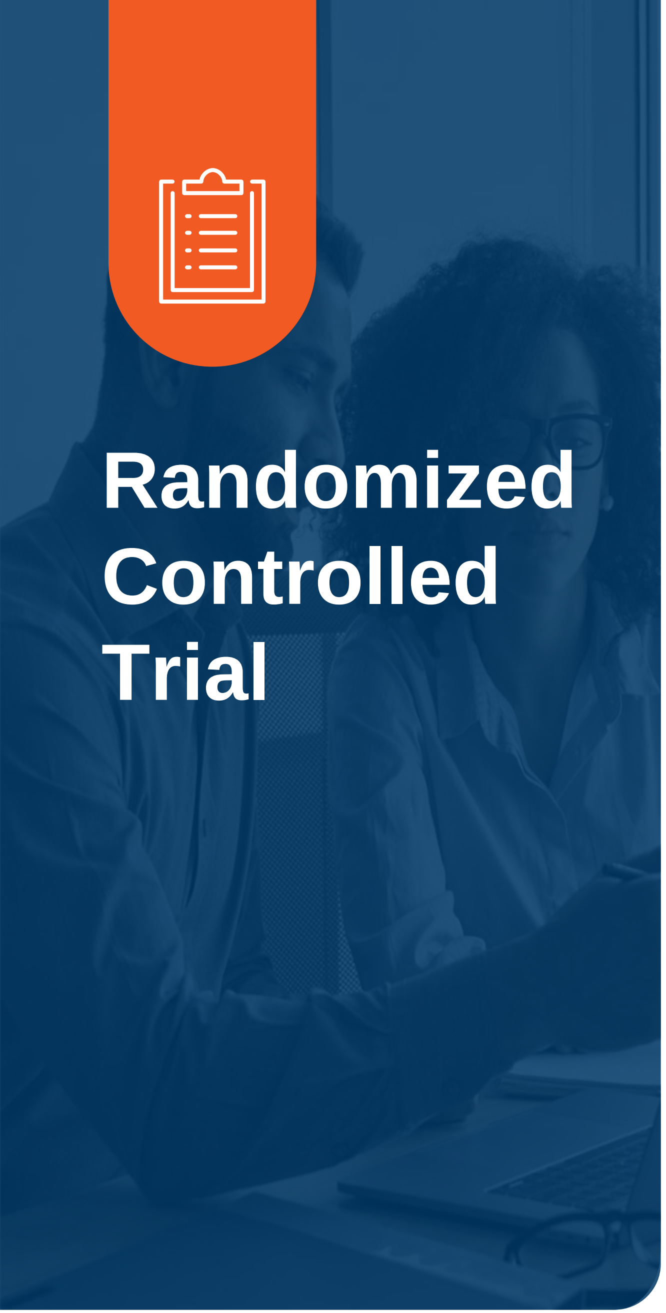
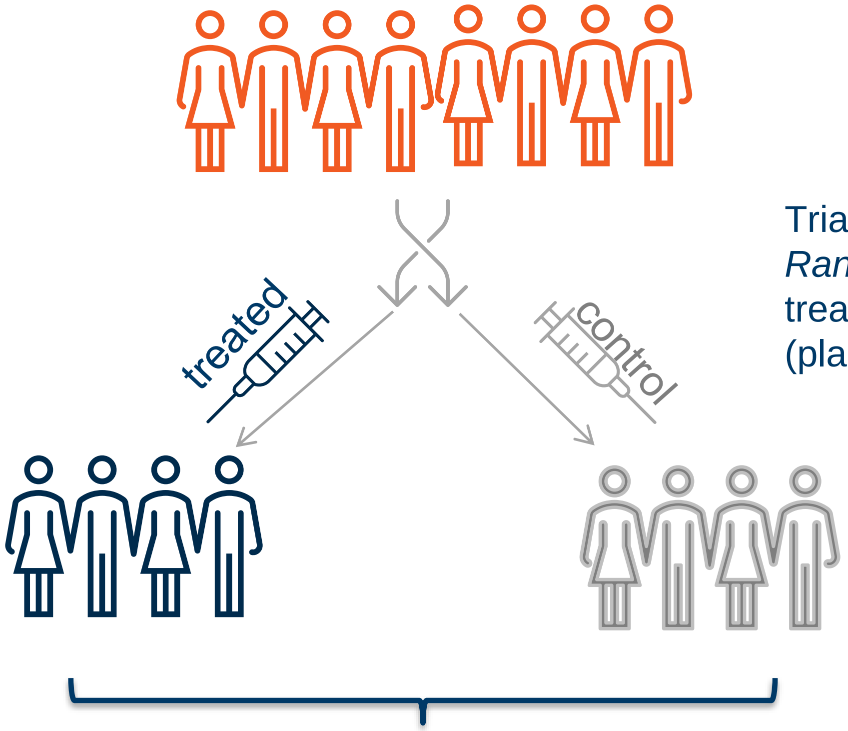
Brief Overview of Methods for Bayesian Power Borrowing



Randomized Controlled Trial

Trial study population



Trial enrollees *Randomized* into treatment or control (placebo) arms

Follow-up: Measurement of outcomes (efficacy, safety)

Treatment effect

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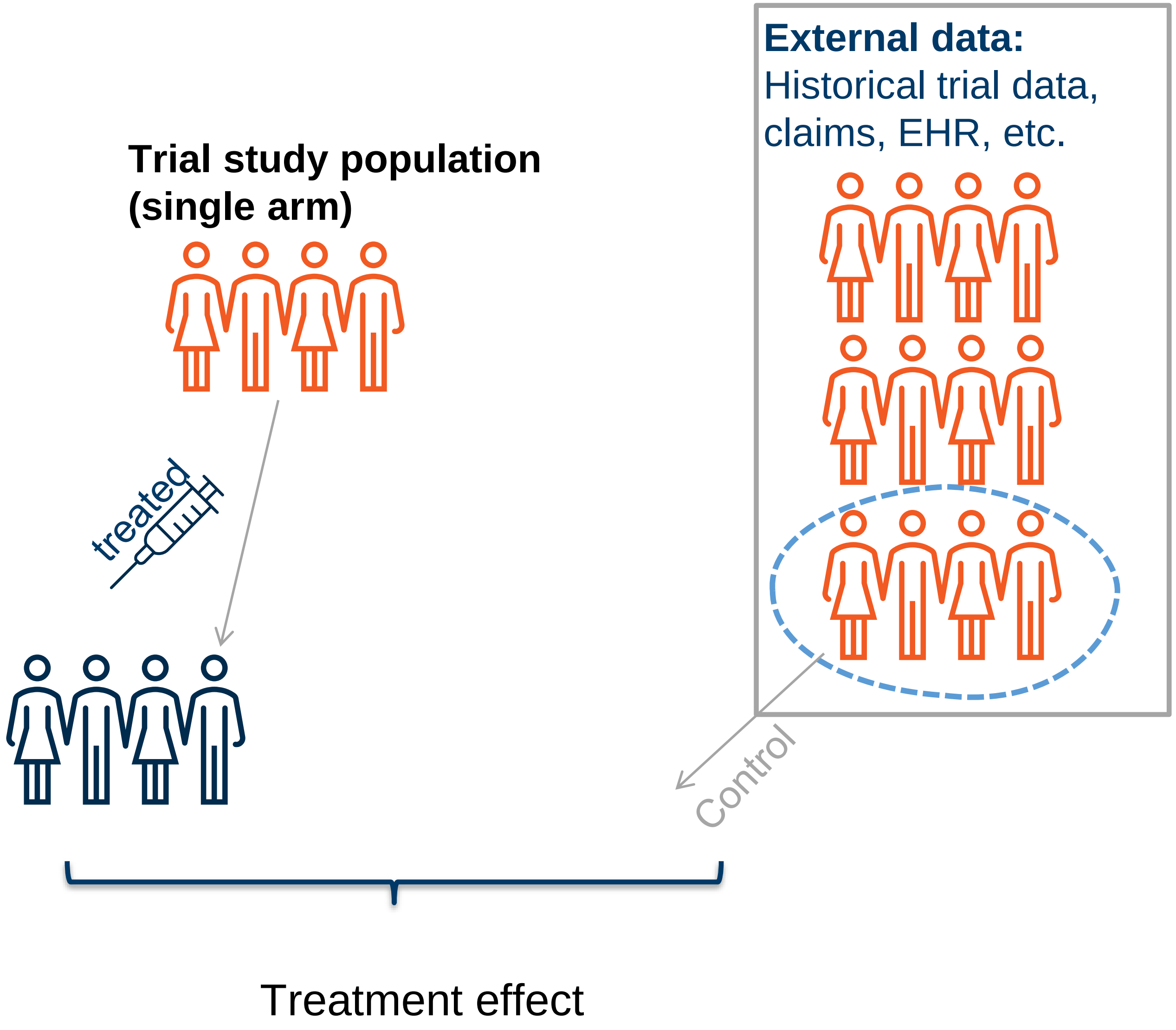
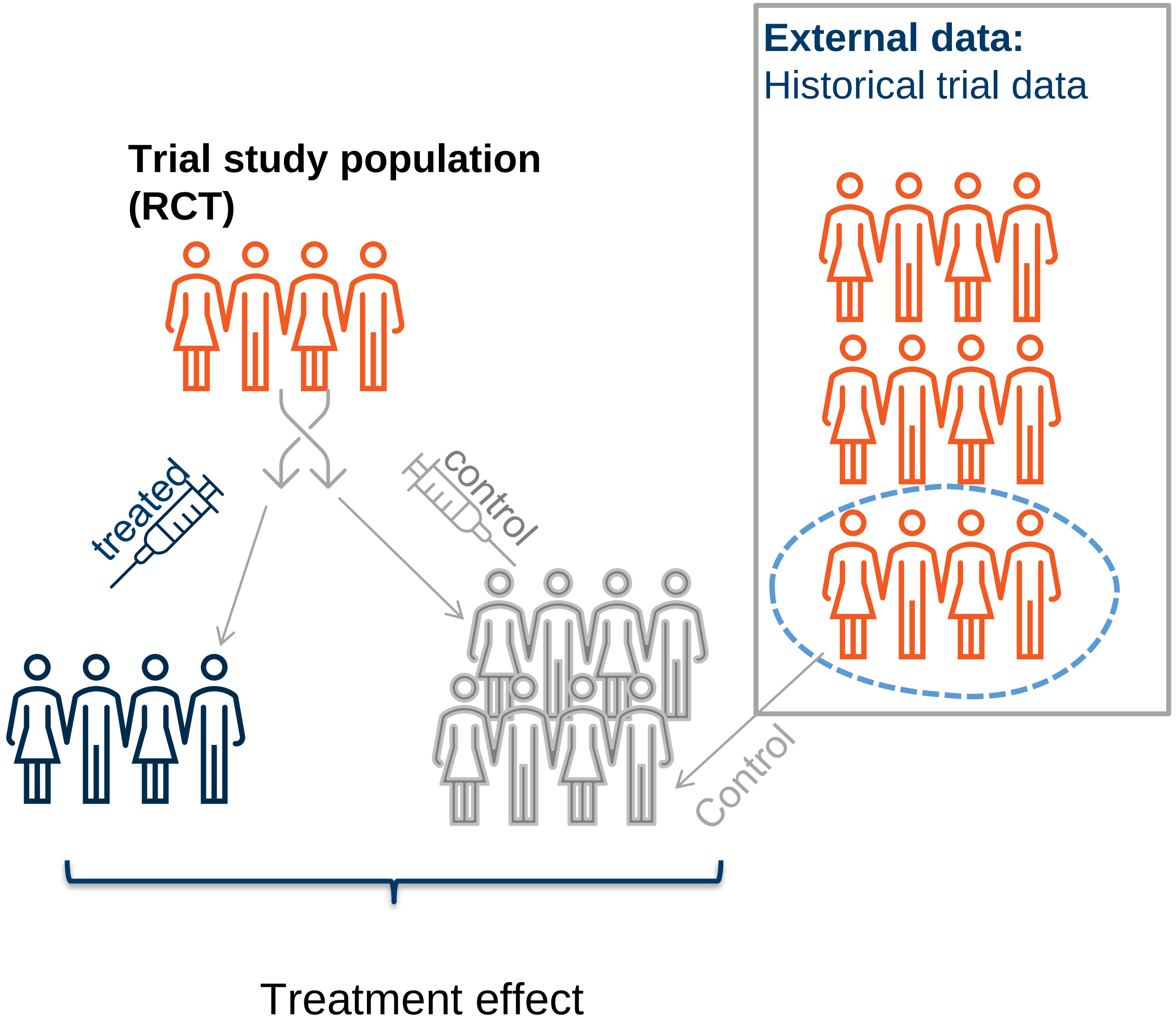
Externally Controlled Trial



Hybrid Trial with Historical Borrowing



Deciding on the Hybrid Approach

Early phase studies

- Increase power for small samples
- Generate hypotheses for later phase studies

Unbalanced randomization

- Higher number of patients randomized to treatment

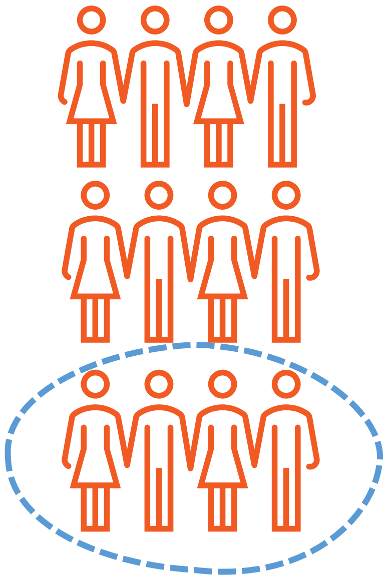
Ethical concerns

Recruitment challenges

- Rare diseases
- Pediatrics

Assessing Suitability of External Data

External data:
Historical trial data



Careful consideration of external data is key

- Are the datasets compatible?
- Are there notable differences?
  - Populations
  - Geographies
  - Temporal
  - Baseline characteristics
  - Same standard of care

Consequences:

- Well-chosen: increased power
- Poorly-chosen: bias, inflated type I error

Statistical methods cannot rescue poorly chosen external data

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What External Data to Consider?

Historical trials are a natural choice

- Placebo group from earlier phase trial
- Placebo group from an earlier trial in the same indication with a different treatment

Can we use real-world data?

- Challenges similar to those found in ECAs
- Weighting difficult; regression adjustment is an option

Approaches

We will discuss the following approaches:

- Power prior
- Hierarchical model / meta-analytic predictive (MAP) approach
- Mixture prior

Bayesian Method #1: Power Prior

How Does the Bayesian Power Prior Work?

Incorporates individual patient data from external data source

Amount of borrowing controlled by a parameter α which downweighs the influence of the external data

- Higher values = more borrowing
- Lower values = less borrowing

Ibrahim, Joseph G., et al. "The power prior: theory and applications." *Statistics in Medicine* 34.28 (2015): 3724-3749.

Analysis without the External Data

$$\underbrace{\pi(\theta \mid D)}_{\text{Posterior distribution for } \theta} \propto \underbrace{L(\theta \mid D)}_{\text{Likelihood (model + data for current trial)}} \underbrace{\pi(\theta)}_{\text{Prior distribution for } \theta}$$

Components of the Bayesian Power Prior

$$\pi(\theta \mid D, H, \alpha) \propto L(\theta \mid D) L(\theta \mid H)^{\alpha} \pi(\theta)$$

Isolating the Effect of the External Data

$$\pi(\theta \mid D, H, \alpha) \propto L(\theta \mid D)\underbrace{L(\theta \mid H)^{\alpha}}_{\text{External data discounted by } \alpha}\pi(\theta)$$

Isolating the Effect of the External Data

$$\pi(\theta \mid D, H, \alpha) \propto L(\theta \mid D) L(\theta \mid H)^{\alpha} \pi(\theta)$$

It must be that $0 \leq \alpha \leq 1$.
If $\alpha = 1$, complete pooling of current and external data
If $\alpha = 0$, external data are ignored

Choosing α

How to choose α

- Set α yourself (fixed power prior)
- Use the data to set a fixed value for α (empirical Bayes power prior)
- Use the data to adaptively choose α (modified power prior)

Note: using a fixed value of α significantly simplifies calculations.

Bayesian Method #2: Hierarchical Model / Meta-Analytic Predictive Approach

Hierarchical Model / MAP approach

Hierarchical models are common in Bayesian methodology

- Allow us to **“borrow”** information from the external data and apply it to our current trial
- The amount of borrowing is controlled by a variance parameter
- Useful when there are several external datasets

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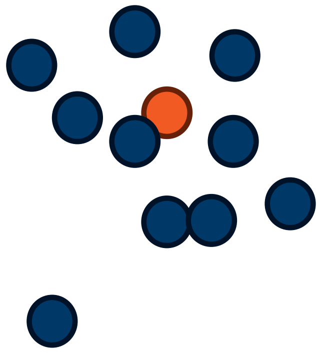
Schmidli, Heinz, et al. "Robust meta-analytic-predictive priors in clinical trials with historical control information." *Biometrics* 70.4 (2014): 1023-1032.

Hierarchical Model / MAP approach

- **Low heterogeneity** between studies (low variance)
- **High** amount of borrowing

Orange dot = Current study
Blue dots = External studies



MAP: Meta-analytic predictive

Hierarchical Model / MAP approach

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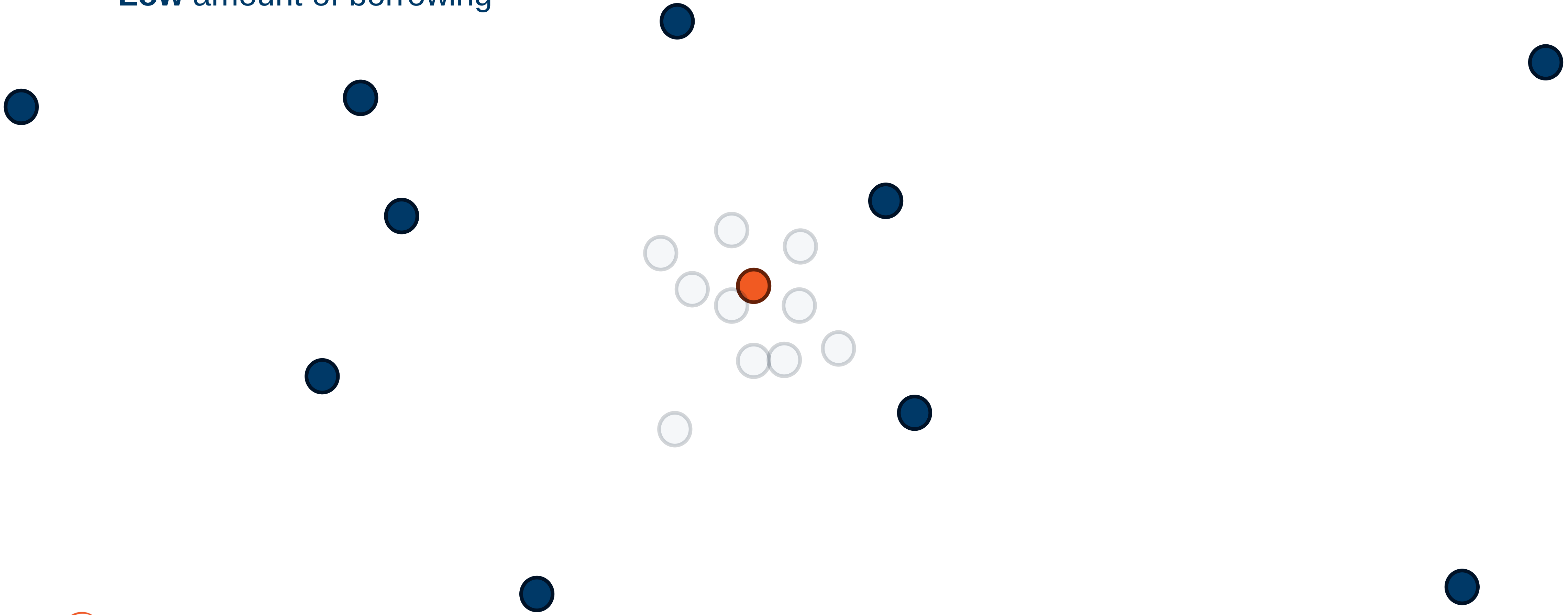

MAP: Meta-analytic predictive

Bayesian Method #3: Mixture Prior

What is a Mixture Prior?

A mixture prior is a prior composed of more than one component.

Component #1: A general, non-informative prior distribution for the current trial

Component #2: An informative prior distribution determined by external data

$$P(\theta) = (1 - a) \cdot P_{current}(\theta) + a \cdot P_{external}(\theta),$$

where $0 \leq a \leq 1$.

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Belimumab for the treatment of systemic lupus erythematosus

CASE STUDY

Disease:

Systemic lupus erythematosus (SLE)

Population: Pediatric (ages 5-17)

Drug:

Benlysta® (belimumab)

Sponsor: Glaxo-Smith-Kline

Endpoint:

Response at week 52

Source: BLA 125370/s-064 and BLA 761043/s-007 Multi-disciplinary Review and Evaluation Benlysta® (belimumab) for Intravenous Infusion in Children 5 to 17 Years of Age with SLE

CASE STUDY

Belimumab for the treatment of systemic lupus erythematosus

Unmet Need in Pediatrics:

“[T]here is a high unmet medical need for efficacious and safe treatments for pediatric patients with SLE.”

“There are currently no treatments specifically approved for this subpopulation.”

Enrollment Difficulties:

“…the Applicant requested to … lower the overall target enrollment from 100 to 70 subjects due to difficulties enrolling pediatric patients between 5 and 17 years of age.”

Source: BLA 125370/s-064 and BLA 761043/s-007 Multi-disciplinary Review and Evaluation Benlysta® (belimumab) for Intravenous Infusion in Children 5 to 17 Years of Age with SLE

Belimumab for the treatment of systemic lupus erythematosus

CASE STUDY

Inadequate Power:

"[The trial] was not adequately powered to make a formal statistical inference on its own due to … enrollment limitations and the rarity of disease in pediatric subjects…."

Similarity with Adults:

"The clinical review team believes that the disease and patient response to treatment are likely to be similar between the adults and pediatric subjects."

Source: BLA 125370/s-064 and BLA 761043/s-007 Multi-disciplinary Review and Evaluation Benlysta® (belimumab) for Intravenous Infusion in Children 5 to 17 Years of Age with SLE

Bayesian Mixture Prior

Idea: Analyze the pediatric study using a mixture prior informed by the adult study

Pediatric study prior:

$$P(\theta) = (1 - a) \cdot P_{peds}(\theta) + a \cdot P_{adult}(\theta)$$

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Bayesian Mixture Prior

Idea: Analyze the pediatric study using a mixture prior informed by the adult study

Pediatric study prior:

$$P(\theta) = (1 - a) \cdot P_{peds}(\theta) + a \cdot P_{adult}(\theta)$$

Non-informative prior

Bayesian Mixture Prior

Idea: Analyze the pediatric study using a mixture prior informed by the adult study

Pediatric study prior:

$$P(\theta) = (1 - a) \cdot P_{peds}(\theta) + a \cdot P_{adult}(\theta)$$

Informative prior
based on adult study

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Bayesian Mixture Prior

$$P(\theta) = (1 - a) \cdot P_{peds}(\theta) + a \cdot P_{adult}(\theta)$$

If a = 0, only noninformative prior is used.

If a = 1, only informative prior based on adult study is used.

Additional steps:

- Vary a between 0 and 1 in steps of 0.05.
- Find the minimum value of a such that credible interval of efficacy parameter does NOT contain 0, i.e., statistical significance.

Bayesian Mixture Prior

Weight (a)	Mean Log Odds	Median Log Odds	*95% Credible Interval*	Posterior Probability of Efficacy
0.00	0.36	0.36	(-0.46, 1.18)	0.81
0.05	0.39	0.42	(-0.41, 1.13)	0.85
0.10	0.41	0.44	(-0.36, 1.08)	0.89
0.15	0.42	0.45	(-0.32, 1.04)	0.91
0.20	0.43	0.46	(-0.27, 1.00)	0.93
0.25	0.44	0.46	(-0.23, 0.95)	0.94
0.30	0.44	0.46	(-0.19, 0.91)	0.95
0.35	0.45	0.46	(-0.15, 0.87)	0.96
0.40	0.45	0.46	(-0.11, 0.84)	0.96
0.45	0.45	0.47	(-0.06, 0.80)	0.97
0.50	0.46	0.47	(-0.01, 0.78)	0.97
0.55	0.46	0.47	(0.04, 0.76)	0.98
0.60	0.46	0.47	(0.09, 0.75)	0.98
0.65	0.46	0.47	(0.14, 0.74)	0.98
0.70	0.46	0.47	(0.17, 0.73)	0.99
0.75	0.47	0.47	(0.19, 0.72)	0.99
0.80	0.47	0.47	(0.21, 0.72)	0.99
0.85	0.47	0.47	(0.22, 0.71)	0.99
0.90	0.47	0.47	(0.23, 0.71)	1.00
0.95	0.47	0.47	(0.24, 0.70)	1.00
1.00	0.47	0.47	(0.24, 0.70)	1.00

Source: [BLA 125370/s-064 and BLA 761043/s-007 Multi-disciplinary Review and Evaluation Benlysta® (belimumab) for Intravenous Infusion in Children 5 to 17 Years of Age with SLE]

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Why choose each method?

Power prior

✓ Most studied
✓ Relatively easy to fit models with fixed weights

Hierarchical/MAP

✓ Convenient when you are incorporating several datasets

Bayesian mixture prior

✓ Has been used in regulatory settings
✓ Don't need IPD

MAP: Meta-analytic predictive; IPD: Individual patient data

Recommendations

Always do a sensitivity analysis

Simulation to determine Type I error and power

- Varying treatment effects
- Varying degrees of heterogeneity
- Varying sample sizes