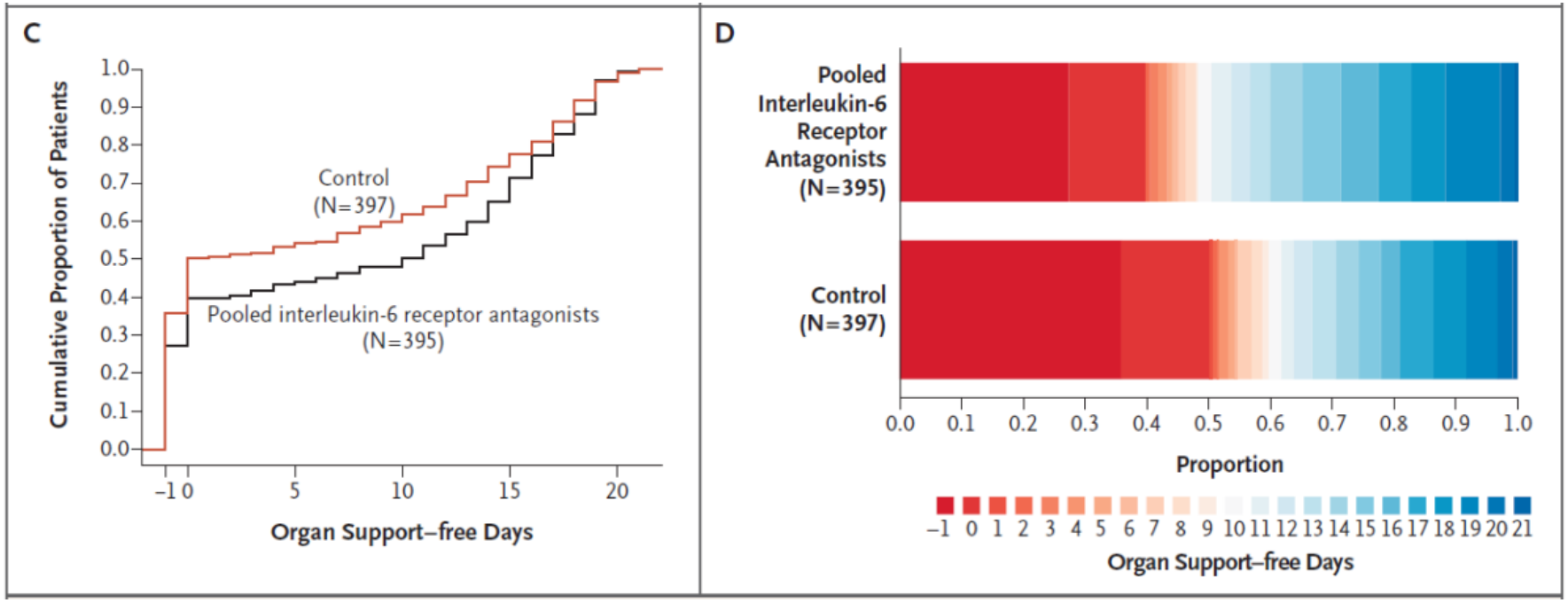


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19

The REMAP-CAP Investigators*

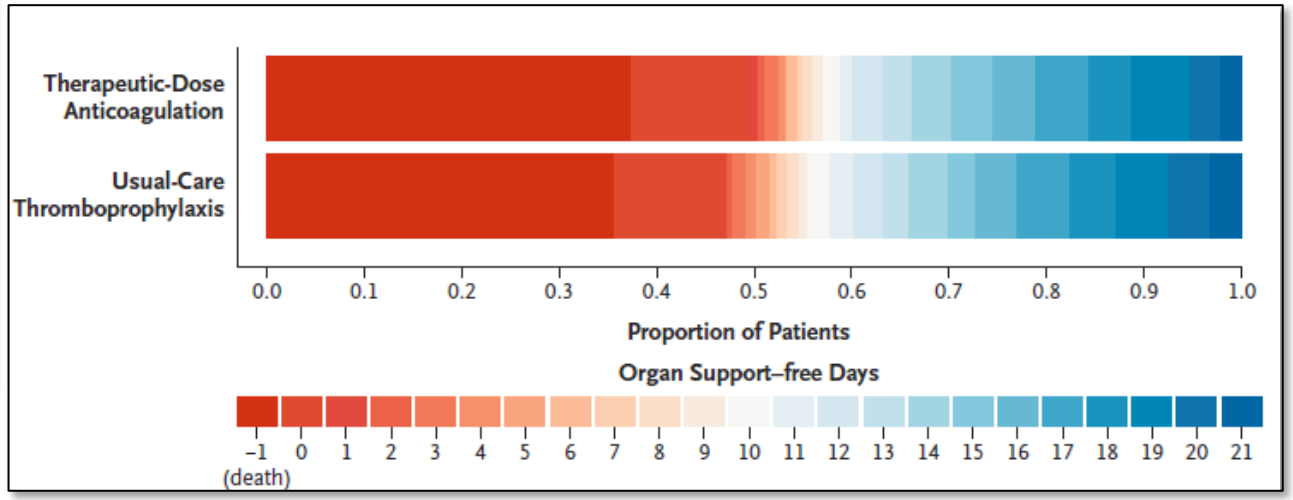


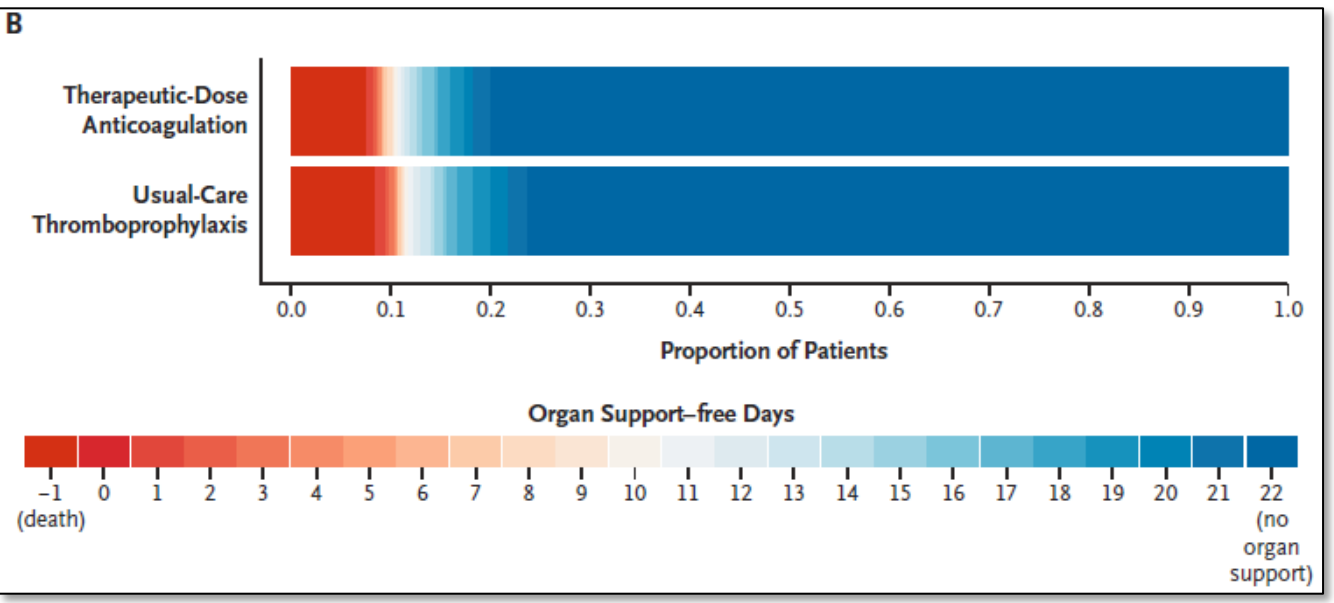
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 26, 2021 VOL. 385 NO. 9

Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19

The REMAP-CAP, ACTIV-4a, and ATTACC Investigators*





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ORIGINAL ARTICLE

Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19

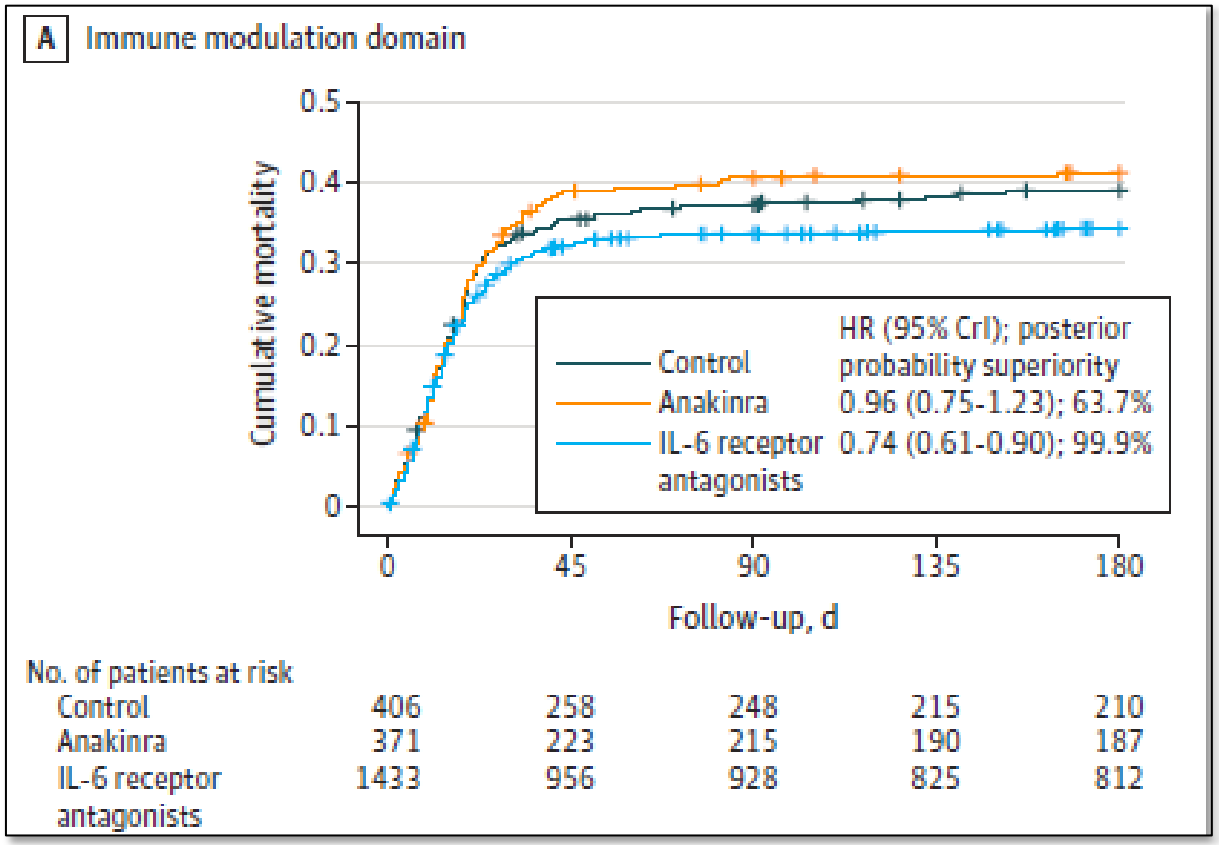
The ATTACC, ACTIV-4a, and REMAP-CAP Investigators*

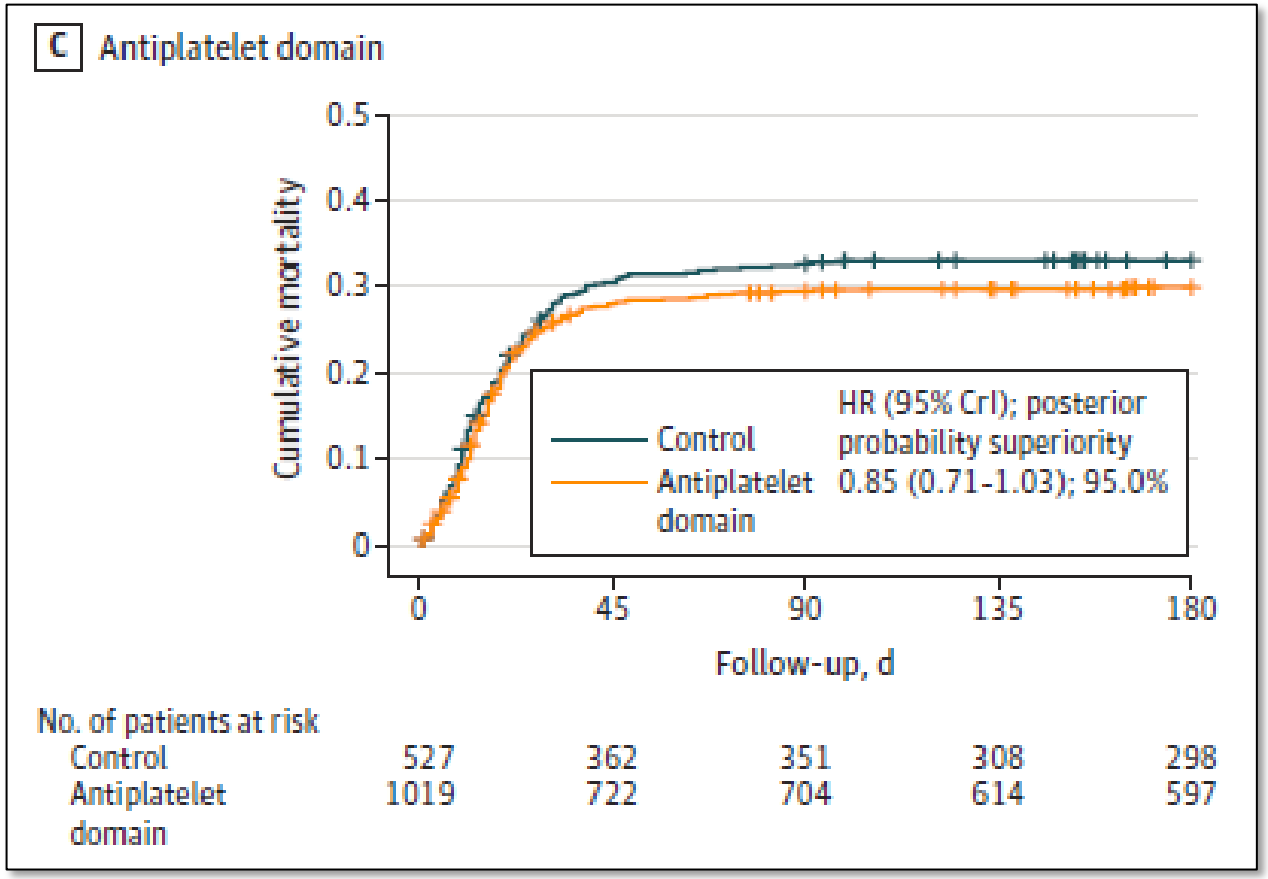
Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Long-term (180-Day) Outcomes in Critically Ill Patients With COVID-19 in the REMAP-CAP Randomized Clinical Trial

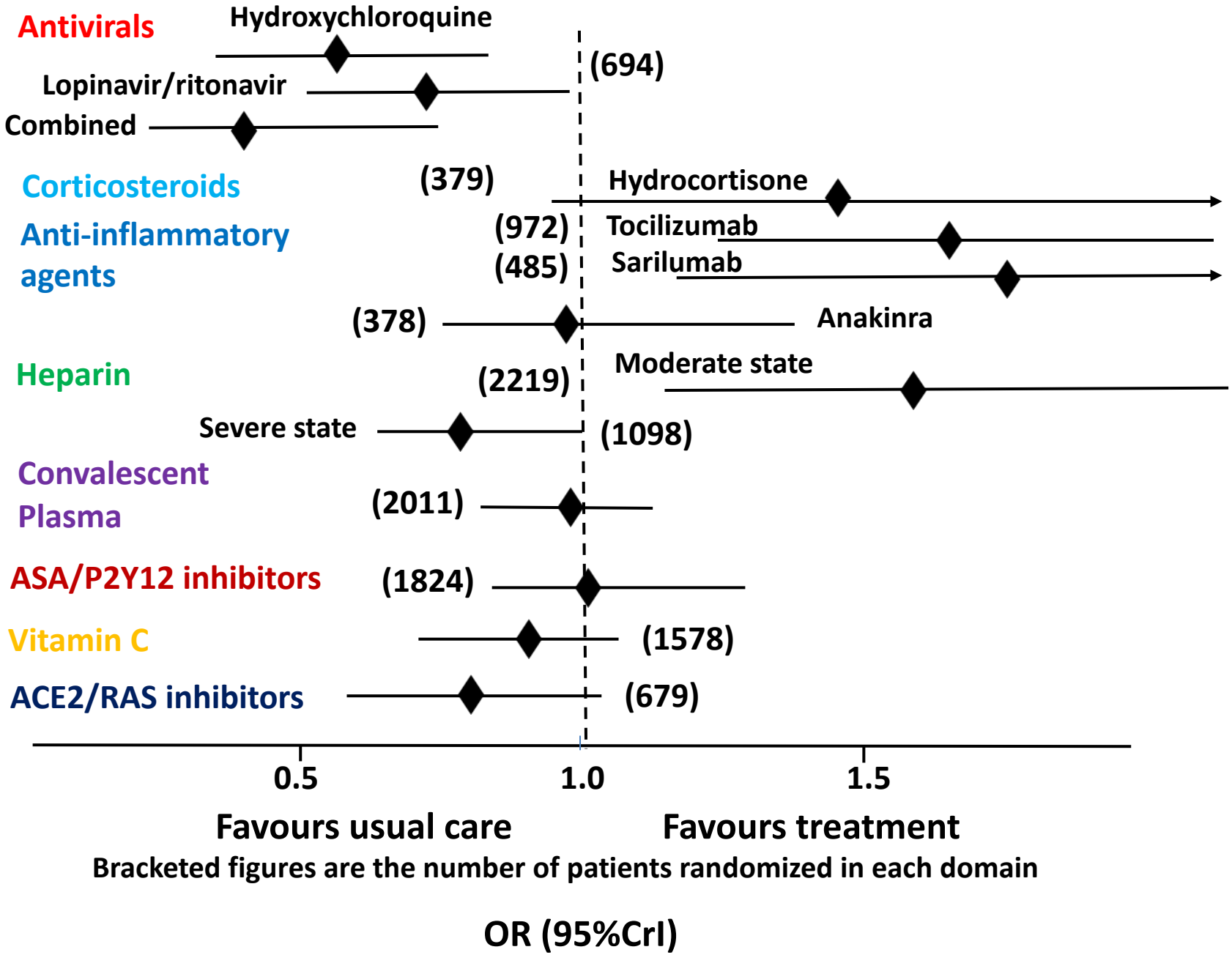
Writing Committee for the REMAP-CAP Investigators





In press …

Vitamin C	**JAMA**
Simvastatin	**New England Journal of Medicine**


Antivirals
Hydroxychloroquine
(694)
Lopinavir/ritonavir
Combined
Corticosteroids
(379)
Hydrocortisone
Anti-inflammatory agents
(972)
Tocilizumab
(485)
Sarilumab
(378)
Anakinra
Heparin
Moderate state
(2219)
Severe state
(1098)
Convalescent Plasma
(2011)
ASA/P2Y12 inhibitors
(1824)
Vitamin C
(1578)
ACE2/RAS inhibitors
(679)
0.5
1.0
1.5
Favours usual care
Favours treatment
Bracketed figures are the number of patients randomized in each domain
OR (95%CrI)

REMAP-CAP Recruitment

UK

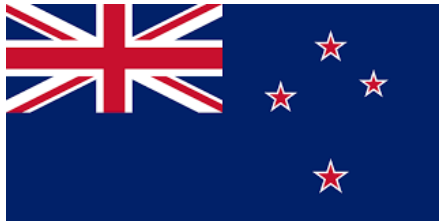
7100 Patients

EU

Australia

1620 Patients

New Zealand



Canada

777 Patients

Nepal

India

Pakistan

1125 Patients

USA

480

Saudi Arabia

200

Japan

90

Colombia

7


AHRC
APPLIED HEALTH RESEARCH CENTRE


ANZICS
Clinical Trials Group


APPRISE


Berry Consultants
Statistical Innovation


CCCTG
Canadian Critical Care
Trials Group


Center for Sepsis
Control & Care


NO BB
COMBACTE
NET


CRISMA


DGIIN
Deutsche Gesellschaft für
Interventionelle Intensivmedizin
und Notfallmedizin


icnarc


INFACT


Imperial College
London


Irish
Critical Care
Clinical Trials
Group


Irish
Critical Care
Clinical Trials
Network


Japanese Association for
Acute Medicine


The Japanese
Association
for Infectious
Diseases


JSICM


NHMRC
Clinical Trials Centre

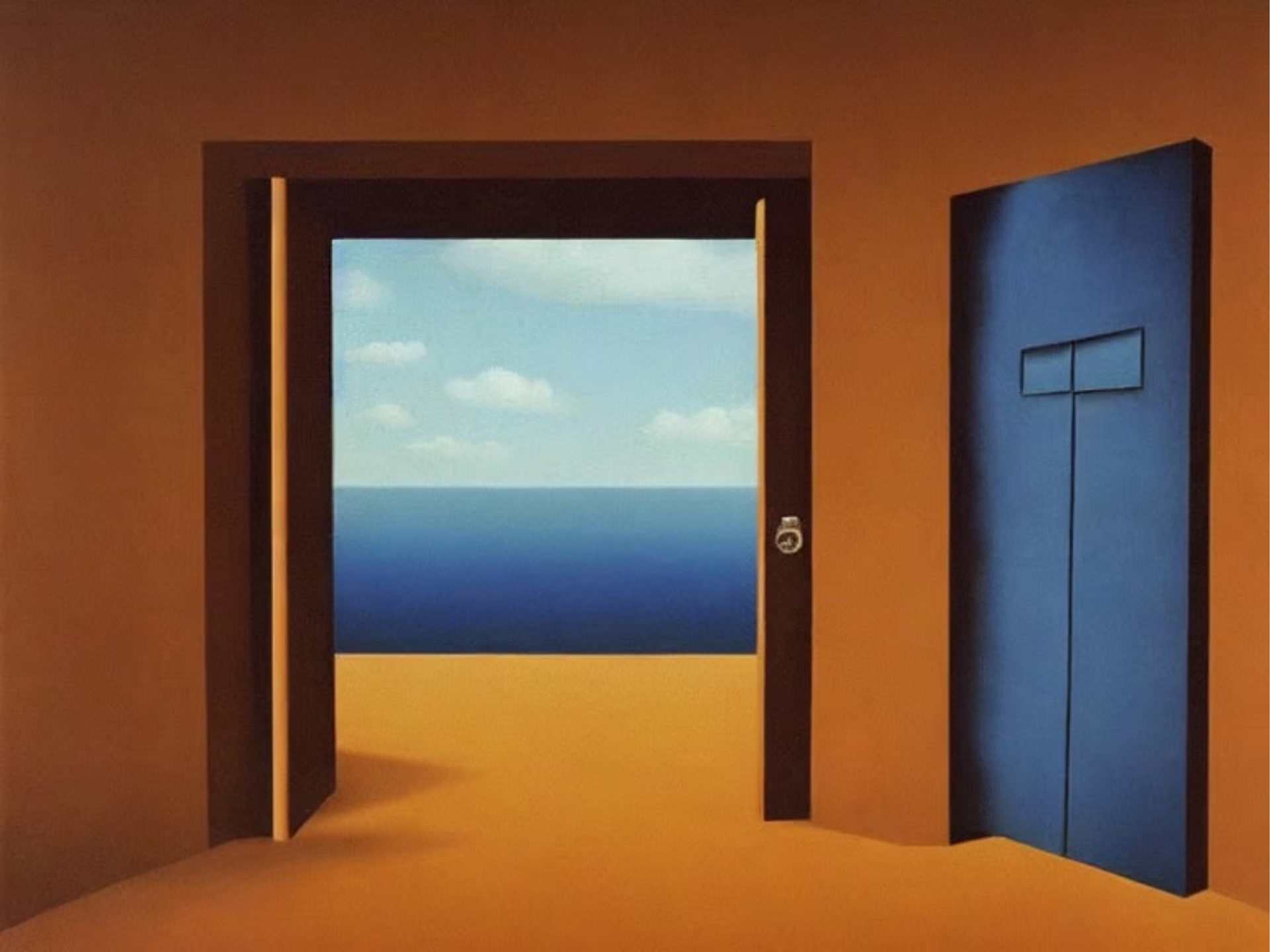

PREPARE


Spinnaker
SOFTWARE


UKCCRG
UK Critical Care Research Group


UPMC
LIFE CHANGING MEDICINE

Supported by



Thank you!