

# The statistical analysis of REMAP-CAP: A platform trial for COVID-19

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SIS 2021

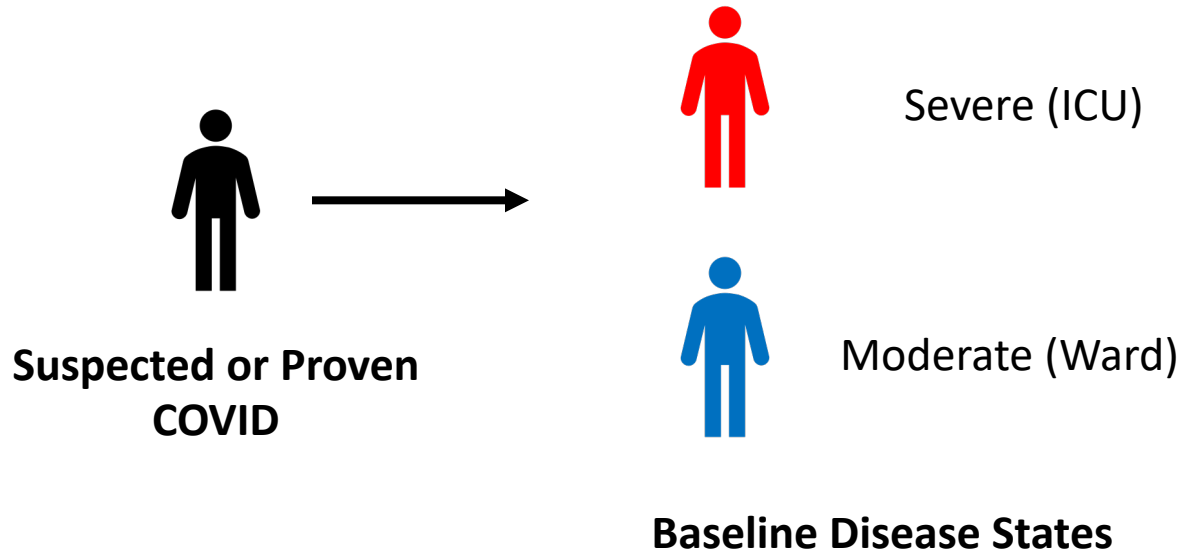
“Light methods for hard problems”



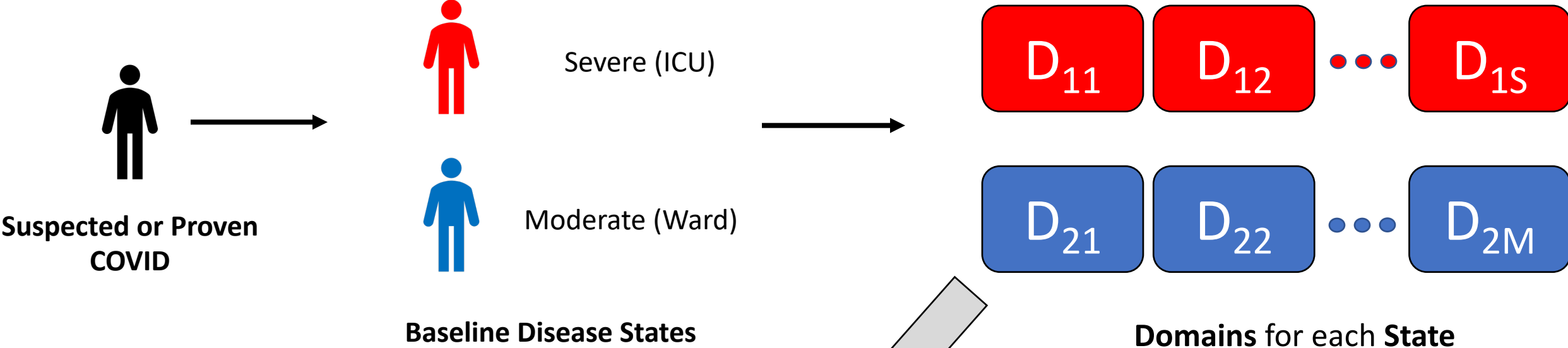
# REMAP-CAP COVID-19 Response

- Pandemic preparedness was a design feature
  - “Sleeping strata” for respiratory pandemic
- Feb 2020 began enrolling COVID-19 ICU patients
  - Initial uncertainty about sample size and enrollment
    - No fixed sample size
    - Frequent adaptive analyses to evaluate success/futility and update randomization probabilities
  - New COVID-19 treatment domains (steroids, antivirals, anticoagulation, etc) and primary outcome
  - Need to incorporate/react to emerging data from external sources

# REMAP-CAP: Patient Journey



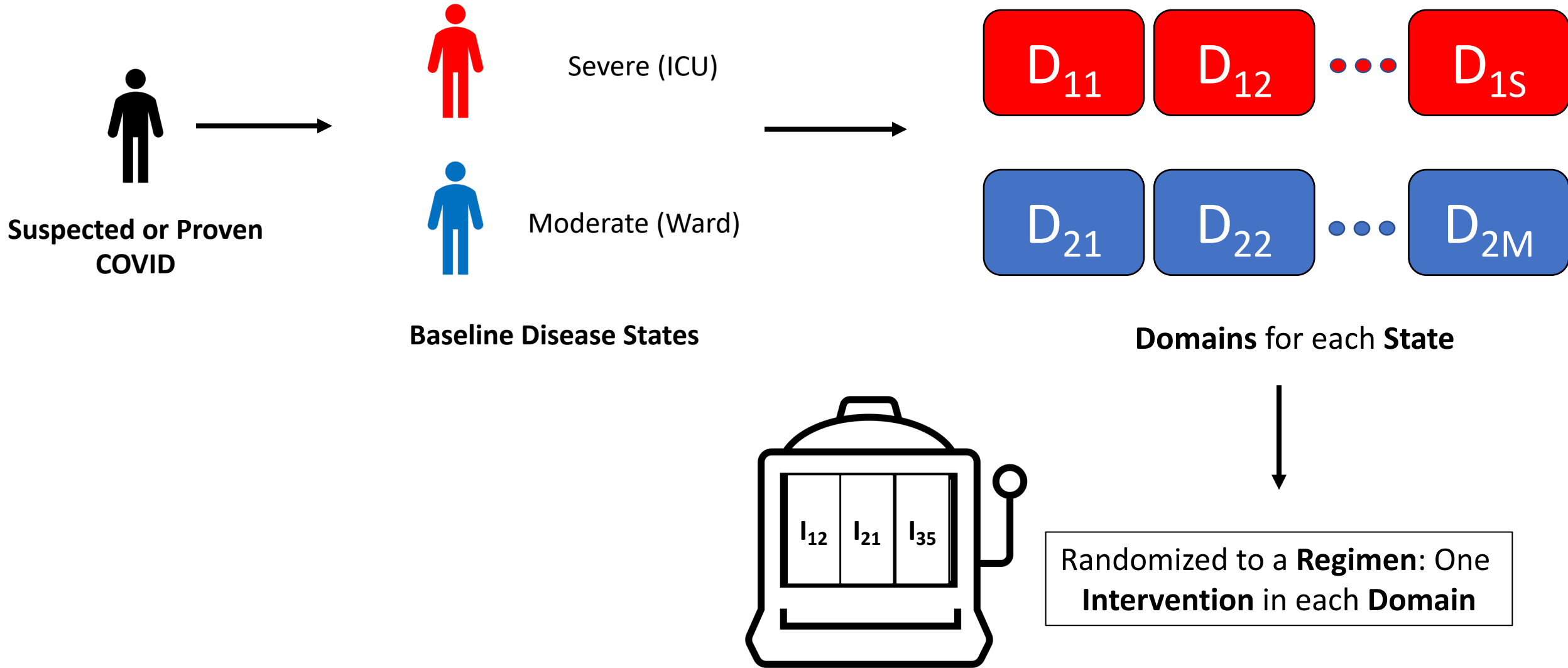
# REMAP-CAP: Domains



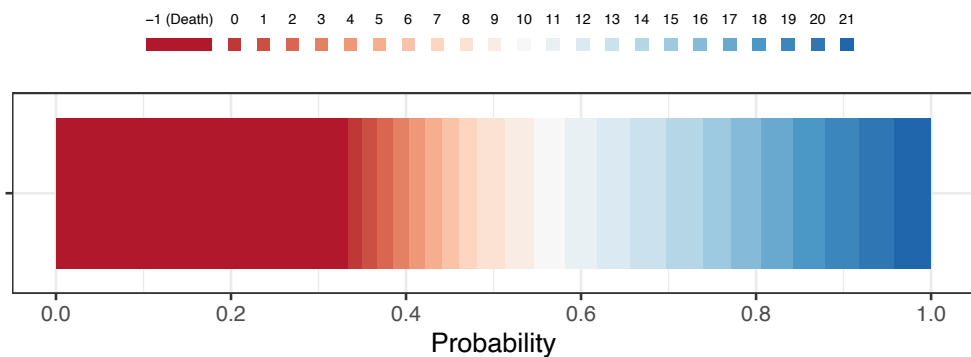
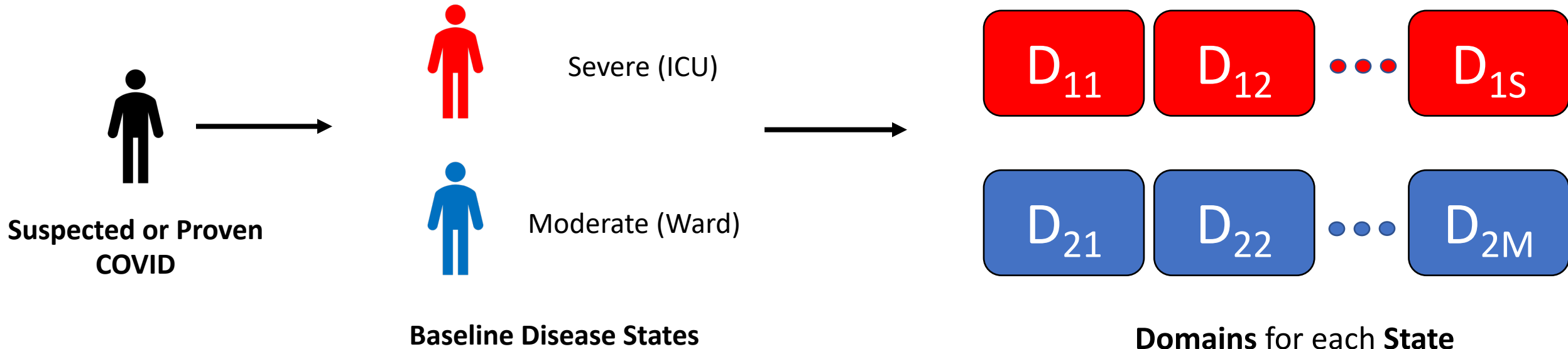
$$D_j = \{I_{j,1}, I_{j,2}, \dots, I_{j,P}\}$$

Interventions within each Domain

# REMAP-CAP: Randomization



# REMAP-CAP: Endpoint

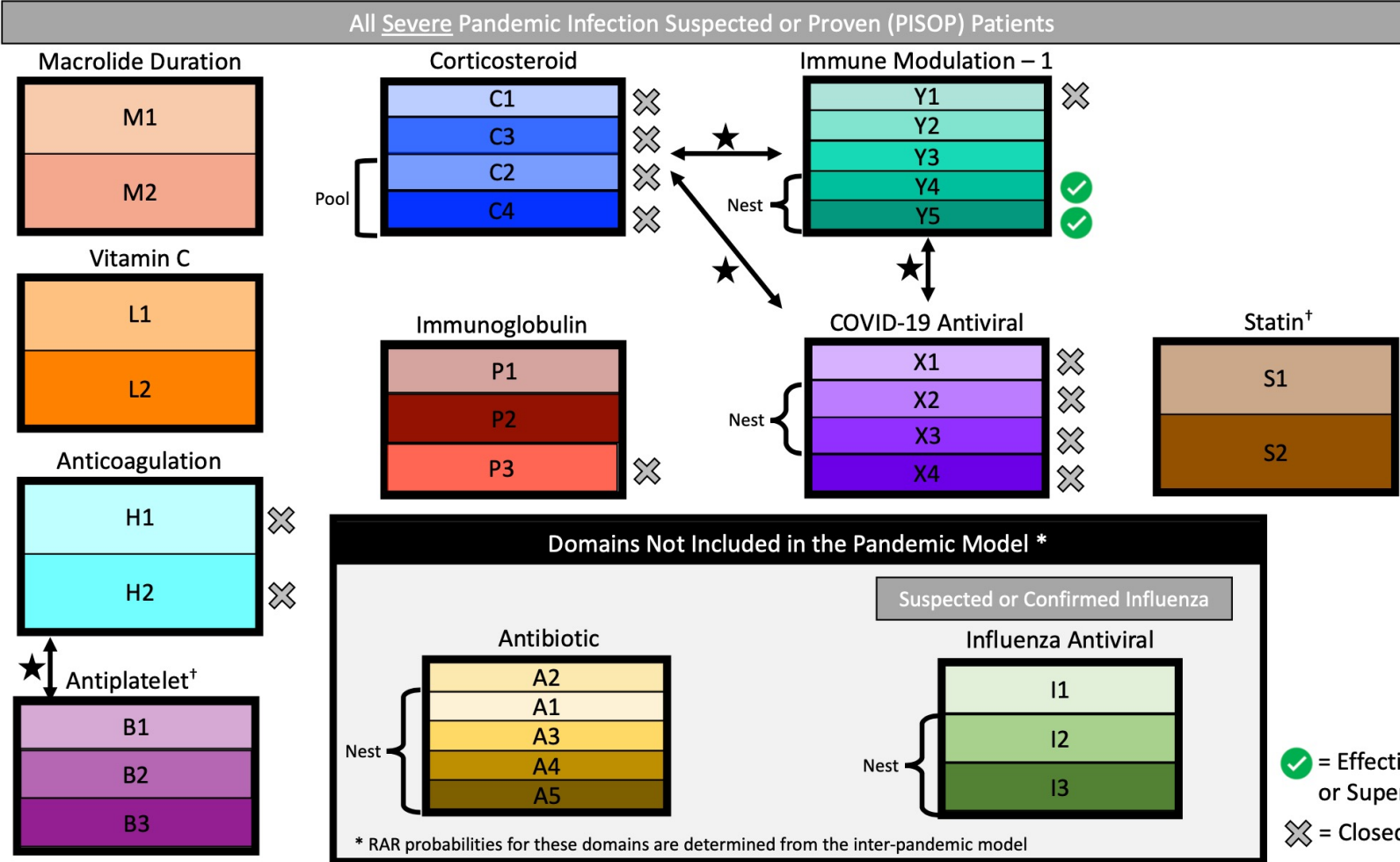


Primary Outcome:  
Organ Support-Free Days (21 days)

Randomized to a **Regimen**: One **Intervention** in each **Domain**

# Domains & Interventions

- Domains/interventions added and removed
- Frequent adaptive analyses
- Drop arms for inferiority/futility
- Superiority in domain or efficacy vs control trigger public disclosure



# Bayesian Analysis Model

- Primary outcome: Organ support-free days, ordinal outcome composite of in-hospital mortality (−1) and OSFD through 21 days
- Cumulative logistic (proportional odds) model

$$\text{logit}\left(\frac{\pi_k}{1 - \pi_k}\right) = [k] + [Site] + [Time] + [Age] + [Sex] + \sum_{j=1}^J [I_j] + \sum [IxI]$$



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- Baseline covariates that explain variability in outcome
- Important in the rapidly evolving pandemic environment

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- Effect of each intervention relative to control/referent within domain
- Assume a proportional effect across ordinal outcome
- Some interventions are “nested” with a hierarchical prior
  - Ex: Two Interleukin-6 receptor antagonists (tocilizumab and sarilumab) are nested based on similar mechanism of action

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- Prespecified *interactions* between interventions
- Ex: Interactions estimated between steroid and antiviral domains based on prior evidence of a negative interaction

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- Response adaptive randomization (RAR) driven by this model
- At each adaptive analysis, compute the posterior probability that each treatment regimen is *optimal*
- Future participants randomized proportionally to this probability; higher probability of receiving effective regimens



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# REMAP-CAP

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

13,911

Patient randomisations

12,460

Patient randomisations with  
suspected or proven COVID-19

48

Current or completed interventions  
in 14 Domains

7,700

Total patients

6,839

Patients with suspected or proven  
COVID-19

320

Active Sites

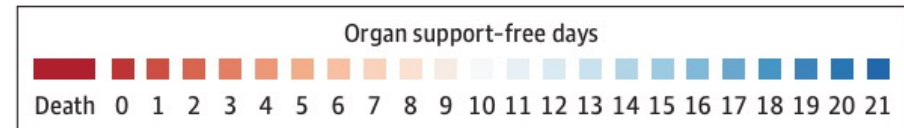
# Analysis of corticosteroids after halting domain based on external data

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

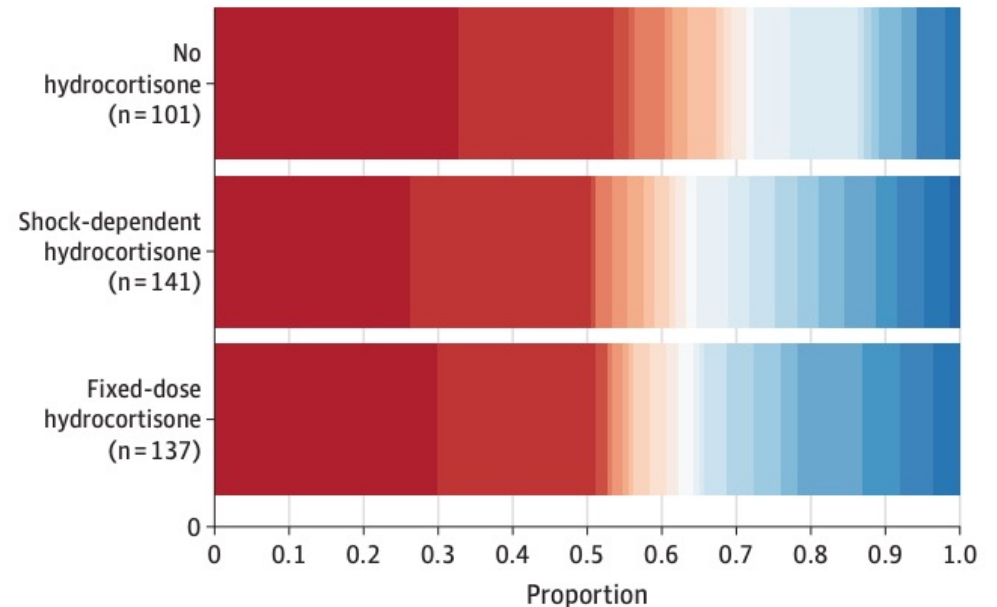
## Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19

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

The Writing Committee for the REMAP-CAP Investigators



**B** Organ support-free days by study group



**Table 2. Primary Outcome**

Outcome/analysis <sup>a</sup>	Fixed-dose hydrocortisone (n = 137)	Shock-dependent hydrocortisone (n = 141)
Primary outcome, organ support-free days		
Median (IQR)	0 (-1 to 15)	0 (-1 to 13)
Subcomponents of organ support-free days		
In-hospital deaths, No. (%)	41 (30)	37 (26)
Organ support-free days among survivors, median (IQR)	11.5 (0 to 17)	9.5 (0 to 16)
Primary analysis of the primary outcome, using covariate data from all severe-state participants with COVID-19 (n = 576) <sup>b</sup>		
Adjusted odds ratio		
Mean (SD)	1.47 (0.35)	1.26 (0.31)
Median (95% CrI)	1.43 (0.91 to 2.27)	1.22 (0.76 to 1.94)
Probability of superiority to no hydrocortisone, %	93	80

# The NEW ENGLAND JOURNAL of MEDICINE

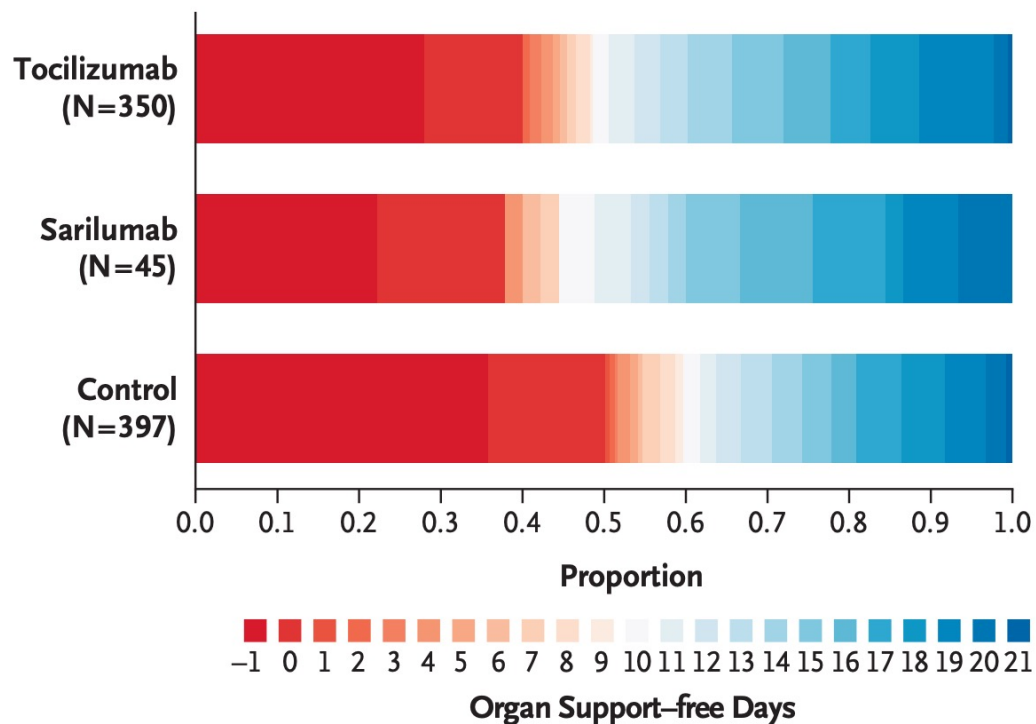
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## Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19

The REMAP-CAP Investigators\*



**Table 2. Primary and Secondary Outcomes.\***

Outcome or Analysis	Tocilizumab (N=353)	Sarilumab (N=48)	Control (N=402)
<b>Primary outcome</b>			
Organ support-free days			
Median (IQR)	10 (-1 to 16)	11 (0 to 16)	0 (-1 to 15)
Adjusted odds ratio			
Mean	1.65±0.23	1.83±0.44	1
Median (95% credible interval)	1.64 (1.25 to 2.14)	1.76 (1.17 to 2.91)	1
Probability of superiority to control — %	>99.9	99.5	—

Tocilizumab and sarilumab continued and met statistical trigger for “equivalence” at a later analysis

# REMAP-CAP COVID-19 results

- Corticosteroids (*JAMA*)
  - Helped confirm benefit in severe patients
- Interleukin-6 receptor antagonists (*NEJM*)
  - Demonstrated benefit in severe patients
  - Later equivalence of toci/sari (paper under review)
- Anticoagulation (medRxiv; under review)
  - Demonstrated benefit in moderate patients; no benefit in severe patients
- Antiviral (under review)
  - Ruled out benefit of HCQ and Kaletra
  - Summarized the data on HCQ despite stopping early
- Immunoglobulin/convalescent plasma (medRxiv; under review)
  - Demonstrated no benefit in severe patients



# Final thoughts

- Bayesian analysis model simplifies many of the challenges of interpreting a complex design in a quickly evolving situation
- Interpretable results with an unknown design, sample size, enrollment rate
- Incorporation of external data/results
- Dynamic borrowing across similar interventions
- Answer more informative questions:
  - What is the optimal treatment regimen for COVID-19?
  - Is there an interaction between corticosteroids and IL-6ra?
  - Are tocilizumab and sarilumab equivalent?

# References

- <https://www.remapcap.org/>
- The Writing Committee for the REMAP-CAP Investigators. [Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial](#). *JAMA*. 2020;324(13):1317–1329. doi:10.1001/jama.2020.17022
- The REMAP-CAP Investigators. [Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19](#). *NEJM*. 2021;384:1491-1502. doi:10.1056/NEJMoa2100433
- The REMAP-CAP, ACTIV-4a, ATTACC Investigators. [Therapeutic Anticoagulation in Critically Ill Patients with Covid-19 – Preliminary Report](#). Pre-print, medRxiv.
- The REMAP-CAP, ACTIV-4a, ATTACC Investigators. [Therapeutic Anticoagulation in Non-Critically Ill Patients with Covid-19](#). Pre-print, medRxiv.
- The REMAP-CAP Investigators. [Convalescent Plasma in Critically ill Patients with COVID-19](#). Pre-print, medRxiv.