

# The REMAP-CAP Adaptive Platform Trial: Recent Insights and Future Directions

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# Disclosures (speaker)

## Related grant funding:

- CIHR, NIH, Heart and Stroke Foundation of Canada, Peter Munk Cardiac Centre, LifeArc Foundation, Thistledown Foundation, Province of Ontario, Research Manitoba, Heart and Stroke Foundation of Canada, Fonds de Recherche du Québec - Santé

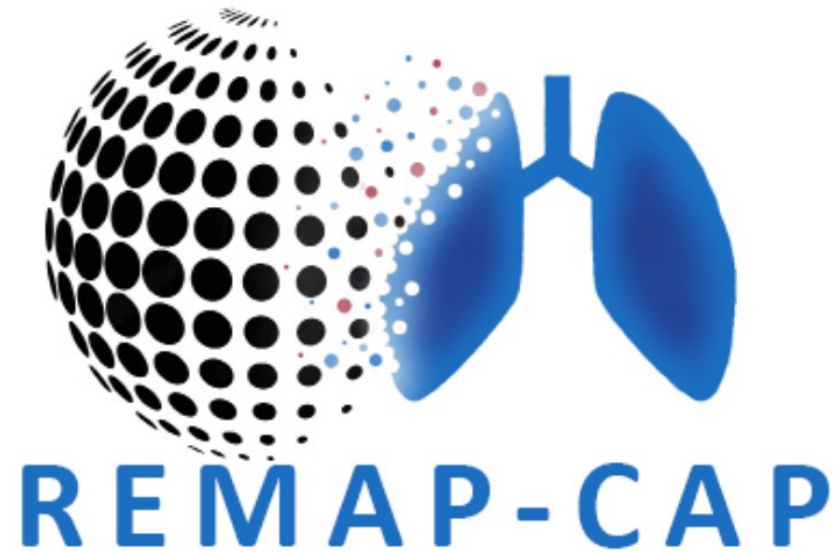
## Related clinical trial roles:

- REMAP-CAP platform trial (International Trial Steering Committee, Design Committee, Protocol/CRF Committee, ACE2 RAS Domain Co-Chair, Antiplatelet Domain Co-Chair), ATTACC trial (Co-PI), NHLBI ACTIV-4a platform trial (Protocol Development Committee, Network Lead)

## Unrelated personal fees:

- Novartis, CorEvitas, Brigham and Women's Hospital, American College of Cardiology, McGraw-Hill

# Thank you



<https://www.remapcap.org/>

# Outline

- Recap: Why an adaptive platform trial?
- Platform experience
- Domain experience evaluating heterogeneity of treatment effect (HTE)
- Conclusions

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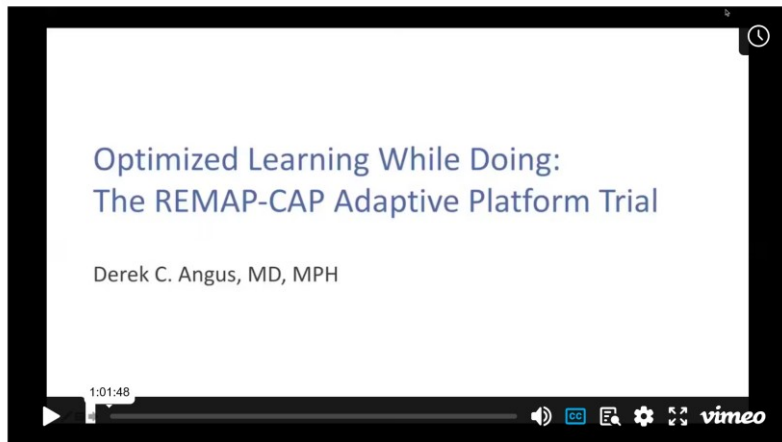
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  - HTE in the TAC and RAS modulation domains
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  - How did the trial address the challenges?
  - Next steps



May 15, 2020: Optimized Learning While Doing: The Platform Trial (Derek Angus, MD, MPH)

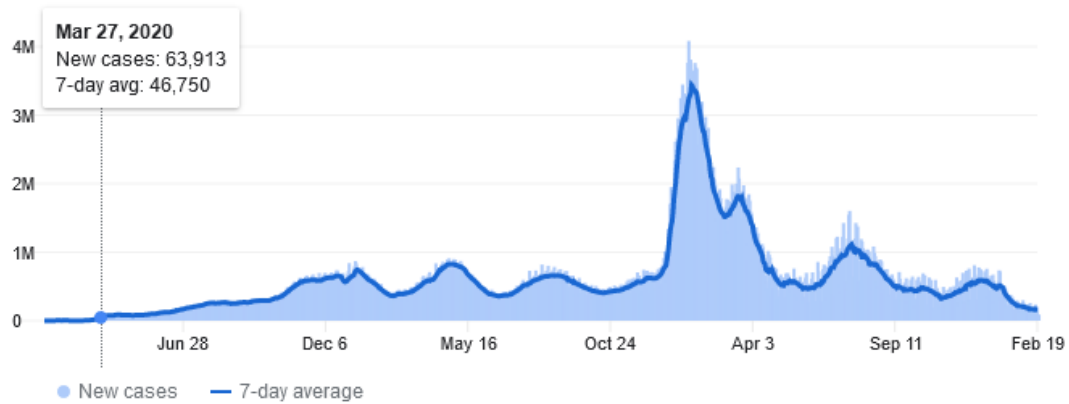


April 2, 2021: Lessons from COVID-19: The First Adaptive Platform Trial (Derek Angus, MD, MPH)



# 6 challenges (...of many) for pandemic RCTs

## 1. Avoiding the shortcoming of prior data (or not having any)



## 6 challenges (...of many)

1. Avoiding the shortcoming of prior data (or not having any)
2. Equipoise: balance learning while doing (exploitation vs exploration)

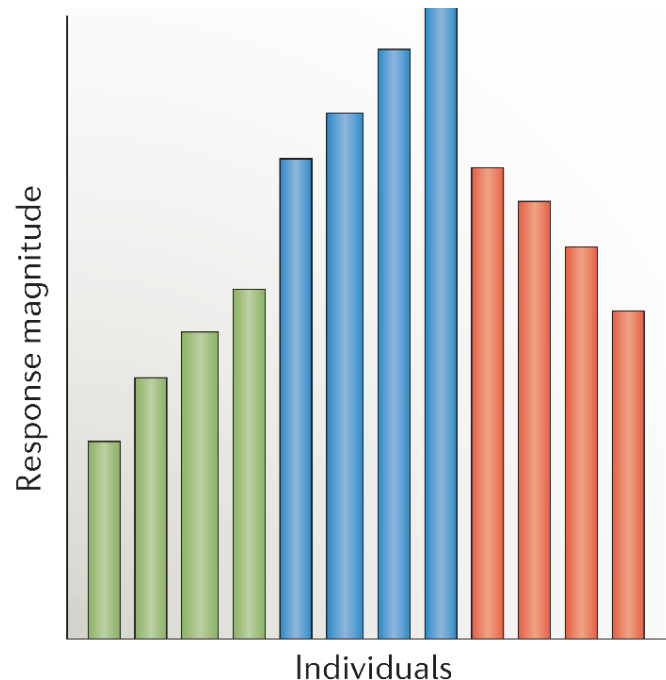
“Many clinicians on the ground felt the urgency of treating the hundreds of patients dying in front of them; researchers, with their literal and intellectual distance from the I.C.U., were pressing them to think about the thousands of patients who were sure to follow — to slow down long enough to build a body of evidence that they knew with more certainty could help.

The tensions between these two ways of thinking about medicine have always existed. But during the early months of the pandemic, the disagreements... provided another layer of painful stress to some doctors already near their limits.”

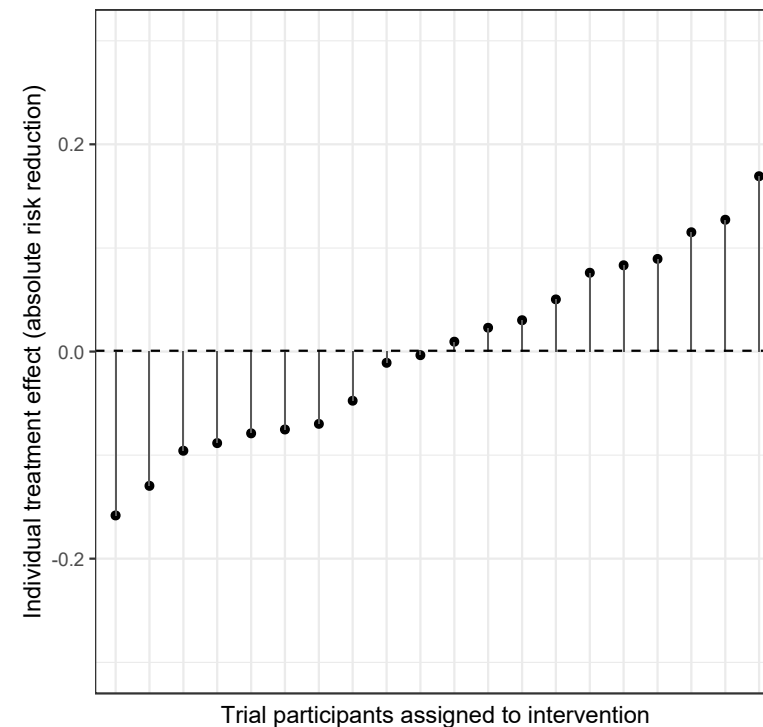
New York Times Magazine, August 8, 2020

# 6 challenges (...of many)

1. Avoiding the shortcoming of prior data (or not having any)
2. Equipoise: balance learning while doing (exploitation/exploration)
3. Heterogeneity of treatment effect – wide syndrome variability



Antman and Loscalzo *Nat Rev Drug Disc* 2016



## 6 challenges (...of many)

1. Avoiding the shortcoming of prior data (or not having any)
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3. Heterogeneity of treatment effect – wide syndrome variability
4. Making trials happen quickly – operationally, evidence generation

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6. Trial conduct: hard to set-up/take-down,  
how to pivot to sustainability/efficiency?



## 6 challenges (...of many)

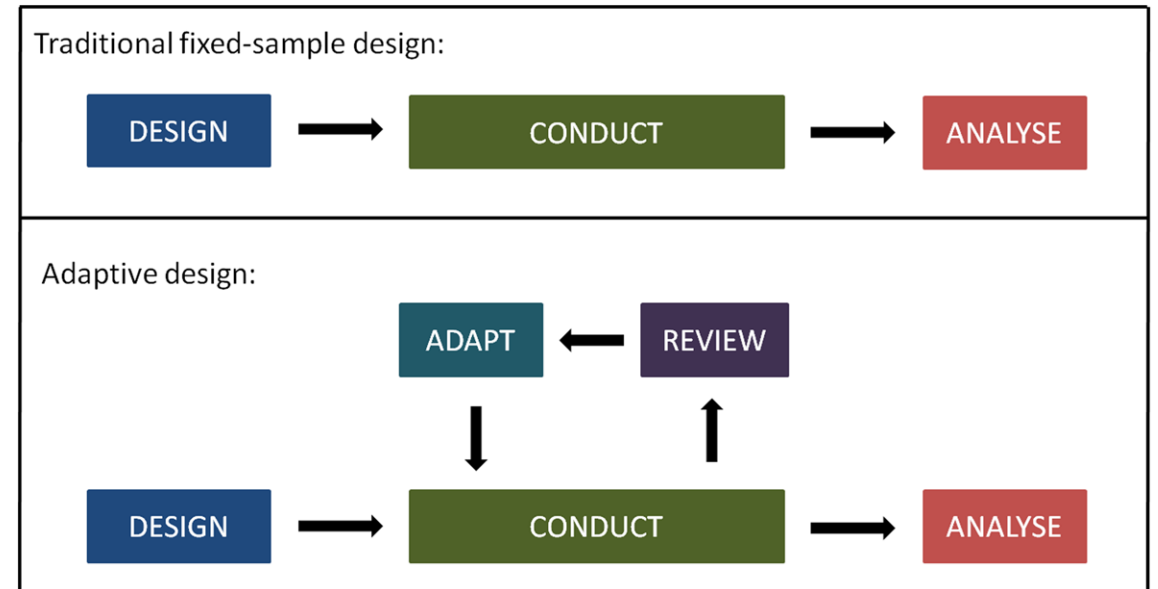
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***So... what approaches may address these challenges?***

***Bayesian Adaptive Platform Trial***

# What is an adaptive RCT?

implies that key features of the trial design are modified during the trial in response to accumulating information for the purpose of maximizing statistical efficiency or achieving better outcomes for trial participants.



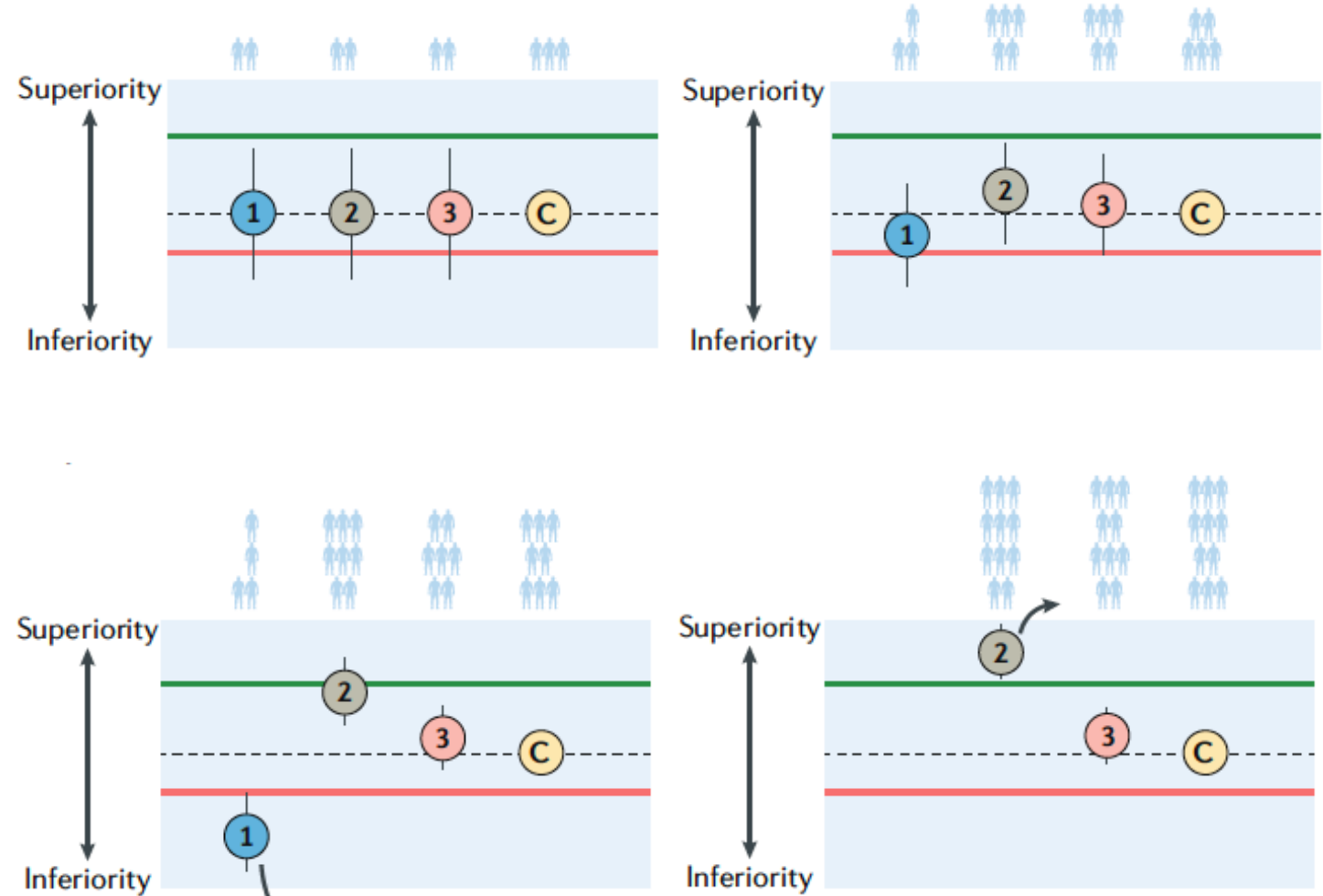
Pallmann P *et al.* *BMC Medicine* 2018

# Adaptive trials: Responsive to accumulated knowledge

## Potential adaptations:

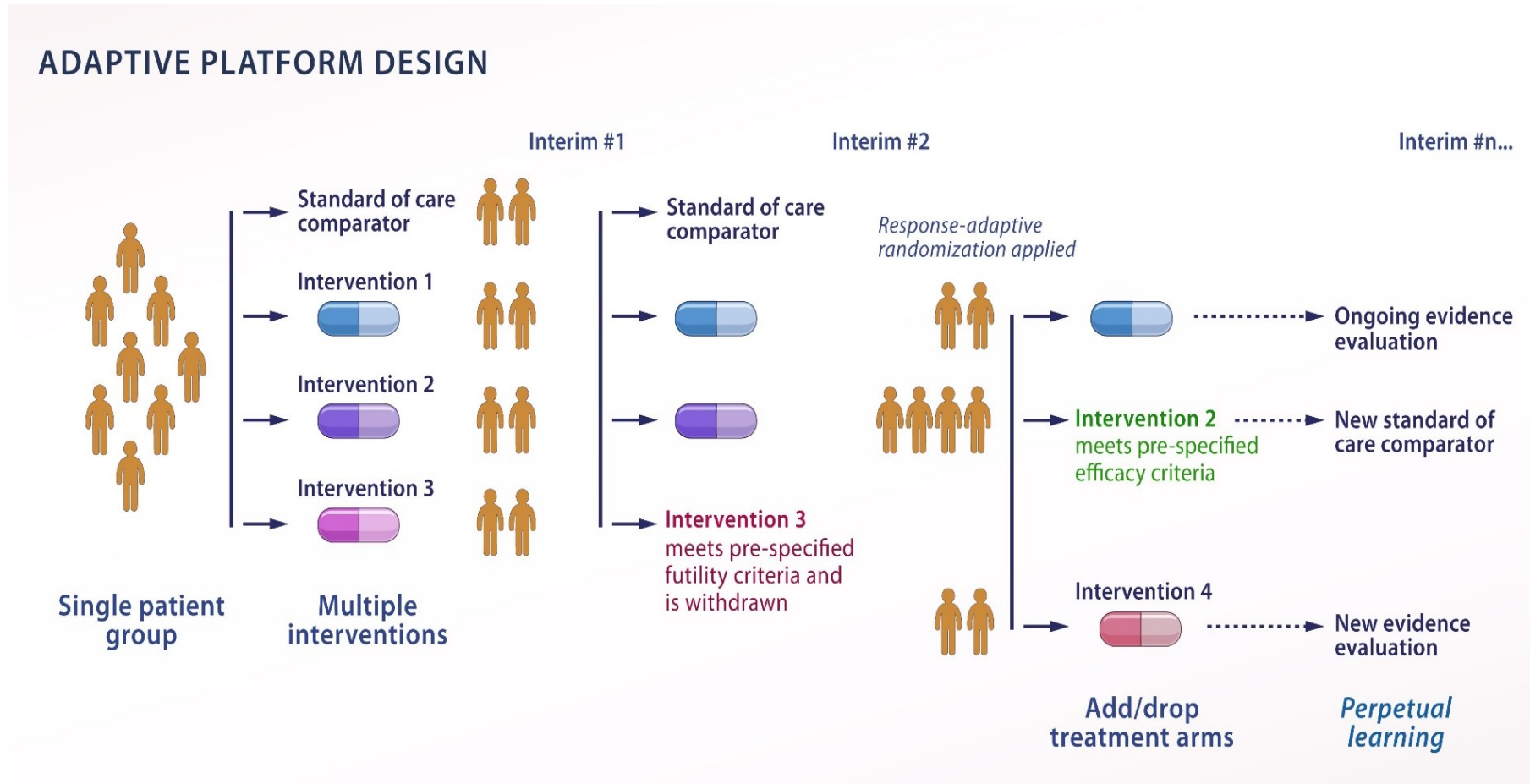
- Response-adaptive randomization
- Sample size reassessment
- Group sequential stopping
- Seamless designs (e.g. seamless phase II/III)
- Enrichment designs
- Multi-arm designs
- Dose-finding phase 1 designs

## Response adaptive randomization



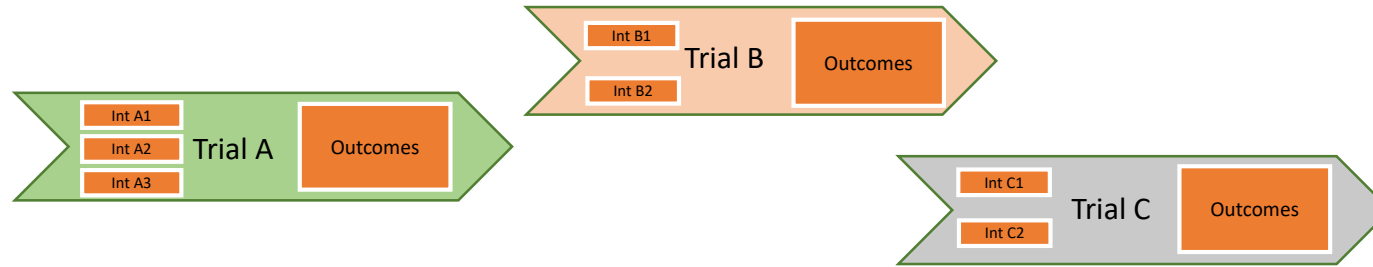
# What is a platform trial?

implies the use of a master protocol as a foundation to study multiple treatments for one disease



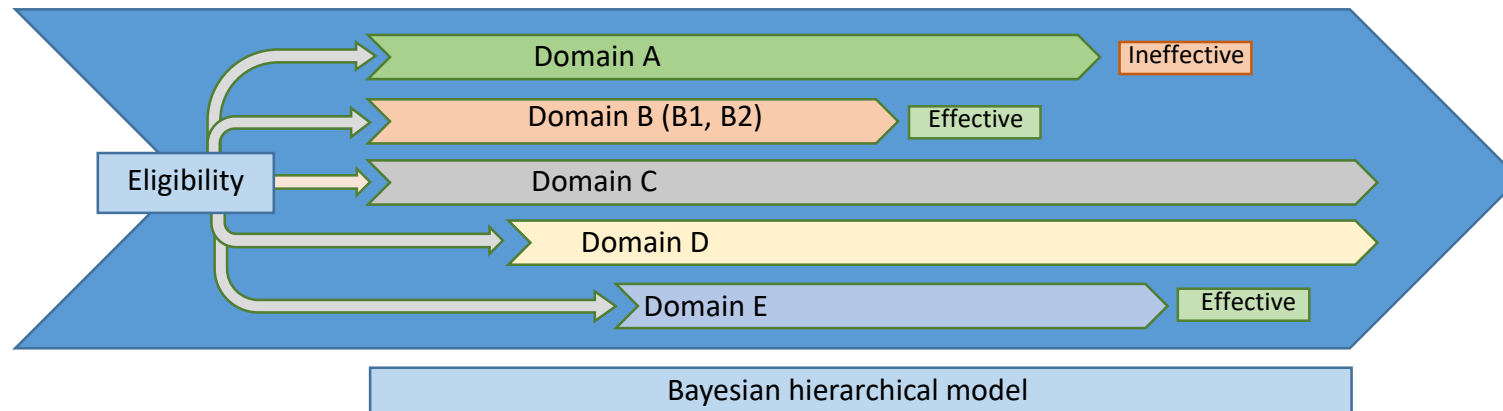
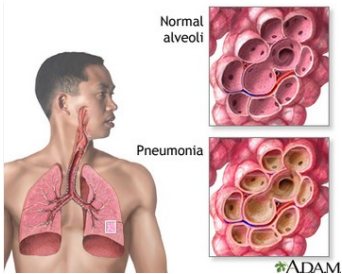
# REMAP-CAP: A platform trial using a master protocol

Traditional RCTs– evaluate treatments sequentially, frequently using operationally and statistically disjoint approaches → ↓ reduces efficiency



**REMAP** – Randomized, EMBEDDED, Multifactorial, ADAPTIVE Platform trial  
simultaneous evaluation of multiple treatments in domains using a **master protocol**

Community-acquired pneumonia (CAP)



# Primary analysis: Single Bayesian hierarchical model

- Primary Endpoint (Organ support-free days): Ordinal endpoint, death worst outcome (−1), followed by number of OSFD through 21 days, modeled with cumulative logistic proportional odds model

$$\log\left(\frac{\pi_y}{1 - \pi_y}\right) = [y] + [Site] + [Time] + [Z] + R_d \sum_{i=1}^{k_d} \theta_{i,S} + R_{d^2} \sum [IxI]$$

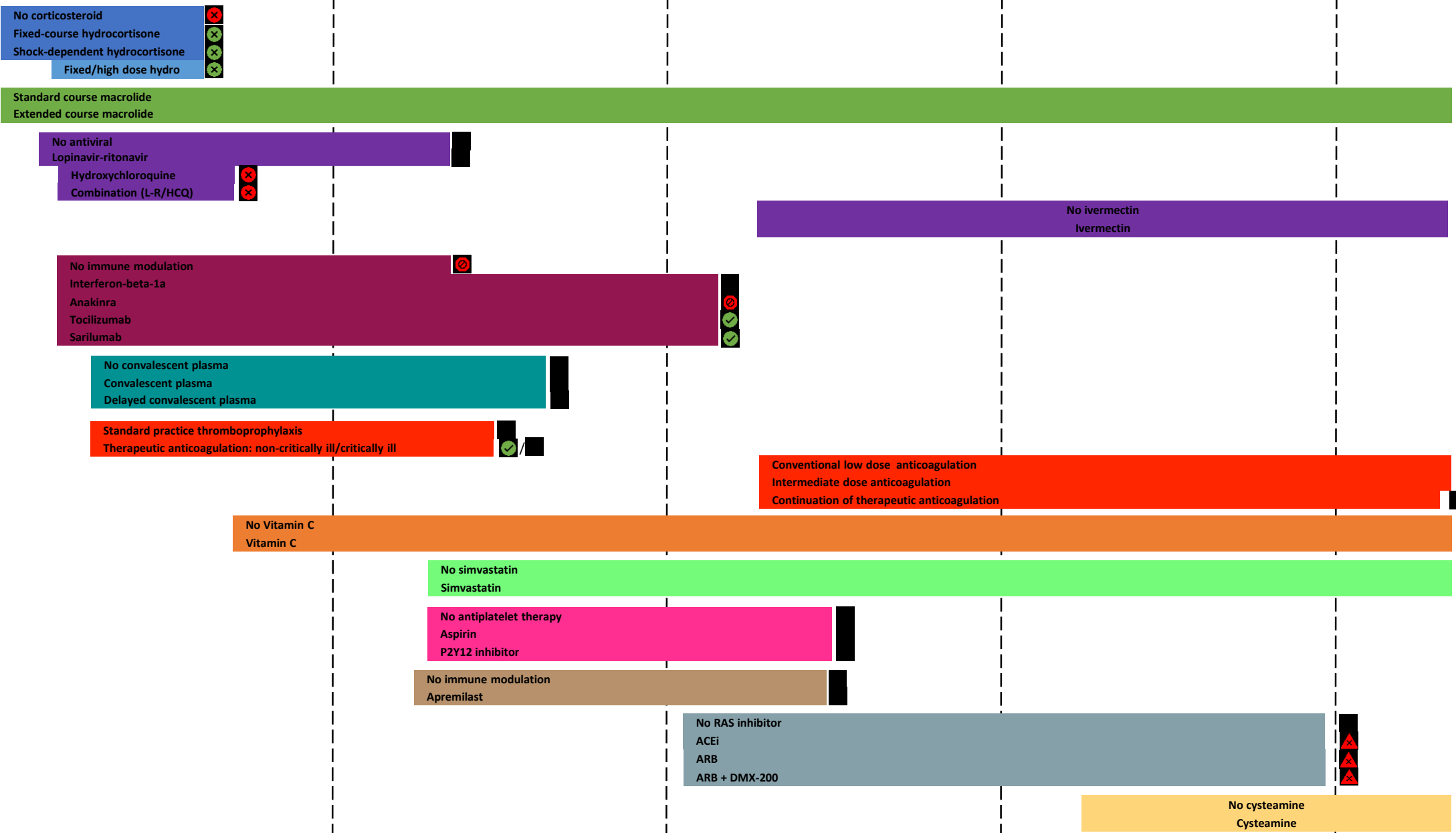
- Scheduled runs of common model by independent, unblinded analysis committee
- Domains specify statistical triggers for adaptation, including:
  - Stopping of one or more arms for: superiority [ $\Pr(\text{OR} > 1) > 99\%$ ]; futility (to detect an at-best modest effect) [ $\Pr(\text{OR} > 1.2) < 5\%$ ]; equivalence
  - Response-adaptive randomization
  - Stage 1 to 2 (i.e., Phase 2 to Phase 3) transition

Platform Conclusions

- Effective
- Futile
- Ineffective/inferior
- Safety concern
- Dropped due to other triggers

Stopped/analyzed due to external results

- External efficacy
- External lack of efficacy



Mar '20

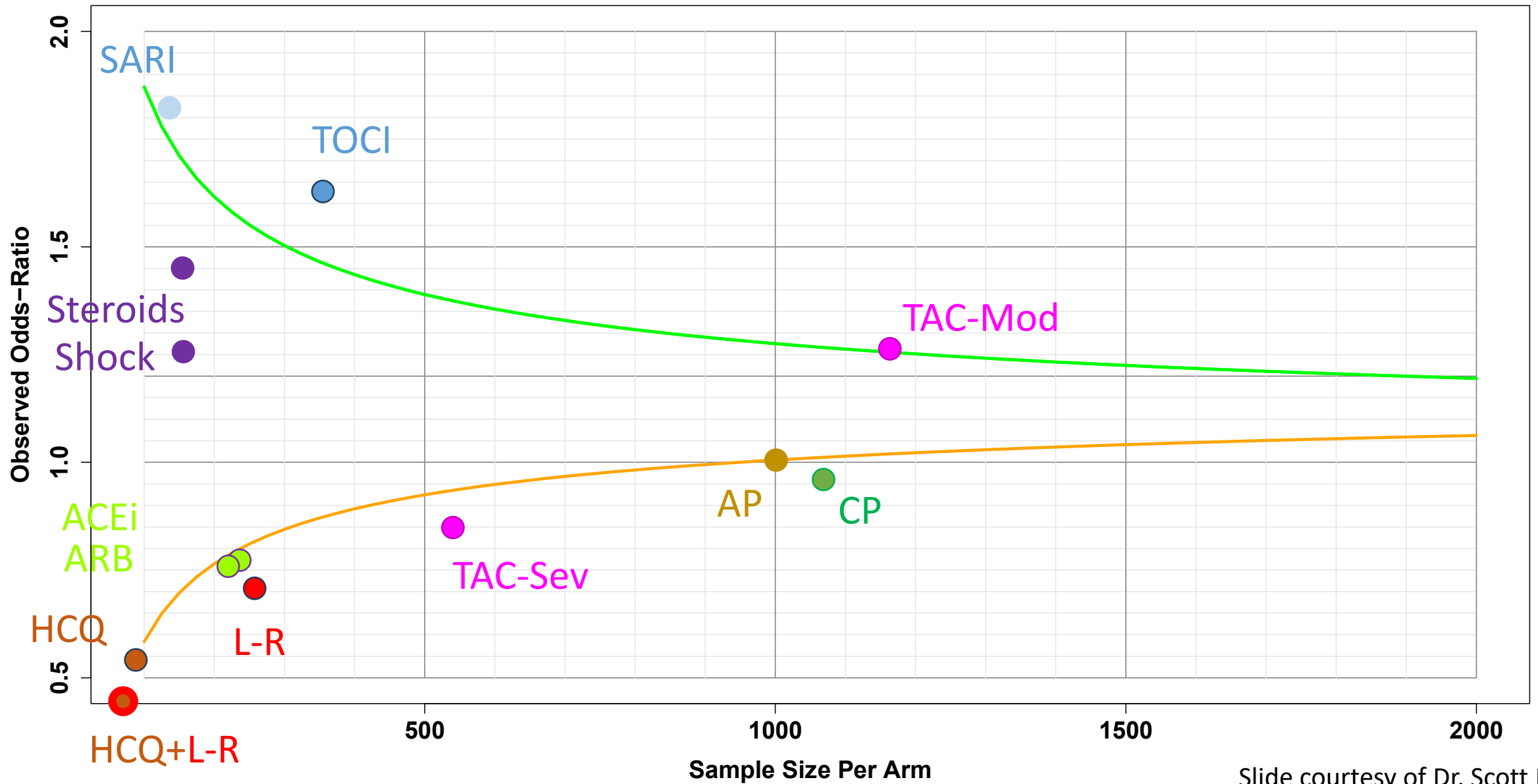
Sept '20

Mar '21

Sept '21

Mar '22

### Example Pathways For Superiority/Futility







22,324

Patient randomisations

18,439

Patient randomisations with suspected or proven COVID-19

61

Current or completed interventions in 17 Domains

12,725

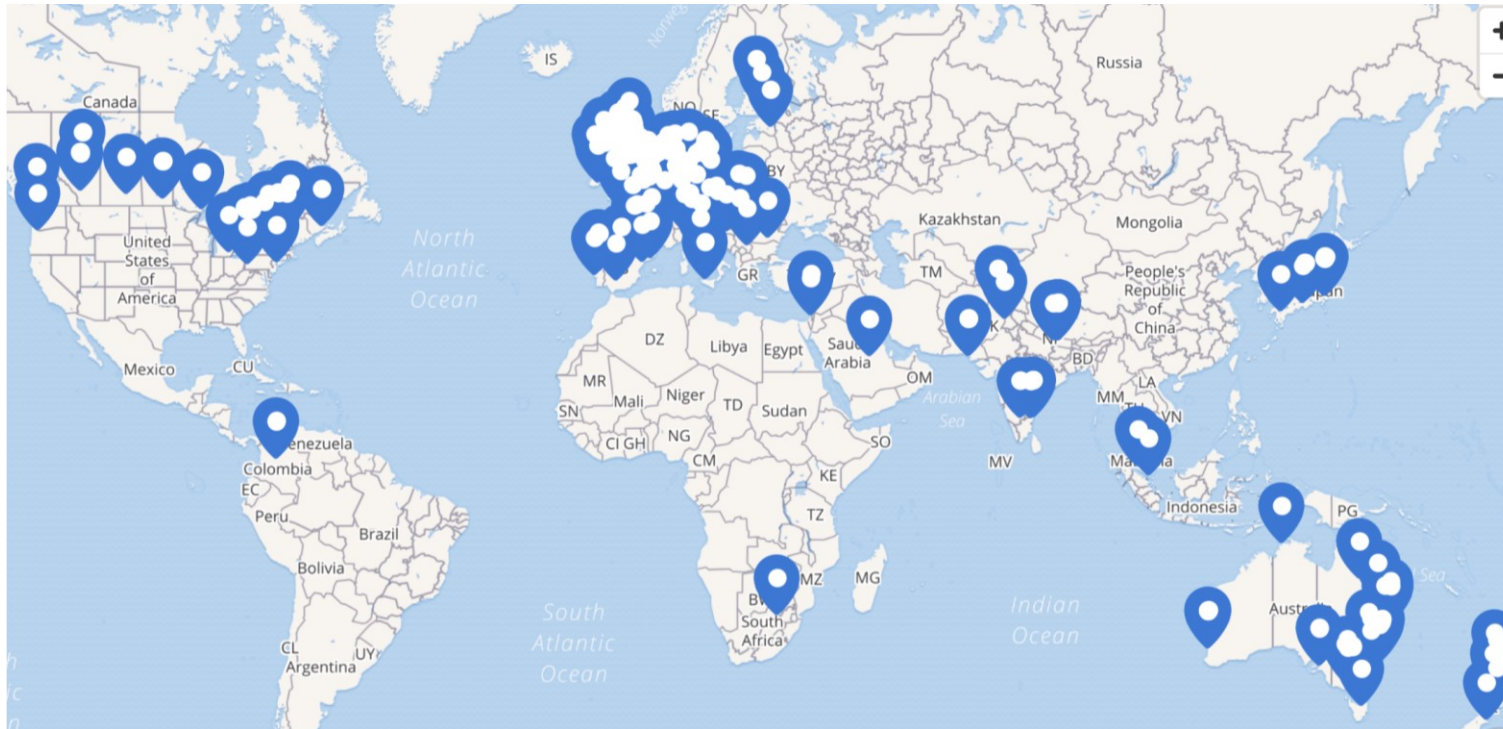
Total patients

10,237

Patients with suspected or proven COVID-19

325

Active Sites



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

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

### Heterogeneous Treatment Effects of Therapeutic-Dose Heparin in Patients Hospitalized for COVID-19

Ewan C. Goligher, MD, PhD; Patrick R. Lawler, MD, MPH; Thomas P. Jensen, MS; Victor Talas, PhD; Lindsay R. Berry, PhD; Elizabeth Lorenz, PhD; Bryan J. McVerry, MD; Chung-Chou Ho Chang, PhD; Eric Leifer, PhD; Charlotte Bradbury, MD, PhD; Jeffrey Bergot, MD; Beverly J. Hunt, MD, PhD; Lana A. Castellucci, MD; Lucy Z. Kornblith, MD; Anthony C. Gordon, MD; Colin McArthur, MD; Steven Webb, MD; Judith Hochman, MD; Matthew D. Neal, MD; Ryan Zarychanski, MD, MSc; Scott Berry, PhD; Derek C. Angus, MD, MPH; for the REMAP-CAP, ATTACC, and ACTIV-4a Investigators

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

ORIGINAL ARTICLE

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

The REMAP-CAP Investigators\*

ORIGINAL

### Lopinavir-ritonavir and hydroxychloroquine for critically ill patients with COVID-19: REMAP-CAP randomized controlled trial

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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A Randomized Clinical Trial

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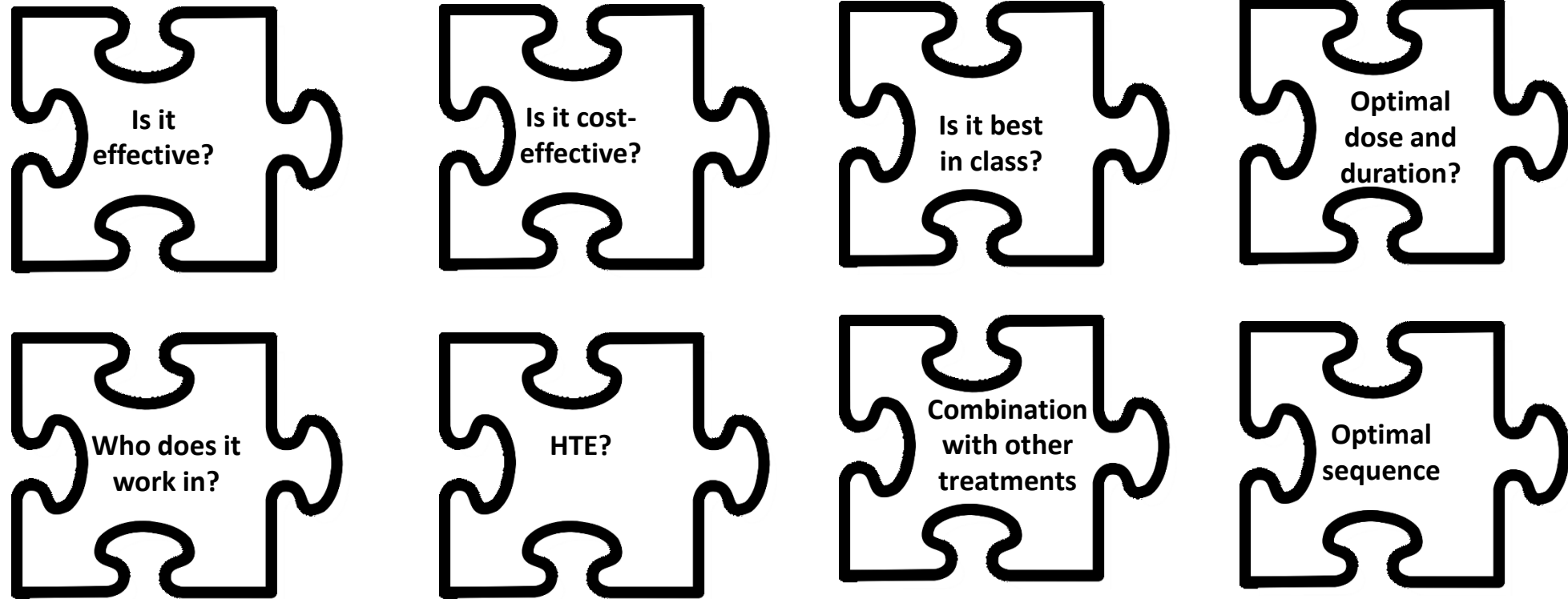
### Effect of Antiplatelet Therapy on Survival and Organ Support-Free Days in Critically Ill Patients With COVID-19

A Randomized Clinical Trial

REMAP-CAP Writing Committee for the REMAP-CAP Investigators

# Beyond operational efficiencies, does REMAP-CAP provide opportunities for trials to address unmet clinical need?

Most diseases have multiple component therapies... for each component:



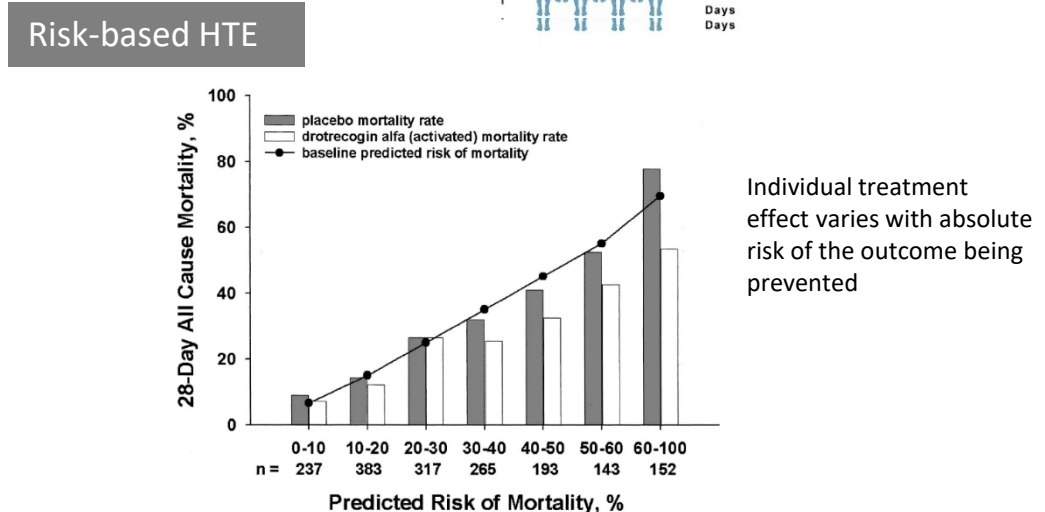
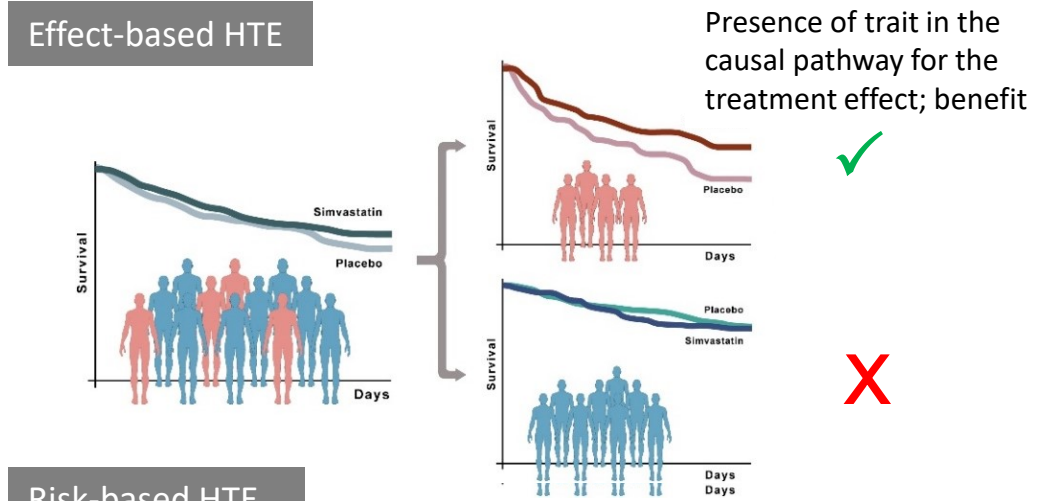
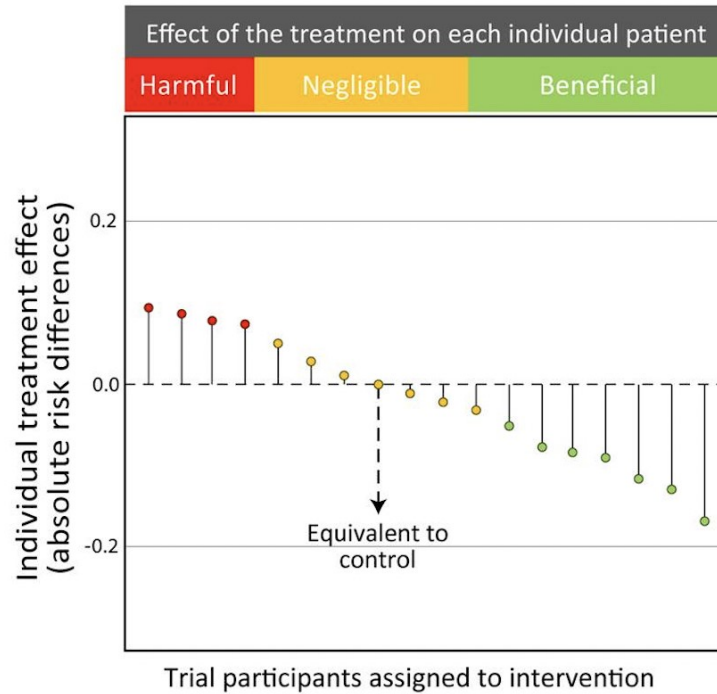
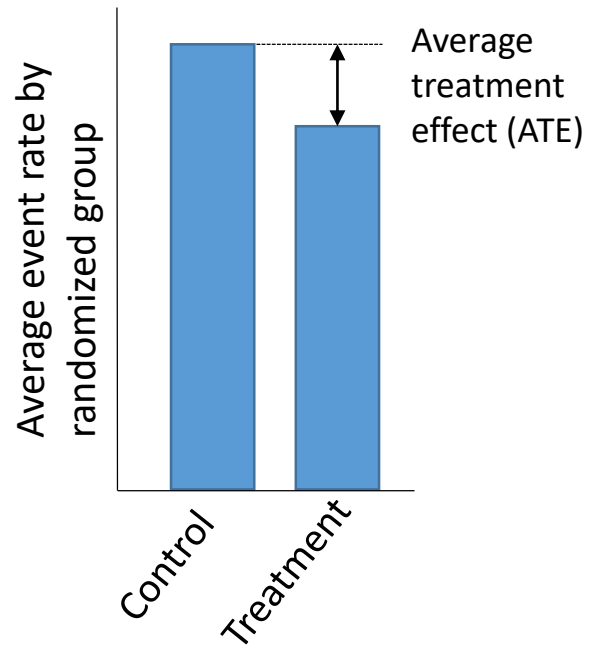
*How can a trial (domain) address this?*

# Heterogeneity of Treatment Effect

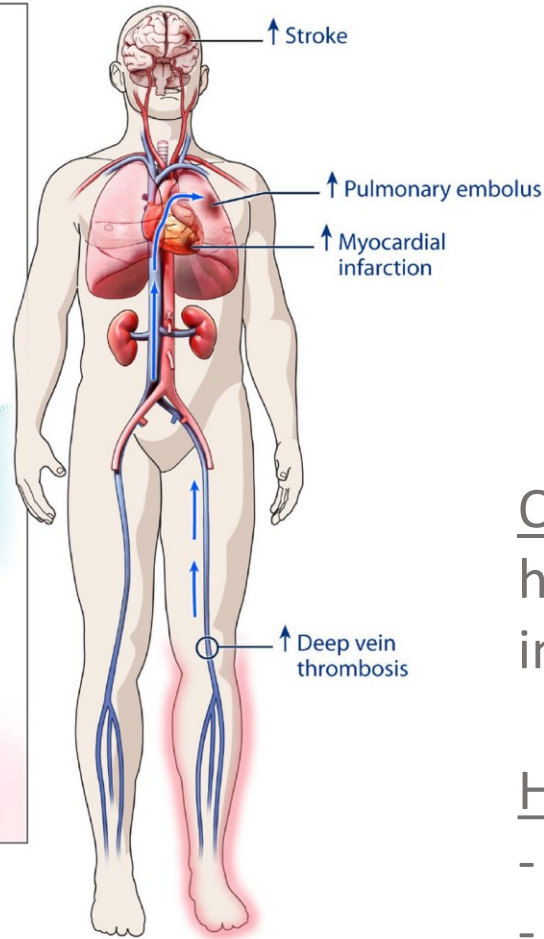
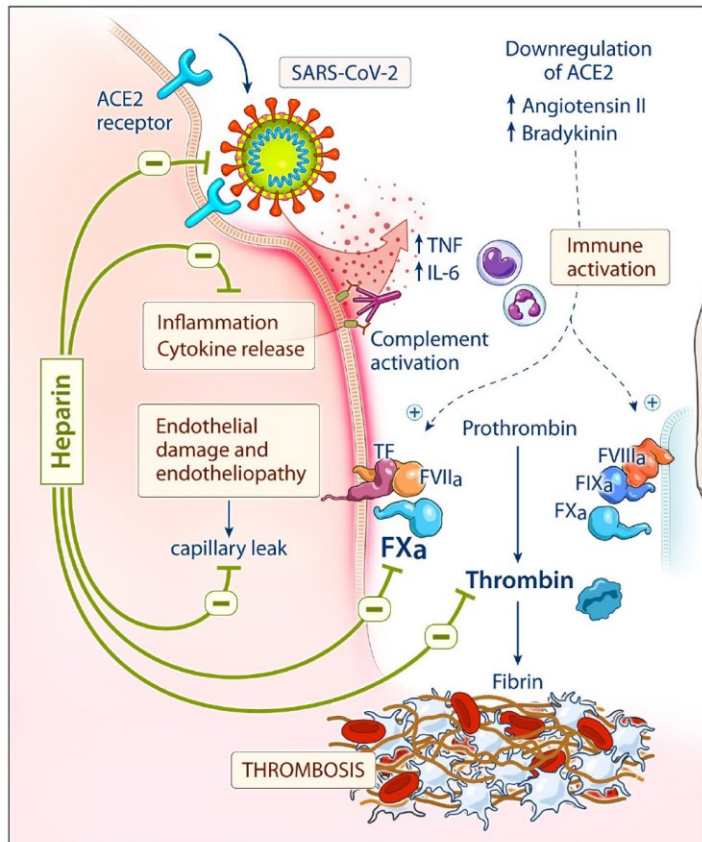
Generally, assume homogenous tx. effect  
Evaluating treatments based on group-level average treatment effect (ATE)

In reality treatment effects are heterogeneous  
Evaluating treatments based on individual treatment effects (ITE)

What determines heterogeneity of treatment effect (HTE)?  
HTE may be effect-based (predictive) or risk-based (prognostic)



# Therapeutic Anticoagulation Domain



## Heparin:

- (1) Antithrombotic
- (2) Direct anti-viral (e.g., Clausen *Cell* 2020)
- (3) Direct anti-inflammatory (e.g., ↓ IL6)

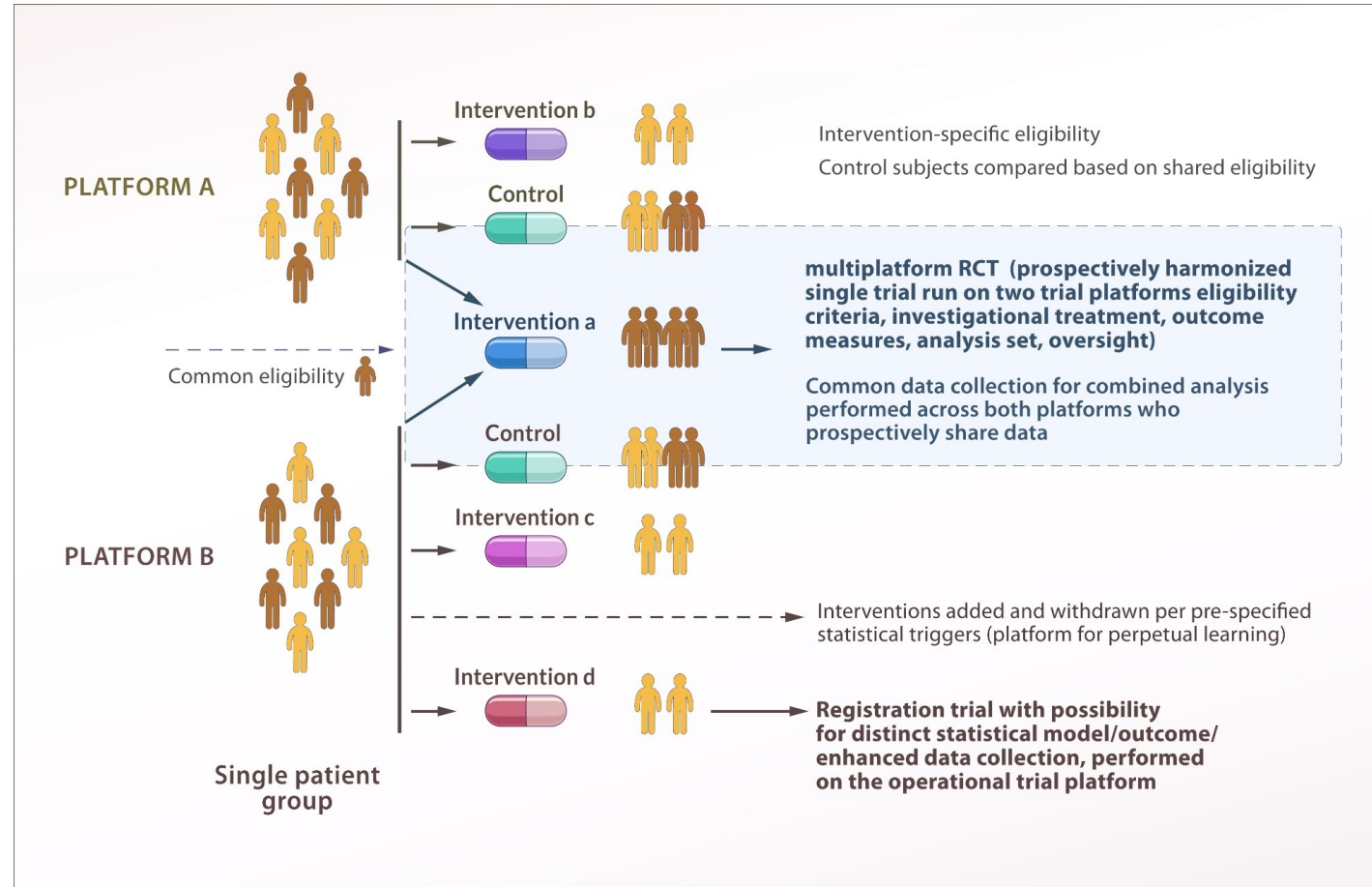
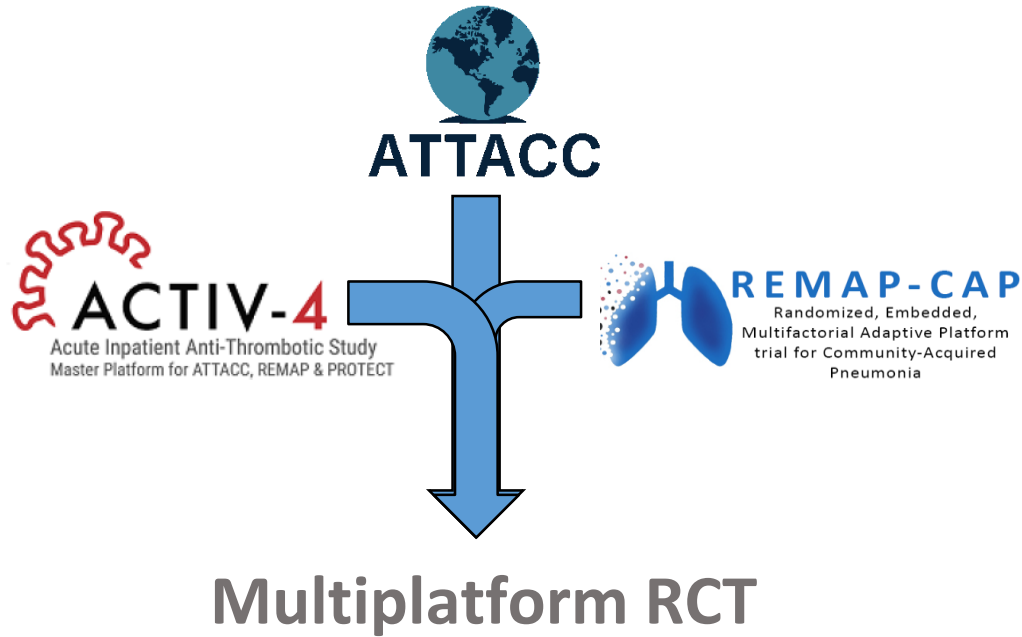
Observation: Highly variable clinical syndrome...  
how to select patients in whom to antagonize  
immunothrombosis host response?

## Heterogeneous treatment effects?

- Treatment effect may vary by severity/risk?
- Treatment effect may vary by mechanism/**effect**?



# Multiplatform randomized controlled trial (mpRCT)

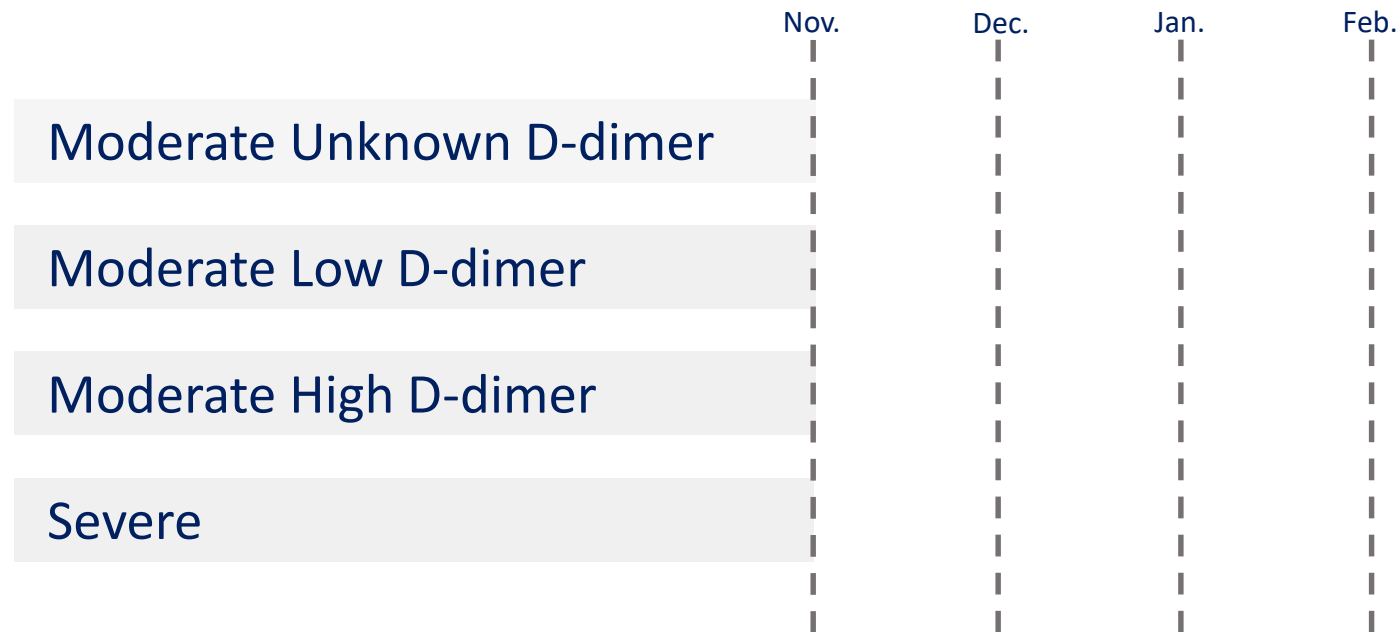


# mpRCT: Adaptive Bayesian Design

*Adaptive stopping criteria: OSFDs examined in each group monthly*

Posterior probability [proportional  $OR > 1.0$ ]  $> 99\%$  = superiority

Posterior probability of proportional [ $OR > 1.2$ ]  $< 5\%$  = futility

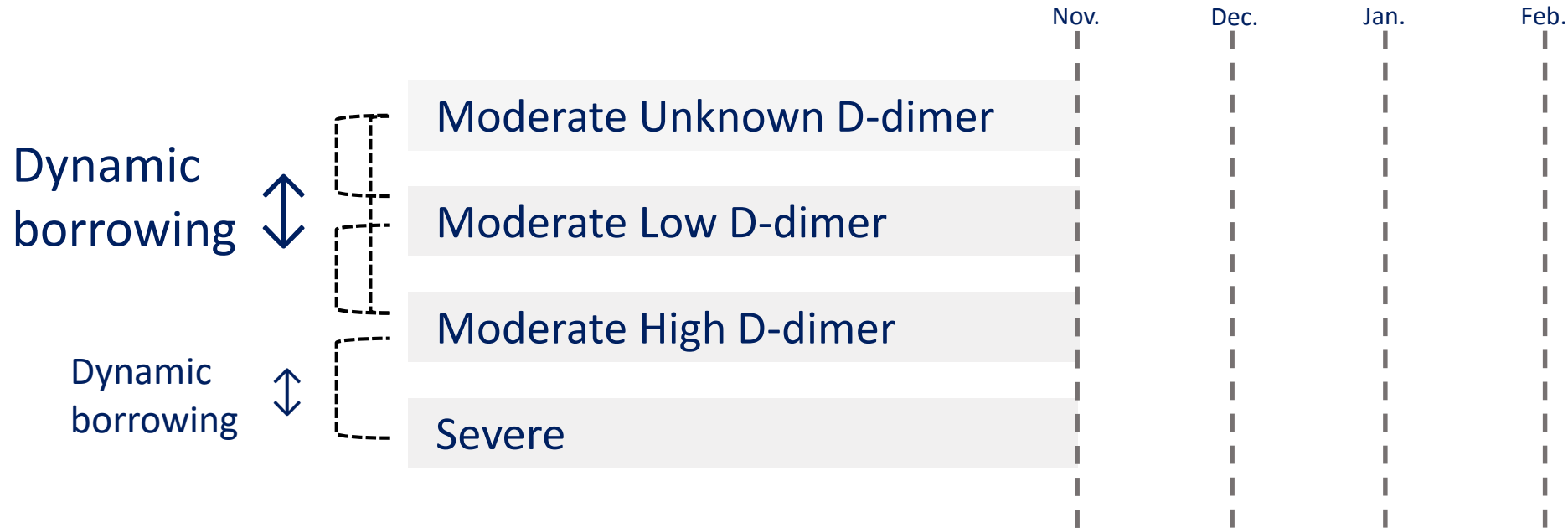


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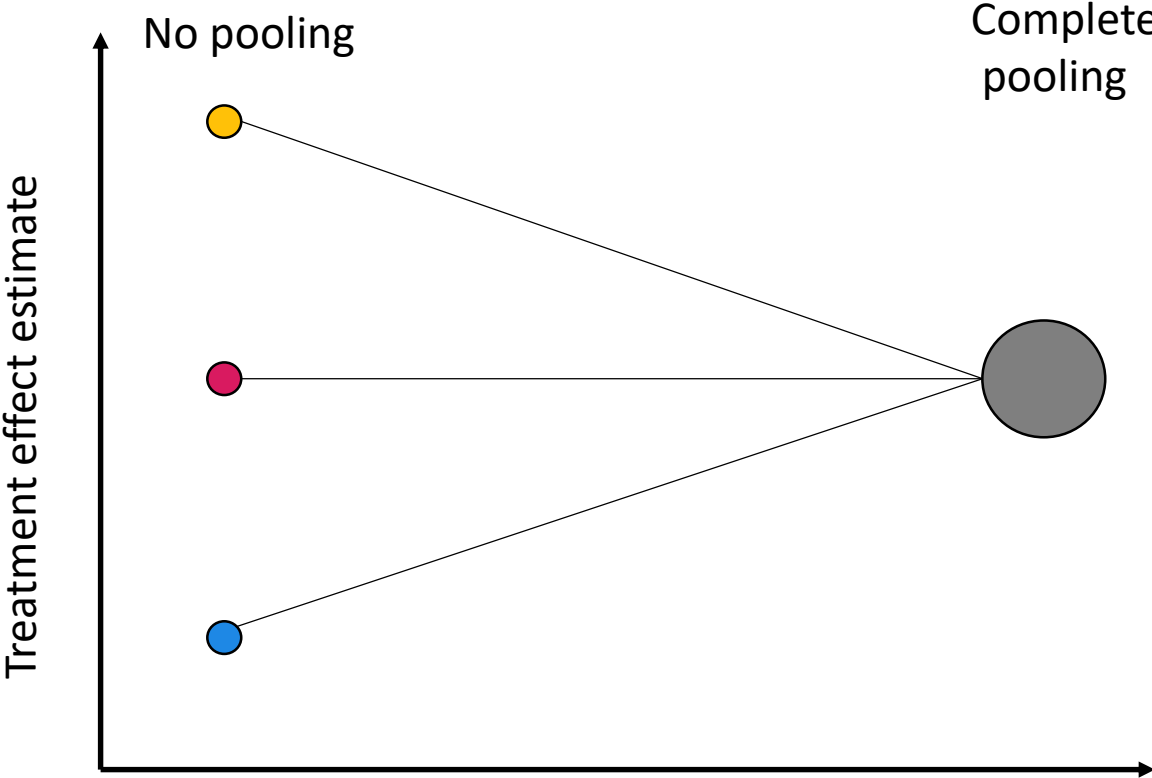
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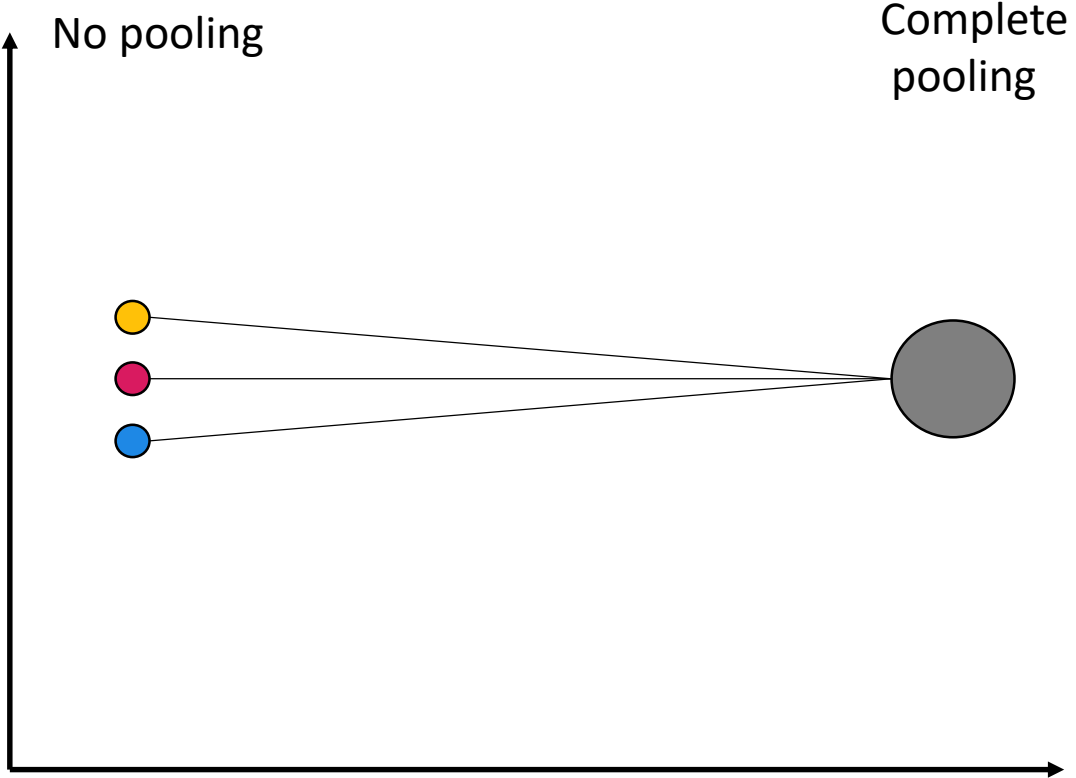
Group 1  
Group 2  
Group 3  
Pooled

# How does dynamic borrowing work?

### A) Variability in treatment effect



### B) Consistent treatment effect

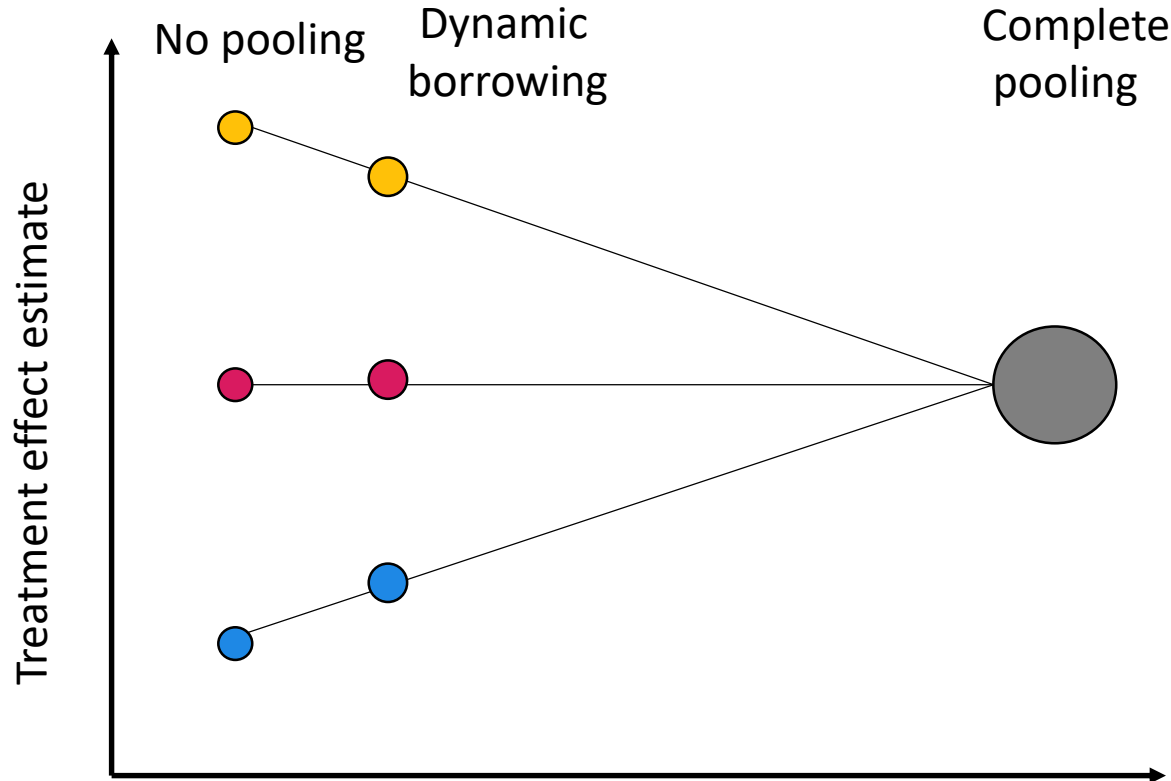




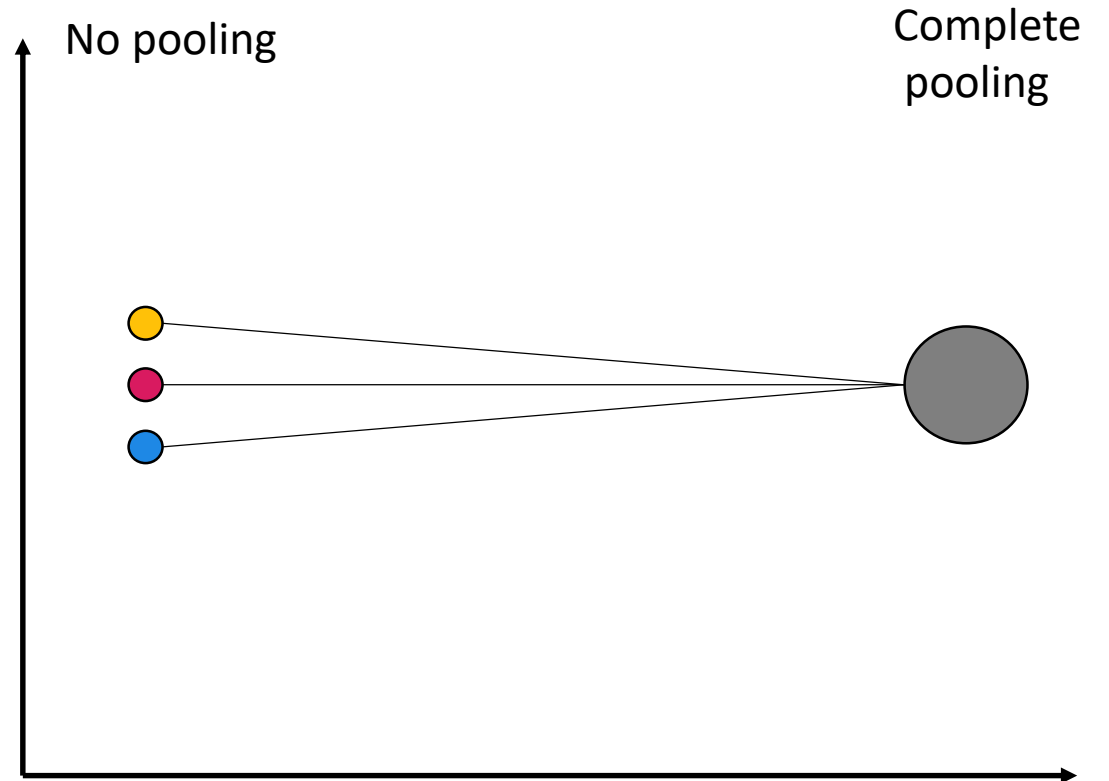
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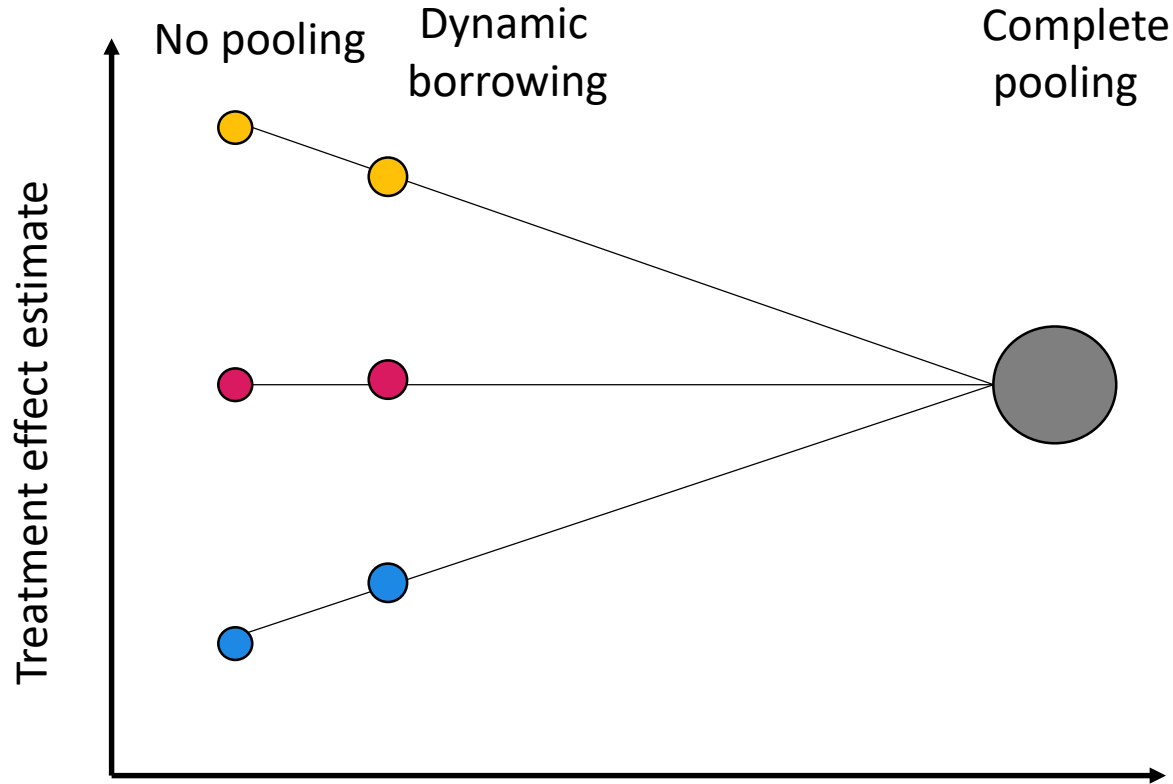
## B) Consistent treatment effect



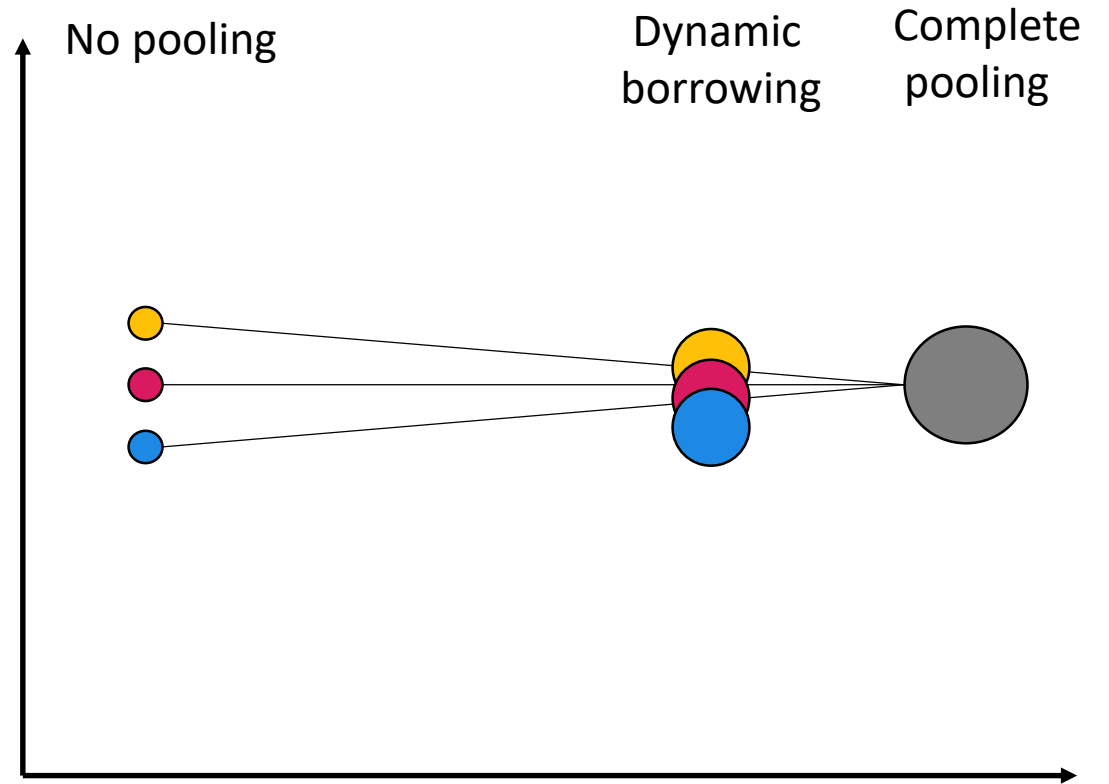
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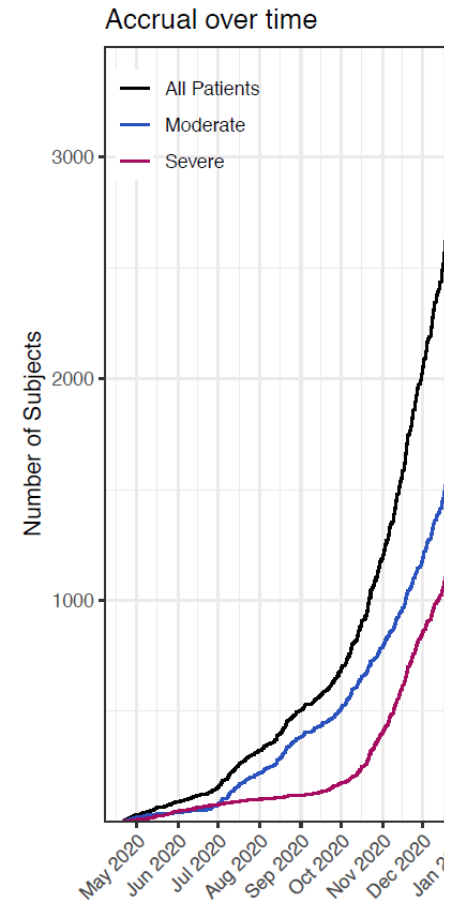
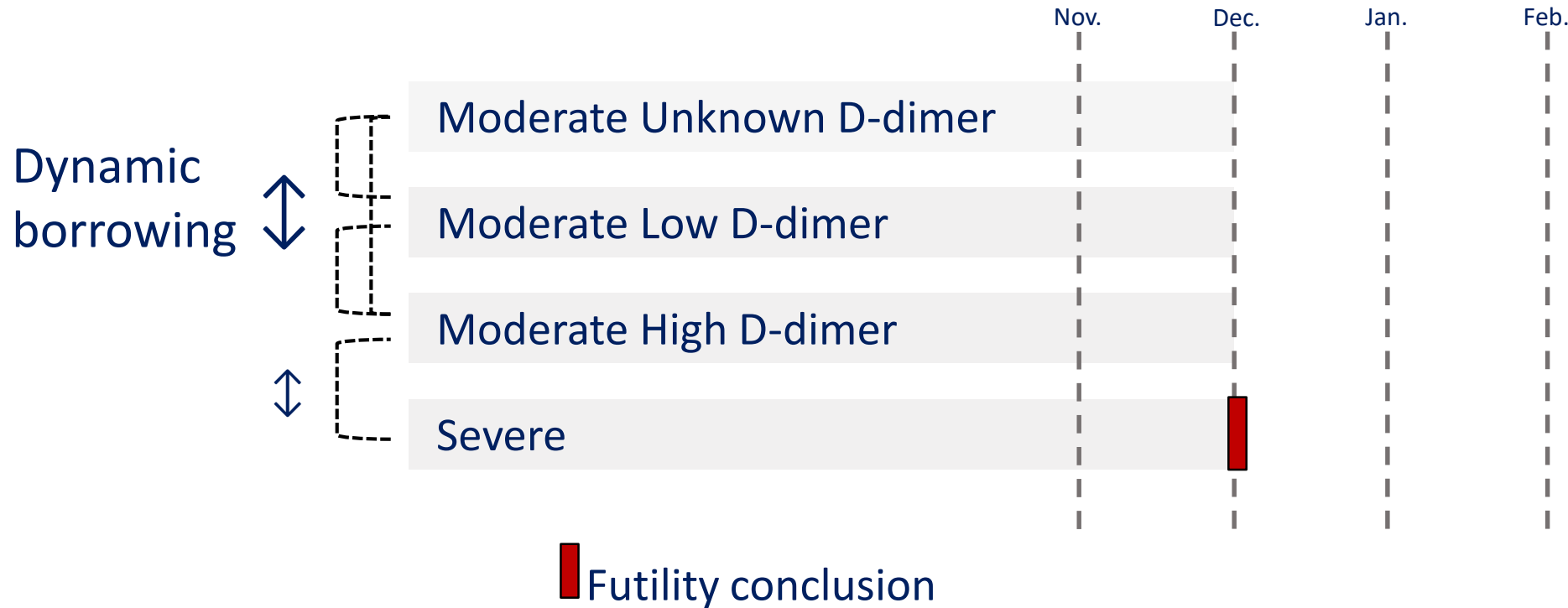


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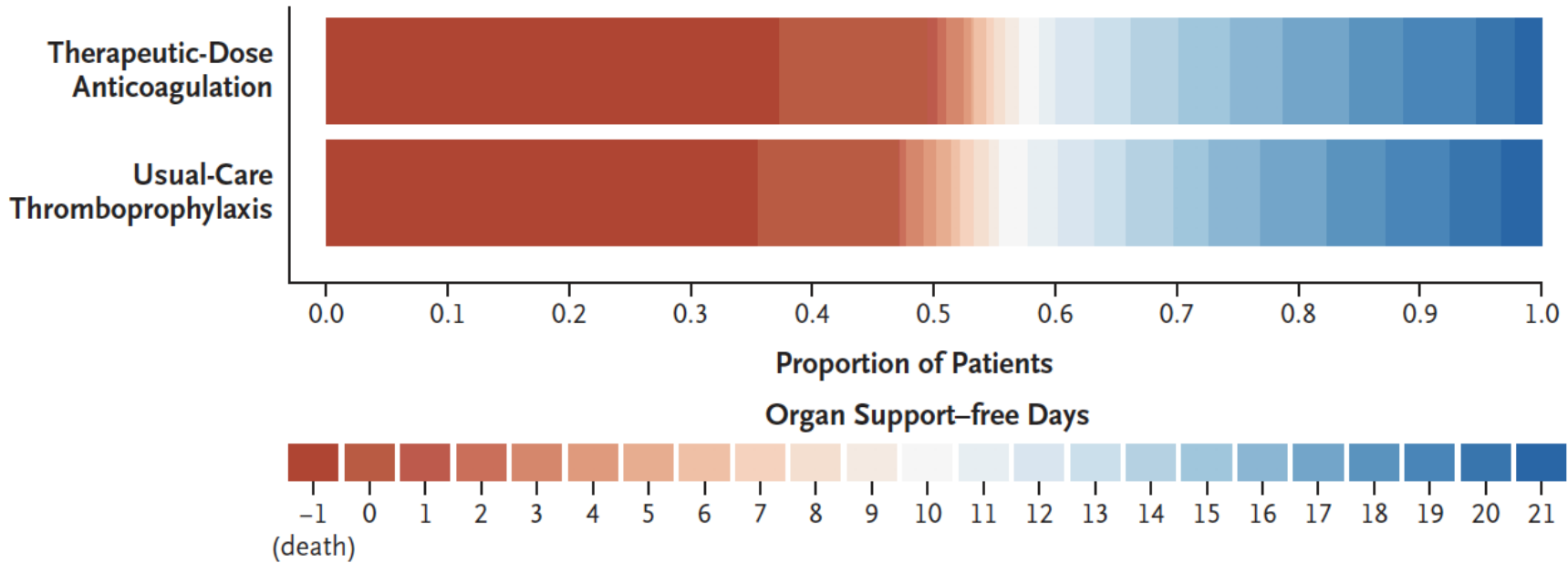


# Primary Endpoint: Organ Support-Free Days in Severe Covid-19

Adjusted OR 0.83 (95% CrI 0.67-1.03)

**Futility:** Prob(OR<1.2) = 99.9%

**Inferiority:** Prob(OR<1) = 95.0%

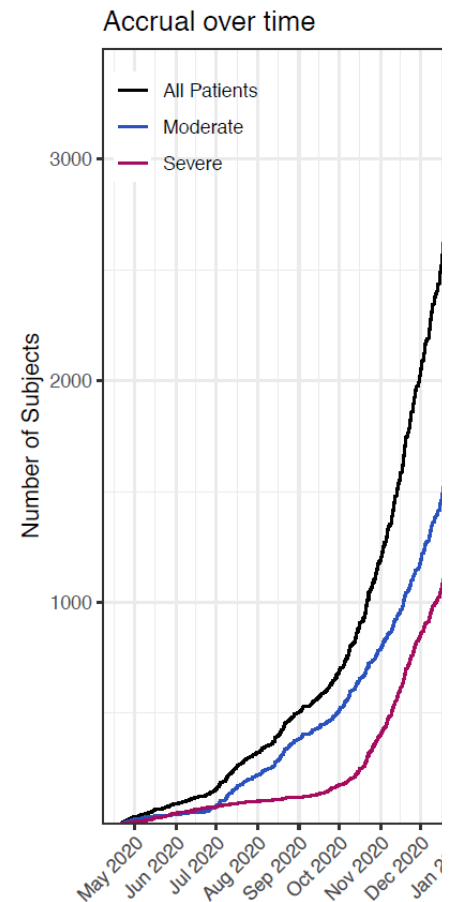
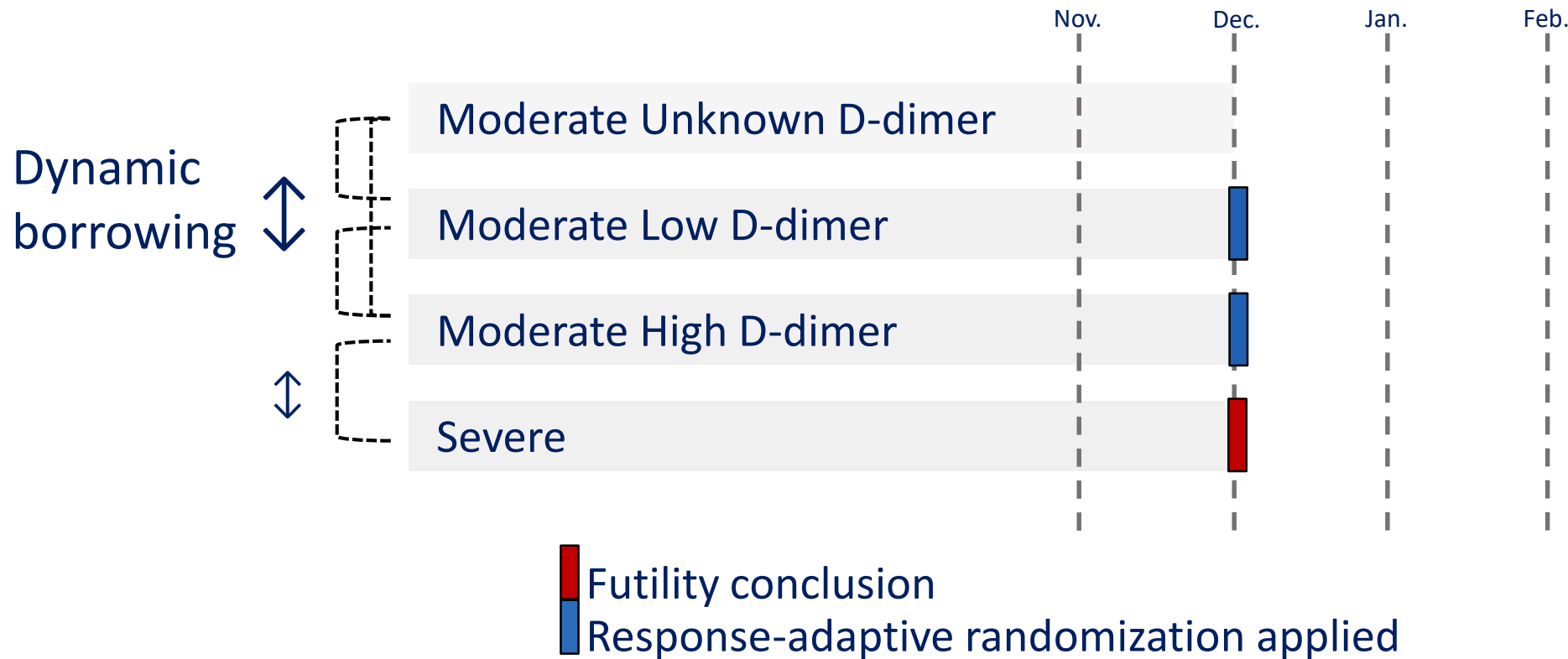


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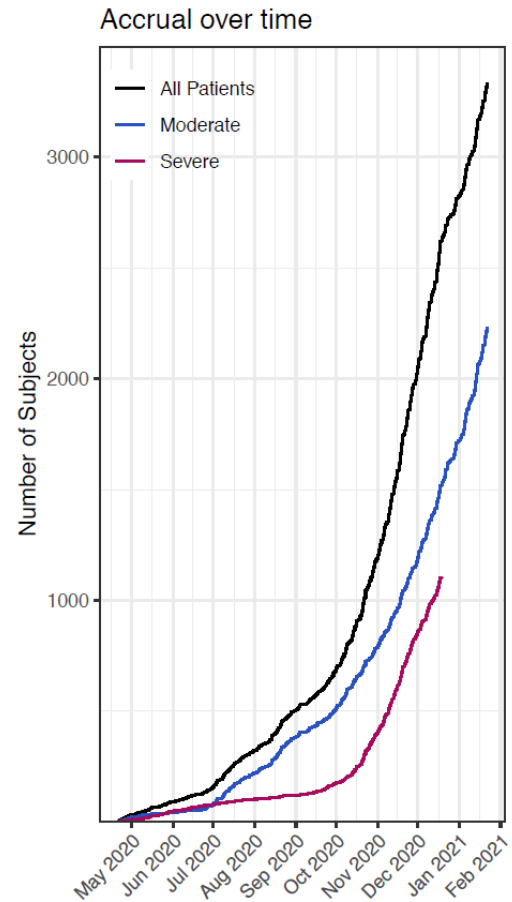
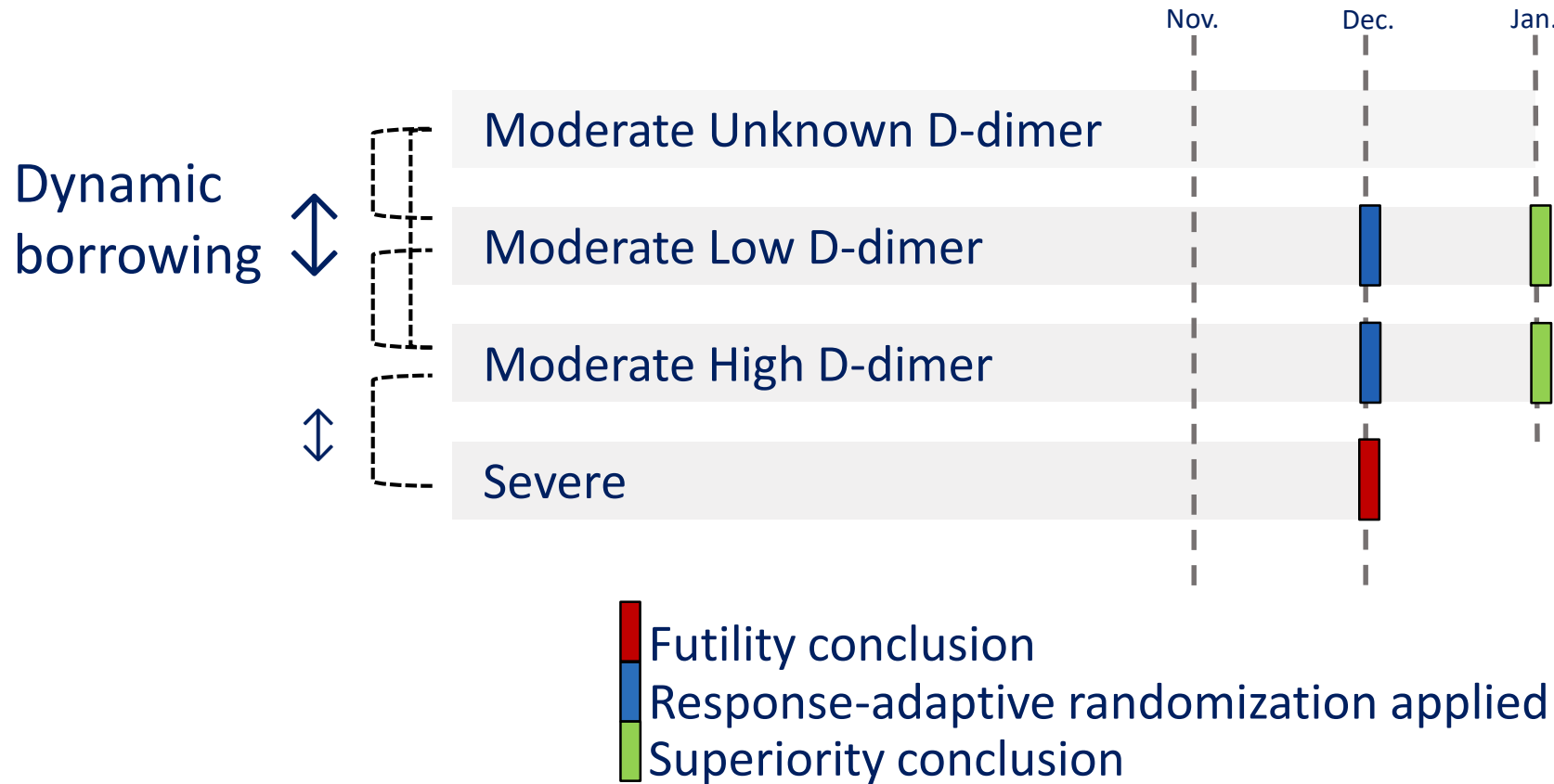


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## The ATTACC/ACTIV-4a/REMAP multiplatform trial

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\*

Adjusted OR 1.27 (95% CrI 1.03-1.58)

**Superiority:** Prob(OR>1) = 98.6%  
4% adjusted difference in risk of  
requiring organ support or dying

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

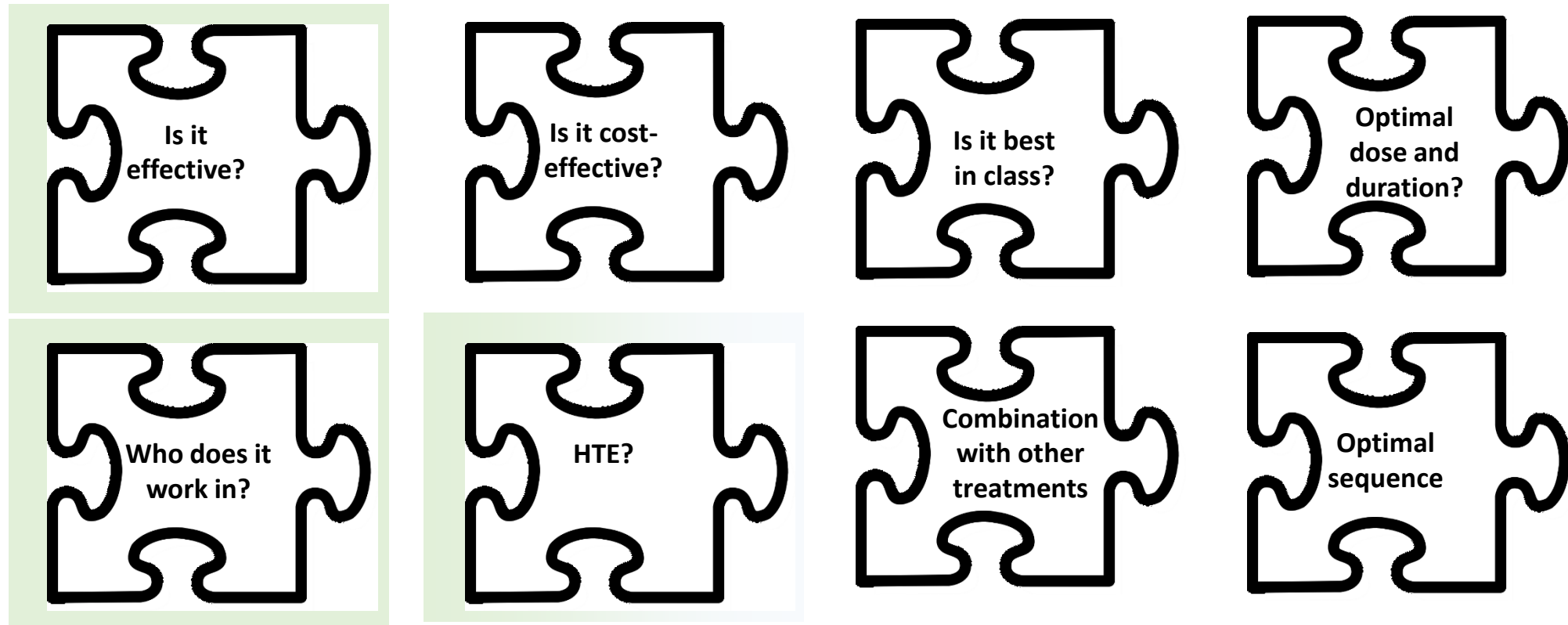
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Most diseases have multiple component therapies...

For each component

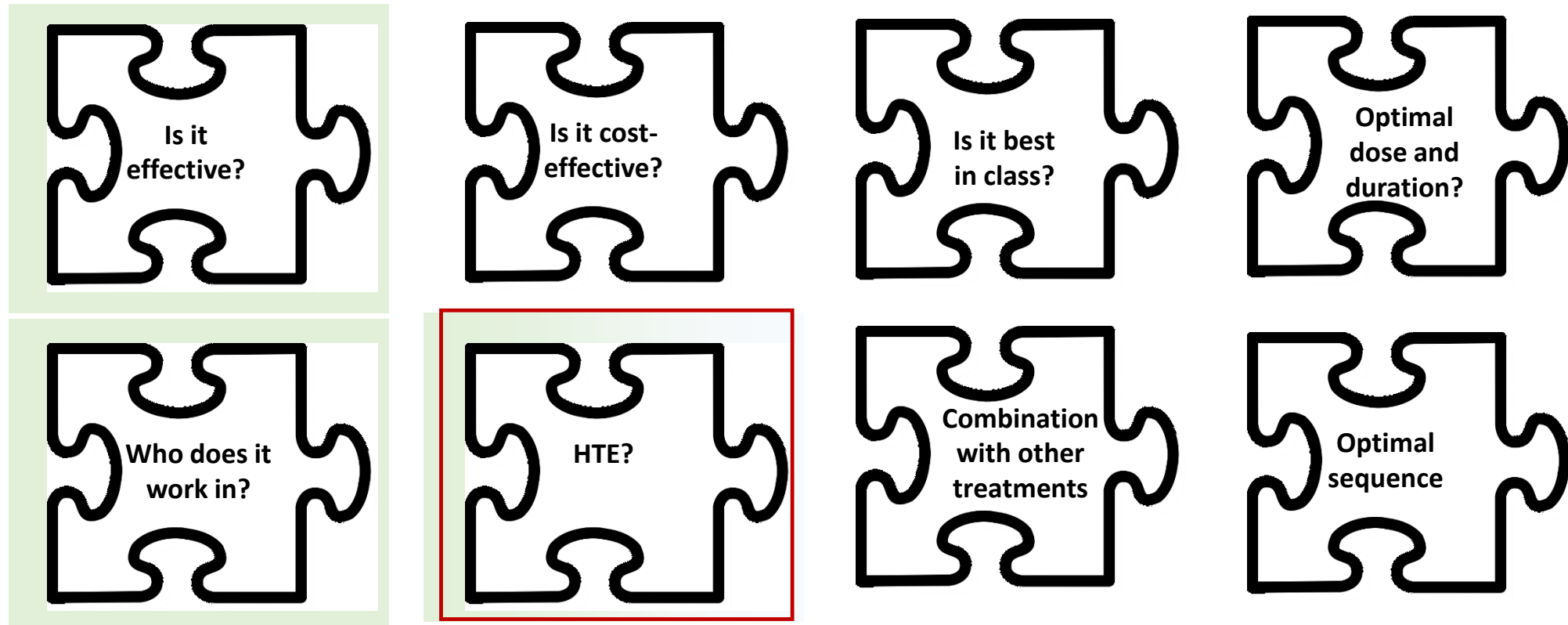


*Can one trial (domain) address this?*



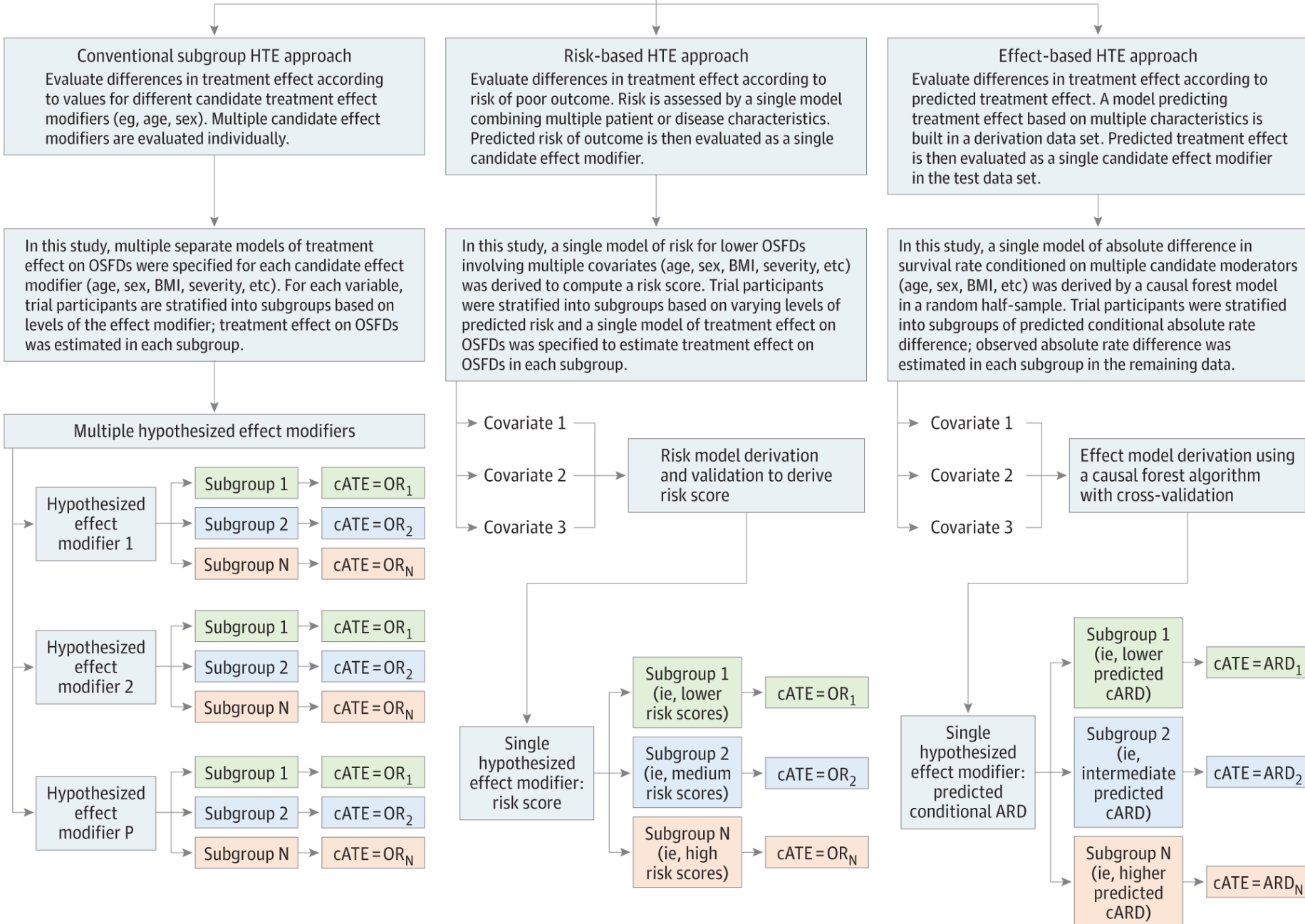
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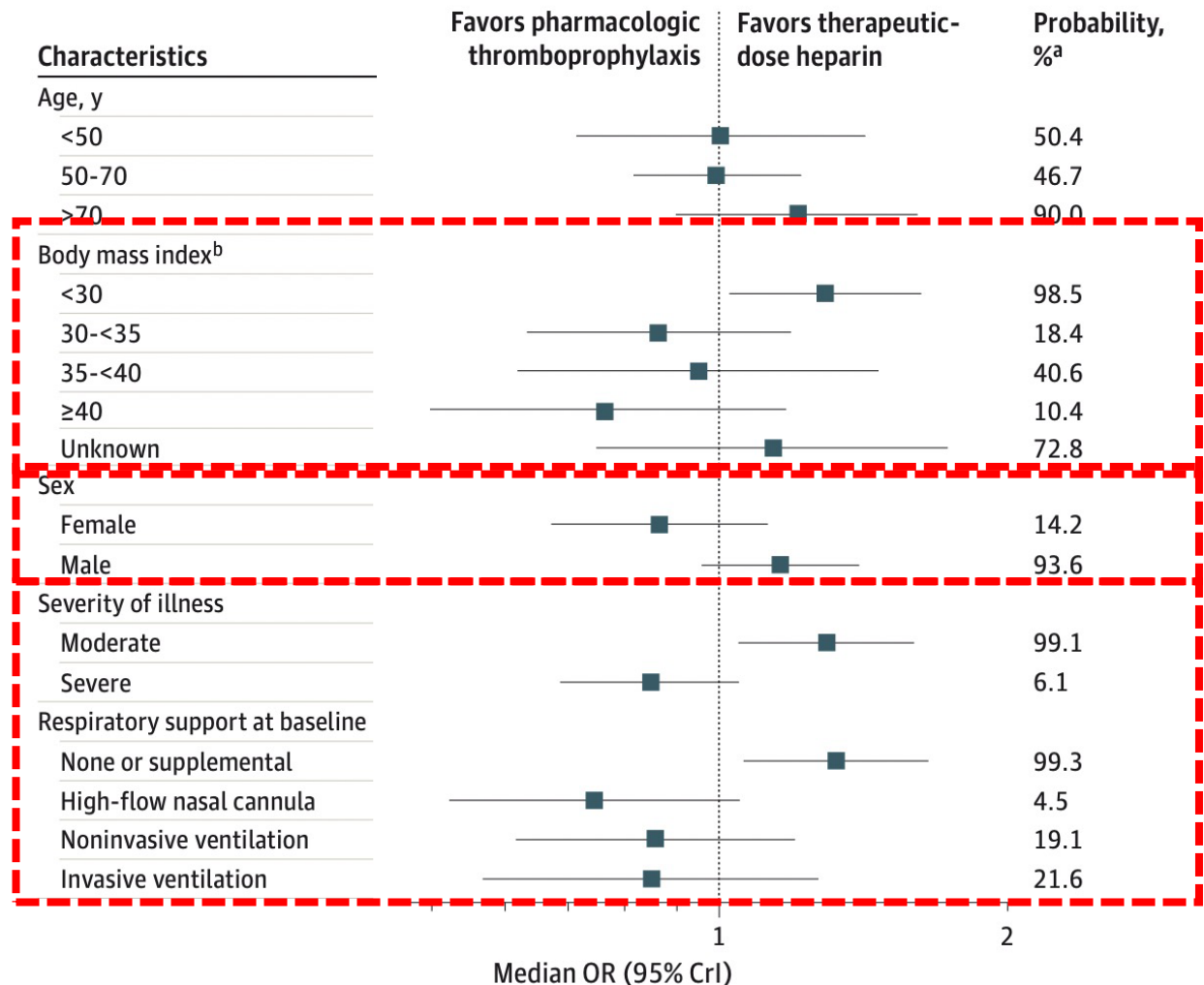
*Can one trial (domain) address this?*

# Strategies for identifying HTE



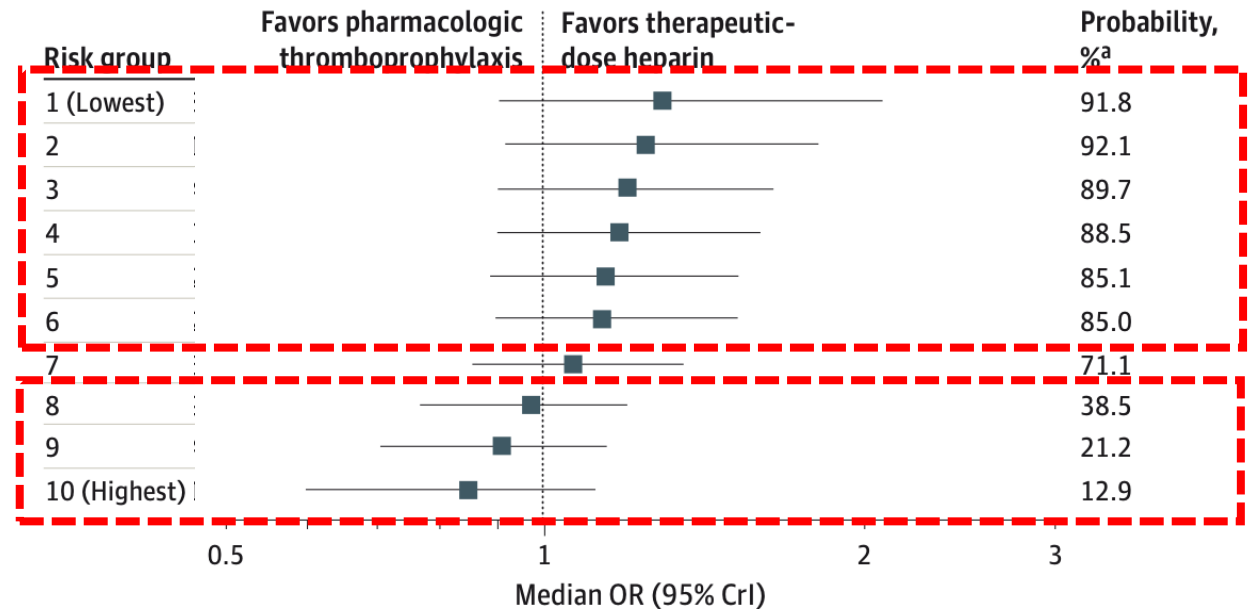
# HTE for TAC: Conventional Subgroup Analysis

- Modifiers of treatment effect
  - Body mass index
  - Sex
  - Severity of illness
    - Respiratory support



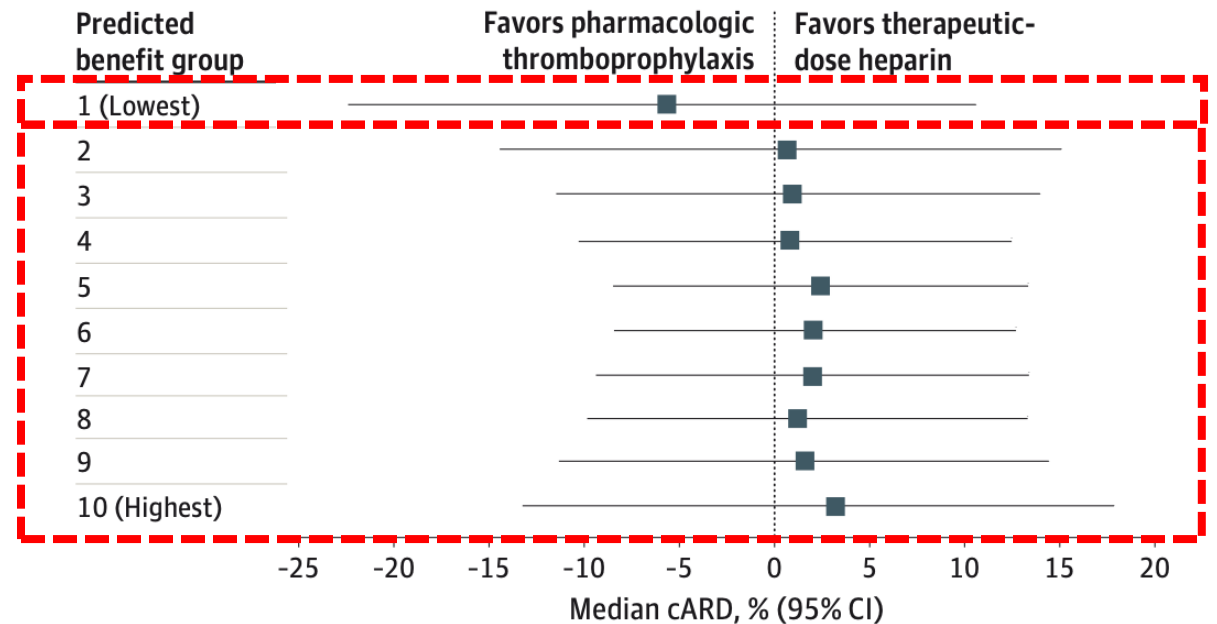
# HTE for TAC: Risk-based Approach

- Treatment effect monotonically related to risk
- Risk groups 1-6 have relatively high probability of benefit
  - No or supplemental oxygen
- Major predictors of risk
  - Age
  - Body mass index
  - Baseline respiratory support



# HTE for TAC: Effect-based

- Lowest predicted cATE decile
  - $P < 0.05$  for difference in treatment effect
  - High BMI
  - High baseline severity of illness



# HTE for RASi: Effect-based

RAS inhibition domain: No benefit of RASi initiation in Covid-19, unfavorable direction of treatment effect

Causal forest heterogeneity of treatment effect (HTE) analysis for survival considering all available baseline variables:

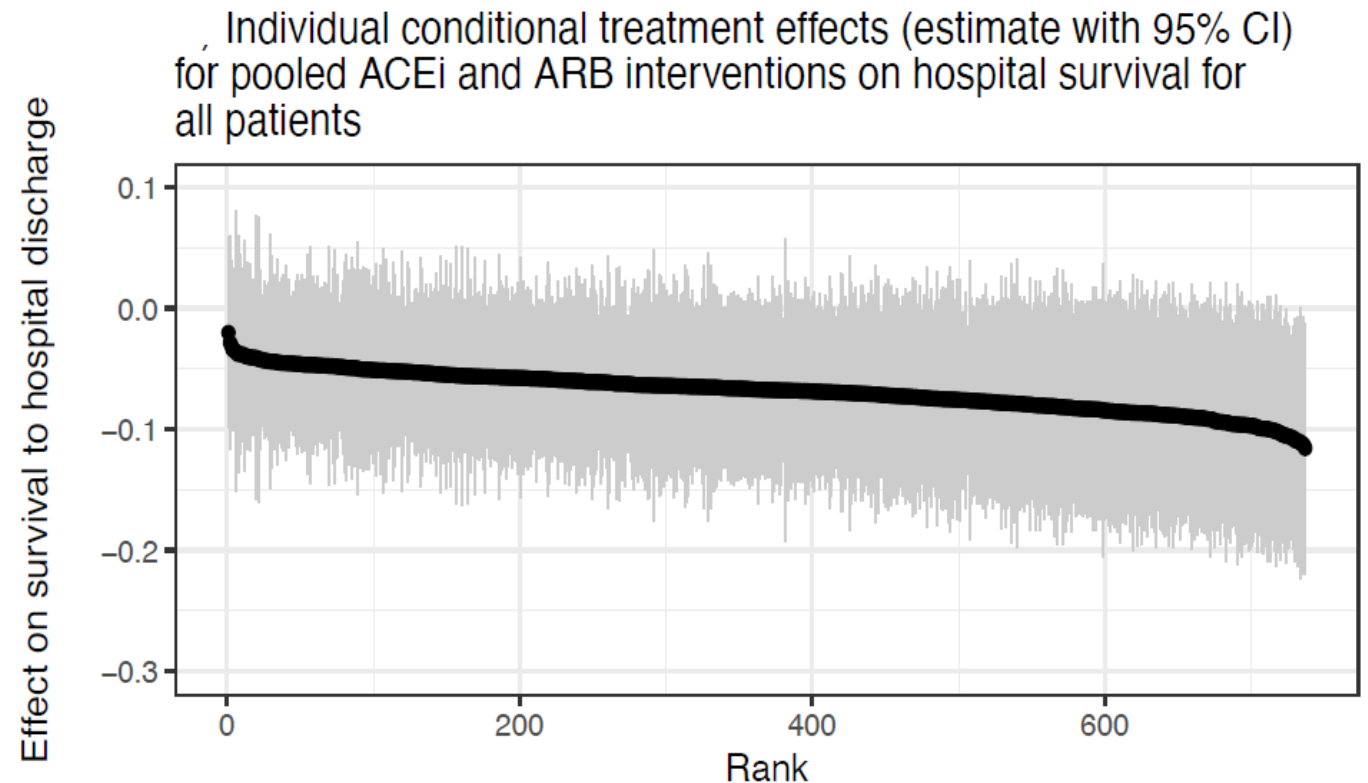
- Individual-level conditional average treatment effect (CATEs) estimates consistently favoured worse outcomes with RAS inhibitors, although 95% confidence intervals included null for the majority of patients

Research

JAMA | **Original Investigation** | CARING FOR THE CRITICALLY ILL PATIENT

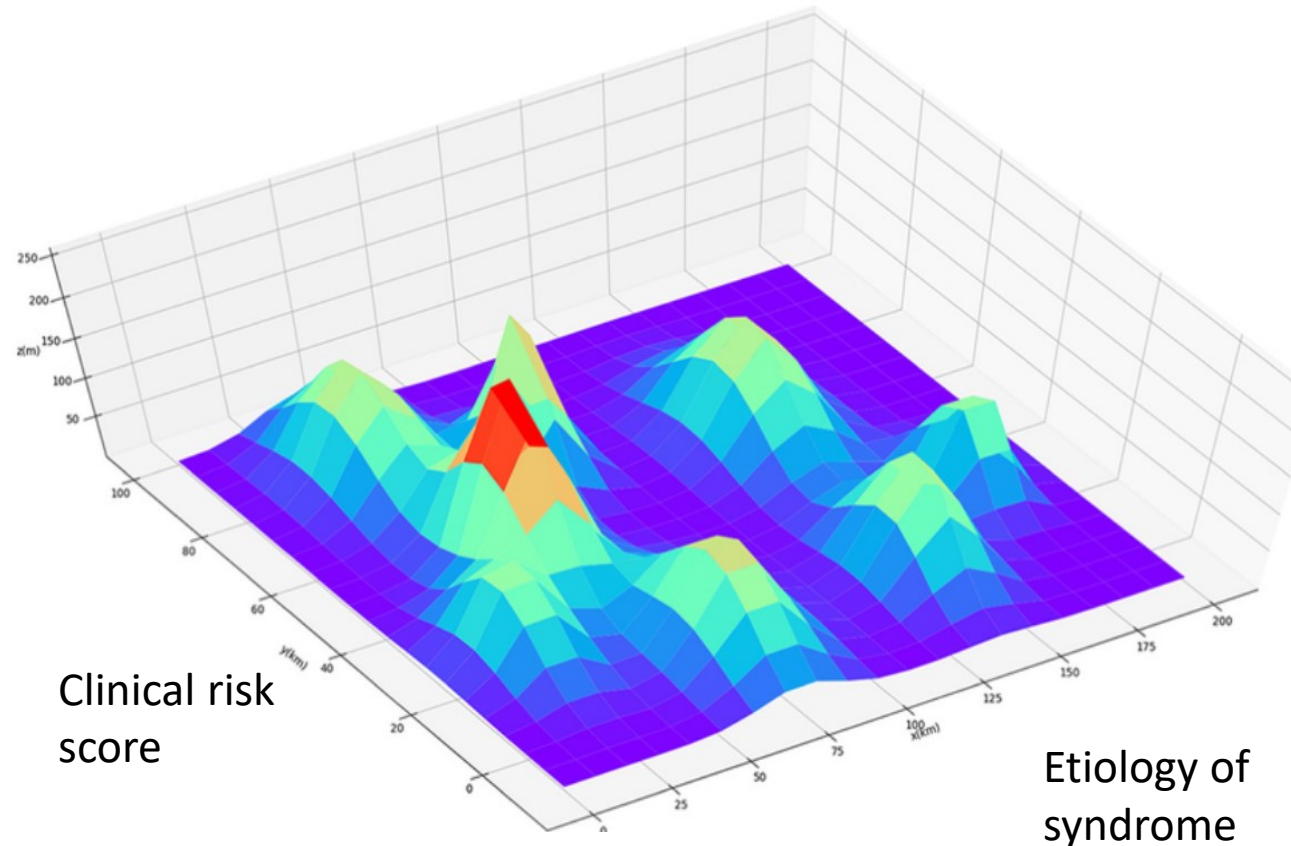
## Effect of Angiotensin-Converting Enzyme Inhibitor and Angiotensin Receptor Blocker Initiation on Organ Support-Free Days in Patients Hospitalized With COVID-19 A Randomized Clinical Trial

Writing Committee for the REMAP-CAP Investigators



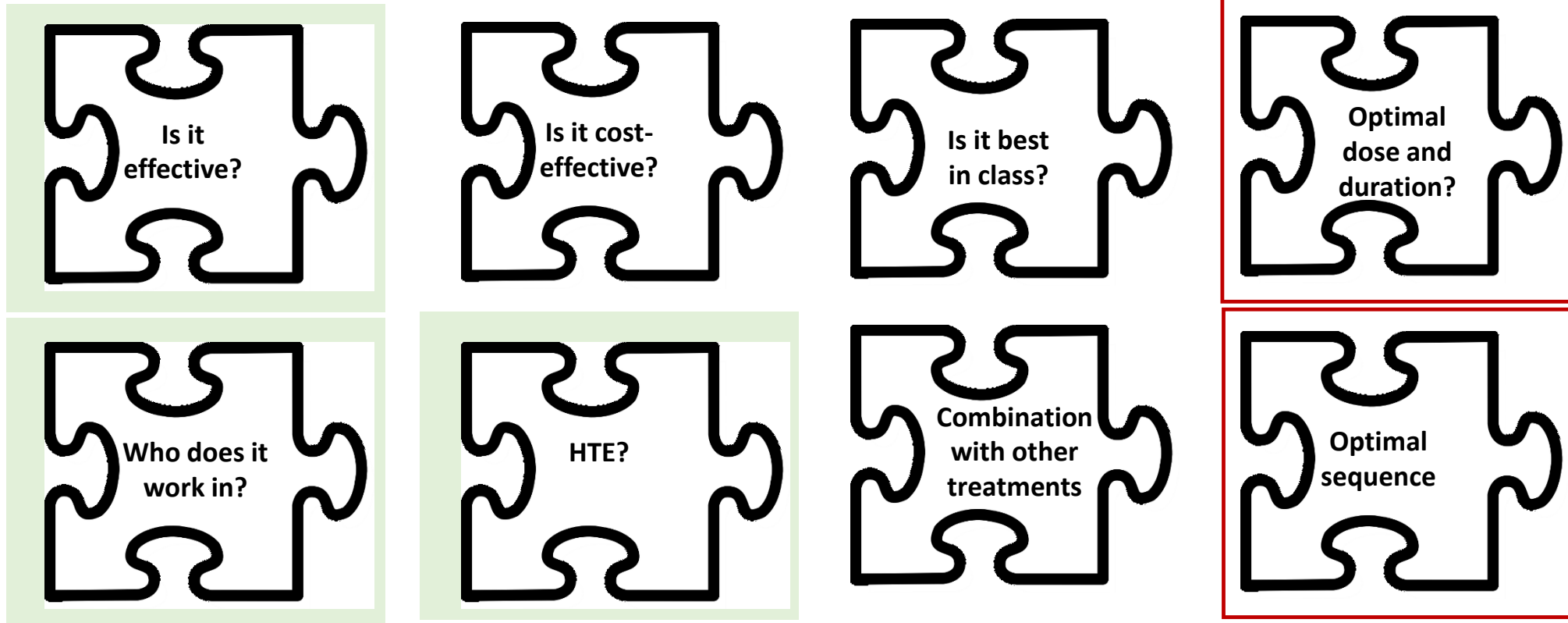
# An aspirational thought: Could we empower trials to even further hunt for HTE?

Predictive biomarker



Most diseases have multiple component therapies...

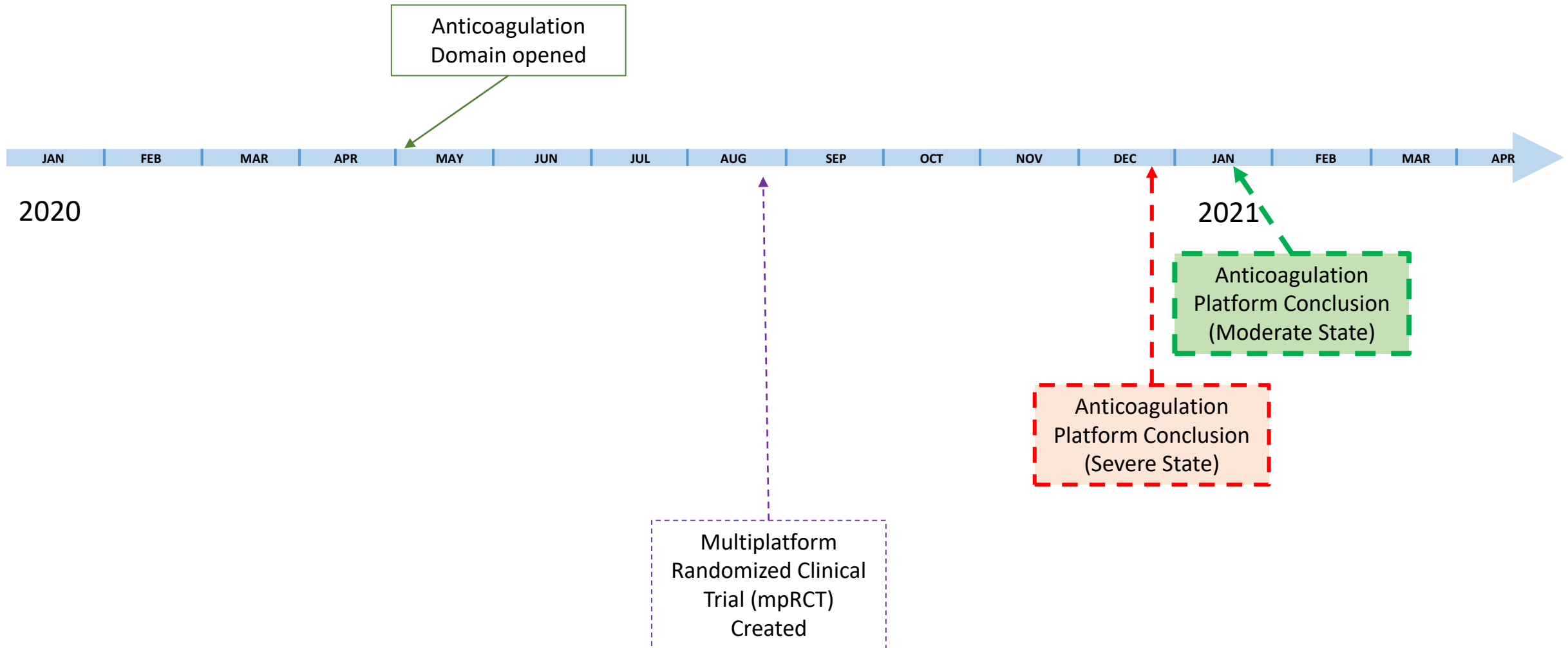
For each component



*Can one trial (domain) address this?*



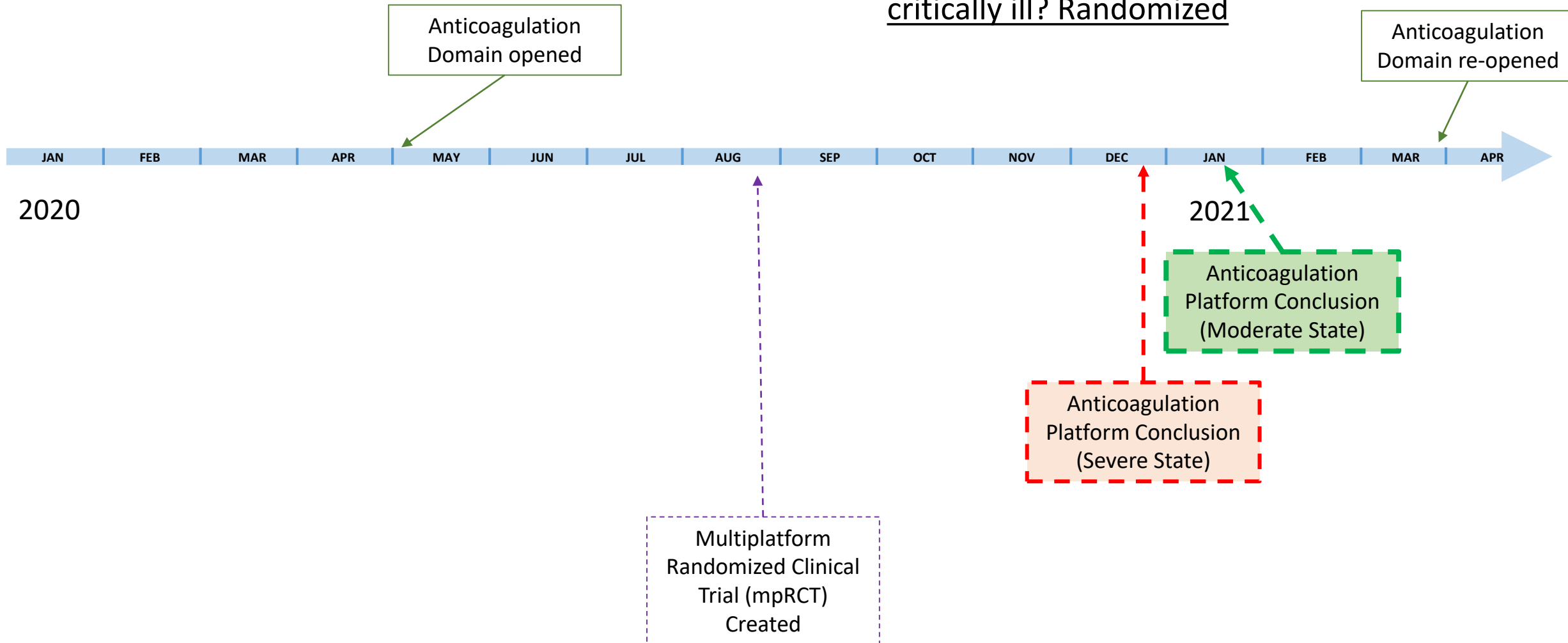
# Pandemic Adaptations in REMAP-CAP



# Pandemic Adaptations

**Observation:** beneficial in non-critically ill patients, non-beneficial in critically ill patients

**Follow-up question:** what to do with TAC dose when non-critically ill patient transitions to critically ill? Randomized



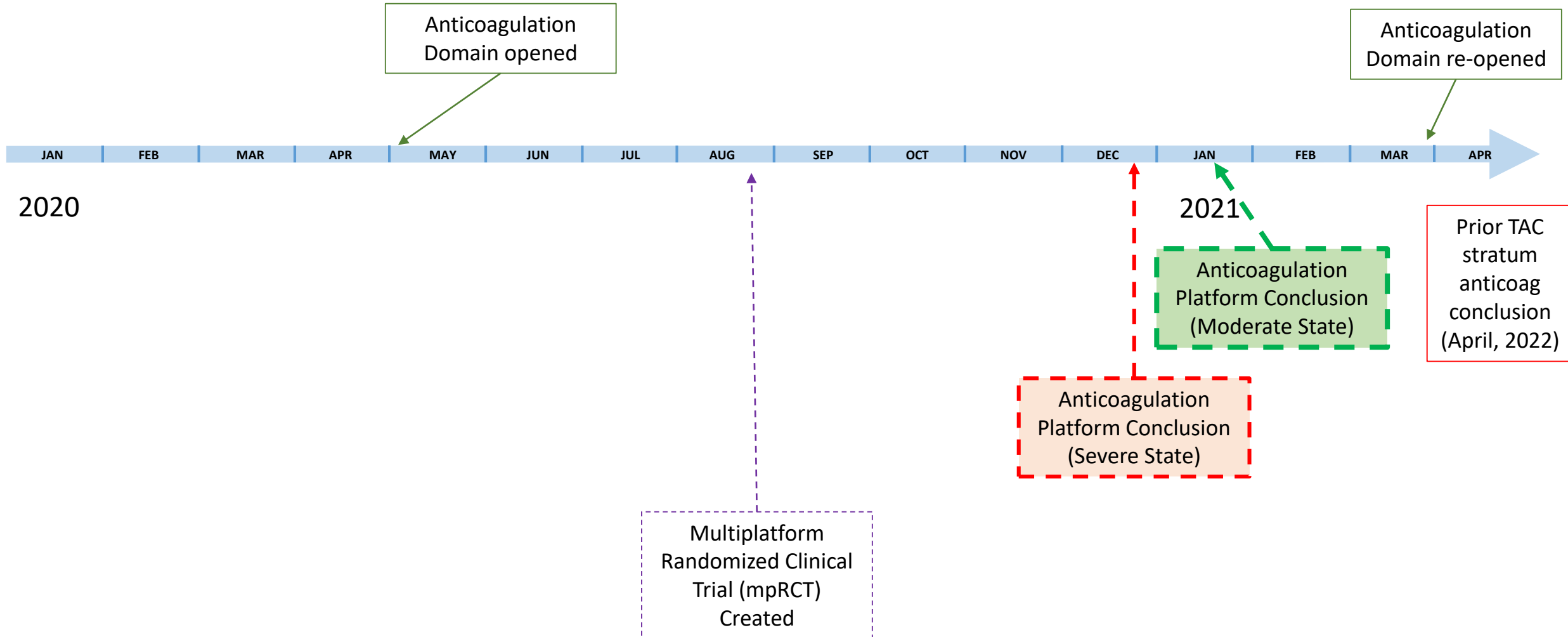
# Pandemic Adaptations

LETTER

## Continuation of therapeutic dose heparin for critically ill patients with COVID-19

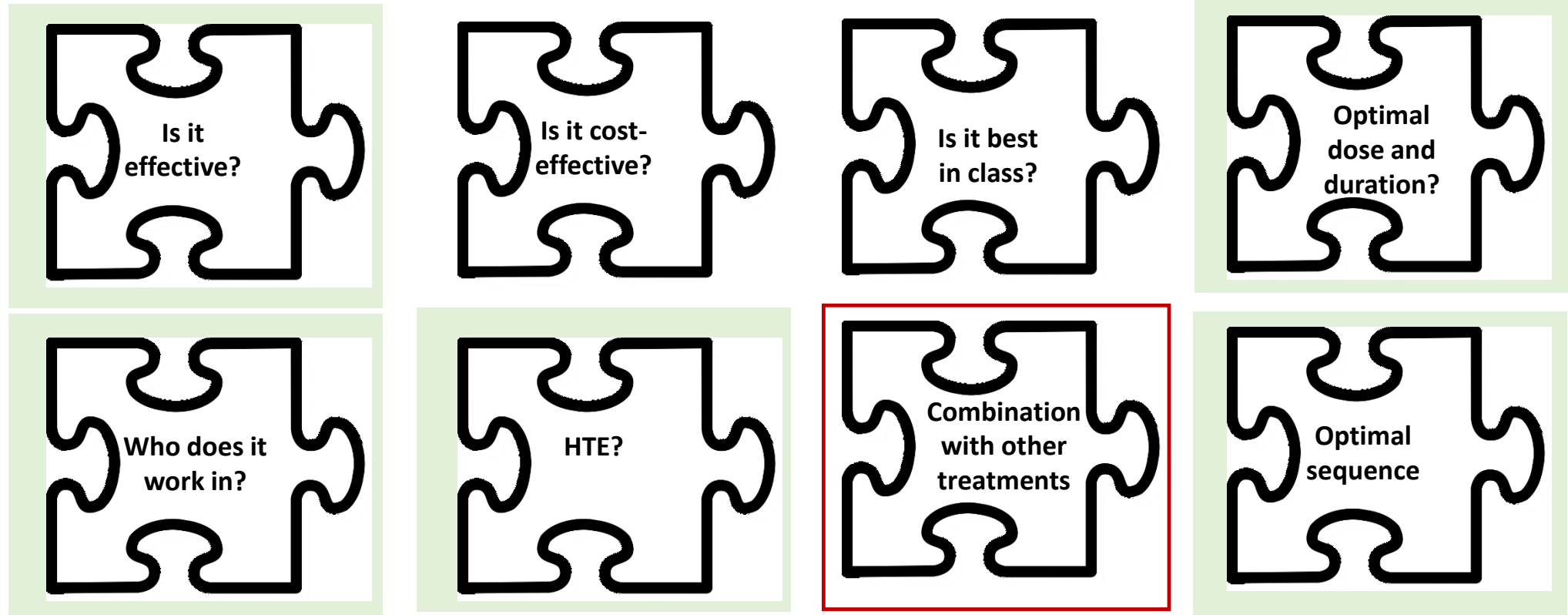


Charlotte A. Bradbury<sup>1,6\*</sup>, Patrick R. Lawler<sup>2,3</sup>, Bryan J. McVerry<sup>4</sup>, Ryan Zarychanski<sup>5</sup> on behalf of the REMAP-C. A. P. Investigators



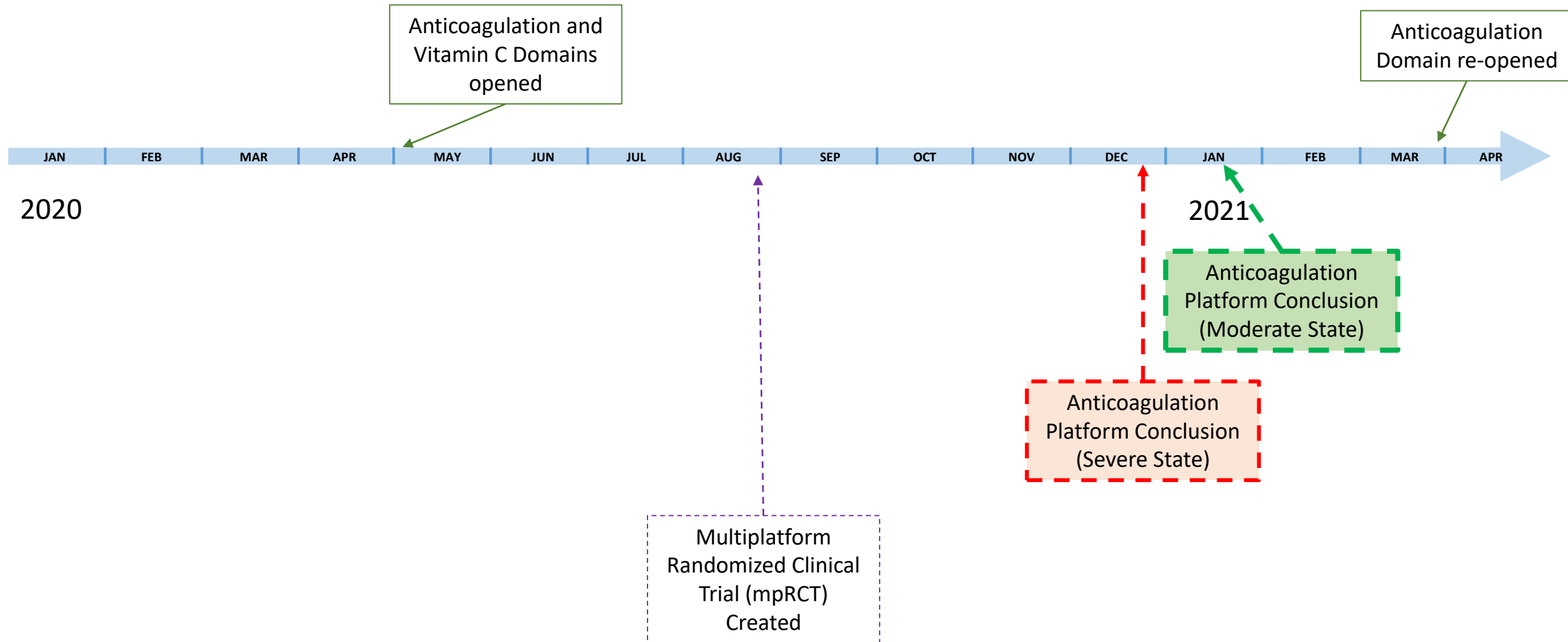
Most diseases have multiple component therapies...

For each component

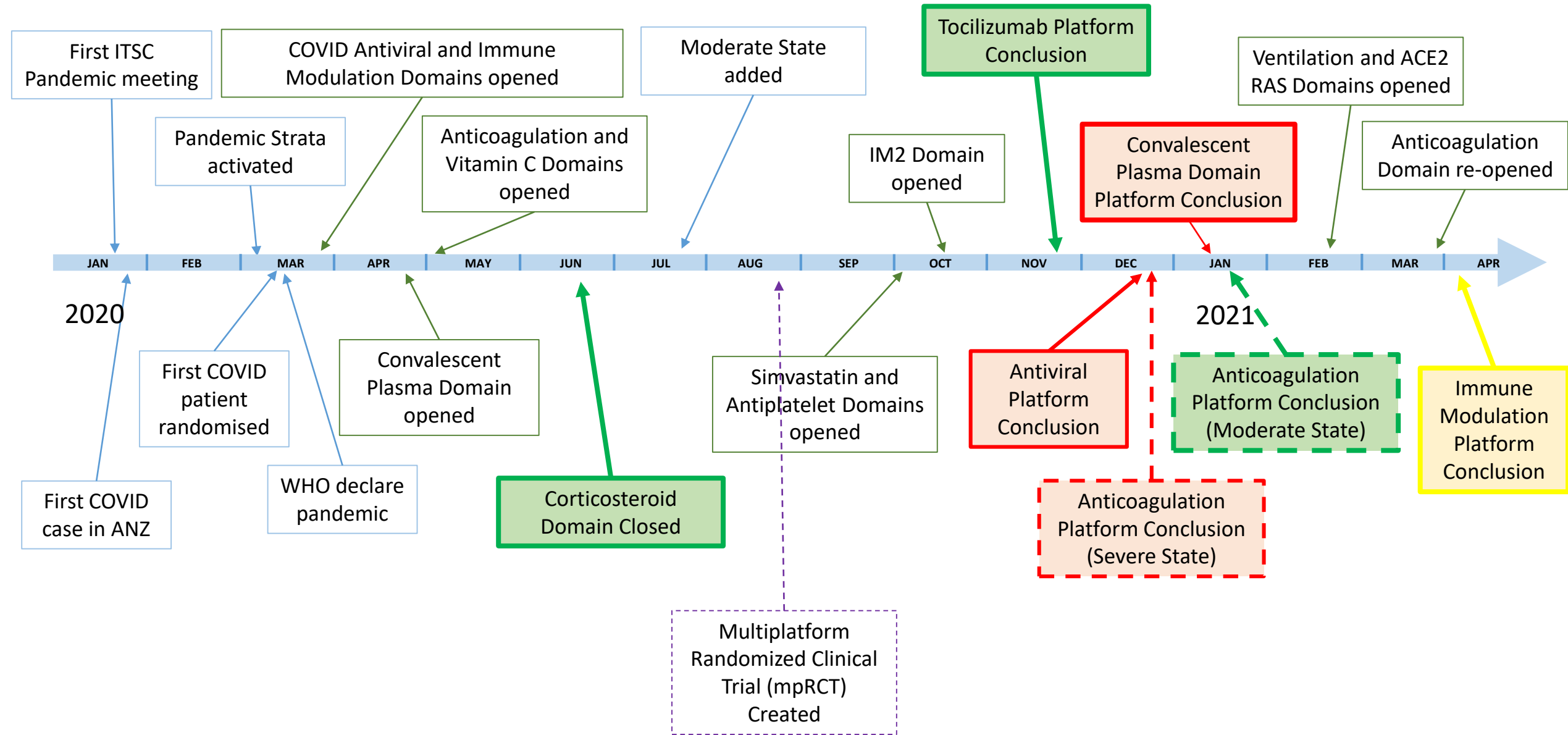


*Can one trial (domain) address this?*

# Pandemic Adaptations



# Pandemic Adaptations



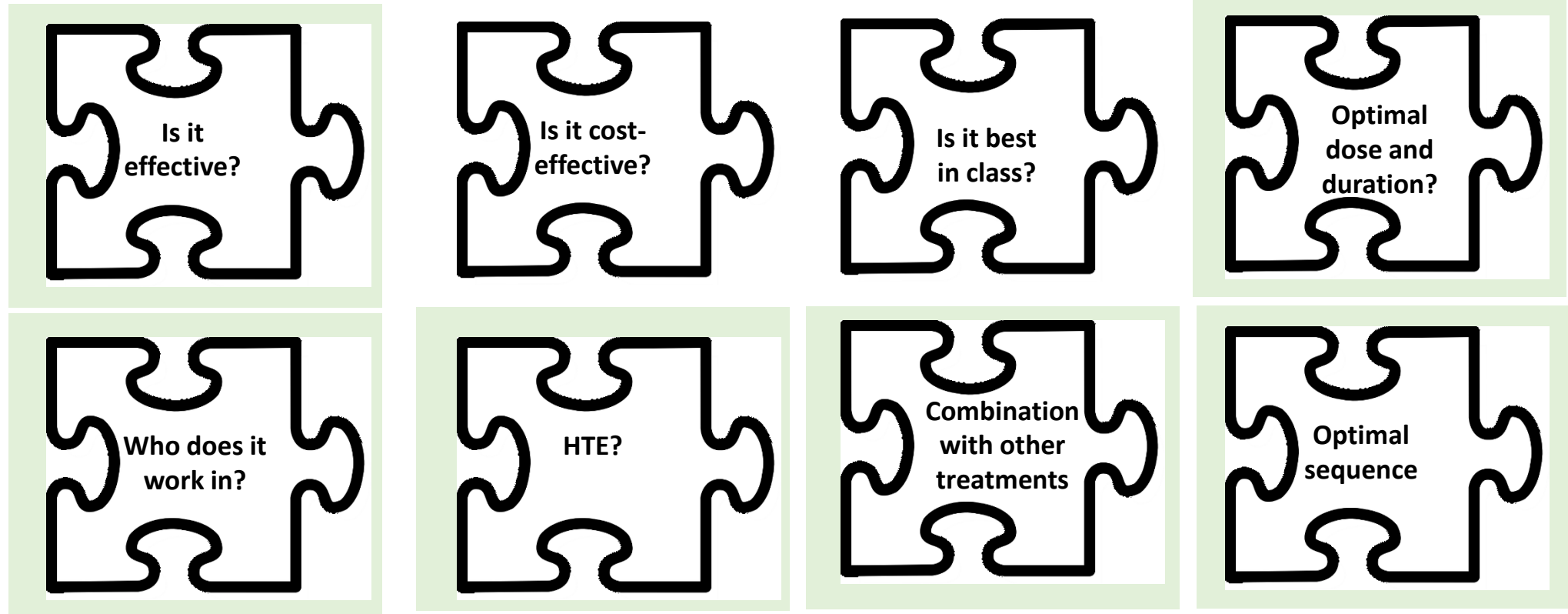
# Effect of Antiplatelet Therapy on Survival and Organ Support-Free Days in Critically Ill Patients With COVID-19

## A Randomized Clinical Trial

| <b>Organ Support Free Days at Day 21</b>                          |                     | <b>Reference</b>                                |
|---|---------------------|---|
| Pooled Antiplatelet Therapy <sup>1</sup>                          | N=1020              | N=529   |
| Adjusted odds ratio, median (IQR)                                 | 1.02 (0.86 to 1.23) | No Antiplatelet                                 |
| Probability of efficacy <sup>2</sup> , %                          | 58                  | -   |
| Therapeutic Anticoagulation <sup>3</sup>                          | N=499               | N=511   |
| Adjusted odds ratio, median (IQR)                                 | 0.90 (0.72 to 1.14) | Usual Care Thromboprophylaxis                   |
| Probability of efficacy <sup>2</sup> , %                          | 19                  | -   |
| Antiplatelet/Anticoagulation Combination <sup>4</sup>             | N=35                | N=26  |
| Adjusted odds ratio, median (IQR)                                 | 0.73 (0.44 to 1.21) | No Antiplatelet / Usual Care Thromboprophylaxis |
| Probability of efficacy <sup>2</sup> , %                          | 12                  | -   |
| <b>Hospital Survival</b>  |                     | Reference                                       |
| Antiplatelet Therapy <sup>1</sup>                                 | N=1020              | N=529   |
| Adjusted odds ratio, median (IQR)                                 | 1.27 (0.99 to 1.62) | No Antiplatelet                                 |
| Probability of efficacy <sup>2</sup> , %                          | 97                  | -   |
| Therapeutic Anticoagulation <sup>3</sup>                          | N=499               | N=511   |
| Adjusted odds ratio, median (IQR)                                 | 0.88 (0.66 to 1.16) | Usual Care Thromboprophylaxis                   |
| Probability of efficacy <sup>2</sup> , %                          | 19                  | -   |
| Antiplatelet/Therapeutic Anticoagulation Combination <sup>4</sup> | N=35                | N=26  |
| Adjusted odds ratio, median (IQR)                                 | 0.72 (0.41 to 1.28) | No Antiplatelet / Usual Care Thromboprophylaxis |
| Probability of efficacy <sup>2</sup> , %                          | 12                  | -   |

Most diseases have multiple component therapies...

For each component



*Can one trial (domain) address this?*



# How did address the challenges presented?

## **1) The shortcomings of prior data (or not having any)**

- Performed well in the face of unknowns, less reliance on initial assumptions (less type II error?)

## **2) Equipoise: balance learning while doing (exploitation/exploration)**

- Learned/adapted while incorporating new knowledge (e.g., response-adaptive randomization)
- Able to generate knowledge sequentially as conclusive results were obtained
- Studied multiple interventions at once, patients may receive multiple potentially effective treatment

## **3) Patient heterogeneity: in outcomes, treatment effects?**

- Treatment effects by group; drop/retain groups with adaptive analyses

## **4) Making trials happen quickly**

- Existing trial infrastructure enabled efficient pivot to emergency response; adaptive design, efficient results

## **5) Complex care: how to study one intervention in “isolation”**

- Offered greater potential to protocolize more aspect of care, and test treatment interactions

## **6) Trial conduct: hard to set-up/take-down, how to pivot to sustainability/efficiency?**

- Platform allowed 61 (and counting!) treatments to be studied in 1 trial: multiple matches in one stadium

# Conclusions

REMAP-CAP offered operational and statistical efficiencies, addressing challenge during the pandemic, and beyond

Shortened the divide between clinical care and research?

Demonstrated capacity for parabiosis with other trials (mpRCT)

Designs increasingly empowered to hunt for heterogeneity of treatment effect, supporting individualizing care

Future directions: ongoing COVID-19 and non-COVID-19 pneumonia studies



# Thank you!

We are very grateful to the patients and investigators who participated in this trial, and to the numerous international funding partners.

## Coordinating Centres



## Partners



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