

Lessons learned from COVID-19:
One year in for the REMAP-CAP global
adaptive platform trial ...

Derek C. Angus, MD, MPH

Who is REMAP-CAP?

- International trial steering committee
 - Trialists, critical care, infectious disease, cardiology, immunology, hematology
- Statistical hub (Berry Consultants)
- Multiple coordinating centers
 - ICNARC/Imperial College London
 - Monash U
 - U Pitt
 - U Toronto
 - Utrecht Medical Centre
- 300 sites in 19 countries
- Tied to several large clinical trials networks
 - CCCTG, COMBACTE, SepNET, ANZICS CTG, ACTIV-4 consortium



Who knew a pandemic was just like baseball?

- It ain't over till it's over
- We made too many wrong mistakes
- The future ain't what it used to be
- Be very careful if you don't know where you're going, because you might not get there
- In theory, there is no difference between theory and practice. In practice, there is.

Outline

- Recap of REMAP-CAP
- Some results from the first year
- A bit more detail on how REMAP-CAP works
- What was good in theory but difficult in practice
- Some reflections and next steps

Last May ...

- The need to optimize the trade-off of providing care (doing) versus conducting trials (learning)
- Consider RCT designs that ...
 - 'Lean in' to clinical care
- Make randomization more comfortable
 - Consider multiple arms or strategies to decrease likelihood of 'no intervention' as controls
 - Consider response-adaptive randomization (increase odds of benefit within the trial)
- Simplify interface between clinical practice and clinical research
 - Master protocols with simple entry criteria
 - 1-stop shopping at sites for data entry, etc.
- Consider whether all research cows are sacred
 - Is placebo always necessary?

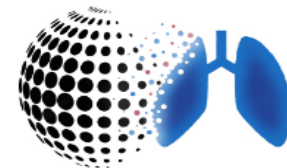
Viewpoint

March 30, 2020

Optimizing the Trade-off Between Learning and Doing in a Pandemic

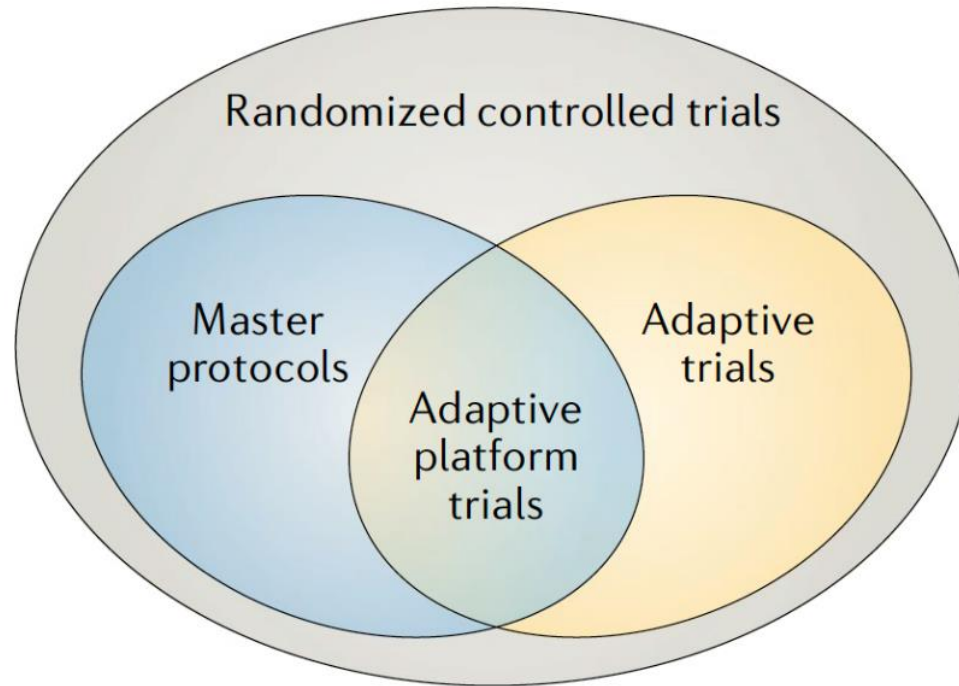
Angus DC, *JAMA* March 30, 2020

REMAP-CAP Executive Summary



- A global adaptive platform trial
- Designed to determine best treatment for severe pneumonia
 - Randomizes multiple interventions simultaneously, nested within domains
 - Uses a multifactorial Bayesian inference model
 - Uses response-adaptive randomization
- Assesses both interpandemic AND pandemic forms of pneumonia
 - Pre-set rules to switch into pandemic mode
- Entered pandemic mode (termed 'REMAP-COVID') in February 2020
 - First COVID patient enrolled in March

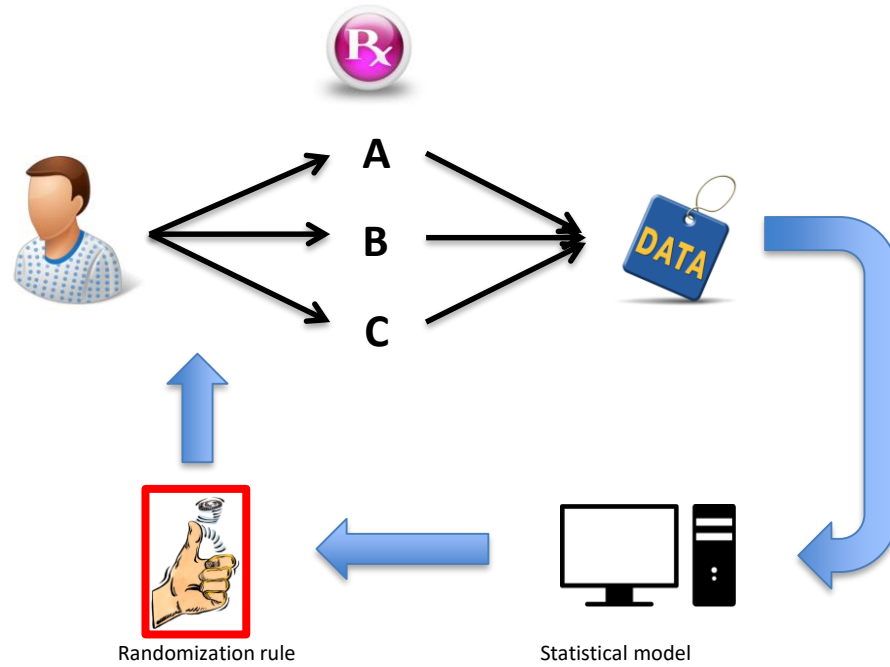
Adaptive Platform Trials



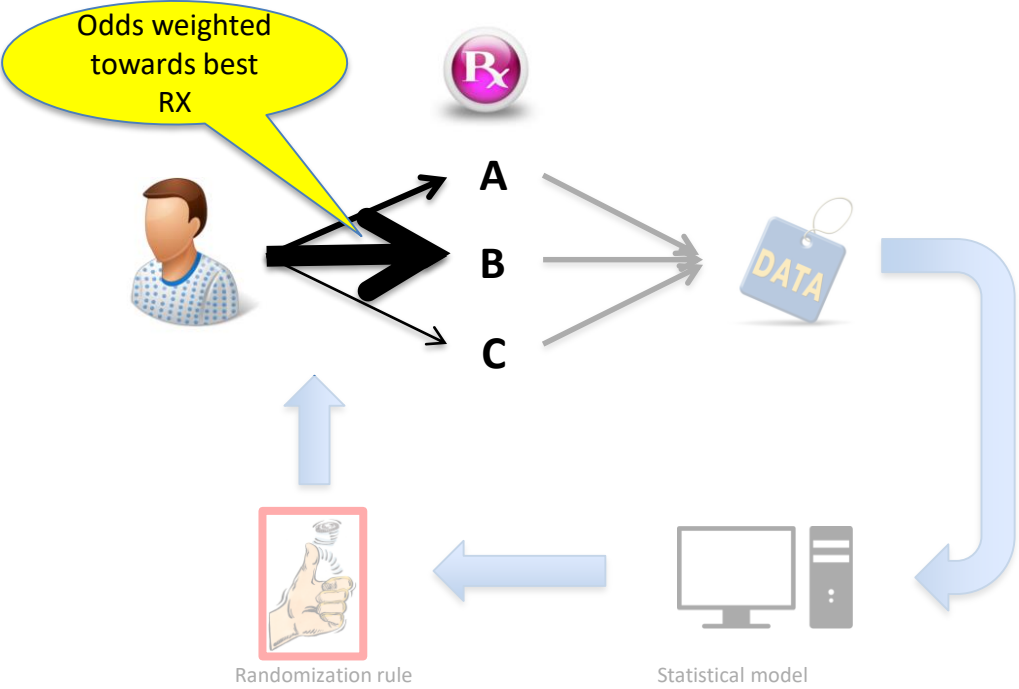
Woodcock and Lavange. *NEJM* 2017

Adaptive Platform Trials Coalition. *Nature Drug Discovery* 2019

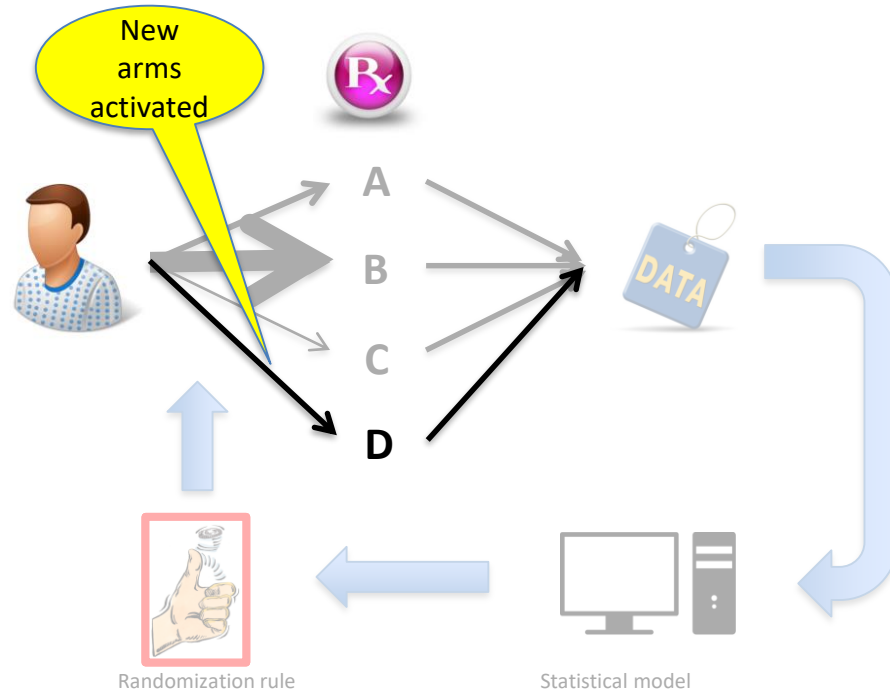
Response-adaptive randomization



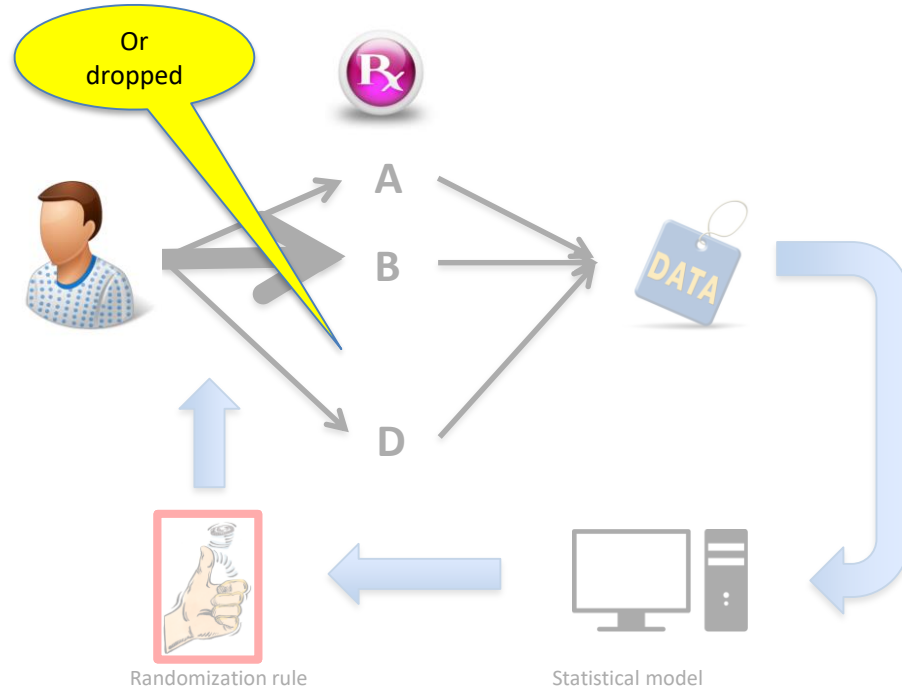
Response-adaptive randomization



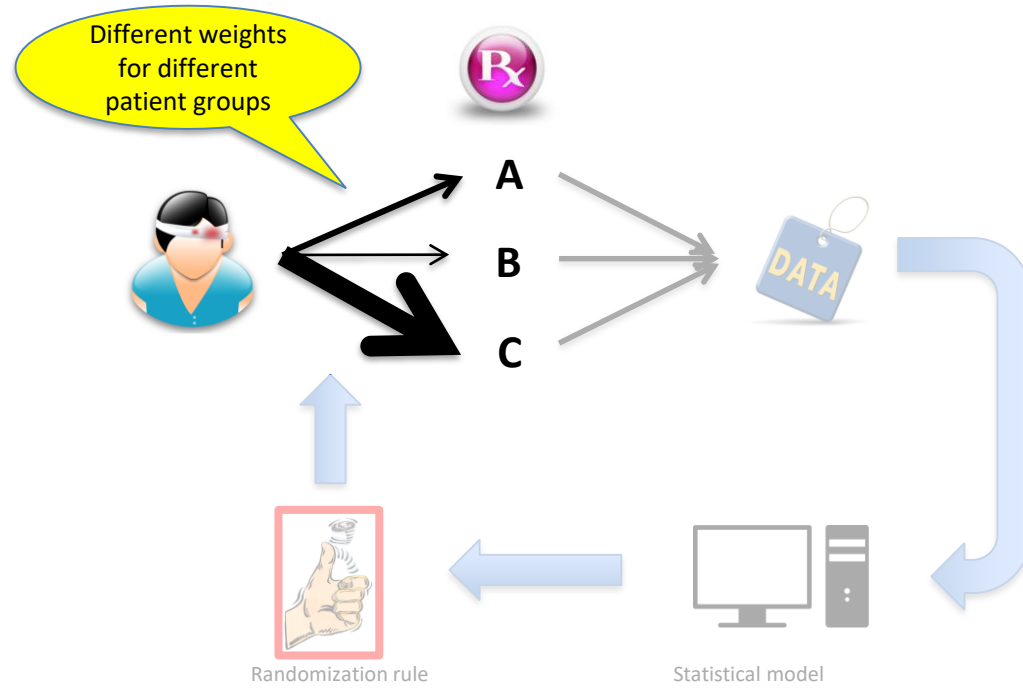
Response-adaptive randomization

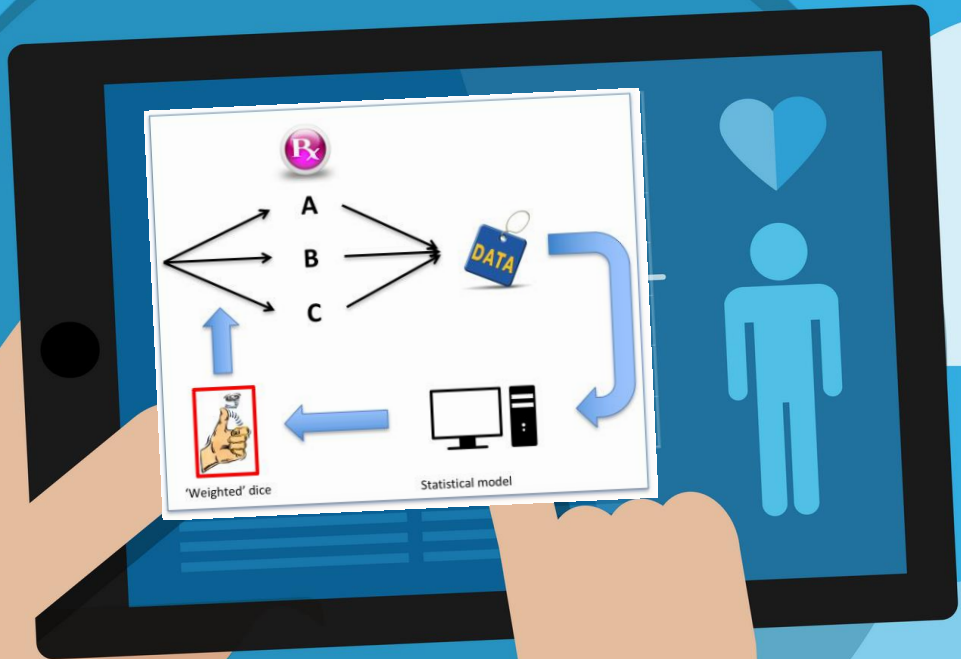


Response-adaptive randomization



Response-adaptive randomization





'Weighted' dice

Statistical model

DATA

A
B
C

Rx

RANDOMIZED
EMBEDDED
MULTIFACTORIAL
ADAPTIVE
PLATFORM

Allow CAUSAL inference

Align with care; leverage the EHR

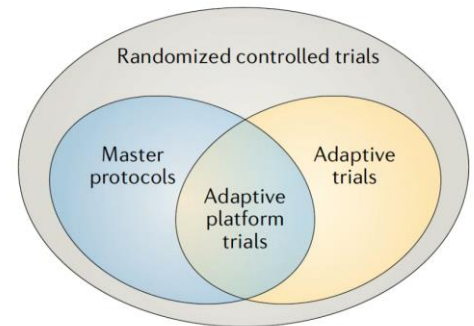
Multiple treatments and subgroups
REMAP

Match odds of success to odds of assignment

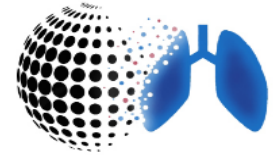
Perpetual enrollment; continuous learning

REMAP designs ...

- Smart
 - Consider many different treatment options
 - Vary the options depending on the patient
- Safe
 - Probably 'play' what is probably the 'winner'
 - On average, safer 'in' the trial than out of it ...

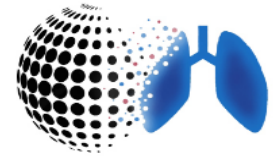


REMAP-CAP:covid, a 'sub-platform' of REMAP-CAP



- Expanded to all hospitalized patients with COVID-19, in 2 strata
 - Moderate (hospitalized but not severe)
 - Severe (requiring ICU care for respiratory failure or shock)

REMAP-CAP:covid, a 'sub-platform' of REMAP-CAP



- Expanded to all hospitalized patients with COVID-19, in 2 strata
 - Moderate (hospitalized but not severe)
 - Severe (requiring ICU care for respiratory failure or shock)
- 1^o endpoint: organ failure-free days
 - Death worst outcome, followed by number of days free of ICU-based cardiovascular or respiratory support through 21 days
 - Modeled with cumulative logistic proportional odds model

$$\log\left(\frac{\pi_y}{1 - \pi_y}\right) = [Site] + [Time] + [Age] + \sum_{i=1}^k [Intervention] + \sum [IxI Interactions]$$

- 2^o endpoints: mortality, WHO ordinal scale, safety

REMAP elements

- Domain – an area where a question is asked ...
 - Domain #1 – choice of antibiotic
 - Domain #2 – whether to give steroids or not
 - Domain #4 – choice of ventilator strategy
 - Etc.
- Intervention
 - Any option within a domain ...
- Regimen
 - Unique combination of interventions within a domain ...
- Stratum
 - Baseline subgroup
 - Ex. Moderate vs. Severe COVID19 at presentation

Multifactorial intervention assignments

Regimen = set of domain-specific interventions

Effect of an intervention is conditional upon

- Stratum
- Interventions within other domains

Regimen	Domain A	Domain B	Domain C
#1	A1	B1	C1
#2	A1	B1	C2
#3	A1	B2	C1
#4	A1	B2	C2
#5	A2	B1	C1
.....			
# <i>n</i>	<i>A_n</i>	<i>B_n</i>	<i>C_n</i>

So ... how have things gone?

Last May ...

- We had enrolled about 200 patients and had ~60 sites in 13 countries
- Randomizing in to 3 relevant domains
- 2 'cross-over' domains from regular CAP
 - Macrolide (azithromycin)
 - Corticosteroids
- 1 COVID-specific domain (anti-virals: HCQ; kaletra)



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REMAP-CAP

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

12,416

Patient randomisations

11,182

Patient randomisations with
suspected or proven COVID-19

46

Current or completed interventions
in 14 Domains

6,781

Total patients

6,051

Patients with suspected or proven
COVID-19

310

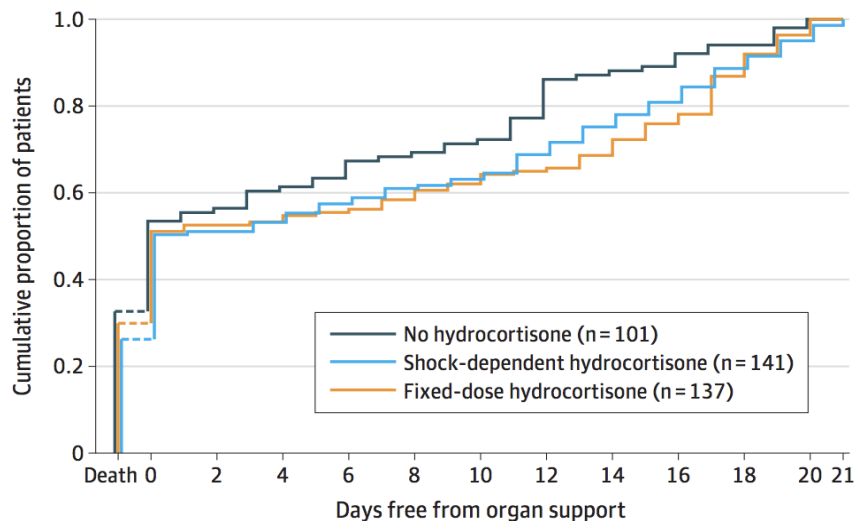
Active Sites

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

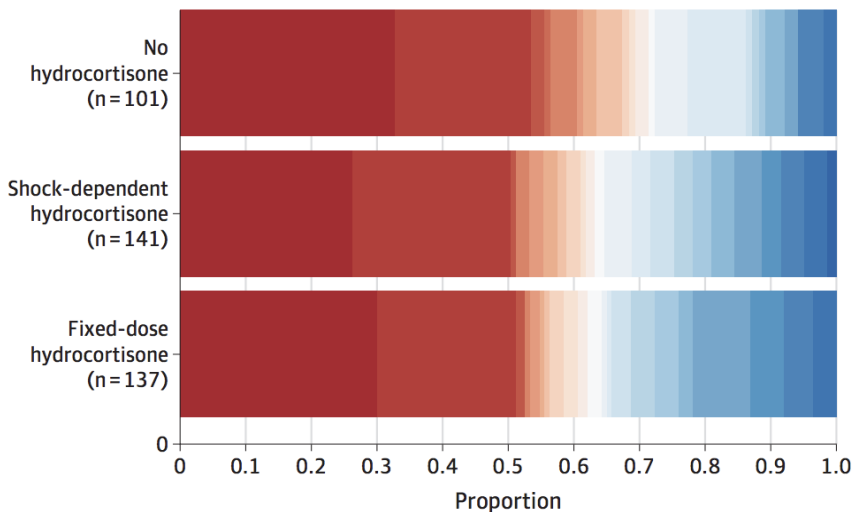
The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial

The Writing Committee for the REMAP-CAP Investigators

A Cumulative distribution of organ support-free days



B Organ support-free days by study group

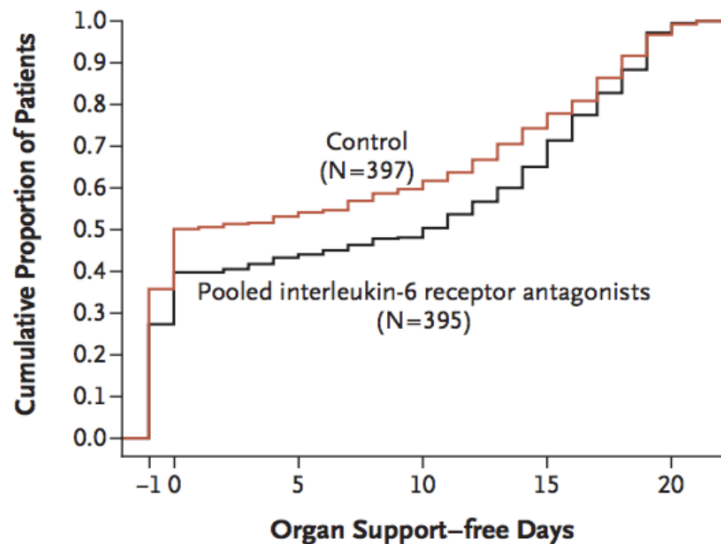


ORIGINAL ARTICLE

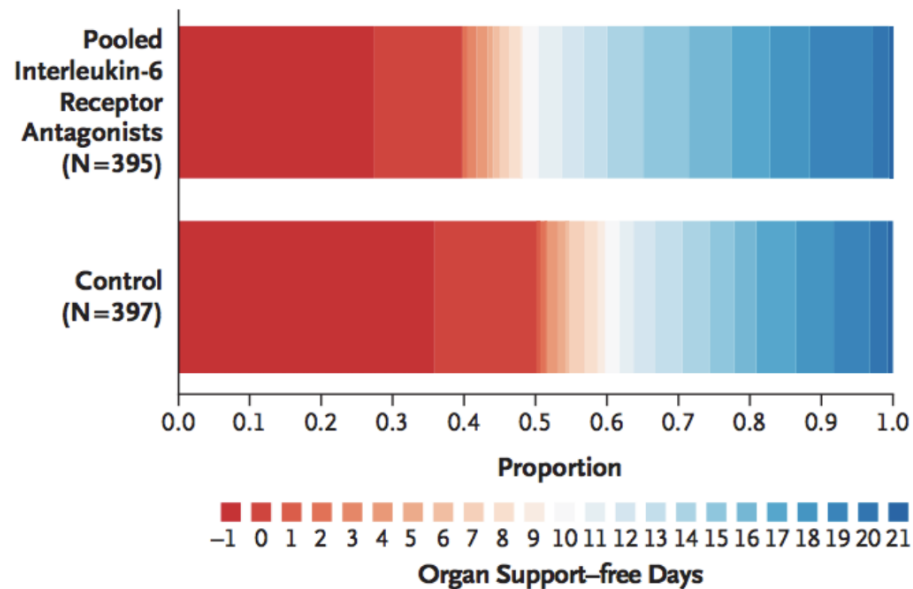
Interleukin-6 Receptor Antagonists
in Critically Ill Patients with Covid-19

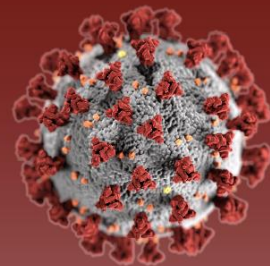
The REMAP-CAP Investigators*

C



D





ATTACC, ACTIV-4a & REMAP-CAP

multiplatform RCT

Results of interim analysis

Release date: January 28, 2021

Results are pre-publication, not from locked databases and not peer reviewed



ATTACC, REMAP-CAP, and ACTIV IV-4a mpRCT

Primary outcome

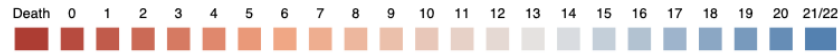
State & D-dimer Strata	Proportional Odds Ratio Median (95% CrI)	Trial Statistical Conclusion
Moderate state, low D-dimer	1.57 (1.14 - 2.19)	Superiority [Probability of OR>1 = 0.997]
Moderate state, high D-dimer	1.53 (1.09 - 2.17)	Superiority [Probability of OR>1 = 0.991]
Moderate state, missing D-dimer	1.51 (1.06 - 2.15)	n/a [⚠]
Severe state	0.76 (0.60 - 0.97)	Futility* [Probability of OR>1.2 < 0.001]

* Posterior probability of **inferiority** [Probability of OR<1 = 0.985]

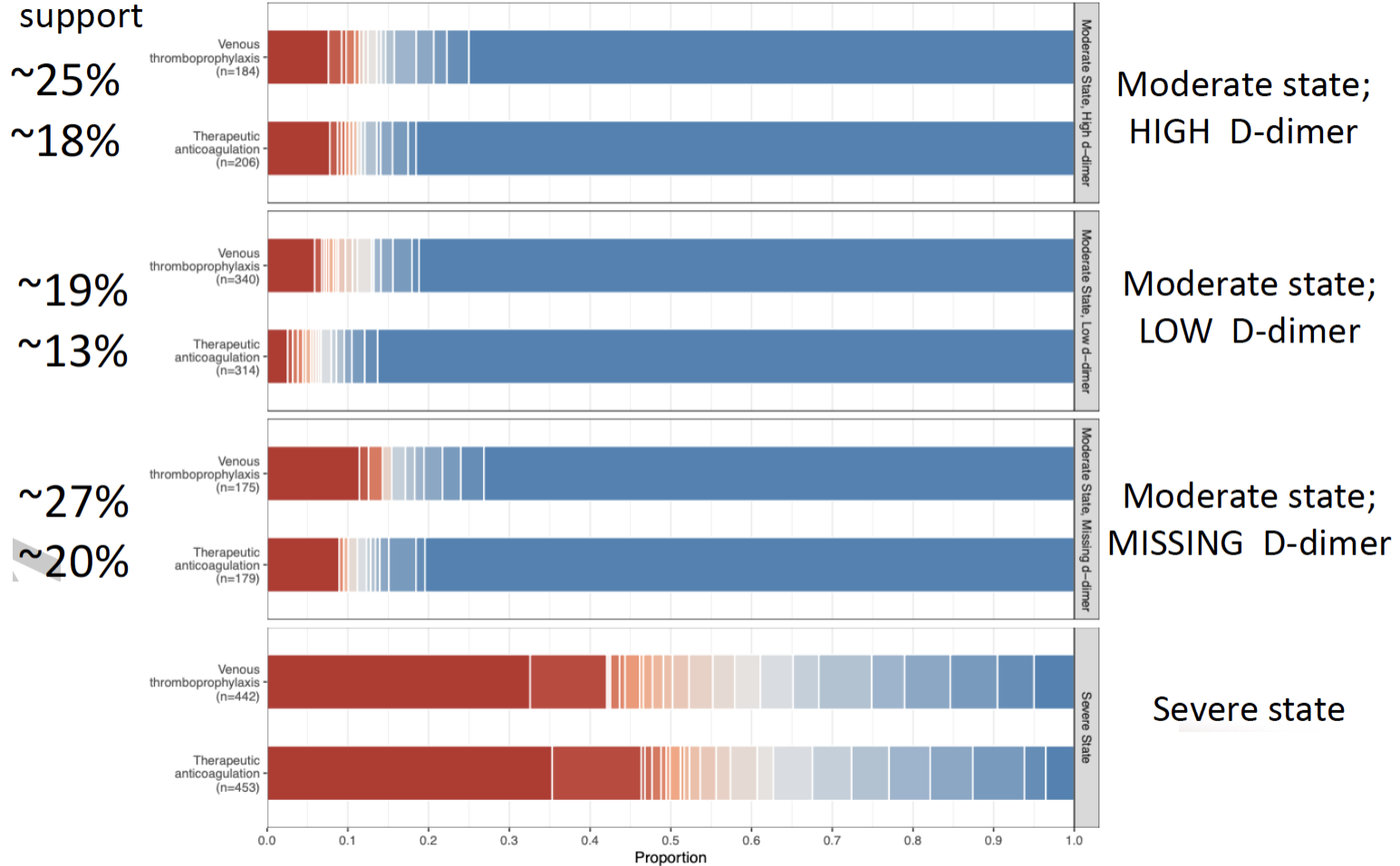
⚠ Not evaluated for stopping at interim

OR >1 represents benefit. A higher OR occurs when either mortality is improved and/or if those who survive have reduced requirement for organ support

Approx. proportion
requiring organ
support



INTERIM



COVID-19 therapies

- Anti-virals (under review; data in Oxfor et al. *Nature Comm* 2021)
 - Helped rule out any benefit with HCQ
 - Helped rule out any benefit with Kaletra
- Immunoglobulin/convalescent plasma (press release; report being finalized)
 - Demonstrated no benefit in severe patients
 - Helped rule out any benefit in moderate patients
- Anti-coagulation (posted on MedRxiv; under review)
 - Demonstrated benefit in moderate patients
 - Demonstrated no benefit/possible harm in severe
- Corticosteroids (*JAMA*)
 - Demonstrated benefit with hydrocortisone in severe state
 - Helped confirm benefits of corticosteroids in sick patients
- Targeted immune suppressor agents (*NEJM*)
 - Demonstrated benefit of IL6 receptor antagonists in severe patients

A bit more about how it all 'works'

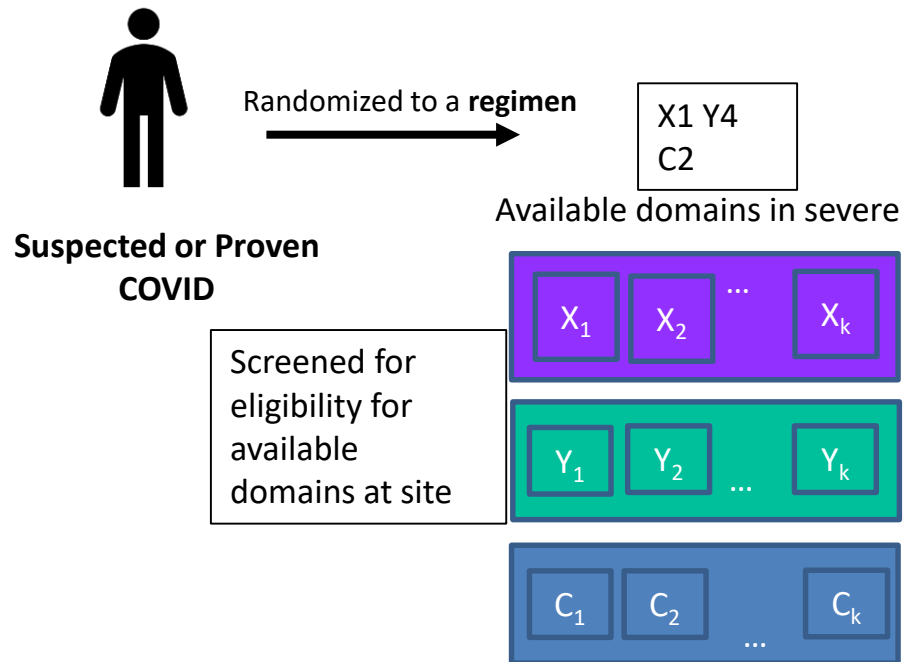
REMAP-CAP journey



**Suspected or Proven
COVID**

**Severe disease –
on organ support
at time of
randomization**

REMAP-CAP journey



REMAP-CAP journey



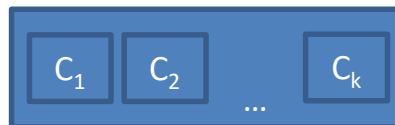
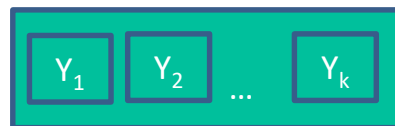
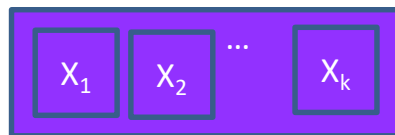
Suspected or Proven
COVID

Randomized to a regimen



X1 Y4
C2

Available domains in severe



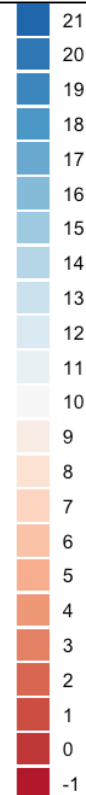
Follow for 21 days
(duration of hospital stay)



Organ Support Free Days (OSFD)

Ordinal endpoint with 23 levels

OSFD =



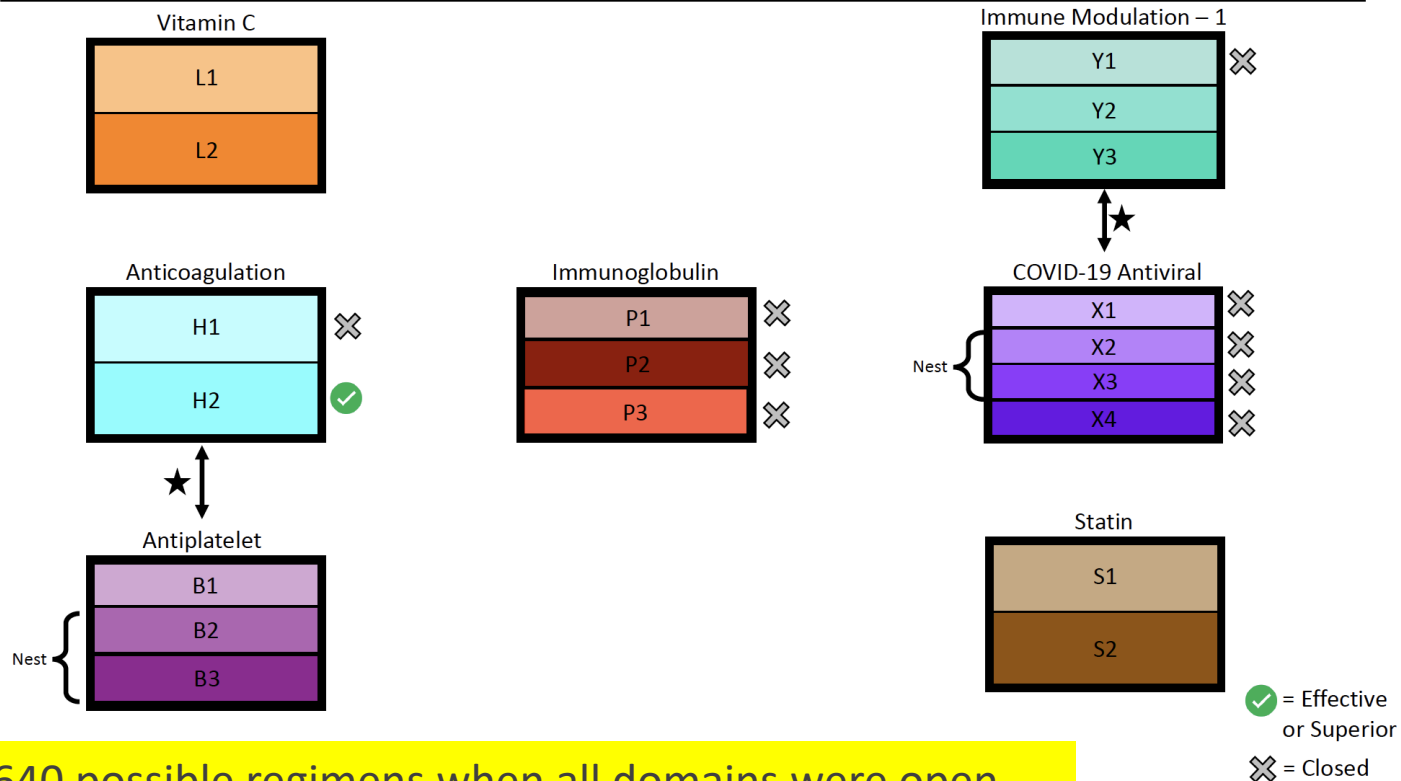
21 — Number of
days on organ
support

- Mechanical ventilation
- HFNO
- Vasopressor/Inotr
opes, ...

-1 for in-hospital mortality

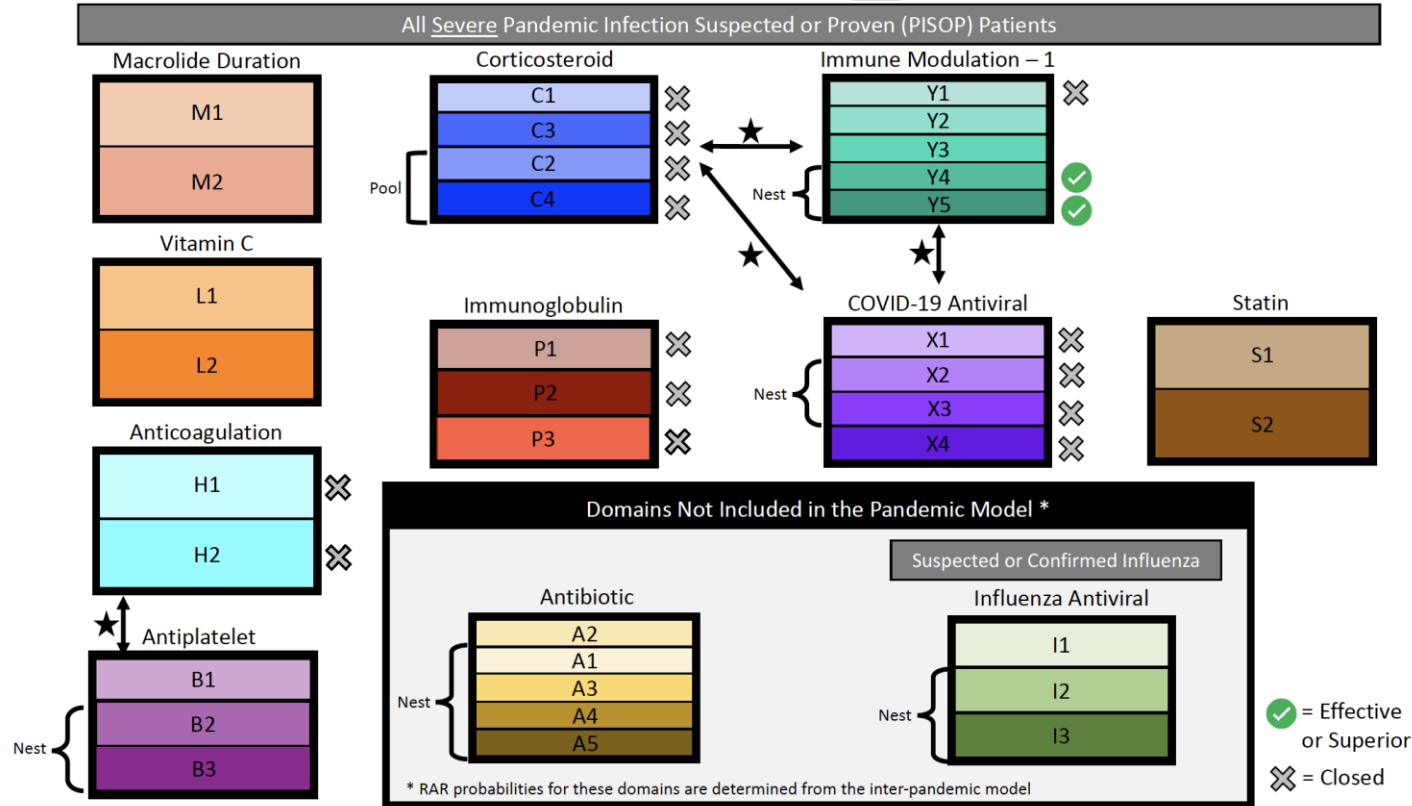
Moderate state (hospitalized, no organ failure)

All Moderate Pandemic Infection Suspected or Proven (PISOP) Patients



• 8,640 possible regimens when all domains were open ...

Severe state (ICU admission with organ failure)



- 194,400 possible regimens, just for COVID, when all domains open!

IL-6ra in REMAP-CAP

- **Immune modulation domain** contained:

1. Standard of care
2. Anakinra
3. Interferon
4. **Tocilizumab**
5. **Sarilumab**

Examples of Questions of interest:

Is tocilizumab superior to standard of care?
Is interferon futile compared to standard of care?
Is sarilumab the most effective immune modulation agent?

- Enrolled in **severe (ICU/organ support at baseline)**

- Comparative effectiveness questions are answered within domain

Bayesian modeling

- 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

$$\log\left(\frac{\pi_y}{1 - \pi_y}\right) = [y] + [Site] + [Time] + [Sex] + [Age] + \sum_{i=1}^k [I] + \sum [IxI]$$

- Model controls for
 - All interventions across domains
 - Cross domain interactions (that are pre-specified)
 - Covariates such as site, time, sex, and age
- Priors specified for all parameters in the model
 - Neutral priors used for estimating treatment effects

Bayesian modeling

- Primary Endpoint: Organ Support Free Days: Ordinal endpoint, death worst outcome (-1), followed by number of OSFD through 21 days
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$$\log\left(\frac{\pi_y}{1 - \pi_y}\right) = [y] + [\textit{Site}] + [\textit{Time}] + [\textit{Sex}] + [\textit{Age}] + \sum_{i=1}^k [I] + \sum [IxI]$$

[Site]
 + **[Time]**
 + **[Sex]**
 + **[Age]**



- All patients used to inform the covariate adjustments
- Important in the changing environment of the pandemic

Bayesian modeling

- 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

$$\log\left(\frac{\pi_y}{1 - \pi_y}\right) = [y] + [\mathbf{Site}] + [\mathbf{Time}] + [\mathbf{Sex}] + [\mathbf{Age}] + \sum_{i=1}^k [\mathbf{I}] + \sum [\mathbf{IxI}]$$

$$\left. \sum_{i=1}^k [\mathbf{I}] \right\}$$

- Each domain contributes interventions to $[\mathbf{I}] = [I_{C,2}, I_{C,3}, \dots, I_{Y,2}, I_{Y,3}, \dots,]$
- Model compares $I_{Y,2}, I_{Y,3}, I_{Y,4}, I_{Y,5}$ to the control arm $I_{Y,1}$ (referent)
- Only patients in domain inform treatment effects

Bayesian modeling

- 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

$$\log\left(\frac{\pi_y}{1 - \pi_y}\right) = [y] + [Site] + [Time] + [Sex] + [Age] + \sum_{i=1}^k [I] + \sum [IxI]$$

$$\sum_{i=1}^k [I]$$

- Model leverages similarities between interventions through nesting
- $I_{Y,4}$ $I_{Y,5}$ are modeled through a hierarchical model where their effect is estimated from a common mean
 - Dynamic borrowing : when effects are different – less borrowing, when effects are similar – more borrowing

Bayesian modeling

- Primary Endpoint: Organ Support Free Days: Ordinal endpoint, death worst outcome (-1), followed by number of OSFD through 21 days
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$$\log\left(\frac{\pi_y}{1 - \pi_y}\right) = [y] + [Site] + [Time] + [Sex] + [Age] + \sum_{i=1}^k [I] + \sum [IxI]$$

$$\sum [IxI]$$

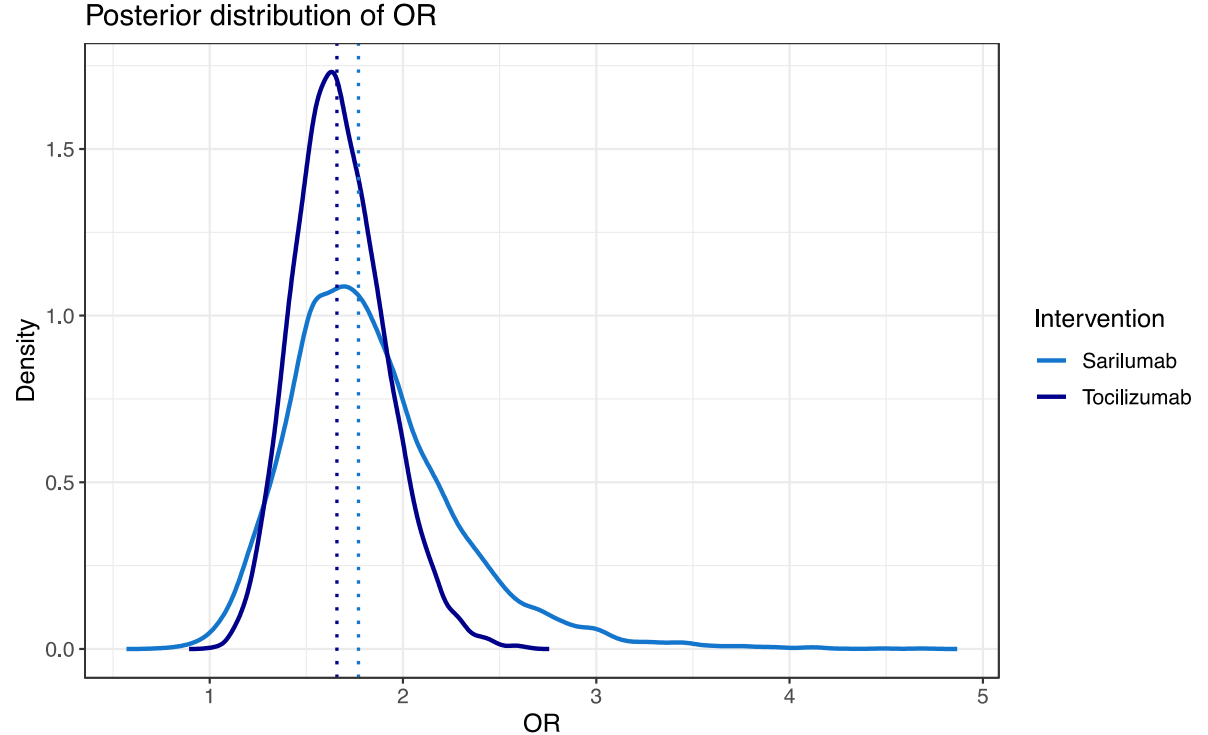
- Pre-specified Interactions across domains are estimated
 - IM has interactions with corticosteroid and antiviral domains

Interpreting Bayesian model

Model returns distribution of the odds ratio (not point estimate)

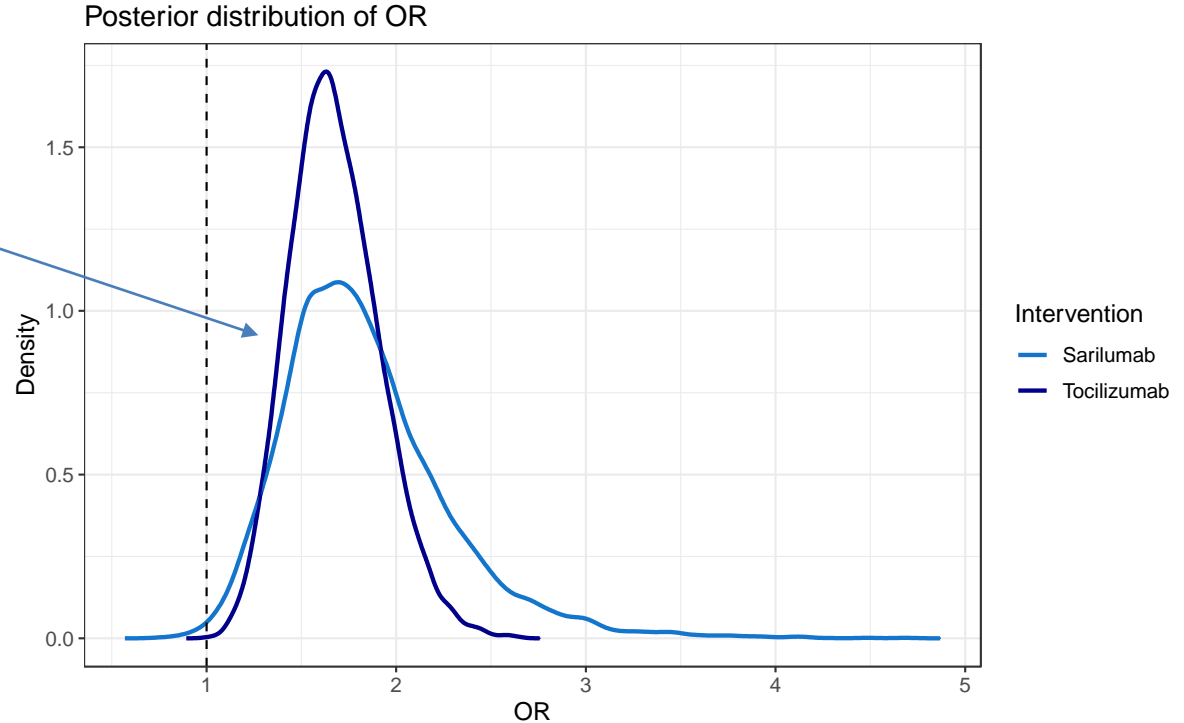
- Summarize effect by taking mean or median of curve

Able to make direct comparisons and quantify with a probability



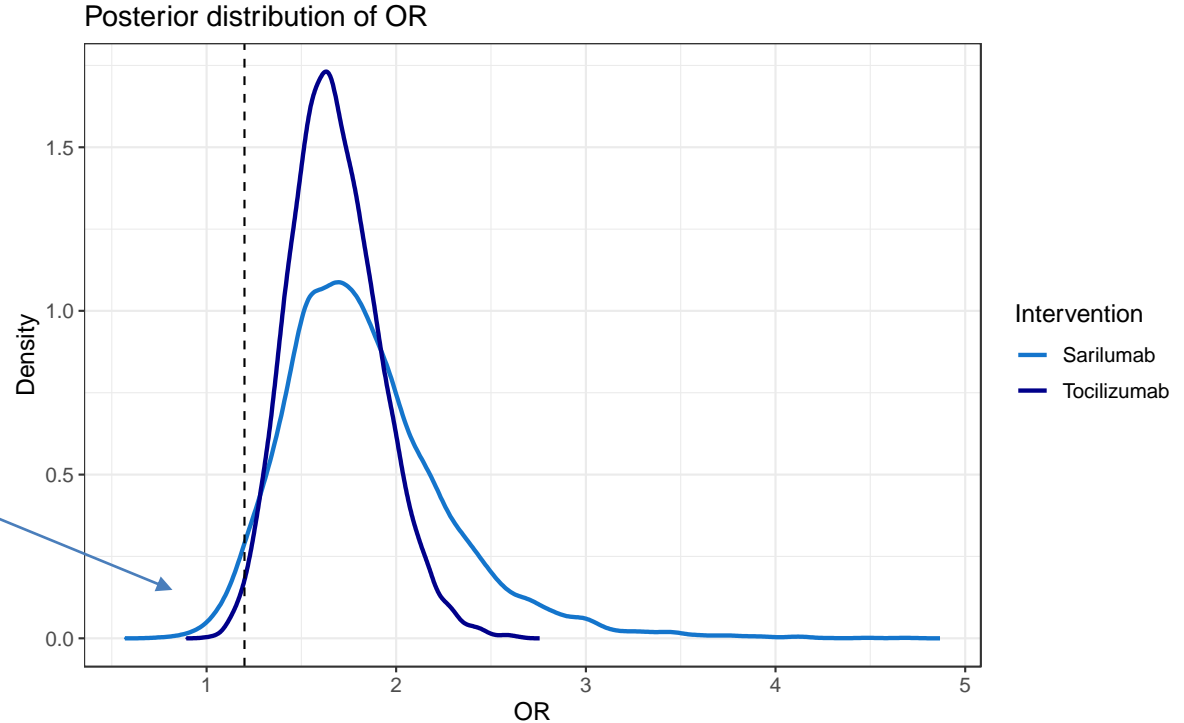
Estimating posterior probabilities

- Probability intervention is superior to control - $\Pr(\text{OR} > 1)$
- Probability intervention is futile – $\Pr(\text{OR} < 1.2)$
- Probability tocilizumab and sarilumab are equivalent



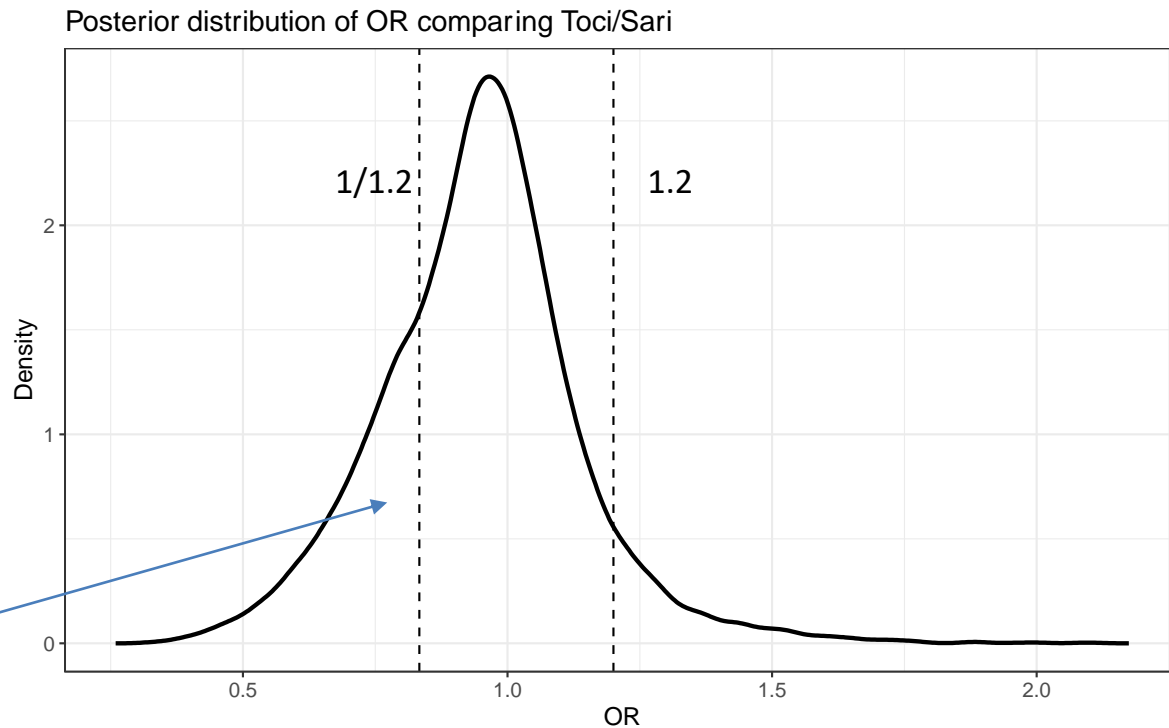
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Estimating posterior probabilities

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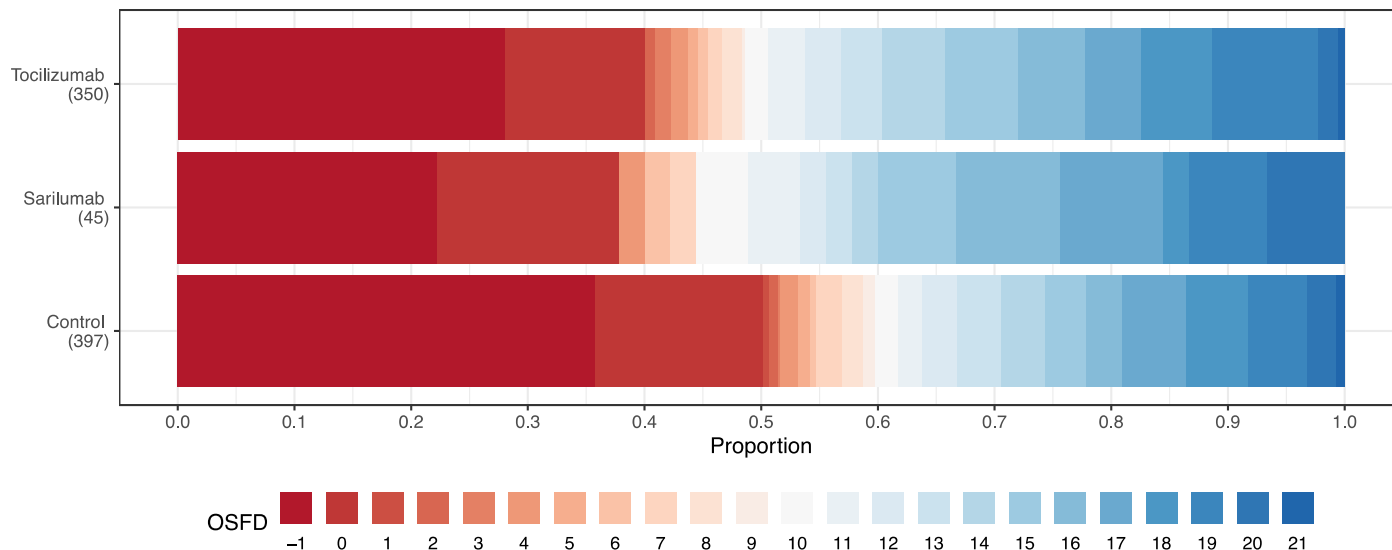
Triggers and Adaptations

- At each interim update, model evaluates
- Superiority to control:
 - posterior probability of superiority is greater than 99%
- Futility:
 - 95% probability of a smaller than 1.2 odds ratio for intervention relative to control
- Equivalence:
 - 90% posterior probability of equivalence (odds ratio of tocilizumab relative to sarilumab is between 1/1.2 and 1.2)
- Response adaptive randomization uses posterior probability regimen is optimal
 - Reassigns randomization weights proportionally
 - 11 updates from fall thru January

Why nesting is important?

Sarilumab- 45
patients with
observed outcomes

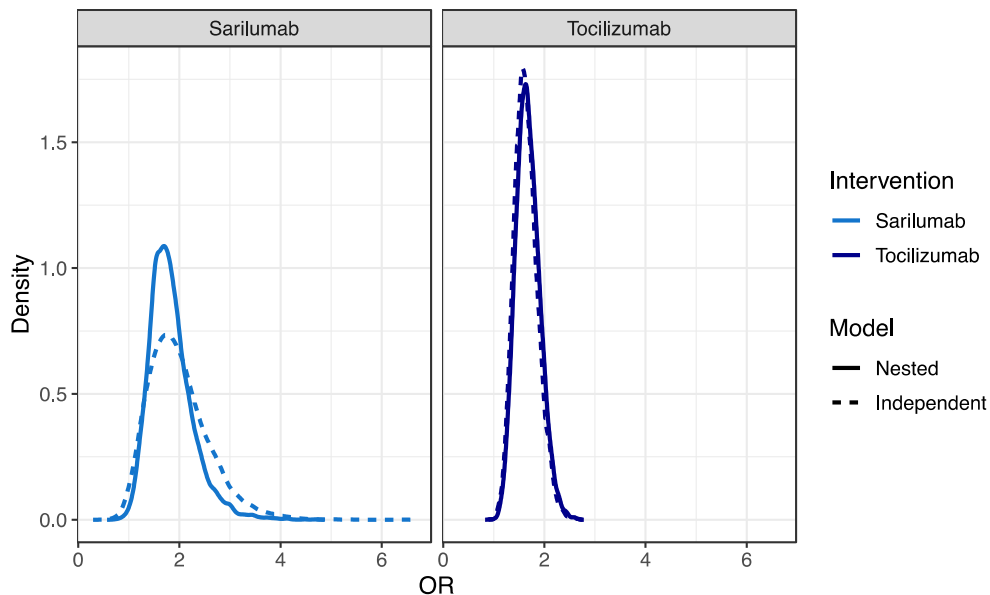
Effects of
tocilizumab and
sarilumab are very
similar



Why nesting is important?

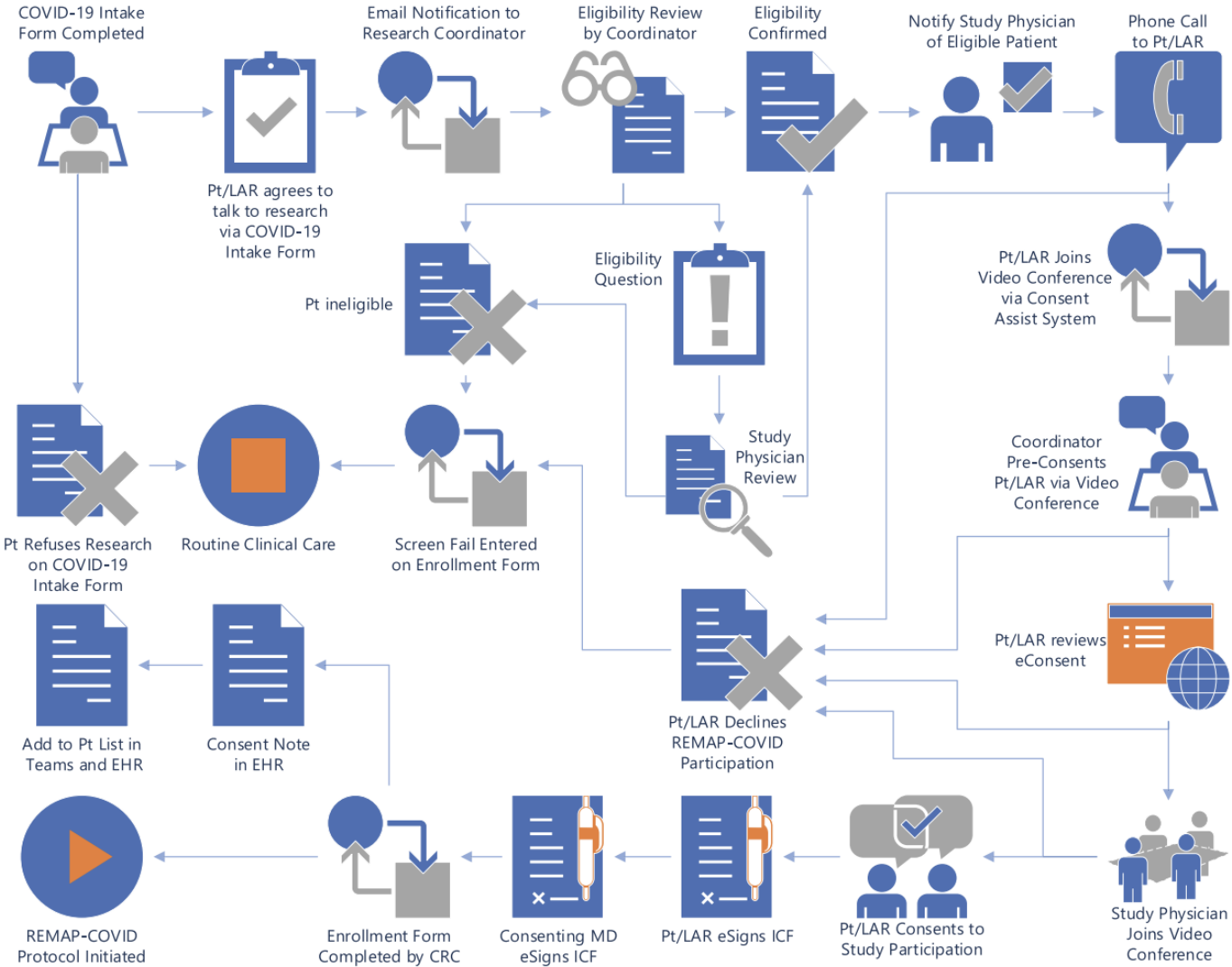
Outcome/Analysis	Tocilizumab (N=353)	Sarilumab (N=48)
Exploratory post-hoc Analysis of Primary Outcome , model restricted to Immune Modulation Therapy Domain participants, with no borrowing between IL-6 RA interventions		
Adjusted OR - mean (SD)	1.64 (0.23)	1.98 (0.60)
- median (95% CrI)	1.62 (1.24 to 2.14)	1.90 (1.08 to 3.41)
Probability of superiority to control, %	>99.9	98.7
Secondary Analysis of Primary Outcome , model restricted to Immune Modulation Therapy domain patients and other closed domains		
Adjusted OR - mean (SD)	1.68 (0.24)	1.84 (0.44)
- median (95% CrI)	1.66 (1.26 to 2.18)	1.77 (1.18 to 2.90)
Probability of superiority to control, %	>99.9	99.6

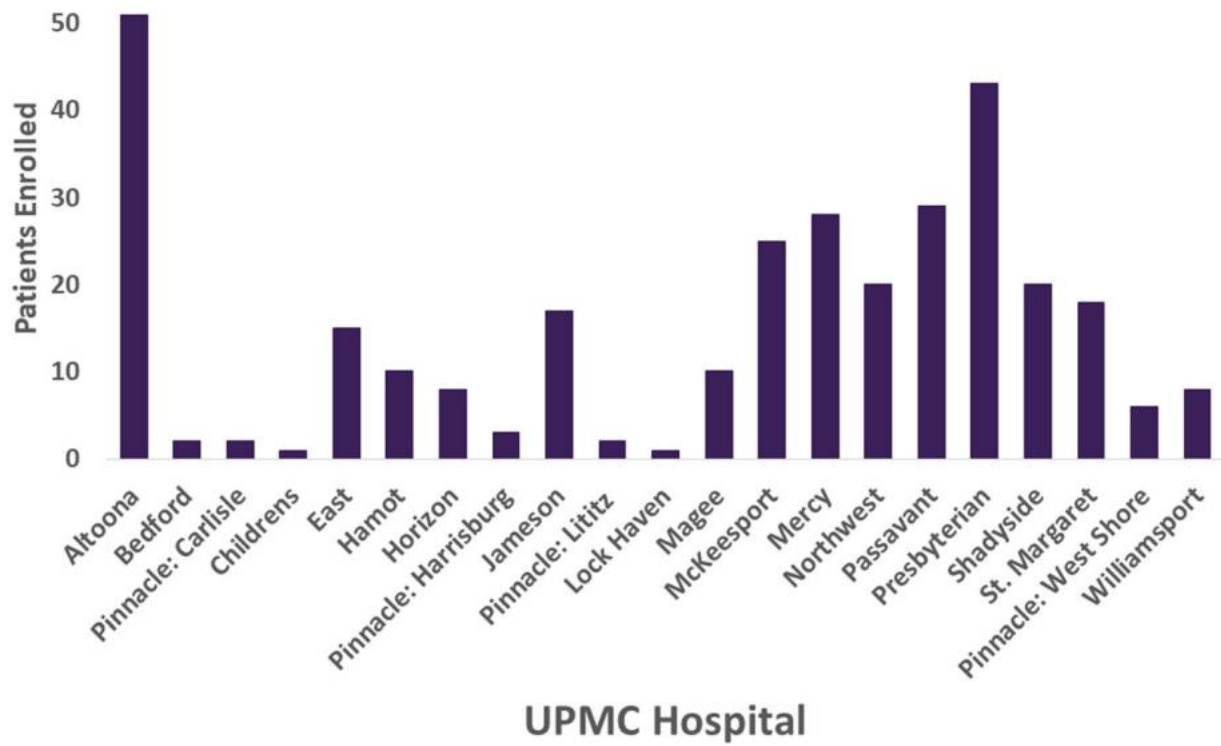
Nesting's influence on posterior distribution of OR



Implementation of the Randomized Embedded Multifactorial Adaptive Platform for COVID-19 (REMAP-COVID) trial in a US health system—lessons learned and recommendations

The UPMC REMAP-COVID Group, on behalf of the REMAP-CAP Investigators¹





Some trials and tribulations ...

- Managing data flow
- Managing model updates
- Variation in enrollment
- Regulatory authorities
- Funding
- Prioritization
- Publication and announcements

Reflections and Next Steps

- Feels like adaptive platform trials are here to stay, but ...
- Need to build comfort level with the modeling, inference, and interpretation
- Need to build appropriate infrastructure to 'keep up' with the power of the engine
- Need to invest in common data models
 - Trial protocols should be 'software', capable of running on any 'hardware' ...
 - Necessary to 'free' the trial from any specific data vendor or IWRT system
- Need to think about incentives for greater research participation

Thanks to the entire (and growing) REMAP-CAP family

- International trial steering committee
 - Trialists, critical care, infectious disease, cardiology, immunology, hematology
- Statistical hub (Berry Consultants)
- Multiple coordinating centers
 - ICNARC/Imperial College London
 - Monash U
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