Adaptive Platform Trials: The Basics

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Adaptive Platform Trials Scientific Meeting
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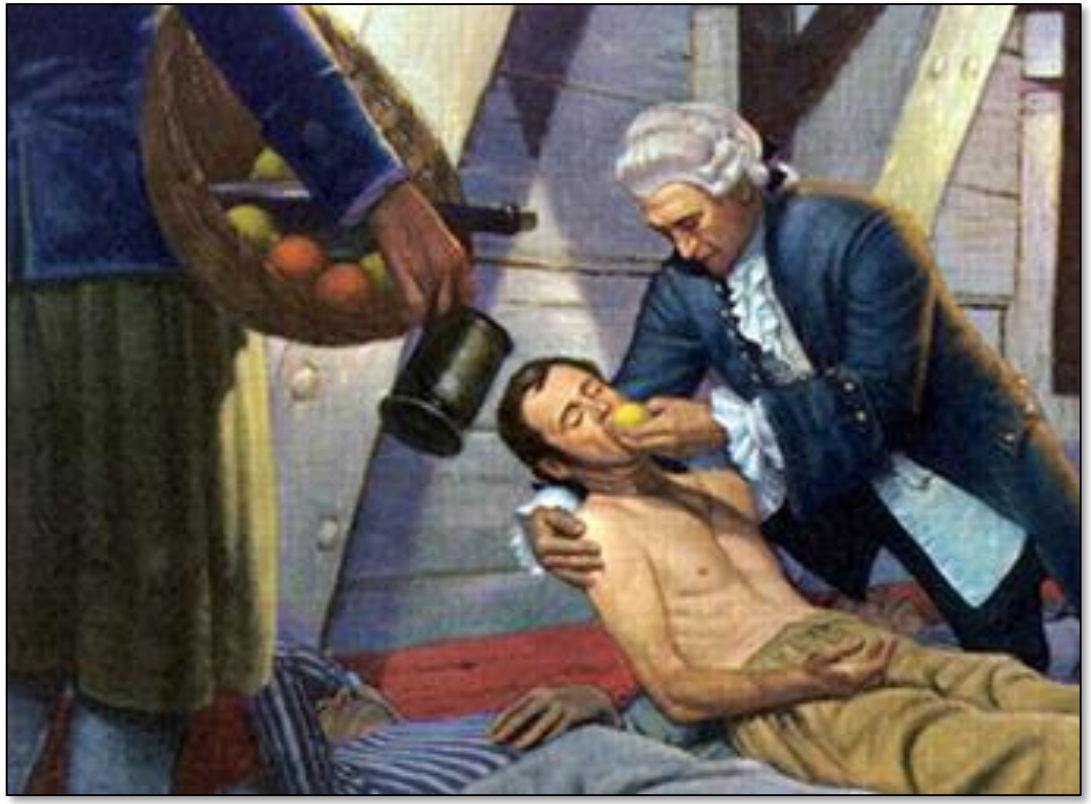
Unity Health Toronto

University of Toronto

Disclosures

- Canadian PI REMAP-CAP
- Chair, InFACT
- Grant funding CIHR
- DSMB chair, AM Pharma



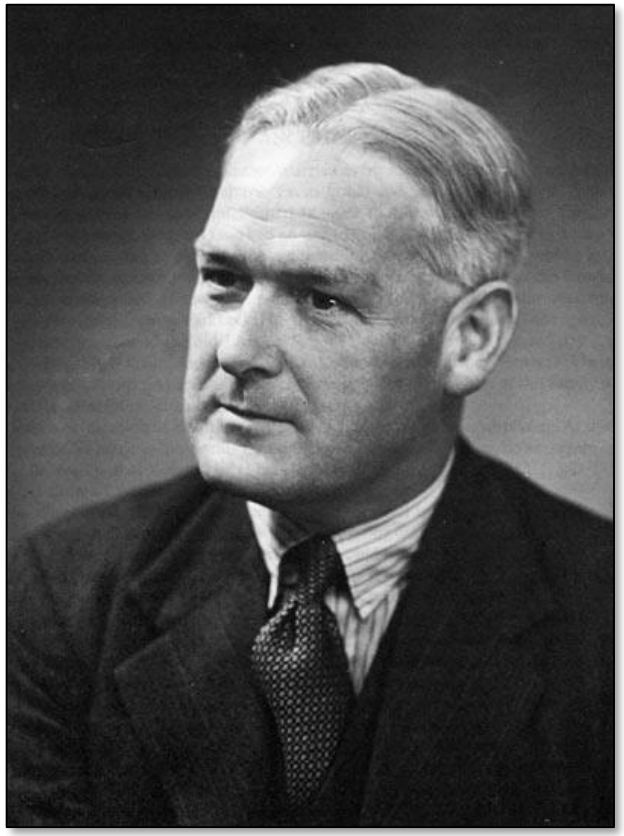
Randomization

The First Clinical Trial

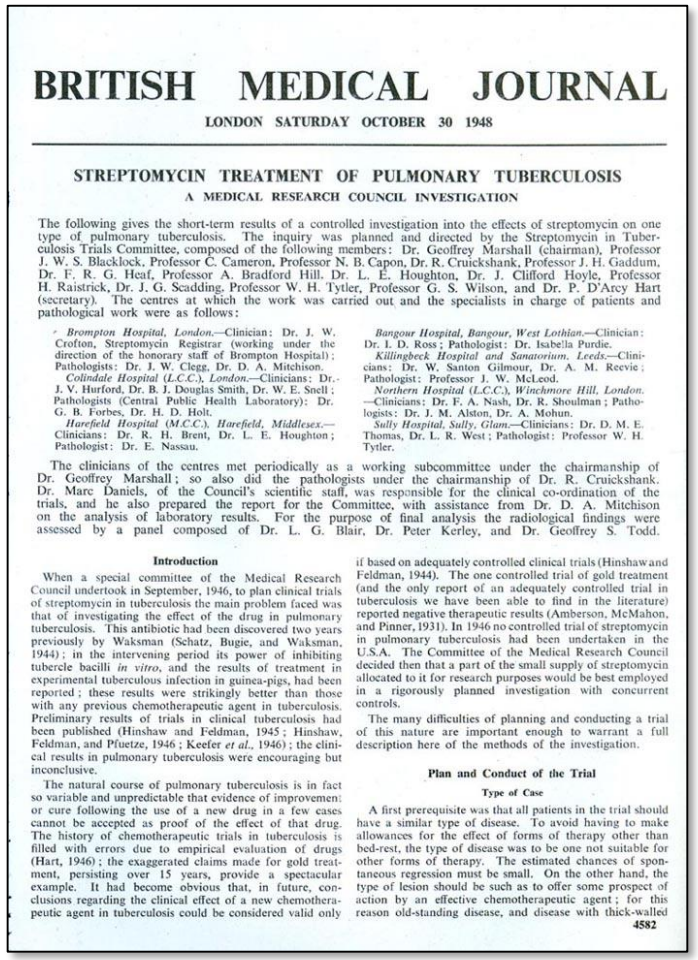
James Lind 1747

2 sailors to each of:

- Cider
- Sulfuric acid
- Vinegar
- Seawater
- Oranges and lemons
- Barley water



Bradford Hill
1948



BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one type of pulmonary tuberculosis. The inquiry was planned and directed by the Streptomycin in Tuberculosis Trials Committee, composed of the following members: Dr. Geoffrey Marshall (chairman), Professor J. W. S. Blacklock, Professor C. Cameron, Professor N. B. Capon, Dr. R. Cruickshank, Professor J. H. Gaddum, Dr. F. R. G. Heaf, Professor A. Bradford Hill, Dr. L. E. Houghton, Dr. J. Clifford Hoyle, Professor H. Raistrick, Dr. J. G. Scadding, Professor W. H. Tytler, Professor G. S. Wilson, and Dr. P. D'Arcy Hart (secretary). The centres at which the work was carried out and the specialists in charge of patients and pathological work were as follows:

Brompton Hospital, London.—Clinician: Dr. J. W. Crofton, Streptomycin Registrar (working under the direction of the honorary staff of Brompton Hospital); Pathologists: Dr. J. W. Clegg, Dr. D. A. Mitchison.
Colindale Hospital (L.C.C.), London.—Clinicians: Dr. J. V. Hurford, Dr. B. J. Douglas Smith, Dr. W. E. Snell; Pathologists (Central Public Health Laboratory): Dr. G. B. Forbes, Dr. H. D. Holt.
Harefield Hospital (M.C.C.), Harefield, Middlesex.—Clinicians: Dr. R. H. Brent, Dr. L. E. Houghton; Pathologist: Dr. E. Nassau.
Bangour Hospital, Bangour, West Lothian.—Clinician: Dr. I. D. Ross; Pathologist: Dr. Isabella Purdie.
Killingbeck Hospital and Sanatorium, Leeds.—Clinicians: Dr. W. Santon Gilmour, Dr. A. M. Reevie; Pathologist: Professor J. W. McLeod.
Northern Hospital (L.C.C.), Winchmore Hill, London.—Clinicians: Dr. F. A. Nash, Dr. R. Shoulman; Pathologists: Dr. J. M. Alston, Dr. A. Mohun.
Sully Hospital, Sully, Glam.—Clinicians: Dr. D. M. E. Thomas, Dr. L. R. West; Pathologist: Professor W. H. Tytler.

The clinicians of the centres met periodically as a working subcommittee under the chairmanship of Dr. Geoffrey Marshall; so also did the pathologists under the chairmanship of Dr. R. Cruickshank. Dr. Marc Daniels, of the Council's scientific staff, was responsible for the clinical co-ordination of the trials, and he also prepared the report for the Committee, with assistance from Dr. D. A. Mitchison on the analysis of laboratory results. For the purpose of final analysis the radiological findings were assessed by a panel composed of Dr. L. G. Blair, Dr. Peter Kerley, and Dr. Geoffrey S. Todd.

Introduction

When a special committee of the Medical Research Council undertook in September, 1946, to plan clinical trials of streptomycin in tuberculosis the main problem faced was that of investigating the effect of the drug in pulmonary tuberculosis. This antibiotic had been discovered two years previously by Waksman (Schatz, Bugie, and Waksman, 1944); in the intervening period its power of inhibiting tubercle bacilli *in vitro*, and the results of treatment in experimental tuberculous infection in guinea-pigs, had been reported; these results were strikingly better than those with any previous chemotherapeutic agent in tuberculosis. Preliminary results of trials in clinical tuberculosis had been published (Hinshaw and Feldman, 1945; Hinshaw, Feldman, and Pfuetze, 1946; Keefer *et al.*, 1946); the clinical results in pulmonary tuberculosis were encouraging but inconclusive.

The natural course of pulmonary tuberculosis is in fact so variable and unpredictable that evidence of improvement or cure following the use of a new drug in a few cases cannot be accepted as proof of the effect of that drug. The history of chemotherapeutic trials in tuberculosis is filled with errors due to empirical evaluation of drugs (Hart, 1946); the exaggerated claims made for gold treatment, persisting over 15 years, provide a spectacular example. It had become obvious that, in future, conclusions regarding the clinical effect of a new chemotherapeutic agent in tuberculosis could be considered valid only if based on adequately controlled clinical trials (Hinshaw and Feldman, 1944). The one controlled trial of gold treatment (and the only report of an adequately controlled trial in tuberculosis we have been able to find in the literature) reported negative therapeutic results (Amberson, McMahon, and Pinner, 1931). In 1946 no controlled trial of streptomycin in pulmonary tuberculosis had been undertaken in the U.S.A. The Committee of the Medical Research Council decided then that a part of the small supply of streptomycin allocated to it for research purposes would be best employed in a rigorously planned investigation with concurrent controls.

The many difficulties of planning and conducting a trial of this nature are important enough to warrant a full description here of the methods of the investigation.

Plan and Conduct of the Trial

Type of Case

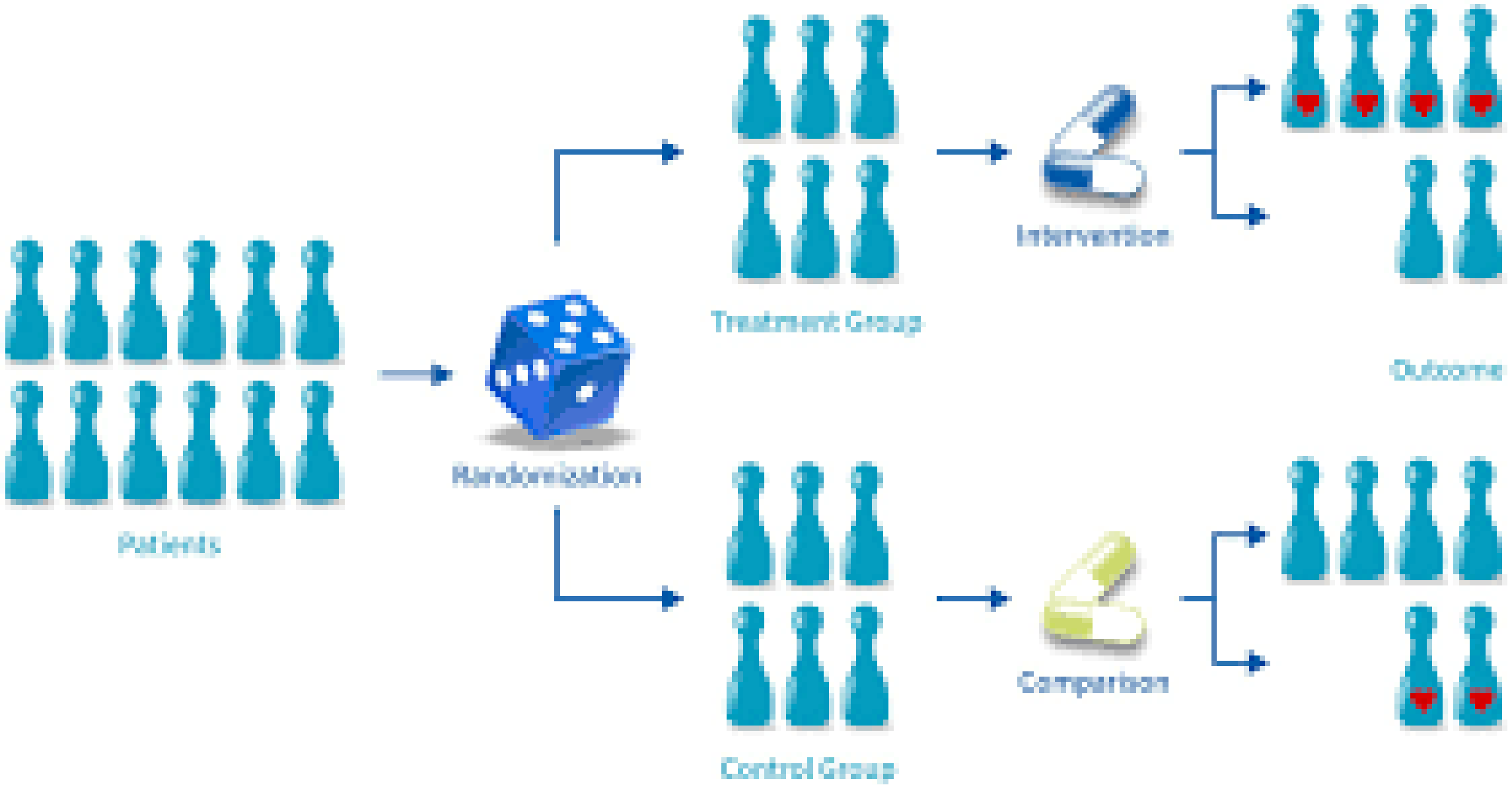
A first prerequisite was that all patients in the trial should have a similar type of disease. To avoid having to make allowances for the effect of forms of therapy other than bed-rest, the type of disease was to be one not suitable for other forms of therapy. The estimated chances of spontaneous regression must be small. On the other hand, the type of lesion should be such as to offer some prospect of action by an effective chemotherapeutic agent; for this reason old-standing disease, and disease with thick-walled

Randomization

Blinding

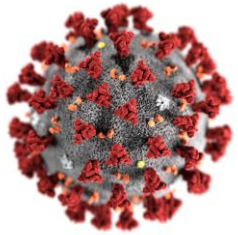
Concealment of allocation

Randomized Controlled Trial



A conventional trial studies an intervention

- Estimate primary event rate
- Specify expected treatment effect
- Calculate sample size
- Develop protocol, CRFs
- Engage sites



Patients at risk of ventilator-associated pneumonia

Probiotics

Recruit until sample size reached

Time

JAMA | Original Investigation

Effect of Probiotics on Incident Ventilator-Associated Pneumonia in Critically Ill Patients

A Randomized Clinical Trial

Jennie Johnstone, MD, PhD; Maureen Meade, MD, MSc; François Lauzier, MD, MSc; John Marshall, MD; Erick Duan, MD, MSc; Joanna Dionne, MD, PhD; Yaseen M. Arabi, MD; Diane Heels-Ansdell, MSc; Lehana Thabane, PhD; Daphnee Lamarche; Michael Surette, PhD; Nicole Zytaruk, RN; Sangeeta Mehta, MD; Peter Dodek, MD, MHSc; Lauralyn McIntyre, MD, MSc; Shane English, MD, MSc; Bram Rochwerg, MD, MSc; Tim Karachi, MD; William Henderson; Gordon Wood, MD; Daniel Ovakim, MD, MSc; Margaret Herridge, MD, MPH; John Granton, MD; M. Elizabeth Wilcox; Alberto Goffi, MD; Henry T. Stelfox, MD, PhD; Daniel Niven, MD, MSc; John Muscedere, MD; François Lamontagne, MD, MSc; Frédérick D'Aragon, MD, MSc; Charles St.-Arnaud, MD; Ian Ball, MD, MSc; Dave Nagpal, MD; Martin Girard, MD, MSc; Pierre Aslanian, MD; Emmanuel Charbonney, MD, PhD; David Williamson, PhD; Wendy Sligl, MD, MSc; Jan Friedrich, MD, MSc; Neill K. Adhikari, MDCM, MSc; François Marquis, MD, MA; Patrick Archambault, MD, MSc; Kosar Khwaja, MD; Arnold Kristof, MD, PhD; James Kutsogiannis, MD; Ryan Zarychanski, MD, MSc; Bojan Paunovic, MD; Brenda Reeve, MD; François Lellouche, MD, PhD; Paul Hosek, MD; Jennifer Tsang, MD; Alexandra Binnie, MD, DPhil; Sébastien Trop, MD, PhD; Osama Loubani, MD; Richard Hall, MD; Robert Cirone, MD; Steve Reynolds, MD; Paul Lysecki, MD; Eyal Golan, MD, PhD; Rodrigo Cartin-Ceba, MD; Robert Taylor, MD; Deborah Cook, MD, MSc; for the Prevention of Severe Pneumonia and Endotracheal Colonization Trial (PROSPECT) Investigators and the Canadian Critical Care Trials Group

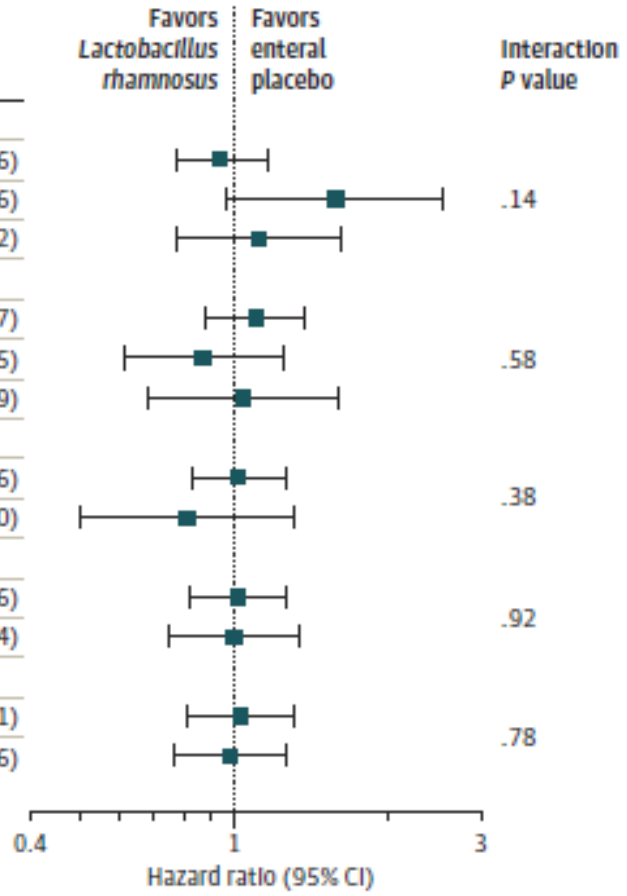
Enrolled patients were at least 18 years old, expected to require mechanical ventilation for at least 72 hours as determined by the treating ICU team (Figure 1). Excluded patients

Statistical Analysis

Based on an estimated 15% VAP rate,[17,22] 2650 patients were enrolled to detect a 25% relative risk reduction (based on results from prior meta-analyses)[10,30] with 80% power ($\alpha = .05$).

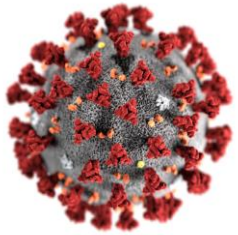
Figure 2. Subgroup Analyses: Ventilator-Associated Pneumonia

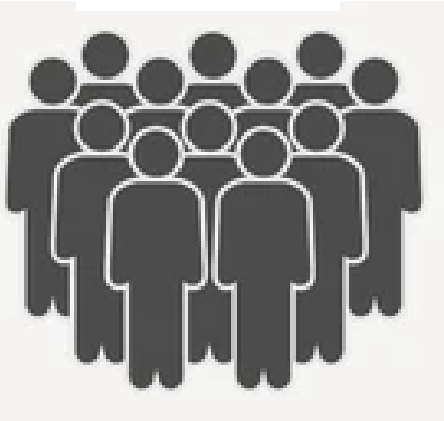
Subgroup	No./total patients: *Lactobacillus rhamnosus*	No./total patients: Enteral placebo	Hazard ratio (95% CI)	Interaction *P* value
Admission type				
Medical	184/1006	199/1021	0.94 (0.77-1.16)	
Surgical	44/141	29/129	1.58 (0.97-2.56)	.14
Trauma	61/171	56/182	1.12 (0.77-1.62)	
Age, y				
<65	173/752	168/767	1.10 (0.88-1.37)	
65-75	69/335	66/319	0.87 (0.61-1.25)	.58
>75	47/231	50/246	1.04 (0.68-1.59)	
Clinical frailty score				
≤4	188/844	191/866	1.02 (0.83-1.26)	.38
≥5	37/240	40/232	0.81 (0.50-1.30)	
Received antibiotics on day of randomization and 2 preceding days				
No	193/766	181/739	1.02 (0.82-1.26)	.92
Yes	96/552	103/593	1.00 (0.75-1.34)	
Prevalent pneumonia as primary diagnosis or comorbid infection				
No	168/542	151/532	1.03 (0.81-1.31)	.78
Yes	121/776	133/800	0.98 (0.76-1.26)	



- **A lot of work**
- **Expensive**
- **Complete – no legacy**

A platform trial studies a disease or a population





Patients at risk of ventilator-associated pneumonia

Endotracheal tube change

Physiotherapy

Positioning

Domain

Probiotics

Prophylactic antibiotics

Intervention

Time

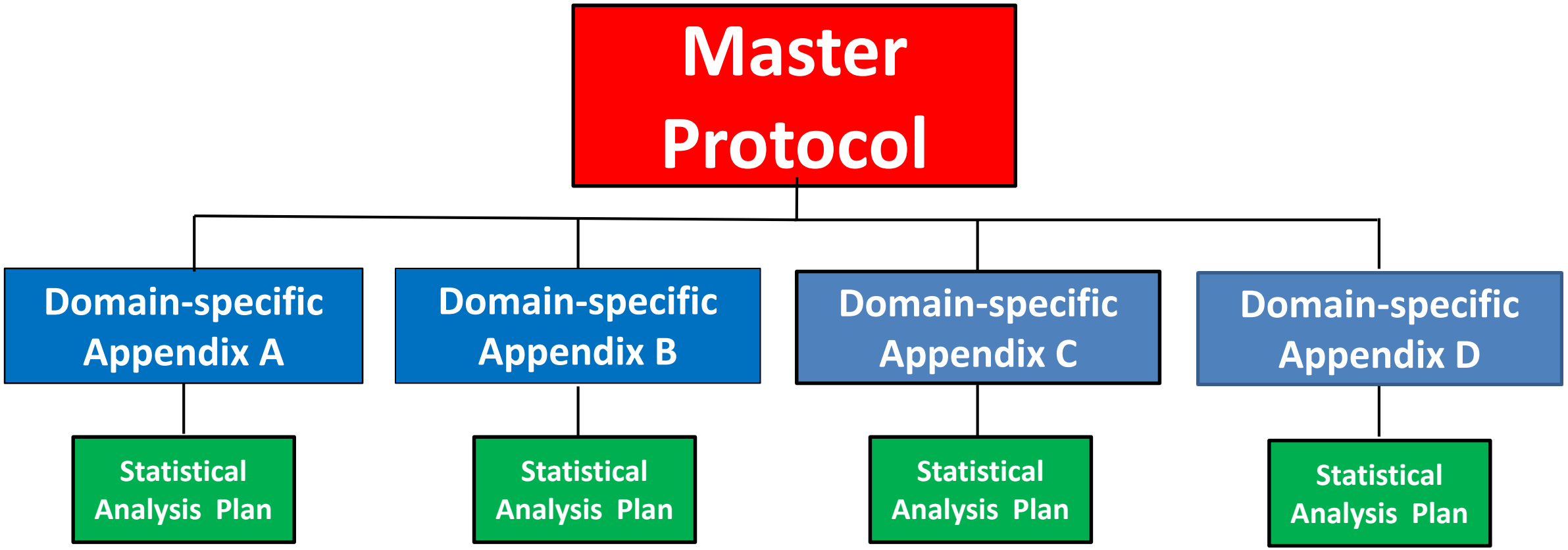
Terminology

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

Platform Trial Structure



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?

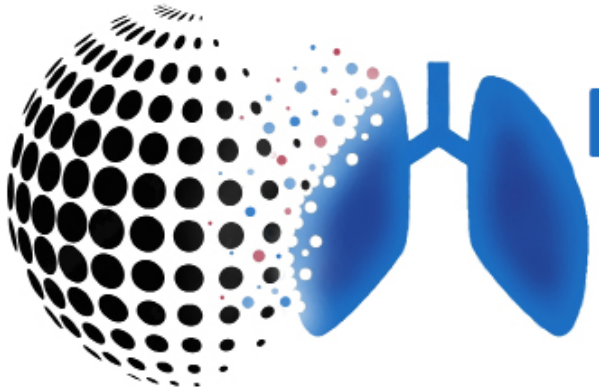
A platform trial is defined by the broad goal of finding the best treatment for a disease by simultaneously investigating multiple treatments, using specialized statistical tools for allocating patients and analyzing results. The focus is on the disease rather than any particular experimental therapy.

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



REMAP-CAP

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

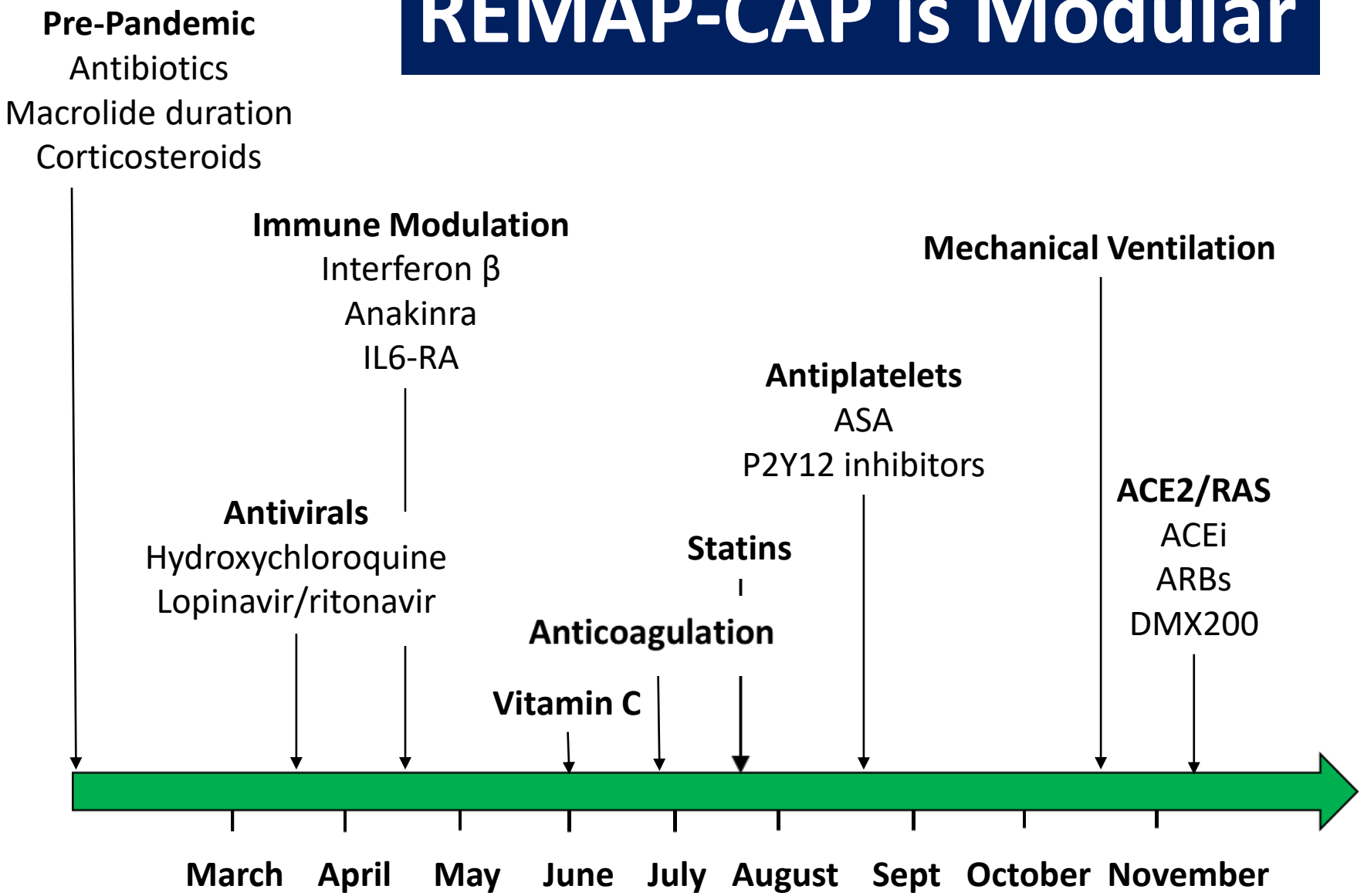
NCT02735707

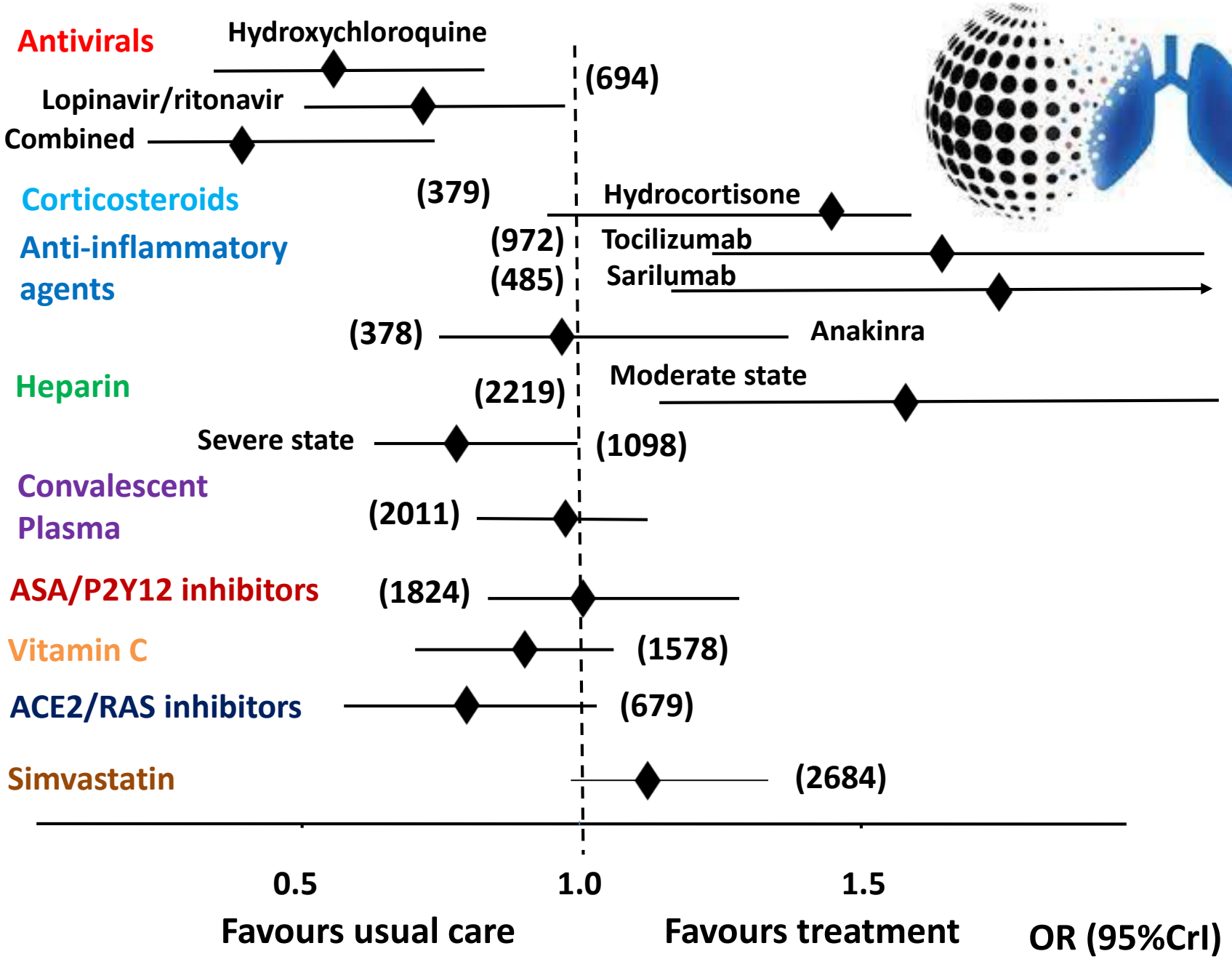
Randomized Embedded Multifactorial Adaptive Platform Trial

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

REMAP-CAP is Modular





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

4 *NEJM*
7 *JAMA*
3 Others

Bracketed figures are the number of patients randomized in each domain

R Randomized

E Embedded in the electronic health record

M Multifactorial - Multiple domains

A Adaptive

P Platform - Perpetual

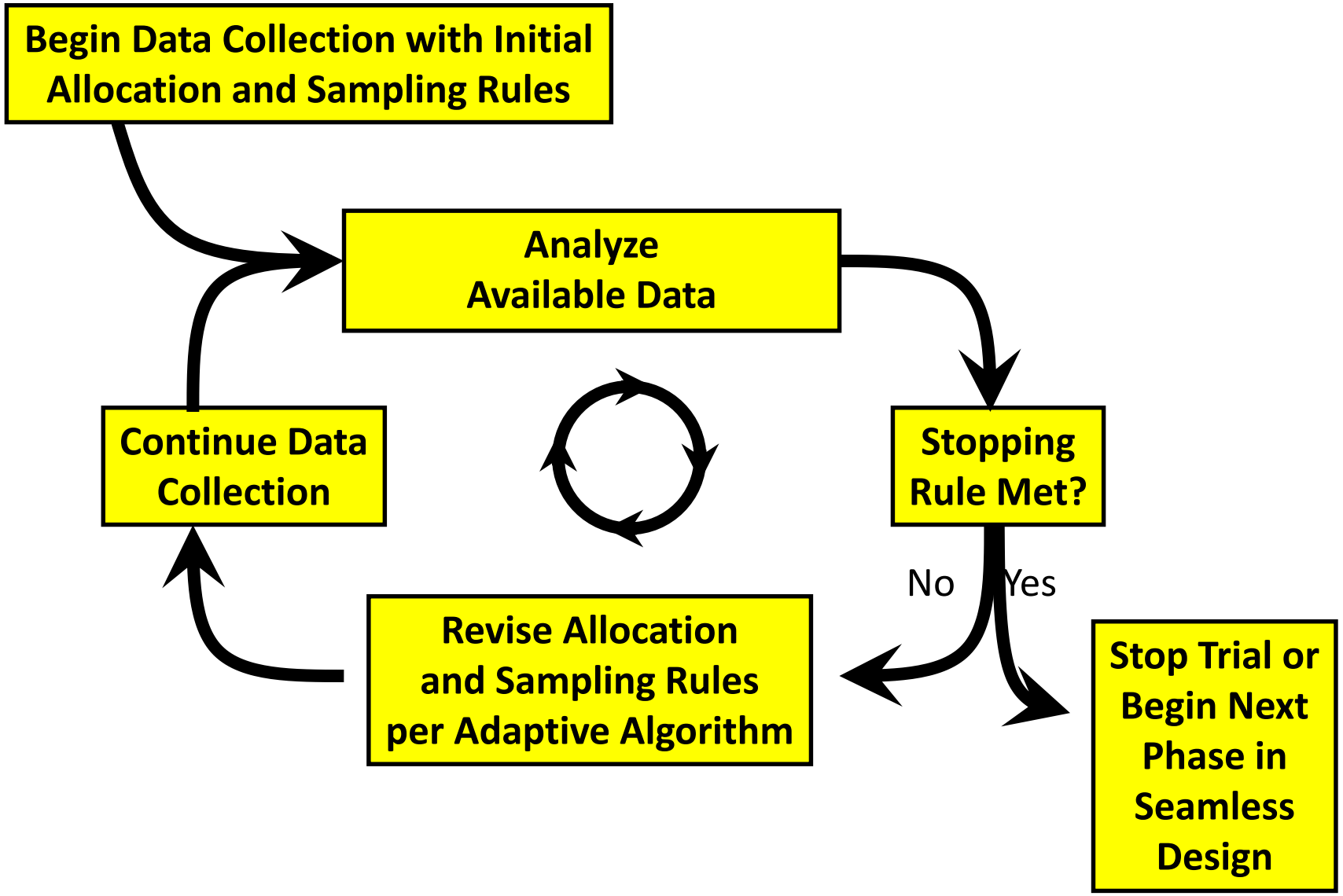
Adaptive Trial

"… a design that allows modifications to the trial and/or statistical procedures of the trial after its initiation without undermining its validity and integrity."

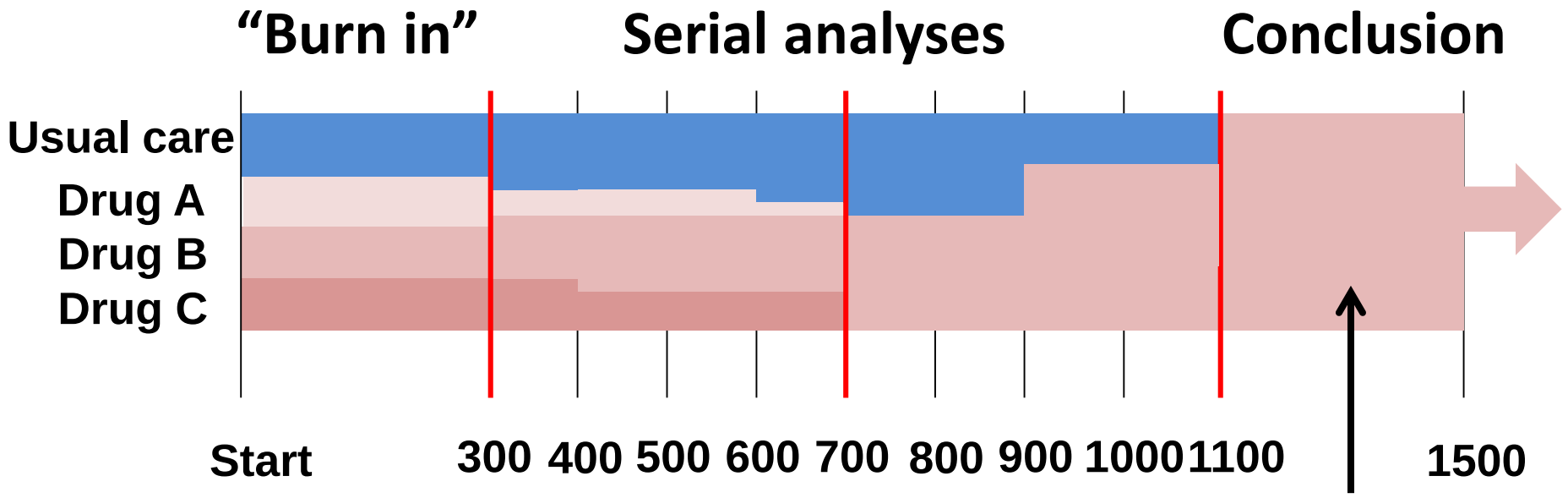
- **Sample size, randomization rates, interventions**

- **Pre-specified**

The Adaptive Process



Response Adaptive Randomization



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

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"

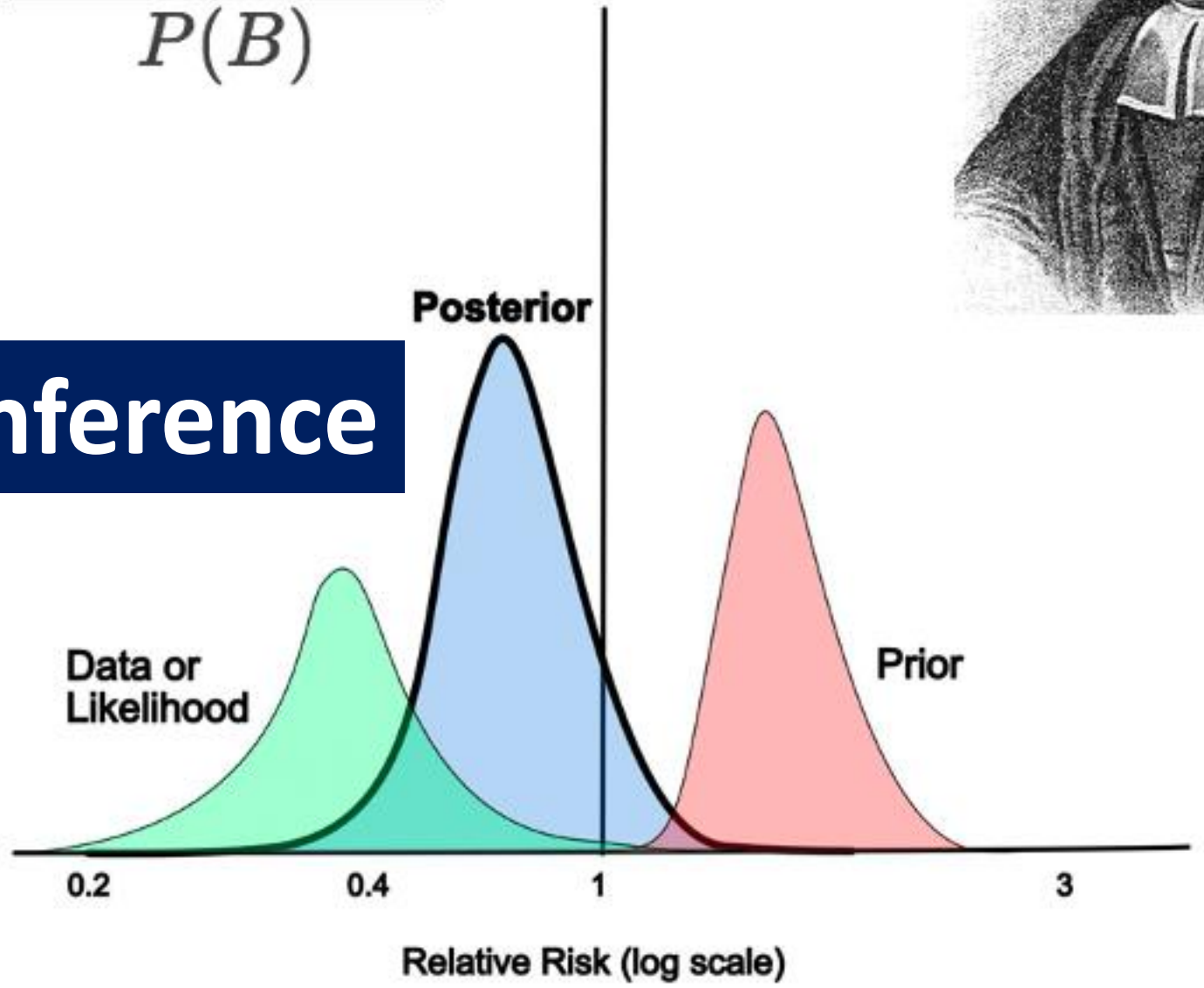
Frequentist versus Bayesian Analyses

Frequentist: The probability of the data given the hypothesis

Bayesian: The probability of the hypothesis given the data

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

Bayesian Inference



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

Frequentist versus Bayesian Approaches

Bayesian posterior probability:

"The probability that the therapy is effective"

Domain Conclusion

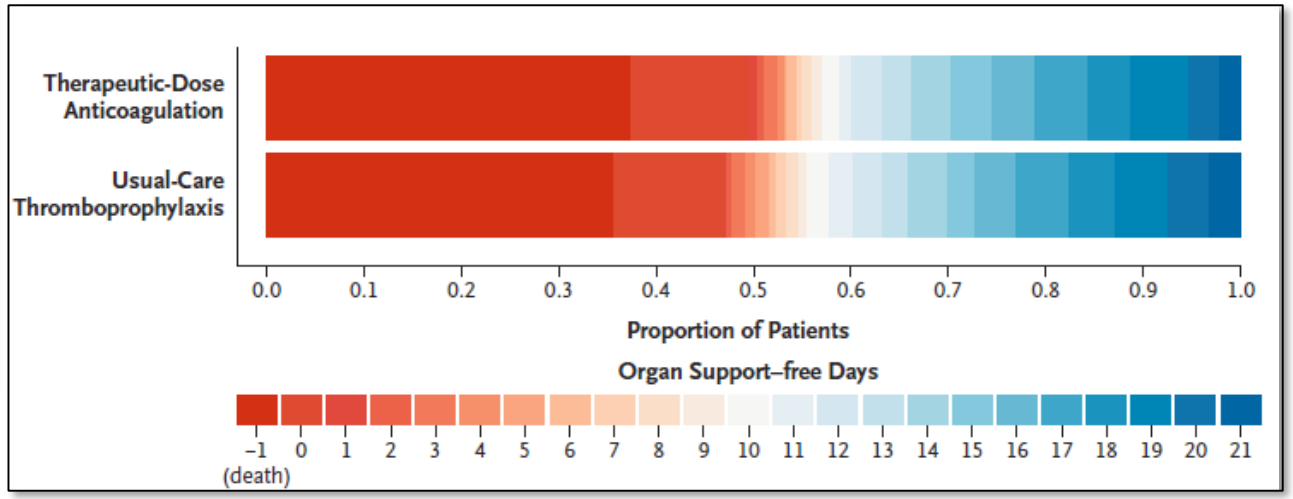
- Domains analyzed independently
- Terminate when a priori stopping boundary for benefit, harm, or equivalence met
- Results reported as for a conventional RCT
- Results inform care of future participants (ie RAR = 100%)

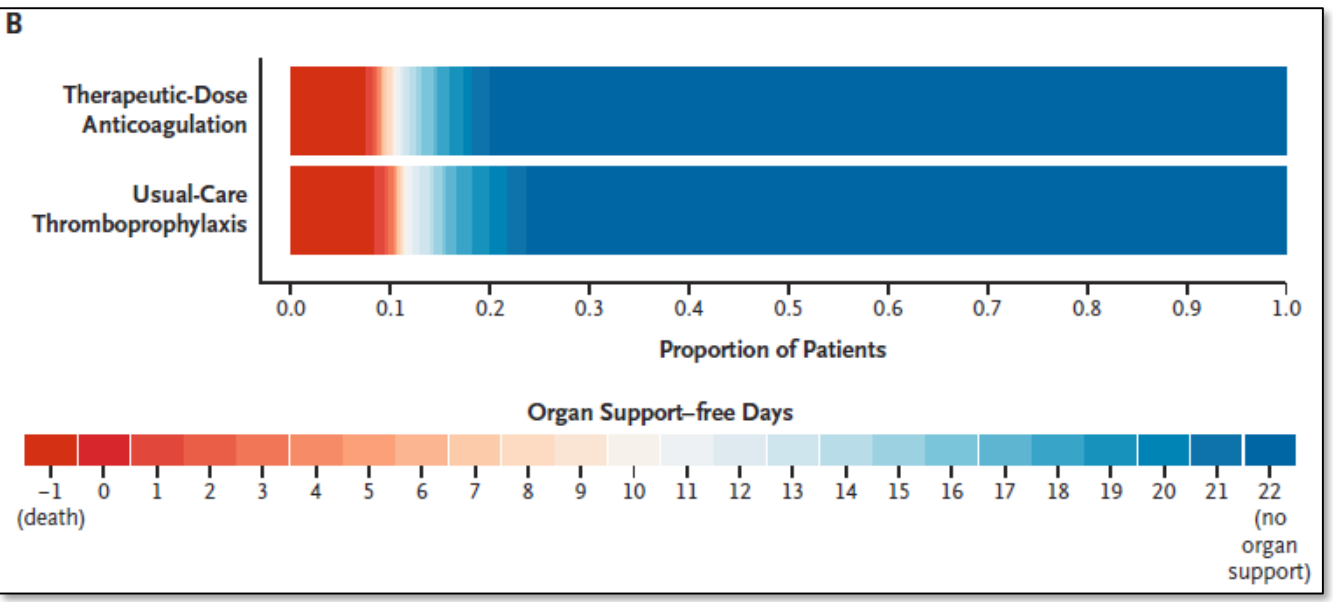
The NEW ENGLAND JOURNAL of MEDICINE

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*





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

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

REMAP-CAP Sites


AHRC


ANZICS


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

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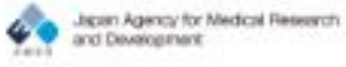

Governance

- Design team
- Statistical Analysis Committee
- Data Coordinating Centre
- DSMB

National/ Regional Centres
Data providers

International Trial Steering Committee

Domain-specific working groups

Operations Committees

When is a Platform Design Appropriate

- When the focus is a disease with many treatment options
- Long term commitment to collaboration
- In supporting multiple research programs within a network
- In supporting international collaboration
- In embedding research within care

Thank you!