AstraZeneca

Bayesian *borrowing* using meta-analytic priors

Aaron Springford

May 7, 2024

CoI statement

- I am an employee of AstraZeneca Global (AZ)
- This presentation contains my own personal views and interpretation and should not be taken as advice in a particular context nor an endorsement of any kind
- Any opinions are my own and not those of AZ

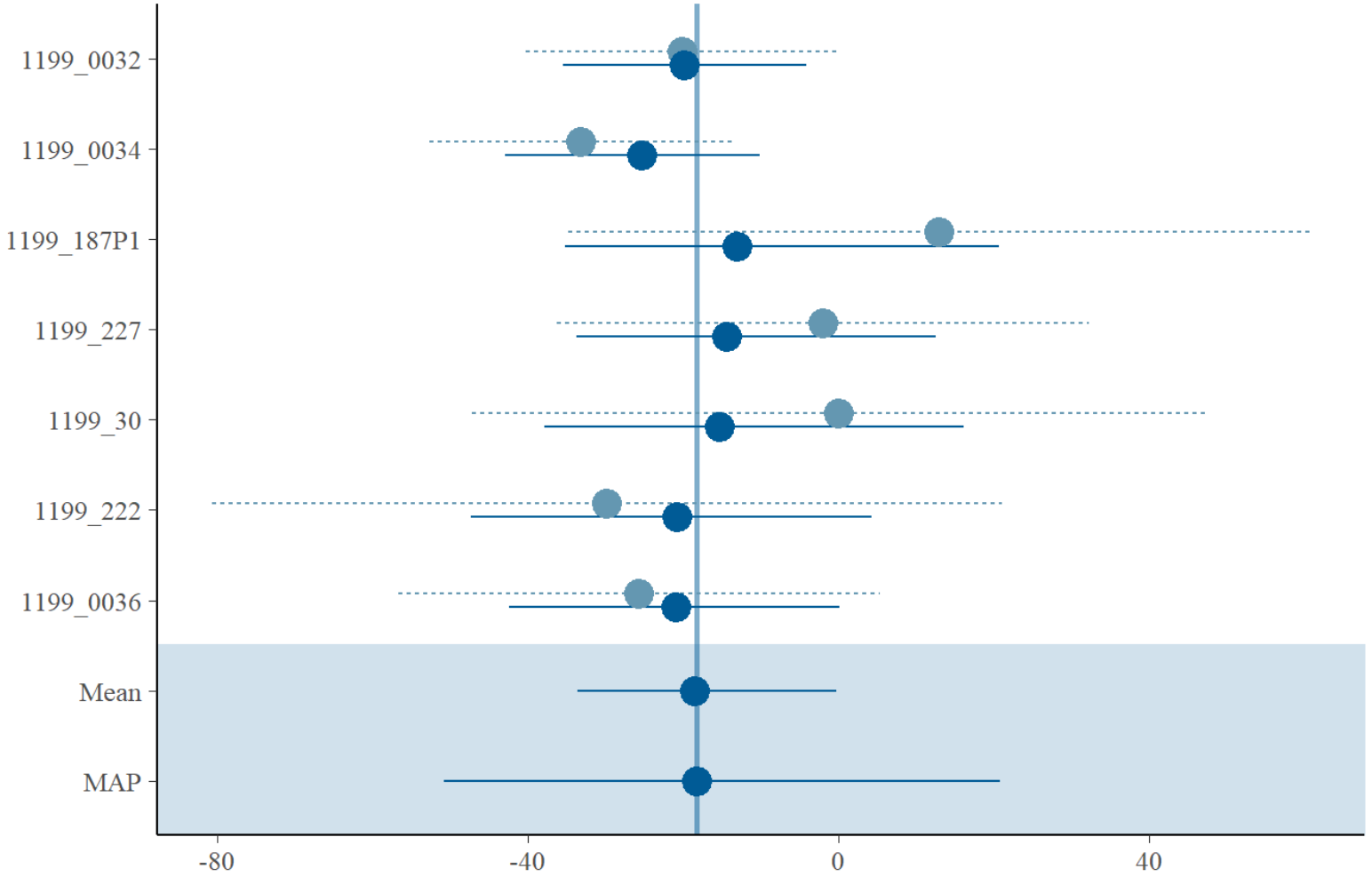
Meta-analytic predictive (MAP) priors

- Two components of the MAP prior to estimate:
  1. Model for historical data given trial-specific parameter $(Y_i|\theta_i)$
  2. Model for the trial-specific parameters across trials $(\theta_1, \ldots, \theta_m, \theta^*|\eta)$
- Using these model components, obtain
  a. Trial-specific parameters $(\theta_i|Y_1, \ldots, Y_m)$
  b. Prediction of the parameter for a new trial $(\theta^*|Y_1, \ldots, Y_m)$
- The prediction of the parameter for a new trial depends on both 1. and 2. That is, there is uncertainty due to within-trial and between-trial variation.
- The MAP prior is sometimes *mixed* with a diffuse prior in case there are substantive differences between the historical and current outcomes

Neuenschwander B, Capkun-Niggli G, Branson M, Spiegelhalter DJ. Summarizing historical information on controls in clinical trials. Clinical Trials. 2010 Feb;7(1):5-18.

Schmidli H, Gsteiger S, Roychoudhury S, O'Hagan A, Spiegelhalter D, Neuenschwander B. Robust meta-analytic-predictive priors in clinical trials with historical control information. Biometrics. 2014 Dec;70(4):1023-32.

Meta-analytic predictive (MAP) priors



1

Borrowing from results of adult trials in pediatrics

Assessment of a monoclonal antibody in children with Systemic Lupus Erythematosus (SLE)

Borrowing from results of adult trials to augment pediatric trials

- Example: Post-marketing trial of a monoclonal antibody which modulates B-cell growth and survival in patients with active systemic lupus erythematosus (SLE)
  - FDA requirement to conduct pediatric study
  - Rare indication in children
  - Two previous studies in adults
  - Identical primary endpoint in three trials
  - Conclusion: Risk/benefit assessment in favour

US Food and Drug Administration. BLA 125370/s-064 and BLA 761043/s-007 Multi-disciplinary Review and Evalaution Benlysta® (belimumab) for Intravenous Infusion in Children 5 to 17 Years of Age with SLE. 2018 Oct.

Study C1109

- Pediatric study in SLE population
- Primary efficacy endpoint:
  - SLE Responder Index (SRI) response rate at week 52.
- Three cohorts (sequential enrolment):
  - 12 patients aged 12-17 years 5:1 ratio
  - 12 patients aged 5-11 years 5:1 ratio
  - 48 patients aged 5-17 years 1:1 ratio (stratified by age group 5-11, 12-17 years)

US Food and Drug Administration. BLA 125370/s-064 and BLA 761043/s-007 Multi-disciplinary Review and Evalaution Benlysta® (belimumab) for Intravenous Infusion in Children 5 to 17 Years of Age with SLE. 2018 Oct.

Studies C1056 and C1057

- Adult studies
- Primary efficacy endpoint:
  - SLE Responder Index (SRI) response rate at week 52 (matches C1109)
- Three arms 1:1:1
  - Placebo
  - Low dose
  - High dose (matches active arm of C1109)

US Food and Drug Administration. BLA 125370/s-064 and BLA 761043/s-007 Multi-disciplinary Review and Evalaution Benlysta® (belimumab) for Intravenous Infusion in Children 5 to 17 Years of Age with SLE. 2018 Oct.

SRI Response Rates

Study	Arm	Response, n(%)	Difference	Odds ratio (95% CI)
C1109 (Pediatric)	Placebo (n=40)	17 (44%)		
	High dose (n=53)	28 (53%)	9%	1.5 (0.6, 3.5)
C1056 (Adult)	Placebo (n=275)	93 (34%)		
	High dose (n=273)	118 (43%)	9%	1.5 (1.1, 2.1)
C1057 (Adult)	Placebo (n=287)	125 (44%)		
	High dose (n=290)	167 (58%)	14%	1.8 (1.3, 2.6)

US Food and Drug Administration. BLA 125370/s-064 and BLA 761043/s-007 Multi-disciplinary Review and Evalaution Benlysta® (belimumab) for Intravenous Infusion in Children 5 to 17 Years of Age with SLE. 2018 Oct.

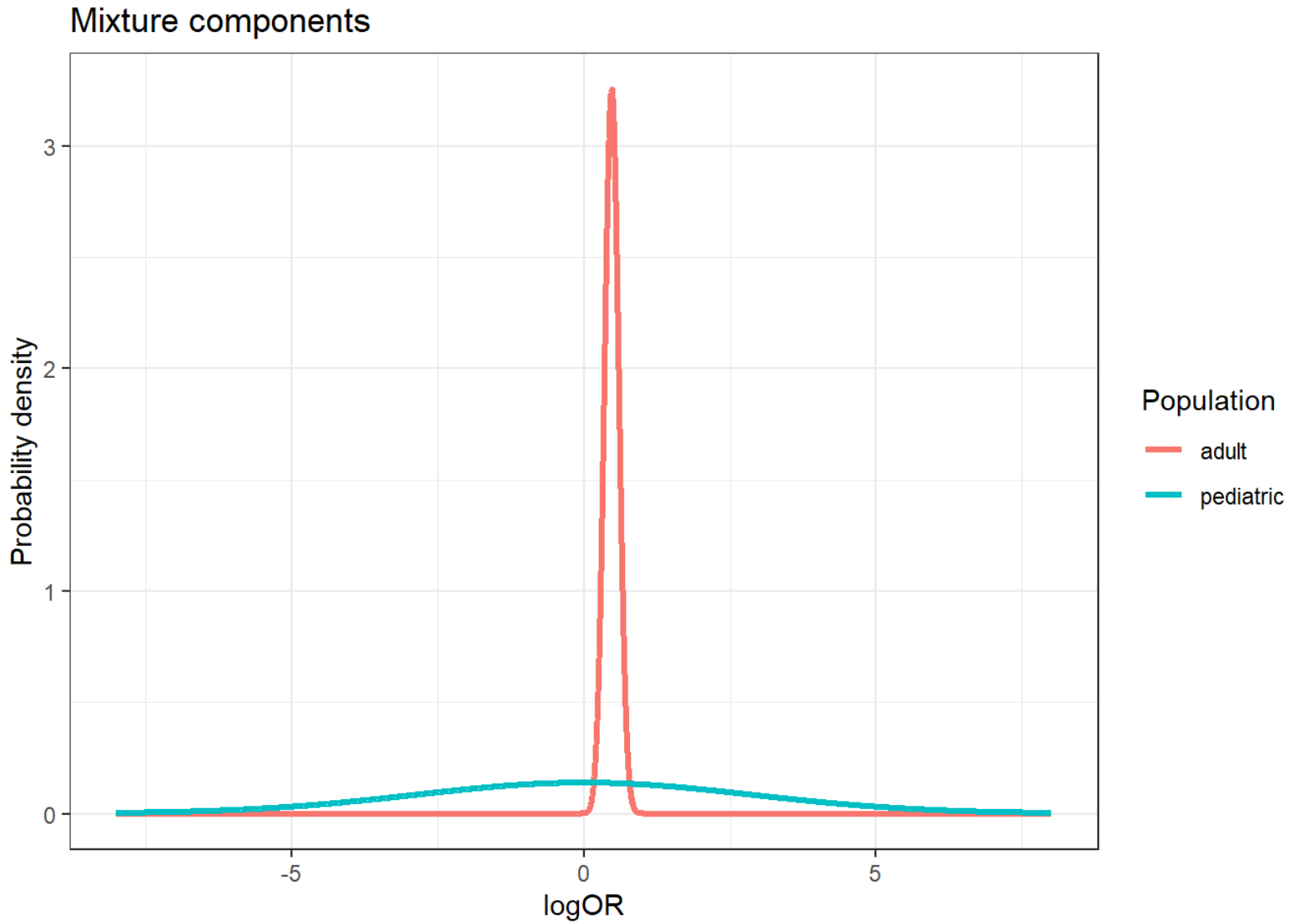
Bayesian meta-analytic mixture prior

… "the clinical division believes that the treatment responses are expected to be similar between the adult and pediatric subjects, therefore, the information from the previous adult studies (C1056 and C1057) could be valuable and relevant to the pediatric population."

- Recommendation: Bayesian mixture prior approach
  1. Meta-analysis of adult studies to obtain single distribution of treatment effect
  2. Skeptical prior for *a priori* distribution of treatment effect in pediatric population
  3. Mixture prior: $p(\theta) = (1 - a) \times f_{\text{pediatric}}(\theta) + a \times f_{\text{adult}}(\theta)$
  4. Explore different values of a, the weight to apply to adult data

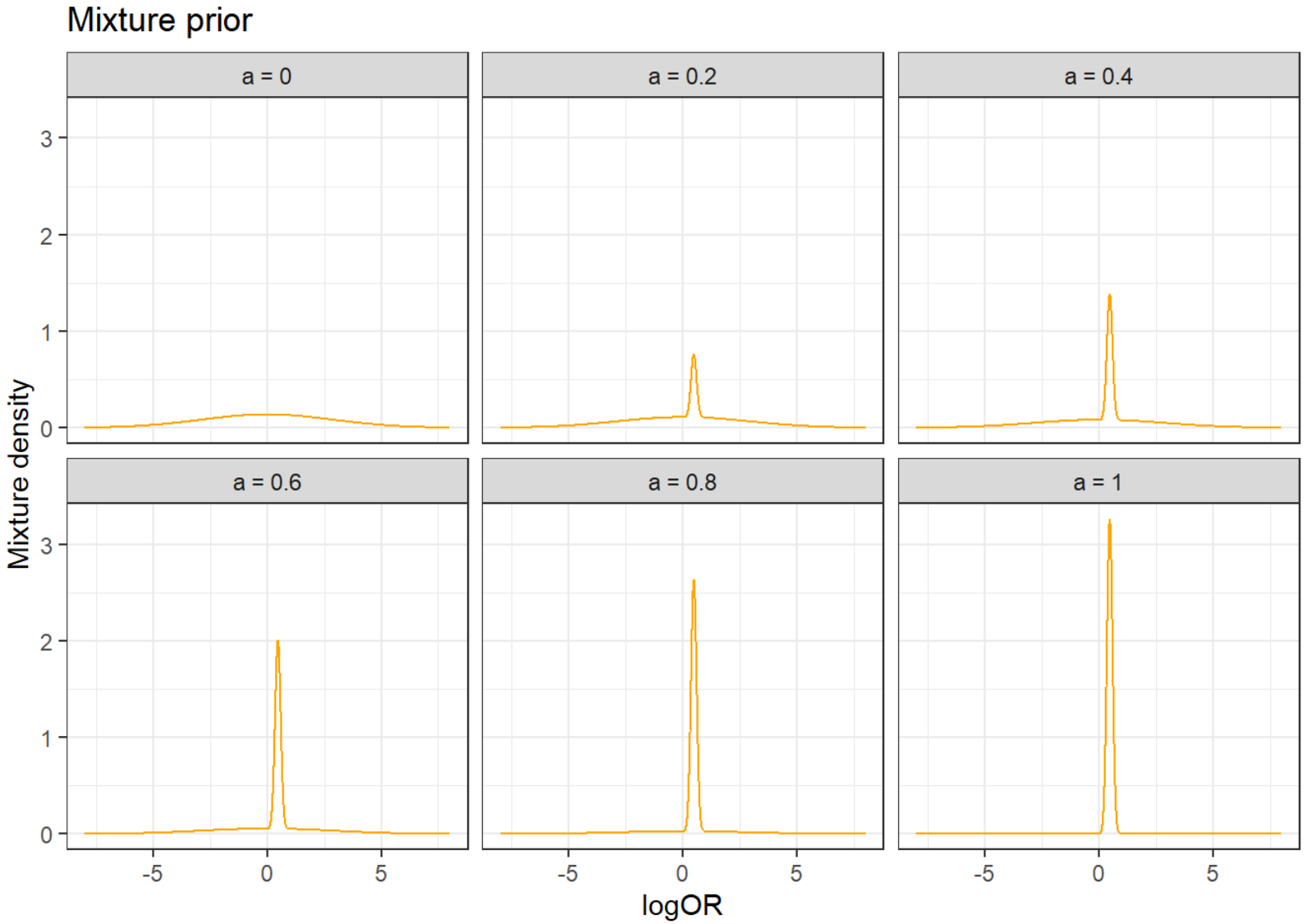
US Food and Drug Administration. BLA 125370/s-064 and BLA 761043/s-007 Multi-disciplinary Review and Evalaution Benlysta® (belimumab) for Intravenous Infusion in Children 5 to 17 Years of Age with SLE. 2018 Oct.

Bayesian meta-analytic mixture prior



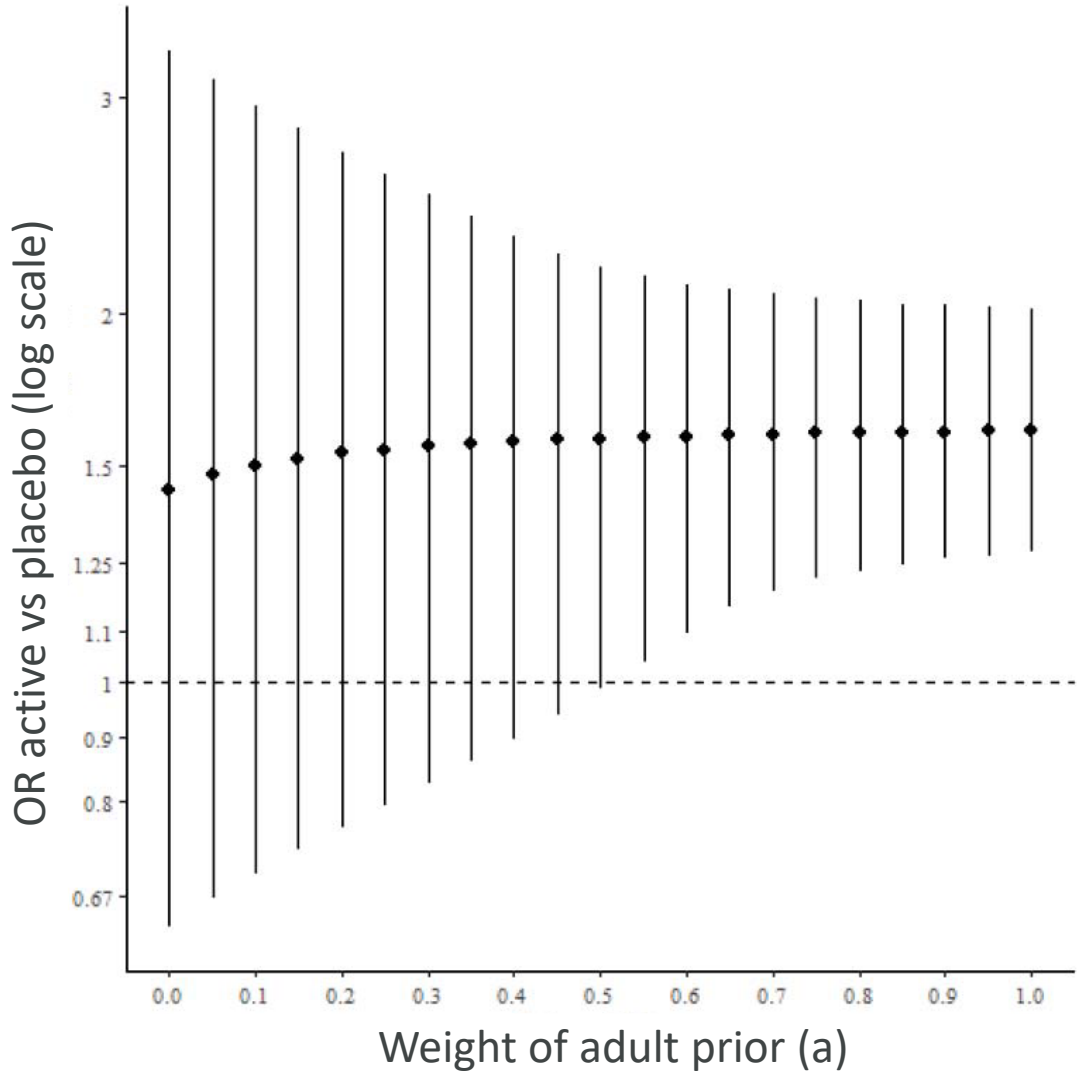
US Food and Drug Administration. BLA 125370/s-064 and BLA 761043/s-007 Multi-disciplinary Review and Evalaution Benlysta® (belimumab) for Intravenous Infusion in Children 5 to 17 Years of Age with SLE. 2018 Oct.

Bayesian meta-analytic mixture prior



US Food and Drug Administration. BLA 125370/s-064 and BLA 761043/s-007 Multi-disciplinary Review and Evalaution Benlysta® (belimumab) for Intravenous Infusion in Children 5 to 17 Years of Age with SLE. 2018 Oct.

Use of adult information improves precision of pediatric estimate



- Posterior means and 95% credibility intervals
- Weight parameter > 0.5 is required to exclude OR = 1

Figure 21 from: US Food and Drug Administration. BLA 125370/s-064 and BLA 761043/s-007 Multi-disciplinary Review and Evalaution Benlysta® (belimumab) for Intravenous Infusion in Children 5 to 17 Years of Age with SLE. 2018 Oct.

2

Borrowing from previous studies in rare disease

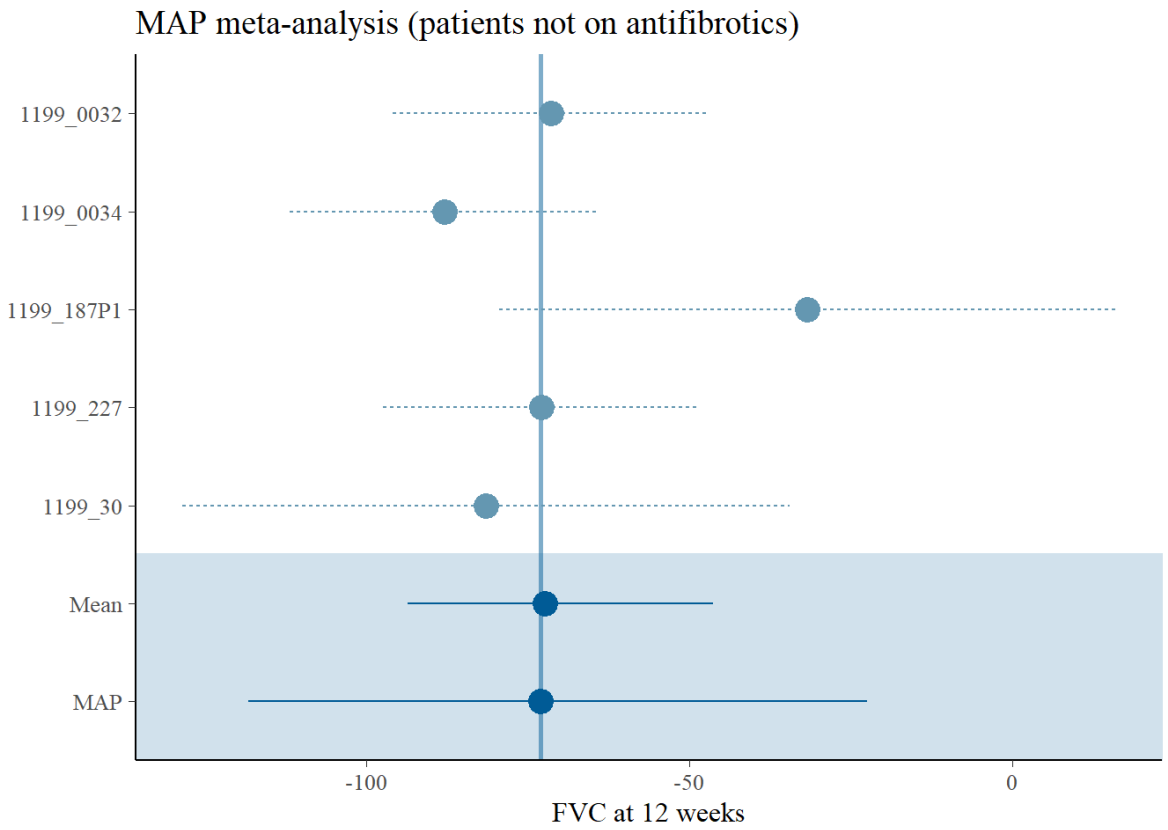
Preferential phosphodiesterase 4B inhibitor for Idiopathic Pulmonary Fibrosis (IPF)

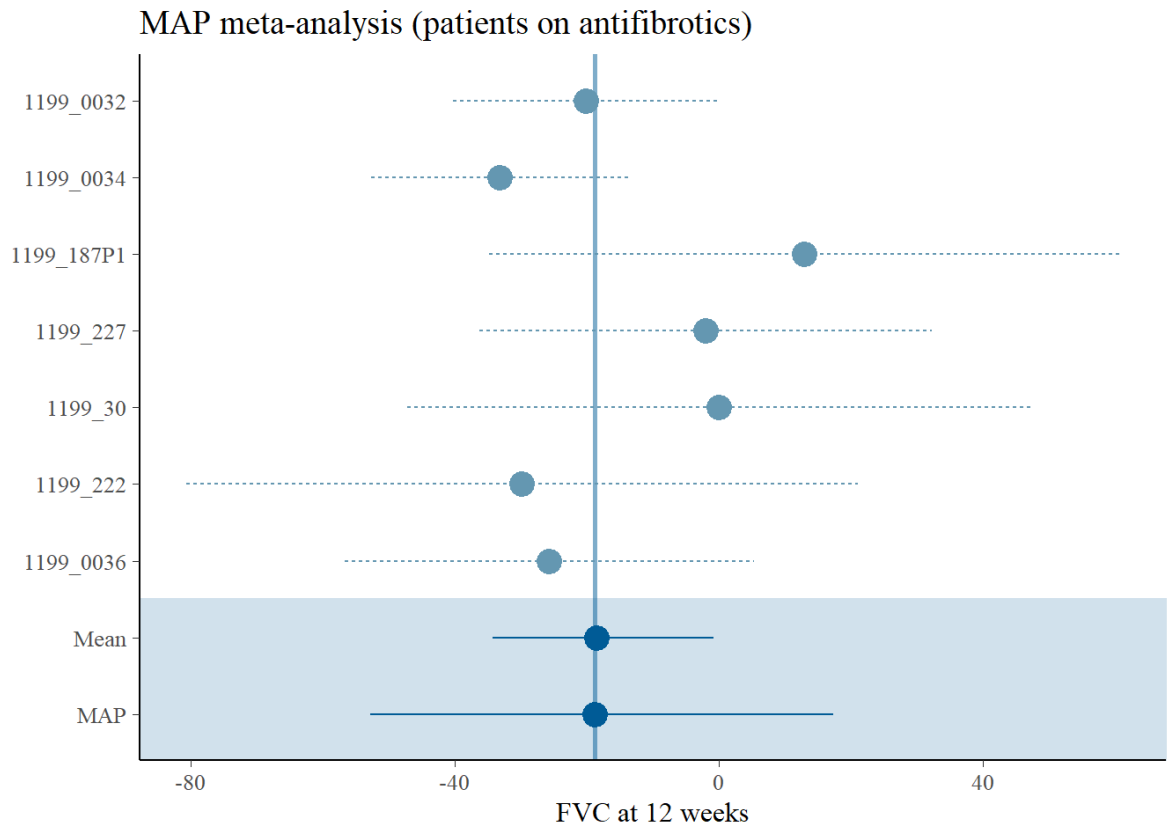
Borrowing control-arm patient information can reduce requirements when designing trials in rare disease

- Recruiting patients to trials in the rare disease setting is difficult
  - Longer trials
  - Promising treatment options are delayed
- Idiopathic pulmonary fibrosis is a rare condition
  - Phosphodiesterase 4 (PDE4) inhibition: antiinflammatory and antifibrotic properties
- Trial of BI 1015550 versus placebo 2:1
  - Goal of 150 patients (actual: 147)
  - Primary endpoint: change from baseline in forced vital capacity (FVC) at 12 weeks

Richeldi L, Azuma A, Cottin V, Hesslinger C, Stowasser S, Valenzuela C, Wijsenbeek MS, Zoz DF, Voss F, Maher TM. Trial of a preferential phosphodiesterase 4B inhibitor for idiopathic pulmonary fibrosis. New England Journal of Medicine. 2022 Jun 9;386(23):2178-87.

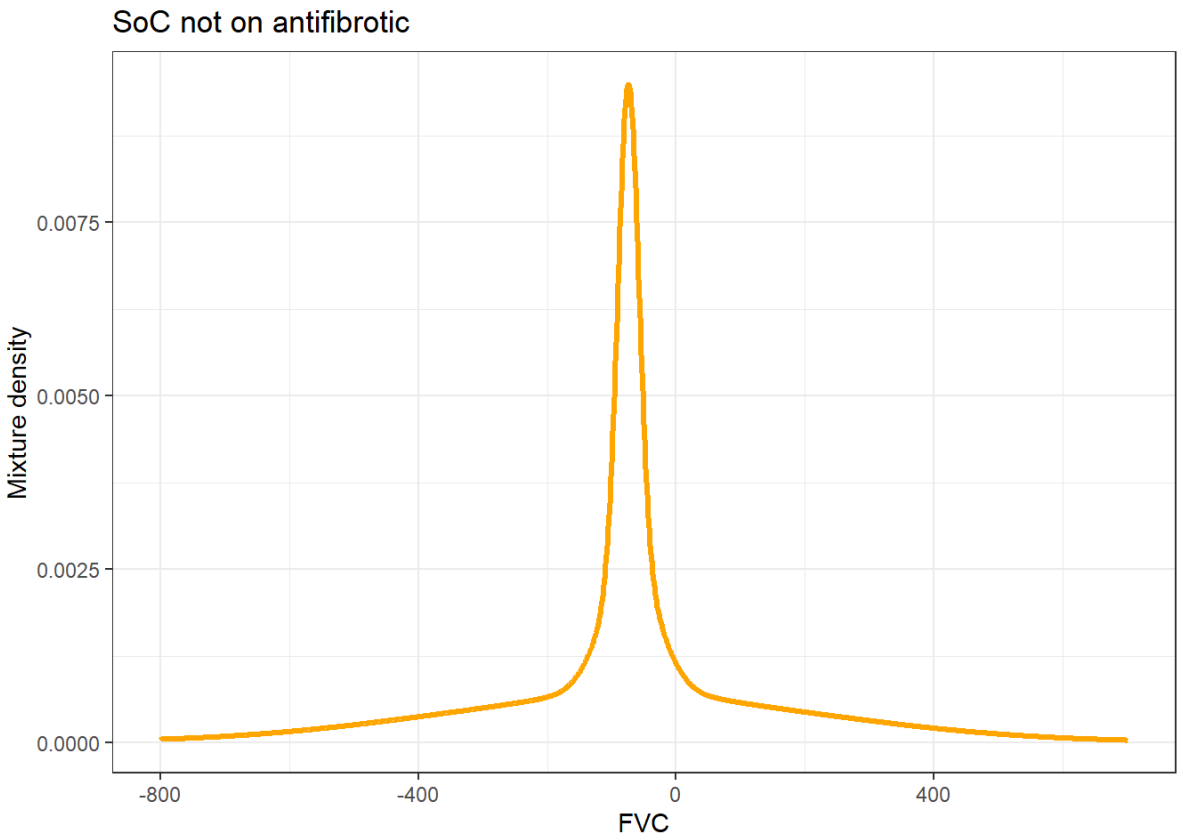
Use control arm outcomes from previous studies to get informative prior when conducting current study

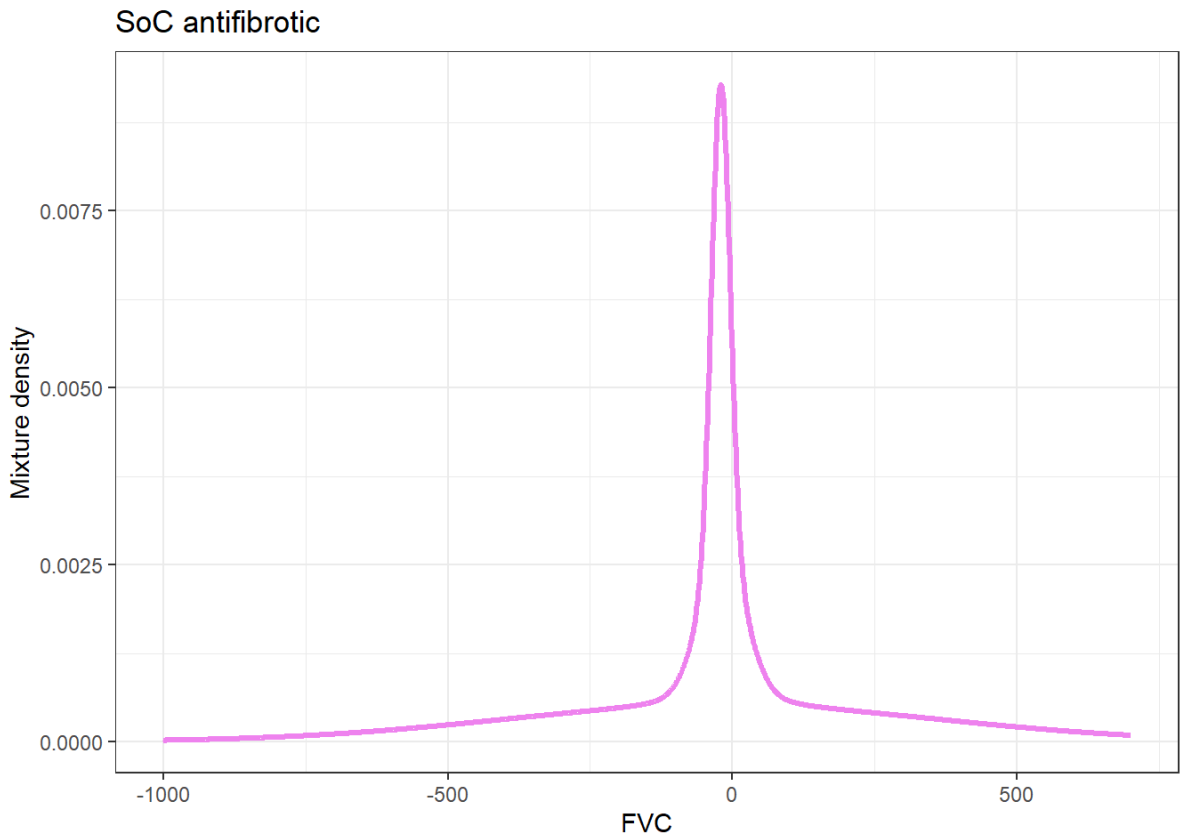




Richeldi L, Azuma A, Cottin V, Hesslinger C, Stowasser S, Valenzuela C, Wijsenbeek MS, Zoz DF, Voss F, Maher TM. Trial of a preferential phosphodiesterase 4B inhibitor for idiopathic pulmonary fibrosis. New England Journal of Medicine. 2022 Jun 9;386(23):2178-87.

Mixture priors for placebo-arm

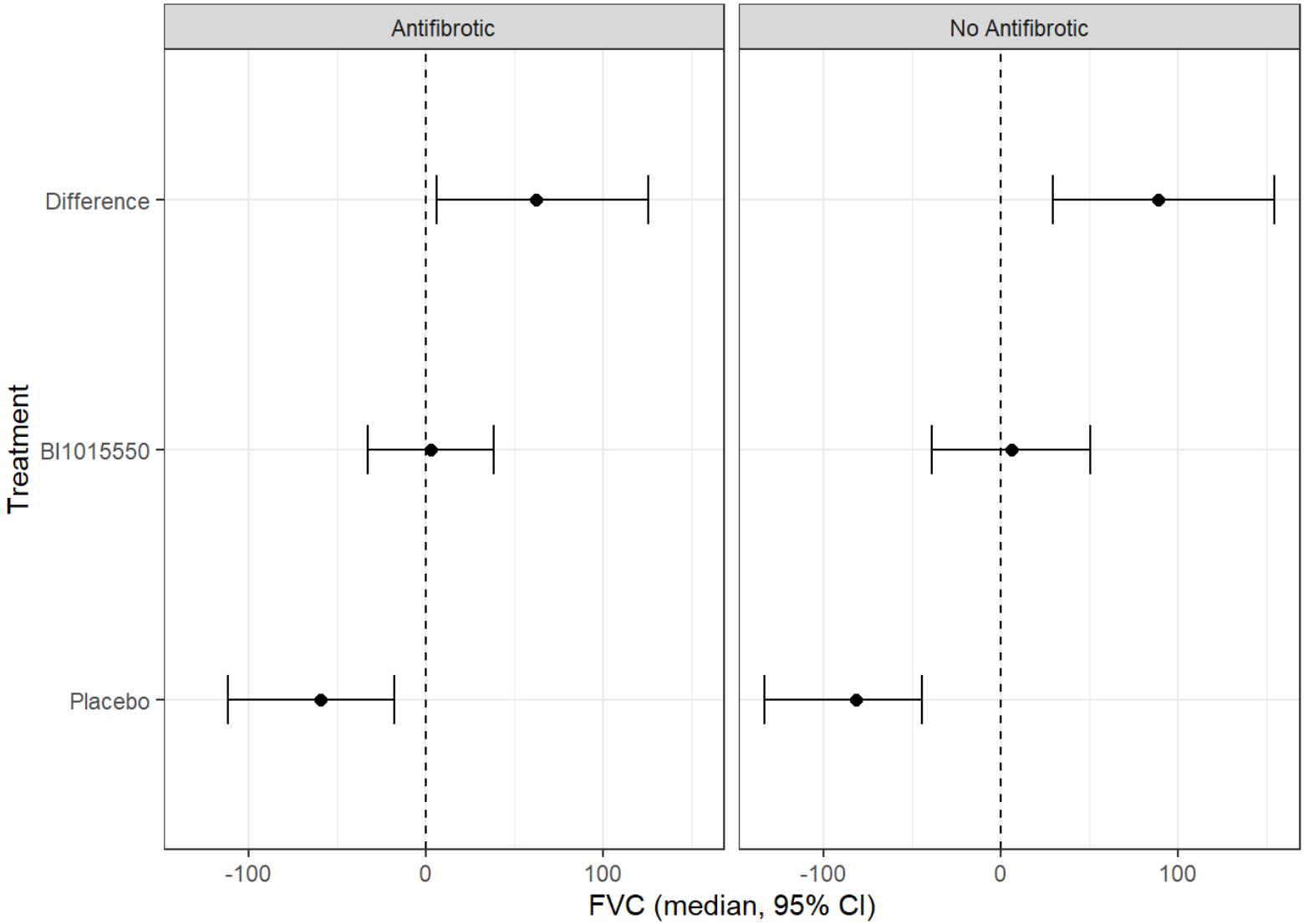




MAP distributions were mixed 50:50 with vague priors, and then further calibrated to represent an approximate effective sample size of 20 patients

Richeldi L, Azuma A, Cottin V, Hesslinger C, Stowasser S, Valenzuela C, Wijsenbeek MS, Zoz DF, Voss F, Maher TM. Trial of a preferential phosphodiesterase 4B inhibitor for idiopathic pulmonary fibrosis. New England Journal of Medicine. 2022 Jun 9;386(23):2178-87.

Results enabled by borrowing approach



- Difference in FVC between treatment arms is demonstrated for both strata
- Variation in Placebo FVC is similar to active treatment despite half the sample size in the Placebo group due to prior information

Richeldi L, Azuma A, Cottin V, Hesslinger C, Stowasser S, Valenzuela C, Wijsenbeek MS, Zoz DF, Voss F, Maher TM. Trial of a preferential phosphodiesterase 4B inhibitor for idiopathic pulmonary fibrosis. New England Journal of Medicine. 2022 Jun 9;386(23):2178-87.

3

MAP prior with covariate adjustment

MAP prior applied to vaccine efficacy, adjusting for differences in patient characteristics

Improving upon the comparability of historical and current control-arm outcomes

- MAP priors are intended to predict the average outcome in a new trial
- Not all trials are conducted in the same population
  - Leads to additional variation in outcomes
- Acknowledgement of this variation leads to the *robust* approaches we have seen
  - Mixture priors which include a vague/diffuse component
  - Adjustment of the prior to target an effective sample size
- Available covariate information could be used to adjust the prior to make it more comparable to the current trial population

Callegaro A, Luo Y, Karkada N, Zahaf T. Dynamic borrowing of historical controls adjusting for covariates in vaccine efficacy clinical trials. Pharmaceutical Statistics. 2024 Apr 9.

Demonstration of covariate adjustment to MAP prior in HPV vaccination study

TABLE 2 HPV case study. ATP cohort sample size (N), number of 1-year persistence with HPV-16 (n) and proportion of events ($\widehat{\theta} \cdot 100$) with 95% confidence interval.

Trial	Group	N	n	$\widehat{\theta} \cdot 100$	LL%	UL%
Historical	CH	7639	405	5.30	4.81	5.83%
Current	CD	1218	41	3.37	2.43	4.54%
Current	V	2464	10	0.41	0.19	0.75%

- Robust mixture prior (RMP) derived from historical control group (CH)
- Three different approaches to adjust for differences in patient characteristics between historical and current:
  1. Inverse probability of treatment weighting (IPTW)
  2. G-computation (G), a form of regression adjustment
  3. Doubly-robust (DR) estimator

Callegaro A, Luo Y, Karkada N, Zahaf T. Dynamic borrowing of historical controls adjusting for covariates in vaccine efficacy clinical trials. Pharmaceutical Statistics. 2024 Apr 9.

Demonstration of covariate adjustment to MAP prior in HPV vaccination study

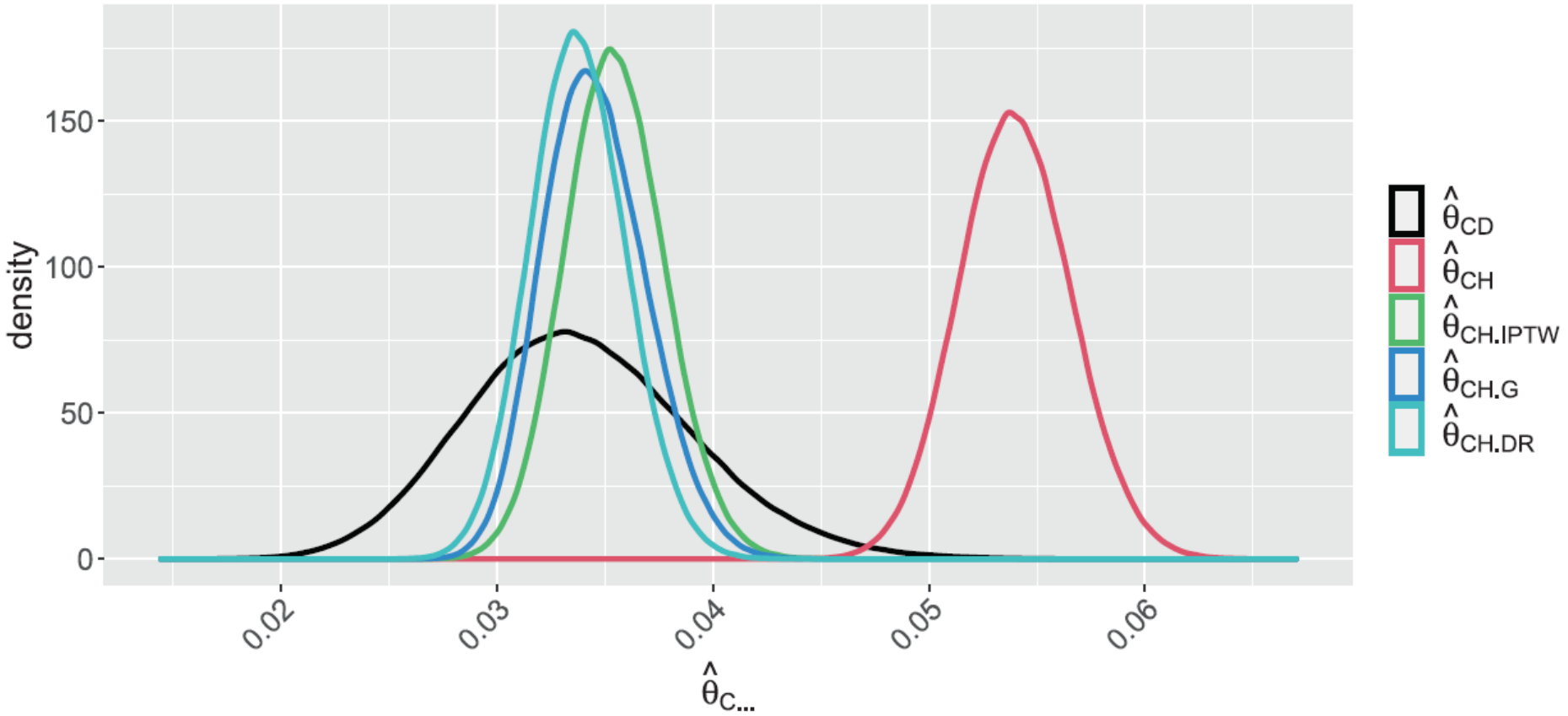


FIGURE 4 HPV case study. Distribution of the estimated control groups parameters with and without adjustment for covariates.

Callegaro A, Luo Y, Karkada N, Zahaf T. Dynamic borrowing of historical controls adjusting for covariates in vaccine efficacy clinical trials. Pharmaceutical Statistics. 2024 Apr 9.

Demonstration of covariate adjustment to MAP prior in HPV vaccination study

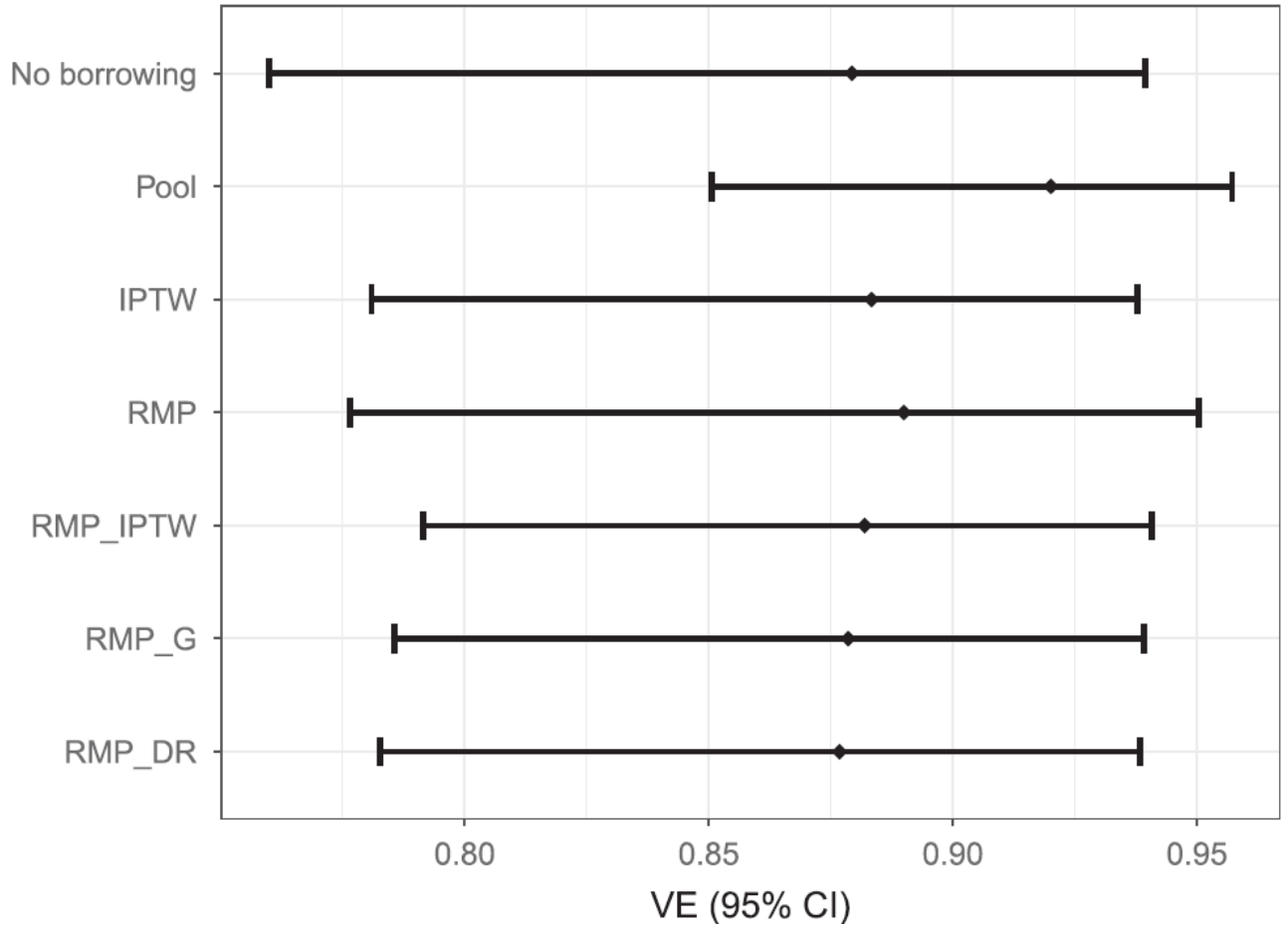


FIGURE 5 HPV case study. Forestplot of the estimated VE (95% CI) by the different methods.

Callegaro A, Luo Y, Karkada N, Zahaf T. Dynamic borrowing of historical controls adjusting for covariates in vaccine efficacy clinical trials. Pharmaceutical Statistics. 2024 Apr 9.

MAP priors for Bayesian borrowing

- Meta-analytic predictive priors are a principled way to include information from historical studies
- Differences in outcomes due to differences in populations, standard of care, etc are a concern
  - *Robustification* by mixing in vague priors
  - Adjustment based on covariate information
- MAP approach can be used at the design-stage, or post-hoc to strengthen results in pediatric or rare disease studies
- Clinical input is crucial at all stages of the analysis

Thank you

aaron.springford@astrazeneca.com