Developing a Bayesian hierarchical model for a prospective individual patient data meta-analysis with continuous monitoring

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Trials are not able to recruit sufficient patients

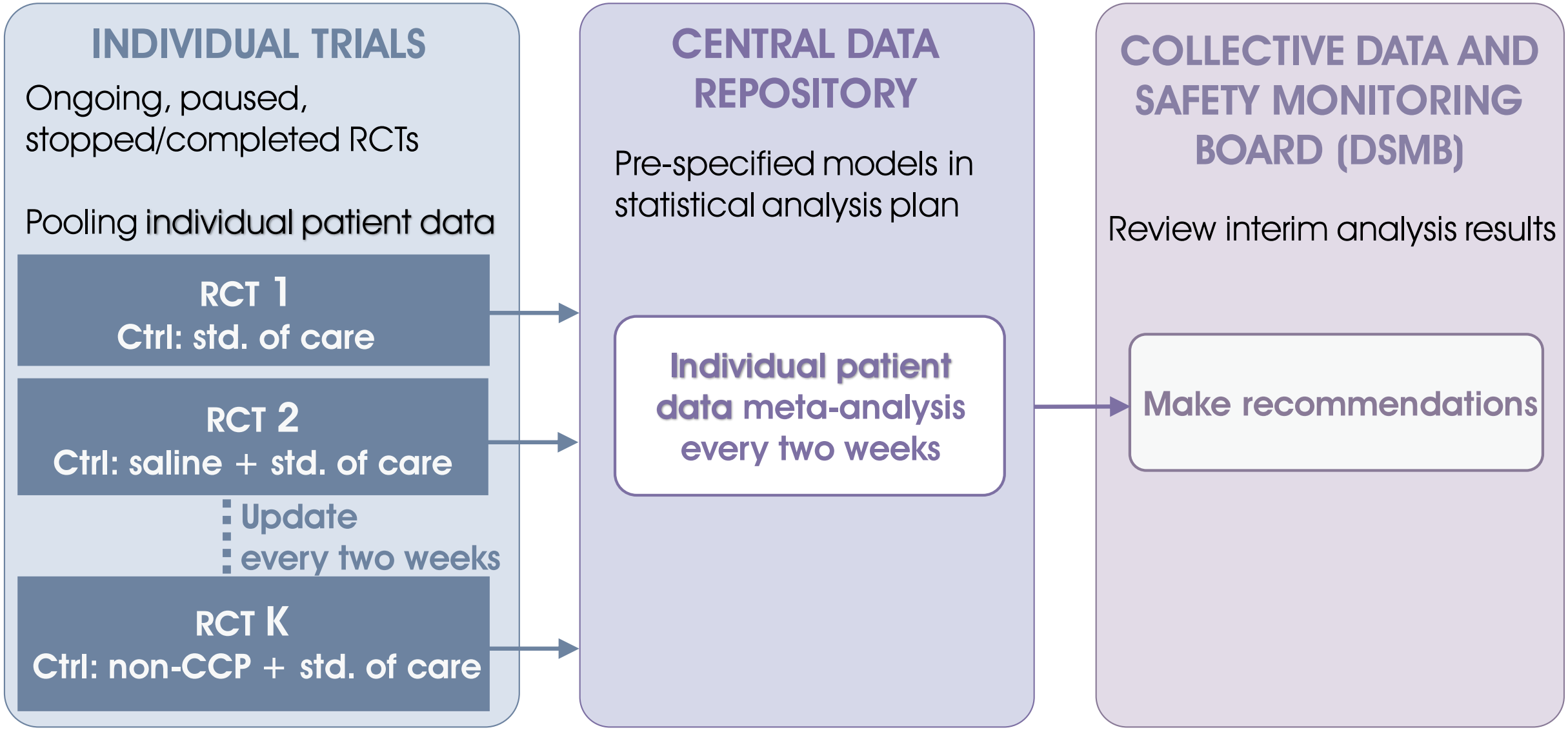
Shifting hotspot of COVID-19 pandemic

Problem: trials are often launched in regions after the pandemic has peaked locally

Consequence: collecting enough data could take additional COVID-19 surges at the same location over several years

Petkova E et al. *JAMA*. 2020
Ortigoza M,…, Wu D et al. *JAMA Internal Medicine*. 2022

COMPILE: Continuous Monitoring of Pooled International Trials of Convalescent Plasma (CCP) for COVID-19 Hospitalized Patients



Troxel A,…, Wu D et al. *JAMA Network Open*. 2022

How to design, monitor a study in the presence of high uncertainty?

Uncertainty:

1. Number of RCTs
2. Number of sites within each RCT
3. Number of RCTs within different control types
4. Number of patients
5. Study duration
6. Number of interim looks
7. Model for three control types
8. Operating characteristics (e.g., type 1 error)

Primary models

- Cumulative proportional odds model (ordinal outcome)
- Logistic model (binary outcome)

Primary outcome: COVID-19 clinical status scale

Patient State	WHO ordinal scale	Binary indicator
Uninfected	0	**No** Mechanical ventilation or death
Ambulatory mild disease	1	
	2	
	3	
Hospitalized: moderate disease	4	
	5	
Hospitalized: severe disease	6	
	7	**Yes** Mechanical ventilation or death
	8	
	9	
Dead	10	

Bayesian cumulative proportional odds model

Denote the WHO score for the i^{th} patient from the k^{th} RCT by Y_{ki}

A_{ki} =1 if this patient was randomized to control arm; $y \in \{1,2,\ldots,10\}$

$$logit\left(P(Y_{ki} \geq \mathrm{y})\right) = \alpha + \tau_{yk} + \boldsymbol{\beta x_{ki}} + \delta_{k_c} A_{ki}$$

Bayesian cumulative proportional odds model

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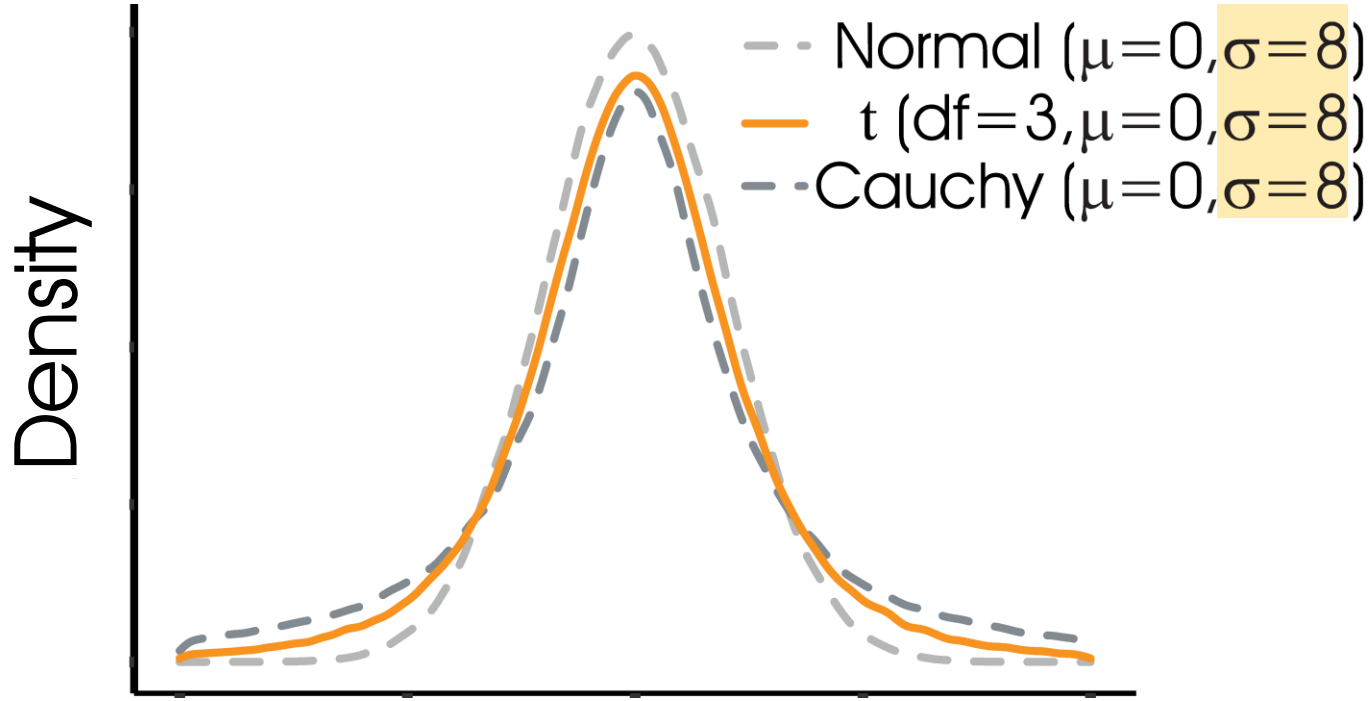
Parameter	Prior distribution
α (global intercept)	Normal $(\mu = 0, \sigma = 0.1)$

Bayesian cumulative proportional odds model

$$logit\left(P(Y_{ki} \geq \mathrm{y})\right) = \alpha + \tau_{yk} + \boldsymbol{\beta x_{ki}} + \delta_{k_c} A_{ki}$$

Parameter	Prior distribution
α (global intercept)	Normal $(\mu = 0, \sigma = 0.1)$
τ_{yk} (RCT-specific intercept)	$\mathrm{t}_{\mathrm{student}}(\mathrm{df} = 3, \mu = 0, \sigma = 8)$



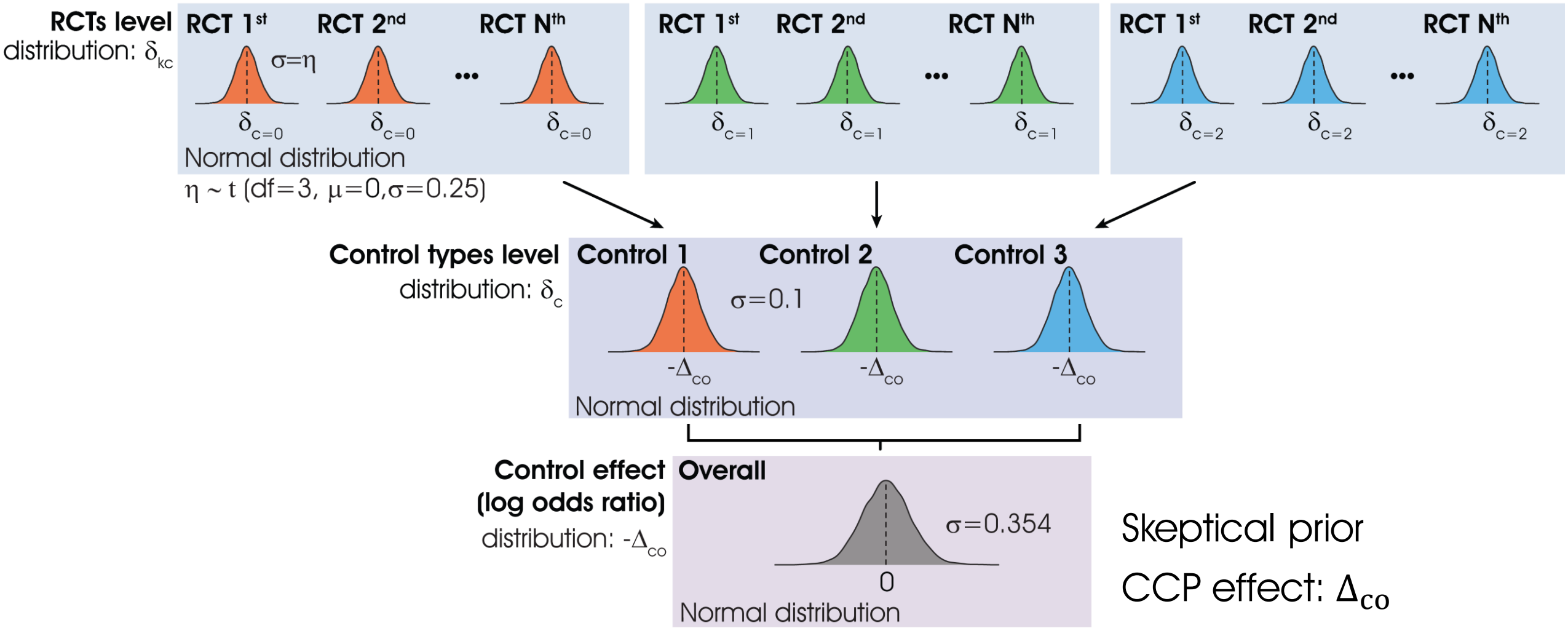
Bayesian cumulative proportional odds model

$$logit\left(P(Y_{ki} \geq \mathrm{y})\right) = \alpha + \tau_{yk} + \boldsymbol{\beta}\boldsymbol{x_{ki}} + \delta_{k_c} A_{ki}$$

Parameter	Prior distribution
α (global intercept)	$\mathrm{Normal}\ (\mu = 0, \sigma = 0.1)$
τ_{yk} (RCT-specific intercept)	$\mathrm{t_{student}}(\mathrm{df} = 3, \mu = 0, \sigma = 8)$
$\boldsymbol{\beta}$ (covariates coefficients)	$\mathrm{Normal}\ (\mu = 0, \Sigma = 2.5^2 \mathrm{I_{m \times m}})$

Bayesian cumulative proportional odds model

$$logit\left(P(Y_{ki} \geq \mathrm{y})\right) = \alpha + \tau_{yk} + \boldsymbol{\beta x_{ki}} + \delta_{k_c} A_{ki}$$



Skeptical prior

CCP effect: Δ_{co}

Bayesian logistic model

- More easily interpreted by clinicians
- $W = 1$ if the patient needs mechanical ventilation or dead

$$logit\left(P(W_{ki} = 1)\right) = \tau_k + \boldsymbol{\beta x_{ki}} + \delta_{k_c} A_{ki}$$

Simulation (n=900)

CCP treatment

VS

3 control types

Standard of care (SOC)

Non convalescent plasma + SOC

Saline solution + SOC

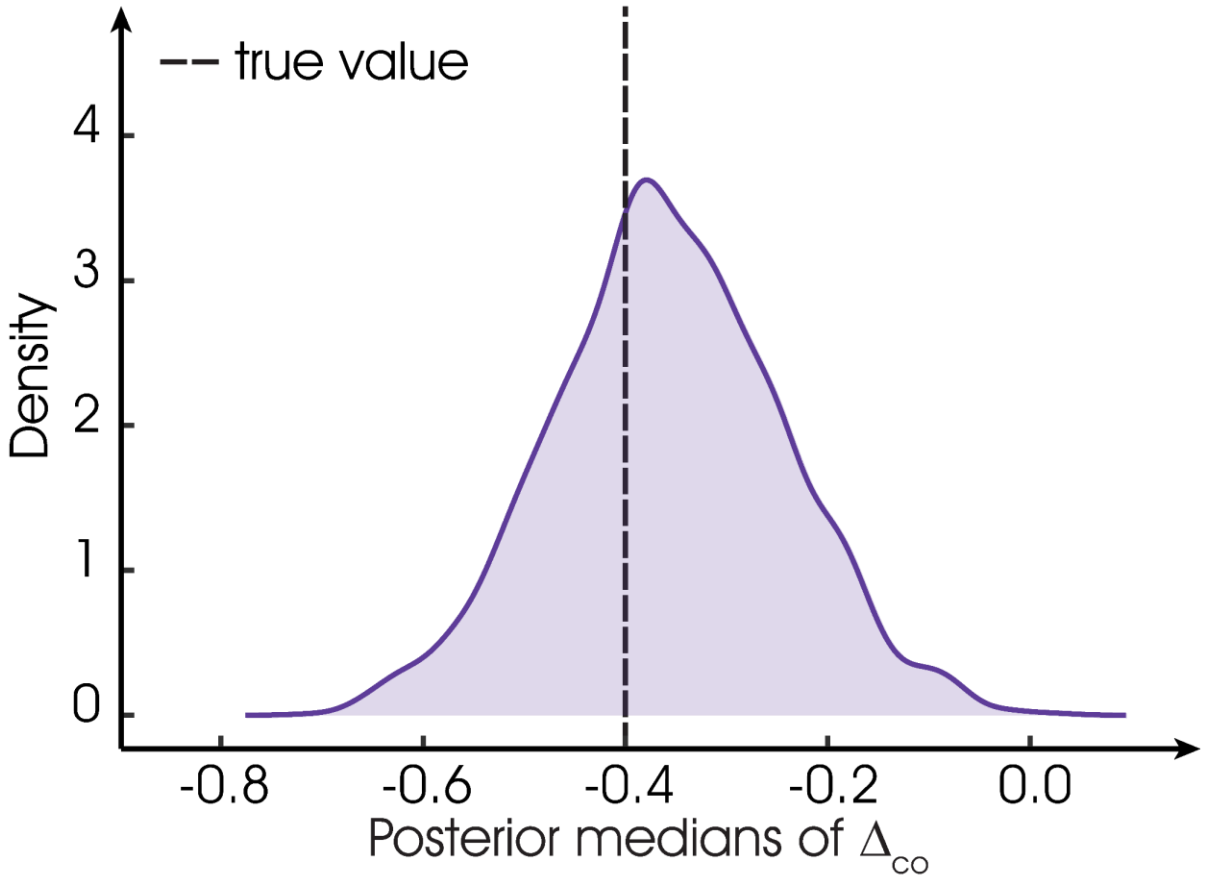
3 RCTs within each control type

3 x

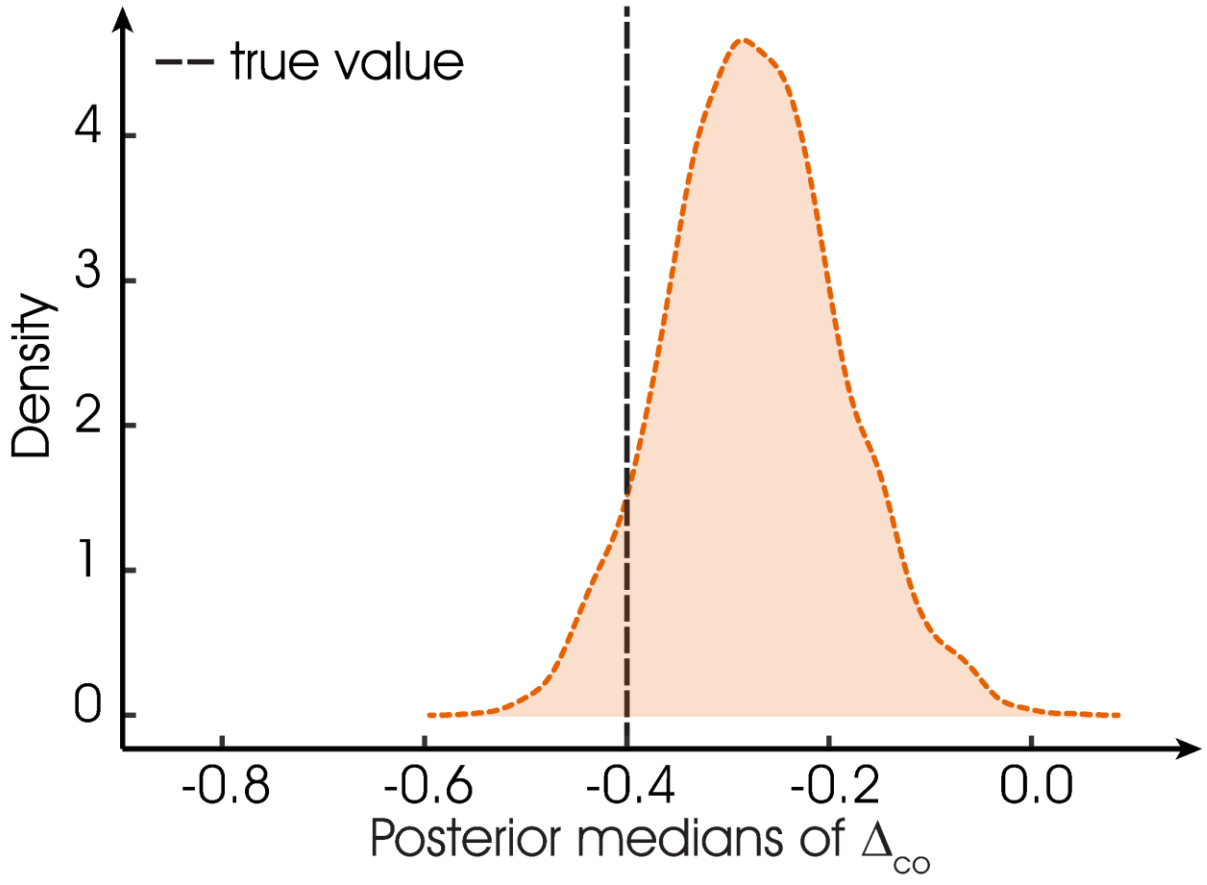
3 x

3 x

Criteria for selecting prior distribution assumptions

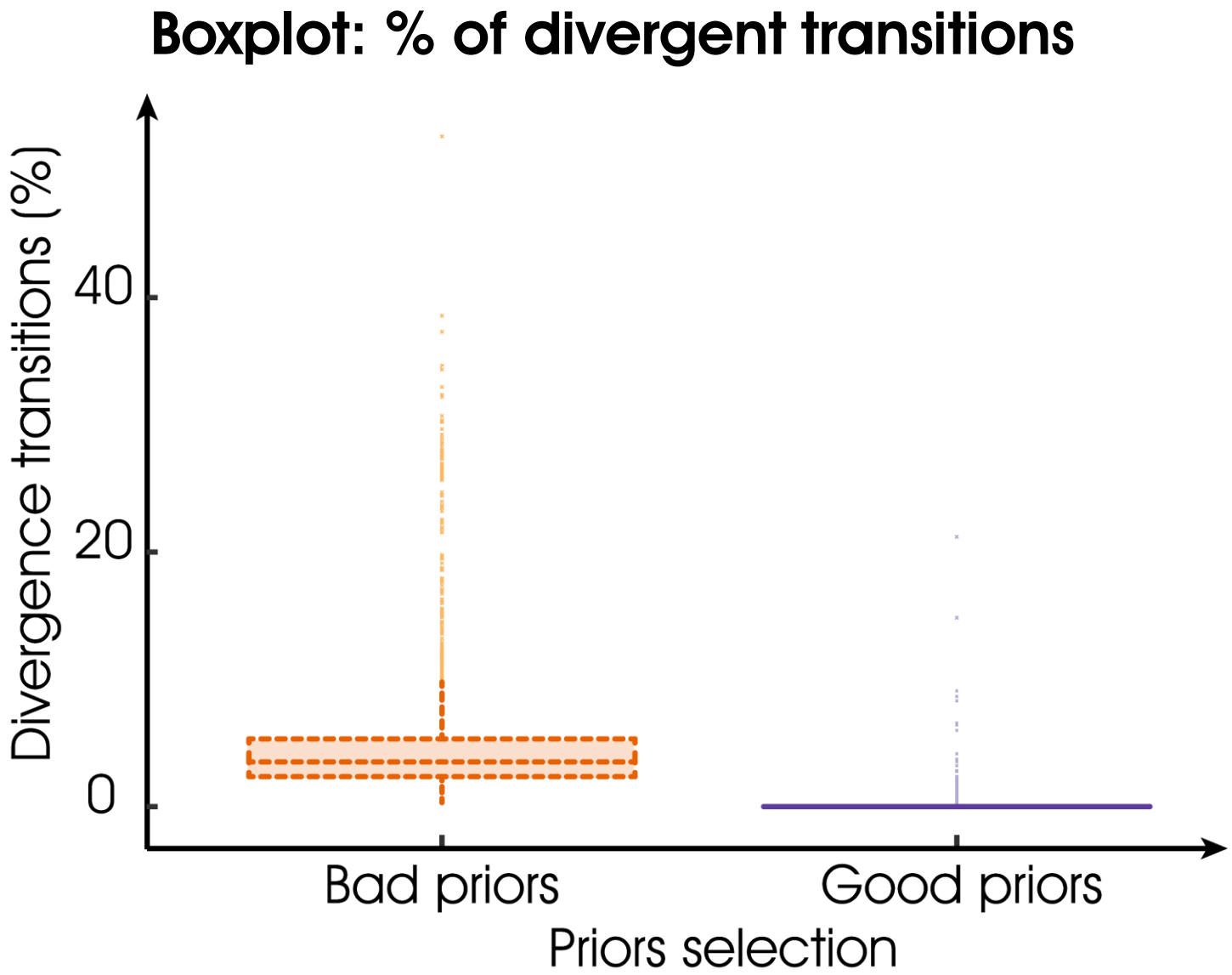


Good priors



Bad priors

Criteria for selecting prior distribution assumptions



Interim monitoring by Bayesian stopping rule

There was no predetermined sample size.

When can we stop the study?

How to monitor the study?

Bayesian stopping rule for efficacy

- Stopping the study for efficacy if the posterior probabilities for OR $(OR_{co} = e^{\Delta_{co}}; OR_l = e^{\Delta_l})$

$$\mathrm{P}(OR_{co} < 1) \geq 0.95 \quad \& \quad \mathrm{P}(OR_{co} < 0.8) \geq 0.5$$

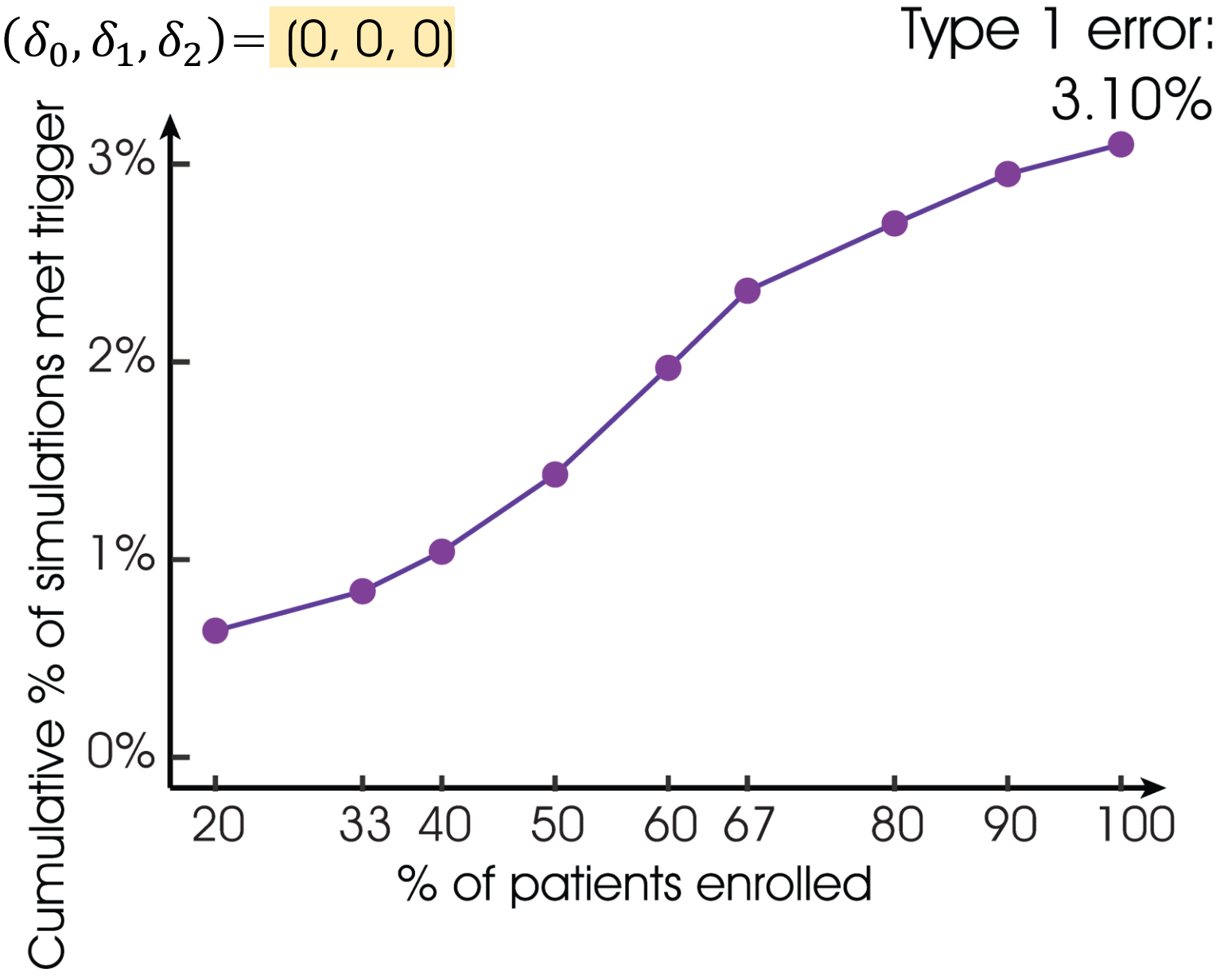
and

$$\mathrm{P}(OR_l < 1) \geq 0.95 \quad \& \quad \mathrm{P}(OR_l < 0.8) \geq 0.5$$

Goldfeld K, Wu D et al. *Statistics in Medicine*, 2021

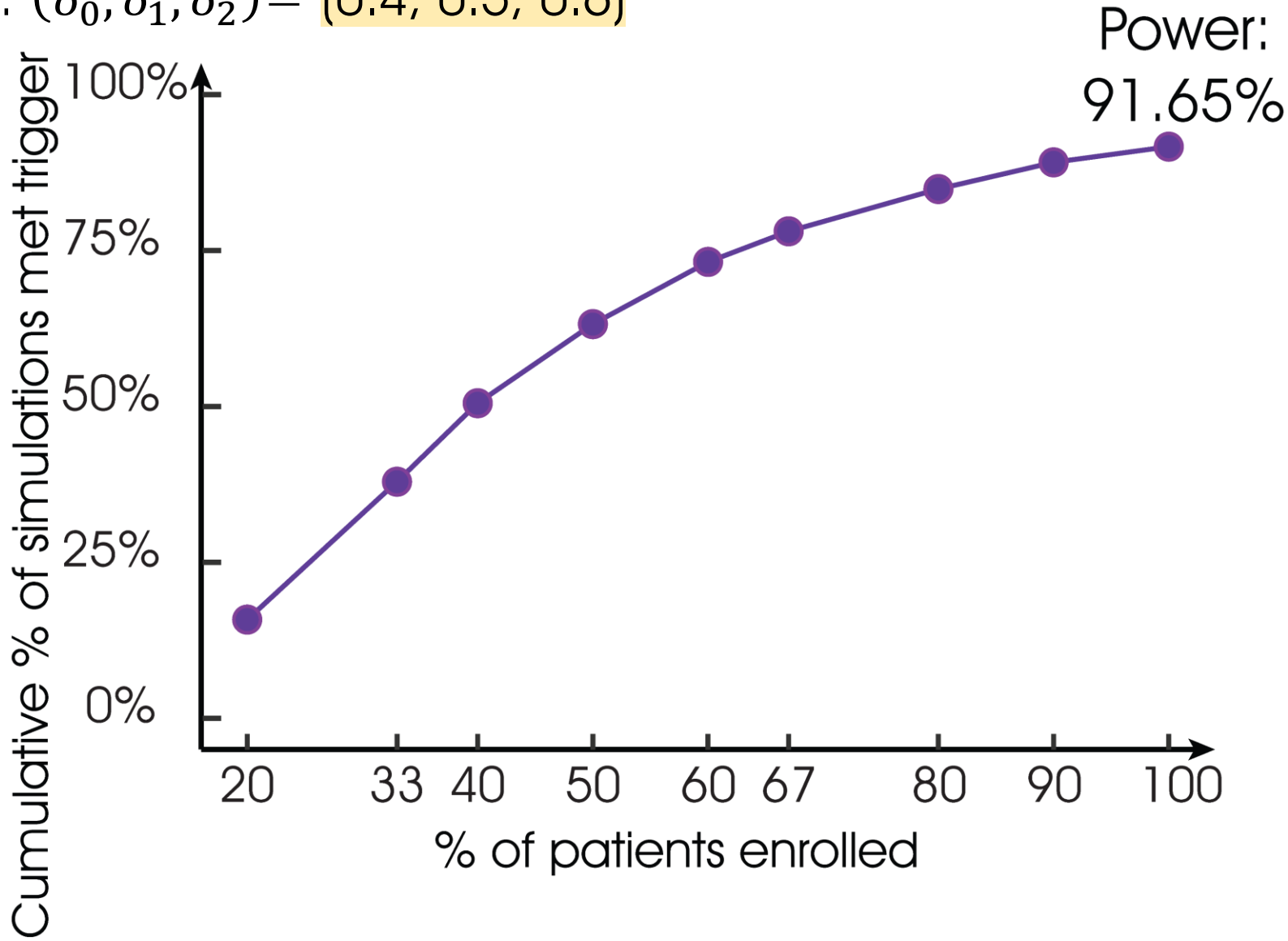
Type 1 error using Bayesian stopping rules

Effect size: $(\delta_0, \delta_1, \delta_2) =$ (0, 0, 0)



Power using Bayesian stopping rules

Effect size: $(\delta_0, \delta_1, \delta_2) =$ (0.4, 0.5, 0.6)



Conclusions

- Prepare a meta-analysis using RCTs at different stages (discontinued or ongoing enrollment)

- This approach would be used in clinical trials where response to treatment for infectious disease can be collected rapidly

- Our method not only can be a valuable tool for assessing new treatment options for COVID-19 but can also be useful for other diseases/treatments

Acknowledgments

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- I convey my sincere gratitude to

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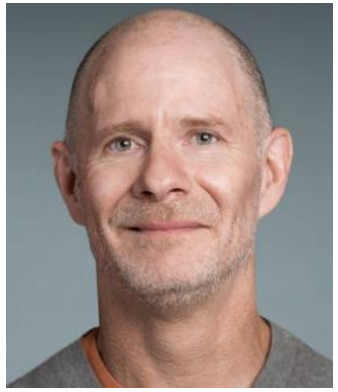

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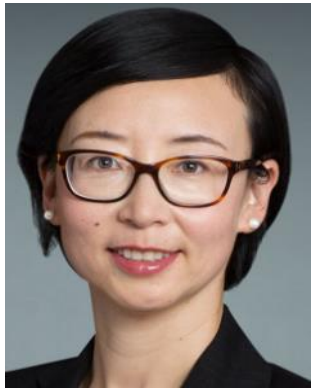

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Thank you!