

Meta-Analytic Approaches to Using Historical Data in Clinical Trials

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Outline

- Introduction with Examples
- Overview of Approaches
- Meta-Analytic Approaches
 - Meta-Combined and Meta-Analytic-Predictive Approach
 - Prior Effective Sample Size
 - Robustness
- More on Meta-Analytic-Predictive (MAP) Priors
- Conclusions

Introduction with Examples

1. Introduction and Examples

Informed Decision Making

- Informed decisions should be based on all relevant information
- In particular, when
 - information is sparse
 - new information is difficult to obtain
- Contextual or complementary data are often available

1. Introduction and Examples

Historical Data

- These data often referred too as «historical data»
 - But they may be come from a parallel experiment
 - Or, from data in the same experiment.
E.g., in a clinical trial, from a similar subgroup
- Considering historical and current data is an example of evidence synthesis
- Various aspects to consider
 - methodological and practical issues and challenges
 - pros and cons

1. Introduction and Examples

Use of Historical Data: Pros & Cons

■ Pros

- **Design:** historical data are always used
 - This information puts the current experiment into perspective
 - For example: information about variability and expected effect sized drives sample size calculations
- **Analysis:** historical data are rarely used. However, these data can improve the inference for key parameters
 - adjusted estimates (safeguard against extremes)
 - better precision

1. Introduction and Examples

Use of Historical Data: Pros & Cons

■ Cons

- What is relevant historical data?
 - Requires judgment about similarity of historical and current setting
 - Requires interaction between subject matter experts
- How to incorporate historical data?
 - Requires a statistically principled approach
- How much is the historical data worth?
- What if historical data and actual data are in conflict?
 - Requires careful evaluation of the reasons
 - Problem can be mitigated by using a robust statistical approach

1. Introduction and Examples

Clinical Trials

- Use of historical data is attractive
 - Smaller sample sizes: e.g., smaller placebo group
 - More **ethical** (less placebo patients), or more **scientific** trials (learn more about new treatment)
 - Decreased costs and trial duration
- Historical data: various formats, e.g.
 - for control group only (our focus)
 - for effect parameter (mean difference, risk-ratio,...)
 - aggregate and/or individual data

1. Introduction and Examples

Novartis Experience

- Use of historical data
 - In all phase I oncology trials (to inform prior distributions)
 - In a substantial percentage of phase II trials
 - In special cases (e.g. non-inferiority trials)
- Experience overall positive
- However, there are challenges
 - Practical: drug development is highly regulated (company internal and external standards)
 - Practical: more time needed for study design
 - Methodological: innovative statistics

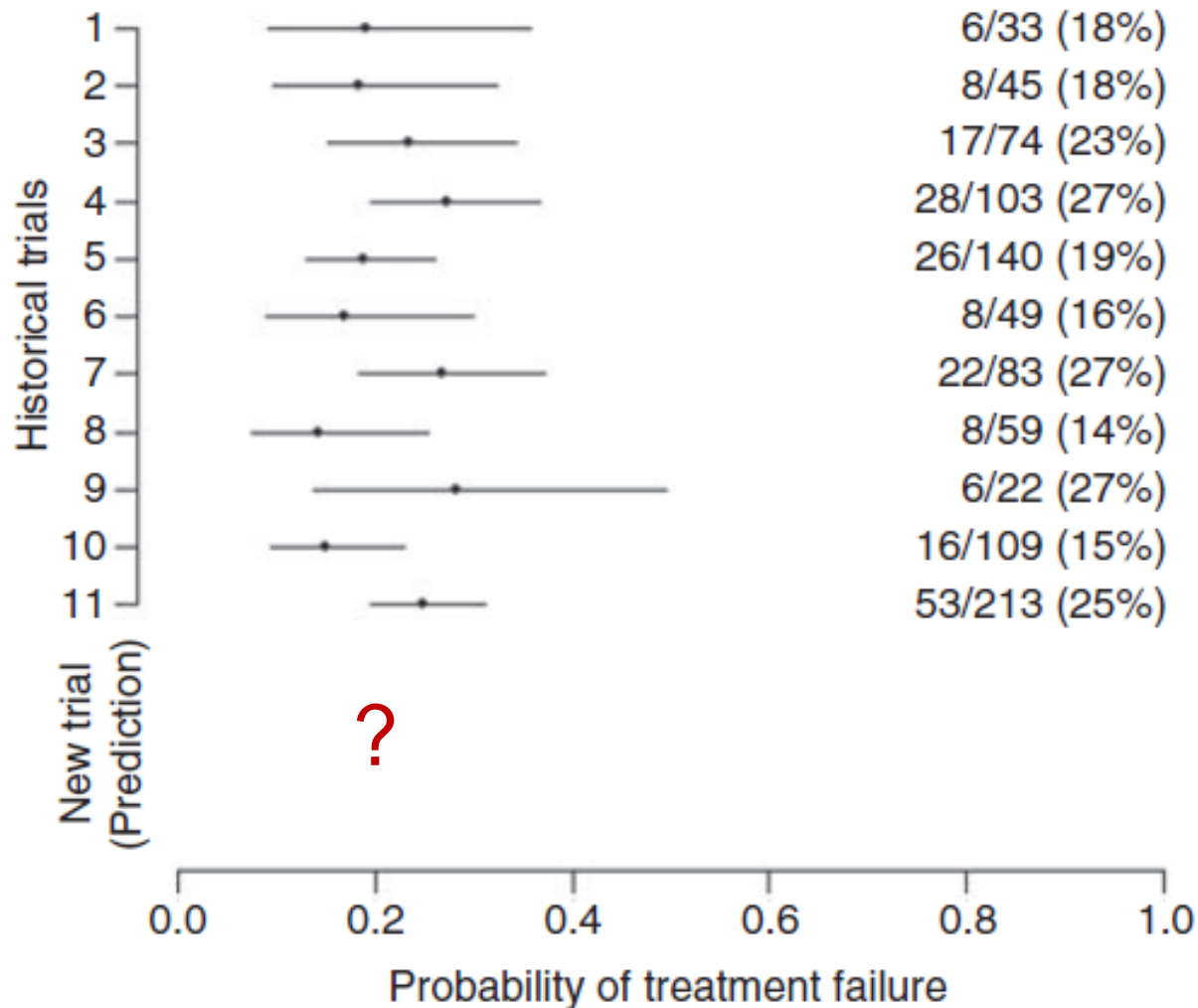
Example 1

Phase IV Trial

- Phase IV transplantation trial
- Binary outcome: treatment failure
- New treatment (T) vs. standard of care (C)
- Standard design: requires 450 patients per arm
- Historical data
 - 930 historical controls from 11 internal trials
 - Can these data be used to make control arm smaller?
 - See N et al. 2010

Example 1

Phase IV Trial: Control Data from 11 Historical Trials



Example 2

Phase II Design

- Phase II Trial in Ulcerative Colitis
- Outcome: clinical remission at week 8
- Placebo data from 4 external trials (363 historical controls) of similar design

Source	r/n	%
VanAssche (2007)	6/56	10.7
Feagan (2005)	9/63	14.3
Rutgeerts <i>et al.</i> I (2005)	18/121	14.9
Rutgeerts <i>et al.</i> II (2005)	7/123	5.7
Total	40/363	11.0

Example 3

Design of a Phase I Oncology Trial in Japan

- **Western** (on-going) first-in-human study
 - Objective: determine the maximum tolerated dose (**MTD**)
 - Endpoint: frequency of dose-limiting toxicity (**DLT**)
- Phase I study in **Japan** to find Japanese MTD
 - Often, no ethnic differences
 - For Japanese trial, can we make use of Western data?

Dose	100	200	400	800	1500	3000	TOTAL
# Patients	5	6	5	9	8	4	37
# DLT	0	0	0	0	1	3	4

↑ Tentative Western MTD

Overview of Approaches

2. Overview of Approaches

Find Relevant Historical Data

- 1st step: identify relevant historical data
 - Systematic Reviews methodology
 - E.g. Cochrane Handbook (Higgins and Green 2011)
 - Pocock's (1976) criteria
 - Inclusion/exclusion criteria for patient population
 - Type of study design
 - Exact definition of the outcome
 - Quality of study execution and management;
 - Potential biases due to time trends
 - Requires cross-functional expertise
 - A psychological barrier for many statisticians
 - May not lead to a unique set of trials (→ sensitivity analyses)

2. Overview of Approaches

Basic Notation

■ Index for

- Historical data from H trials: $1, \dots, H$
- Current/new trial: $*$

■ Data

- Historical: Y_1, \dots, Y_H Current: Y_*

■ Parameters

- Historical: $\theta_1, \dots, \theta_H$ Current: θ_*

- Use of historical data requires an assumption of similarity: formally expressed by parameter model for

$$\theta_1, \dots, \theta_H, \theta_*$$

2. Overview of Approaches

Approaches

- Original work in pre-clinical applications (1970s)
- The main approaches are
 1. Pocock's approach (bias model)
 2. Ibrahim & Chen Power Priors
 3. Meta-Analytic approaches (hierarchical models)
- Approaches 1-3
 - Are conceptually and mathematically similar
 - Discount the historical data; see Spiegelhalter et al. 2004

2. Overview of Approaches

Pocock (1976)

- Differences between new and historical trial

$$\delta_h = \theta_* - \theta_h \quad (h=1, \dots, H)$$

- Assumption: no systematic biases
This requires careful selection of historical data

$$\delta_h \sim N(0, \tau_\delta^2)$$

- The above model can be extended, but this requires additional assumptions
 - Bias assumptions $\rightarrow \delta_h$ not centered at 0
 - Historical trials of different quality \rightarrow different τ_δ
 - e.g., larger for observational, smaller for randomized controlled trials

2. Overview of Approaches

Power Priors (Ibrahim and Chen 2000)

- Prior for θ_*

- For one historical trial:

$$p(\theta_* | Y_1) \propto L(\theta_* | Y_1)^a \times \pi_0(\theta_*)$$

- Accounts for historical data via discounted likelihood
- $a \in [0, 1]$ determines the amount of discounting
 - $a = 1$: pooling of historical and new data; $a = 0$: no borrowing
- Notes:
 - $\pi_0(\theta_*)$, a default non-informative prior
 - No formal model for θ_1 (historical) and θ_* (but see slides 20-21)
 - Extension to more trials: power parameters a_1, \dots, a_H

2. Overview of Approaches

Power Priors: Two Versions

- Fixed a

- Discounting does not depend on how similar historical and new data are

- What about unknown $a (= \alpha)$?

- Prior on α ?

$$p(\theta_*, \alpha | Y_1) \propto L(\theta_* | Y_1)^\alpha \times \pi(\alpha) \times \pi_0(\theta_*)$$

- This is not correct:

- $L(\theta_* | Y_1)^\alpha$, conditional prior of θ_* given α ; $\pi(\alpha)$ marginal prior of α
- Normalizing constant on right-hand side depends on unknown α
- Derivation of normalizing constant can be difficult
- See Duan et al. 2006, N et al. 2009

2. Overview of Approaches

Power Priors: Unknown Power Parameter

- Simple Example: one trial with binary data
 - Uniform prior for power parameter α
 - Historical data: x_0 responders, y_0 non-responders, $n_0 = x_0 + y_0$
 - New data: x responders, y non-responders, $n = x + y$
 - Power priors
 - Original: $\propto \theta^{\alpha x_0} (1-\theta)^{\alpha y_0}$
 - Normalized: $= \Gamma(\alpha n_0 + 2) \Gamma^{-1}(\alpha x_0 + 1) \Gamma^{-1}(\alpha y_0 + 1) \theta^{\alpha x_0} (1-\theta)^{\alpha y_0}$
 - Data: historical $x_0/n_0 = 20/100$, new $x/n = 20/100$
 - α posterior from original prior: 0.02 (0.00, 0.07)_{95%} ???
 - α posterior from normalized prior: 0.57 (0.07, 0.98)_{95%}

2. Overview of Approaches

Hierarchical Modeling Approaches

- Data (within trials) suggests a hierarchical model that allows for between-trial heterogeneity
 - $\theta_1, \dots, \theta_C, \theta_* \sim N(\mu, \tau^2)$
 - For normal-normal hierarchical model (see later slides), there is a 1-1 mapping between τ and a (power parameter)
 - Historical data: n observations with standard deviation σ (known)
$$a = \frac{1}{1 + 2n\tau^2/\sigma^2}$$
 - $\theta_1 = \dots = \theta_C = \mu, \theta_* \sim N(\mu, \tau^2)$
 - Commensurate prior approach (Hobbs et al. 2011, 2013)
 - Note:
 - for one historical trial, the above approaches are equivalent

2. Overview of Approaches

1-1 Relationship: Power Parameter a vs. Between-Trial sd τ

■ Example

- Normal data (known standard deviation σ)
- Hierarchical model (between trial sd τ)
- Power parameter a (%) as a function of
 - historical sample size n (one trial)
 - between trial-heterogeneity (σ^2/τ^2 , see N et al 2010)

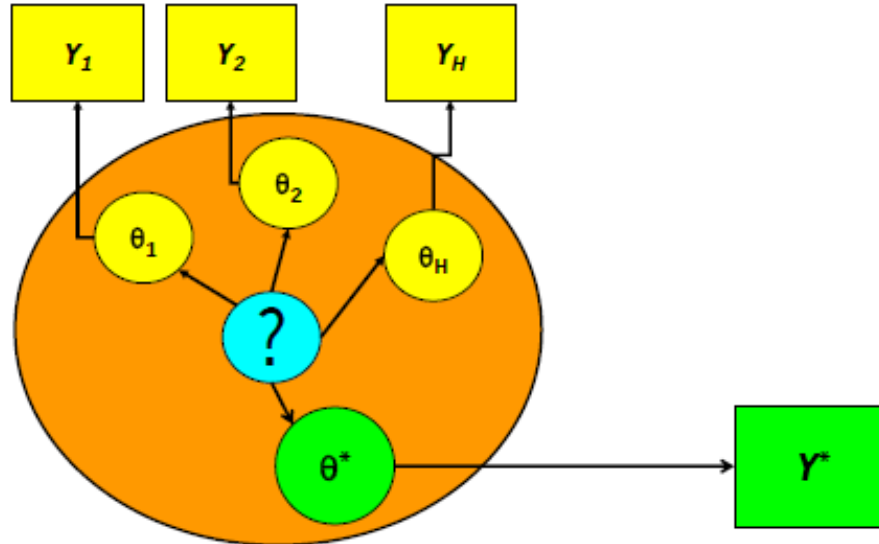
	large (4)	substantial (16)	moderate (64)	small (256)
n=25	7.0	20.0	60	80
n=50	4.0	10.0	40	70
n=100	2.0	7.0	20	60
n=250	0.8	3.0	10	30
n=500	0.4	2.0	6	20
n=1000	0.2	0.8	3	10

- For moderate between-trial sd: historical data are worth
 - 20 subjects if $n=100$ ($a=0.20$),
 - 30 subjects if $n=1000$ ($a=0.03$)

Meta-Analytic Approaches

3. Meta-Analytic Approaches

Framework



■ Meta-Analytic Approach

- uses a data model $Y|\theta$, and a parameter model ?
- infers the parameter of interest θ_*
 - at the end of the new trial (with Y_*),
 - or, at the design stage (without Y_*) \rightarrow prior of θ_*

3. Meta-Analytic Approaches

Retrospective or Prospective Use of Historical Data

- Two MA approaches

- **Meta-Analytic-Combined (MAC)** is **retrospective**

- Perform a meta-analysis of historical data and current trial data
- Parameter of interest: the parameter in the actual trial

$$\theta_* | Y_1, \dots, Y_H, Y_*$$

- **Meta-Analytic-Predictive (MAP)** is **prospective**

- 1) At design stage of current trial:
Perform MA of historical data data and obtain distribution of θ_*

$$\text{MAP Prior: } \theta_* | Y_1, \dots, Y_H$$

- 2) Combine MAP prior with current trial data Y_* (Bayesian analysis)

3. Meta-Analytic Approaches

MAC or MAP?

- ***Meta-Analytic-Combined (MAC)***

- No prior for θ^* required at design stage
- Only one analysis required, can be (non-)Bayesian

- ***Meta-Analytic-Predictive (MAP)***

- Historical information about θ^* is explicitly stated at design stage
- Historical data can then be ignored
- Fully Bayesian analysis required

- ***MAC*** or ***MAP*** ? Which one is better?

3. Meta-Analytic Approaches

MAC and MAP Are Equivalent

- For a hierarchical model, MAC and MAP are equivalent
 - HM \rightarrow data conditionally independent given parameters
 - That is: $Y_h \mid \theta_1, \dots, \theta_h, \dots, \theta_H, \theta_* = Y_h \mid \theta_h$
 - Proof:

$$\begin{aligned} p(\theta_* \mid Y_*, Y_{\mathcal{J}}) &\propto p(\theta_*, \theta_{\mathcal{J}} \mid Y_*, Y_{\mathcal{J}}) \\ &\propto p(Y_*, Y_{\mathcal{J}} \mid \theta_*, \theta_{\mathcal{J}}) \times p(\theta_*, \theta_{\mathcal{J}}) \\ &= p(Y_* \mid \theta_*) \times p(Y_{\mathcal{J}} \mid \theta_{\mathcal{J}}) \times p(\theta_*, \theta_{\mathcal{J}}) \\ &\propto p(Y_* \mid \theta_*) \times p(\theta_*, \theta_{\mathcal{J}} \mid Y_{\mathcal{J}}) \\ &\propto p(Y_* \mid \theta_*) \times p(\theta_* \mid Y_{\mathcal{J}}) \end{aligned}$$

3. Meta-Analytic Approaches

Normal-Normal Hierarchical Model (NNHM)

NNHM, very popular model

- Sampling model

$$Y_h | \theta_h \sim N(\theta_h, s_h^2) \quad h = 1, \dots, H, *$$

- Parameter model

$$\theta_h | \mu, \tau \sim N(\mu, \tau^2) \quad h = 1, \dots, H, *$$

- Inference: for θ_*

- Challenge: what is τ ? (in particular if H is small)
- Classical: various ways to estimate τ
- Bayesian: priors on μ (often flat) and τ (contextual)

3. Meta-Analytic Approaches

*Inference for **known** τ (with improper prior for μ)*

Basic formulas for fixed τ : Classical and Bayesian results are the same

Meta-analytic weights

$$w_h = 1/(s_h^2 + \tau^2)$$

Inference for μ

$$\hat{\mu} = \sum_h w_h Y_h / \sum_h w_h, \quad Var(\hat{\mu}) = 1 / \sum_h w_h$$

Shrinkage factors

$$B_h = s_h^2 / (s_h^2 + \tau^2)$$

Inference for θ_h

$$\hat{\theta}_h = B_h \hat{\mu} + (1 - B_h) Y_h, \quad Var(\hat{\theta}_h) = B_h(\tau^2 + B_h Var(\hat{\mu}))$$

Inference for new parameter θ^*

$$\hat{\theta}^* = \hat{\mu}, \quad Var(\hat{\theta}^*) = \tau^2 + Var(\hat{\mu})$$

Special case: 1 historical trial: $\hat{\theta}^* = Y_1, \quad Var(\hat{\theta}^*) = s_1^2 + 2\tau^2$

3. Meta-Analytic Approaches

Unknown τ

- Discounting of historical data depends on τ
- For small number of trials
 - Classical
 - The various estimates can differ substantially
 - It is unclear how to adjust for estimation uncertainty
 - Proposal: for θ_* , t distribution with H-2 df (Higgins et al. 2009)
 - Bayesian
 - Conclusions can be sensitive to the prior
 - Judgment required about plausible values for τ

3. Meta-Analytic Approaches

τ -Priors. Spiegelhalter et al. 2004, Gelman 2006

- Various priors for τ
 - Uniform, inverse-sqrt-gamma, Half-Normal, Half-Cauchy...
 - Recommendation: use prior that puts
 - most of its mass to values that represent plausible heterogeneity
 - remaining probability to unanticipated heterogeneity (e.g. large)
 - Example: binary data, parameter = logit(p)
 - $\tau = 2$ (1) correspond to very large (large) heterogeneity
 - Half-Normal priors (Spiegelhalter et al. 2004)
 - $\tau \sim \text{Half-Normal}(\text{scale}=1.0) \rightarrow \Pr(\tau < 2) \approx 0.95$
 - $\tau \sim \text{Half-Normal}(\text{scale}=0.5) \rightarrow \Pr(\tau < 1) \approx 0.95$

3. Meta-Analytic Approaches

Prior Effective Sample Size (ESS)

- Idea:

- express prior as an equivalent number of subjects
- the **prior effective sample size (ESS)**

- What we know from conjugate analyses:

- Binomial(n, p) data, Beta(a, b) prior
 - **Prior ESS: $n_0 = a+b$**
 - Posterior mean is a weighted average of prior mean and sample mean (with weights n_0 and n)
- Similar results for normal, Poisson, exponential data, ...

3. Meta-Analytic Approaches

Approximating ESS

- More generally: ESS for MAP prior $\theta^* | Y_1, \dots, Y_H$
 - Approximate prior effective sample size n_*
 - Idea: sample sizes are (approximately) proportional to precisions
 - Under completely homogeneous trials, $\tau = 0$
 - $\Rightarrow n_* = N = \sum_h n_h =$ total # of historical subjects
 - $\Rightarrow \text{Var}_{\tau=0}(\theta_* | Y_1, \dots, Y_H)$ is proportional to $1/N$
 - If $\tau > 0$ (reality!) $\Rightarrow \text{Var}_{\tau>0}(\theta_* | Y_1, \dots, Y_H)$ is proportional to $1/n_*$

$$n_* = \frac{\text{Var}_{\tau=0}(\theta_* | Y_1, \dots, Y_H)}{\text{Var}_{\tau>0}(\theta_* | Y_1, \dots, Y_H)} \times N$$

- More general approach to ESS, see Morita et al. (2008, 2012)

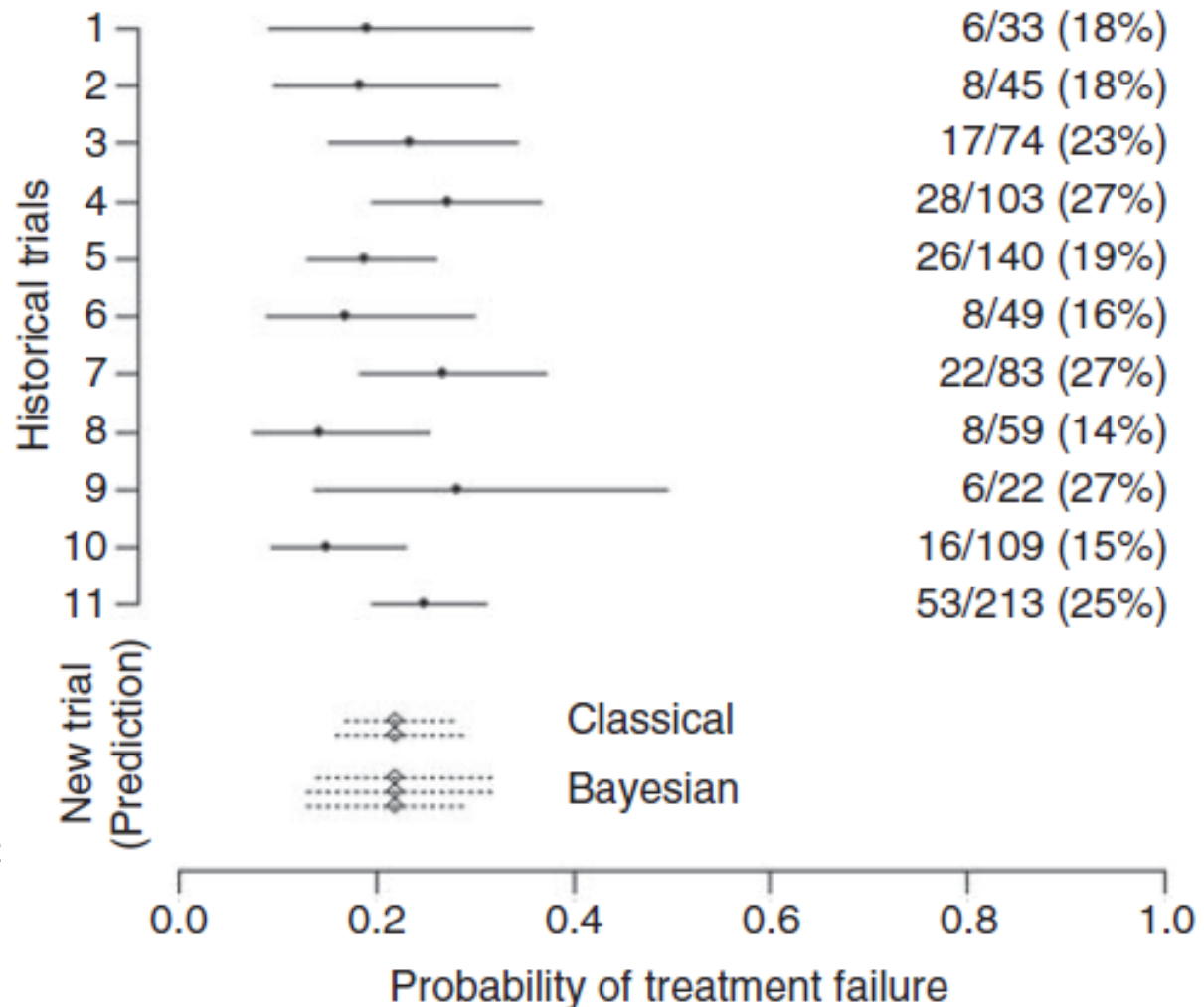
3. Meta-Analytic Approaches

Prior ESS for Example 1

- 11 historical trials with **N=930** patients
- Between-trial sd τ on log-odds scale **0.17 (0.01, 0.50)_{95%}**
- 0.17: small/moderate

Results for log-odds θ_*

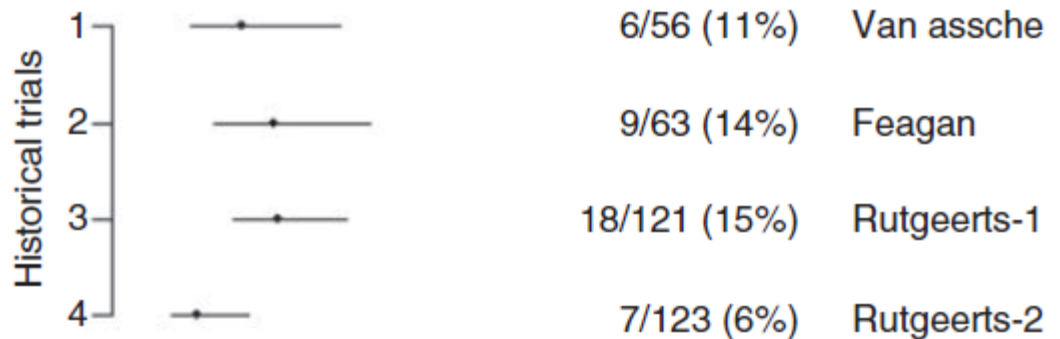
- Pooled: -1.27 (0.080)
- MAP: -1.29 (0.253)
- **Prior ESS**
 $n^* = 930 \times (0.08/0.253)^2$
= 93



3. Meta-Analytic Approaches

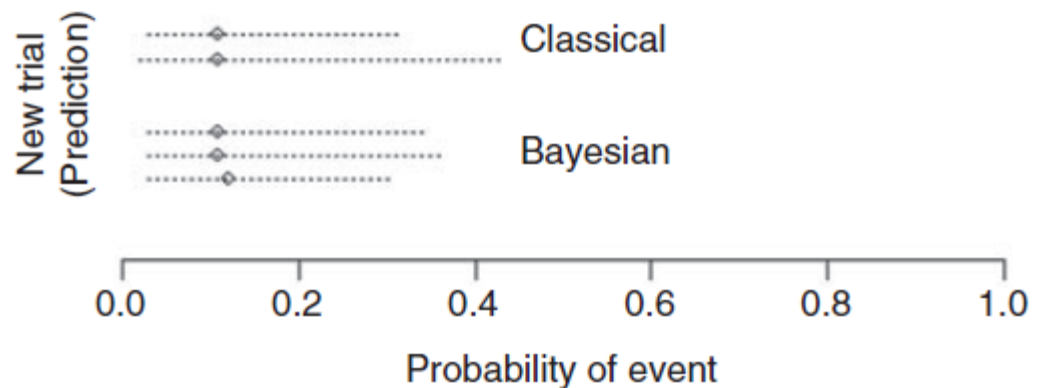
Prior ESS for Example 2

- 4 historical trials with **N=363** patients
- Between-trial sd τ on log-odds scale **0.41 (0.03, 1.39)_{95%}**
- 0.41: substantial



Results for log-odds θ_*

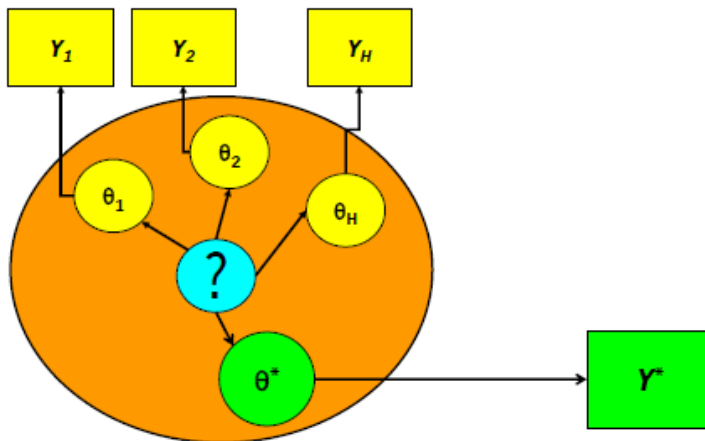
- Pooled: -2.01 (0.169)
- MAP: -2.08 (0.690)
- **Prior ESS**
 $n^* = 363 \times (0.169/0.690)^2 = 22$



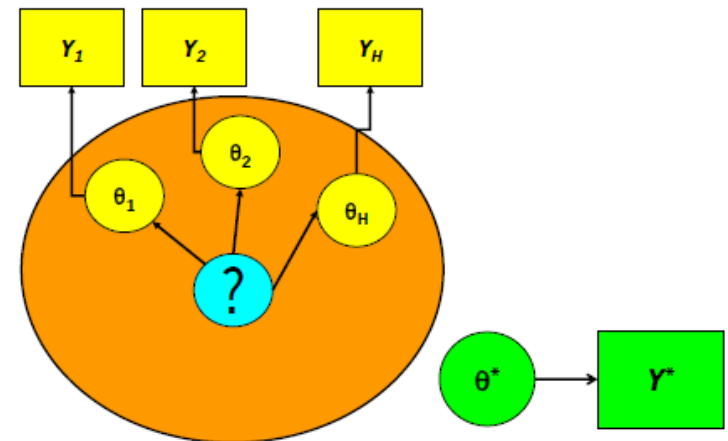
3. Meta-Analytic Approaches

Robust Meta-Analytic Priors

Similarity Scenario (\rightarrow MAP prior)



Dissimilarity Scenario



- Conflict between historical data and actual data
 - Similarity of parameters is violated
 - Solution: robust priors (O'Hagan 1979); heavy-tailed (t or mixture)
- Robustified MAP prior
$$w \times (\text{MAP-prior}) + (1-w) \times (\text{weakly-informative prior})$$

3. Meta-Analytic Approaches

Example 3: Robust MAP Priors

- **Western** (on-going) first-in-human study
 - Objective: determine the maximum tolerated dose (MTD)
 - Endpoint: frequency of dose-limiting toxicity (DLT)
- Phase I study in **Japan** to find Japanese MTD
 - Often, no ethnic differences
 - For Japanese trial, can we use of Western data?

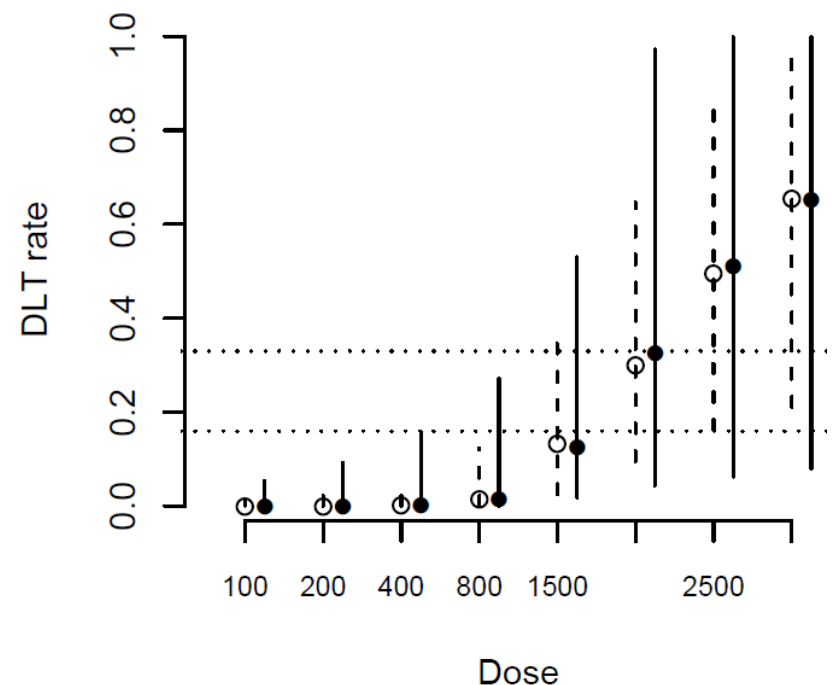
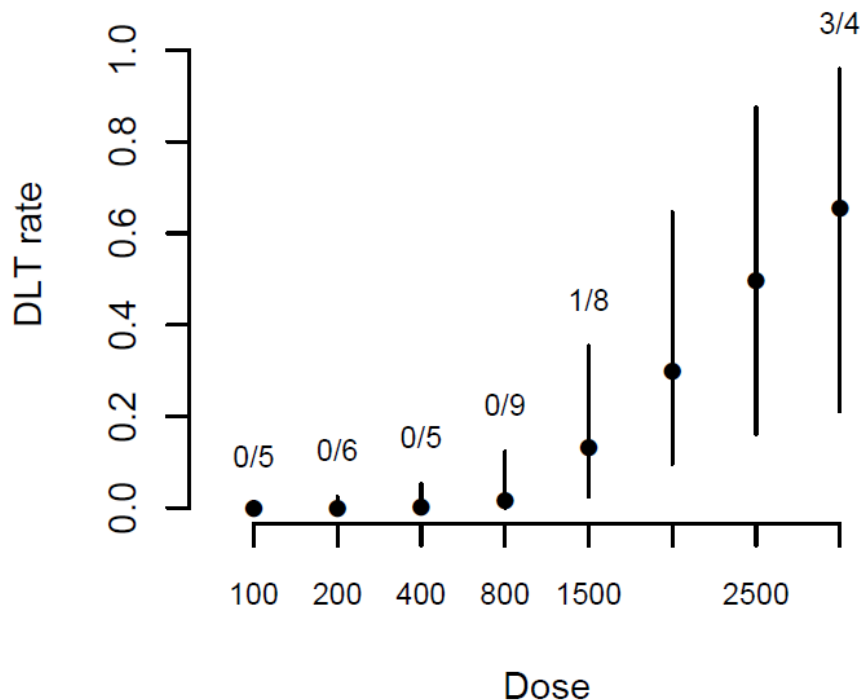
Dose	100	200	400	800	1500	3000	TOTAL
# Patients	5	6	5	9	8	4	37
# DLT	0	0	0	0	1	3	4

↑ Tentative MTD

3. Meta-Analytic Approaches

Example 3: MAP Prior for Similarity Scenario

- Model: logistic regression, with bivariate-normal prior for (α, β)
- Left: posterior from Western data
- Right: posterior from Western data (dotted line), MAP prior for Japan (solid line), under substantial heterogeneity

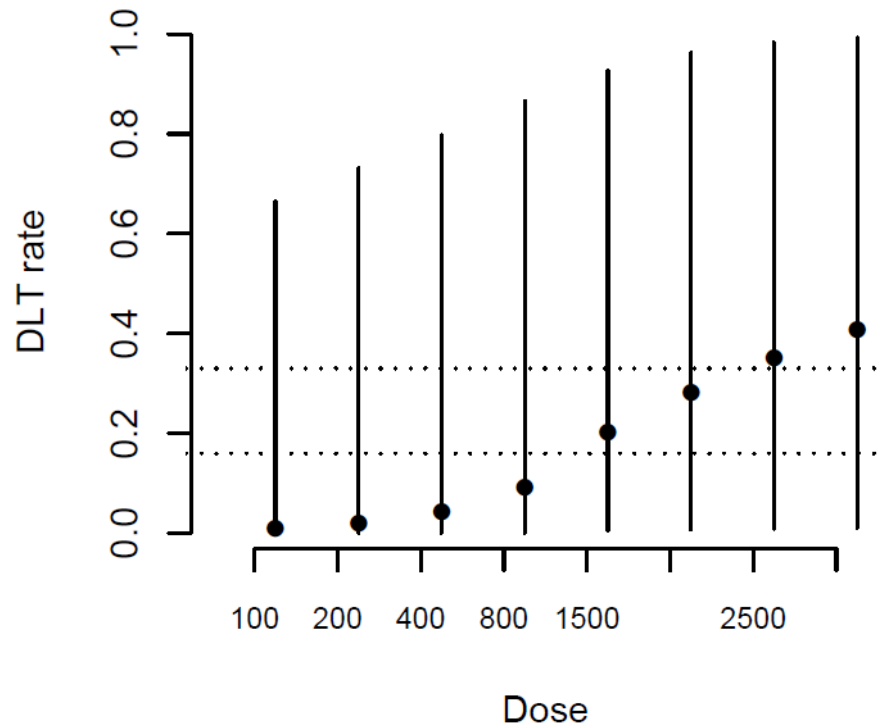


3. Meta-Analytic Approaches

Example 3: Weakly-Inf Prior for Dissimilarity Scenario

But what if ...

- There are relevant ethnic differences
- Better: to use weakly-informative prior (Figure)

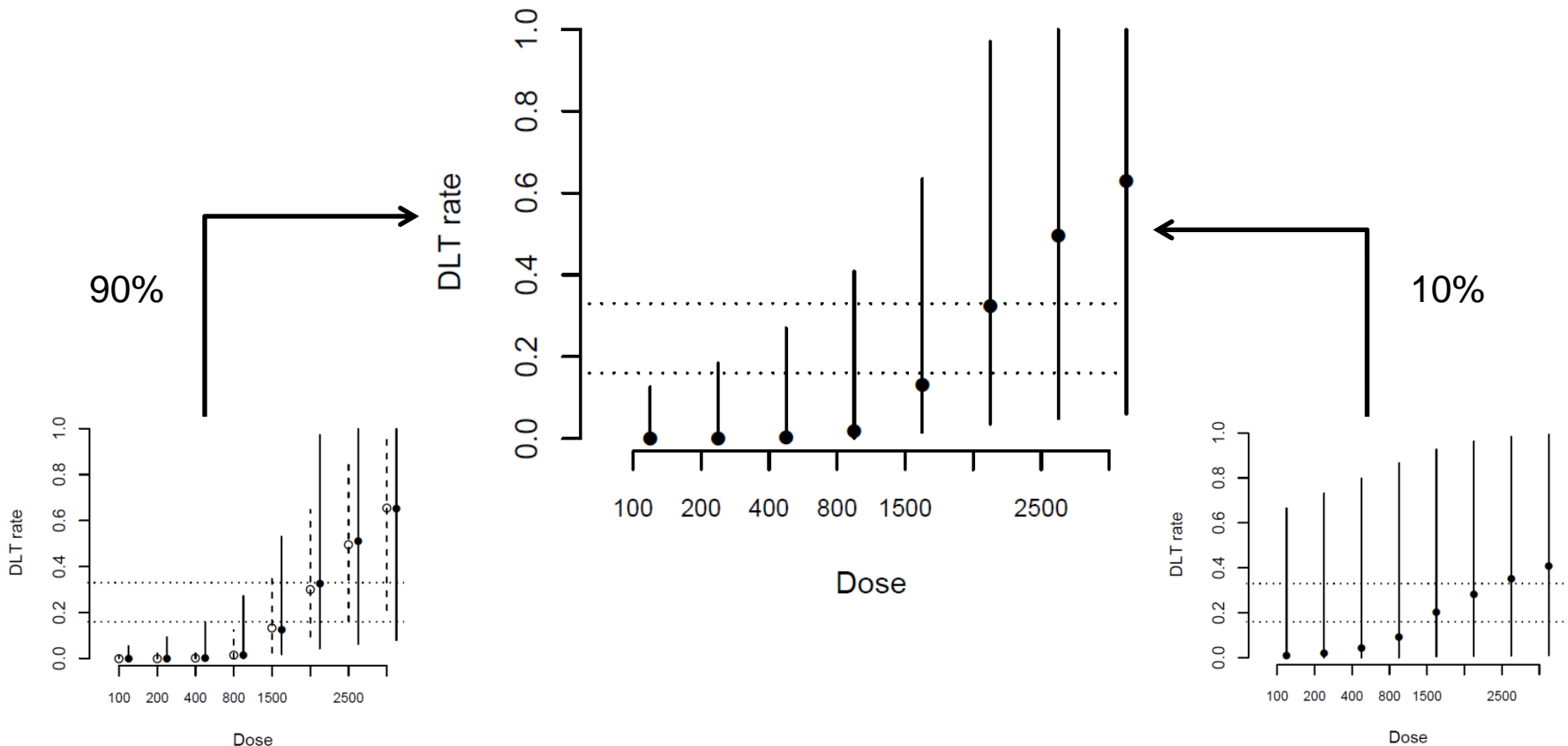


3. Meta-Analytic Approaches

Example 3: Robustification (Mixture Prior)

Mixture prior for the two scenarios, with the weights

- 90% for similarity scenario, 10% for dissimilarity scenario



3. Meta-Analytic Approaches

Example 3: Two Data Scenarios

- Design properties
 - Assess operating characteristics
 - Assess data scenarios that may arise in the trial

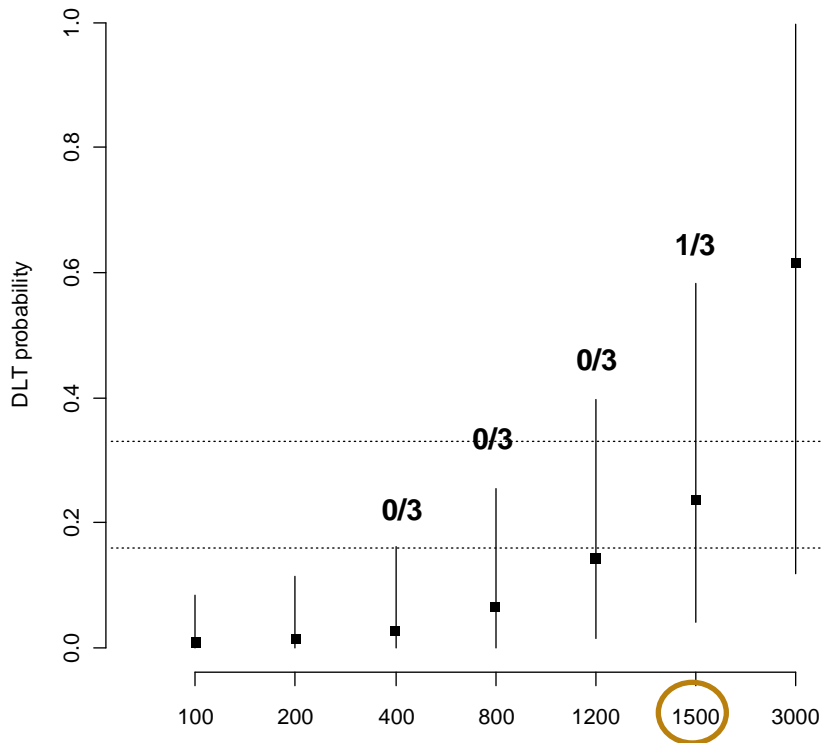
Dose	100	200	400	800	1200	1500	3000
Western Data							
#DLT/#Pts	0 / 5	0 / 6	0 / 5	0 / 9		1 / 8	3 / 4
Japan: scenario 1 (similarity)							
			0 / 3	0 / 3	0 / 3	1 / 3	
Japan: scenario 2 (dissimilarity)							
			0 / 3	2 / 3			

3. Meta-Analytic Approaches

Example 3: Posteriors for Two Data Scenarios

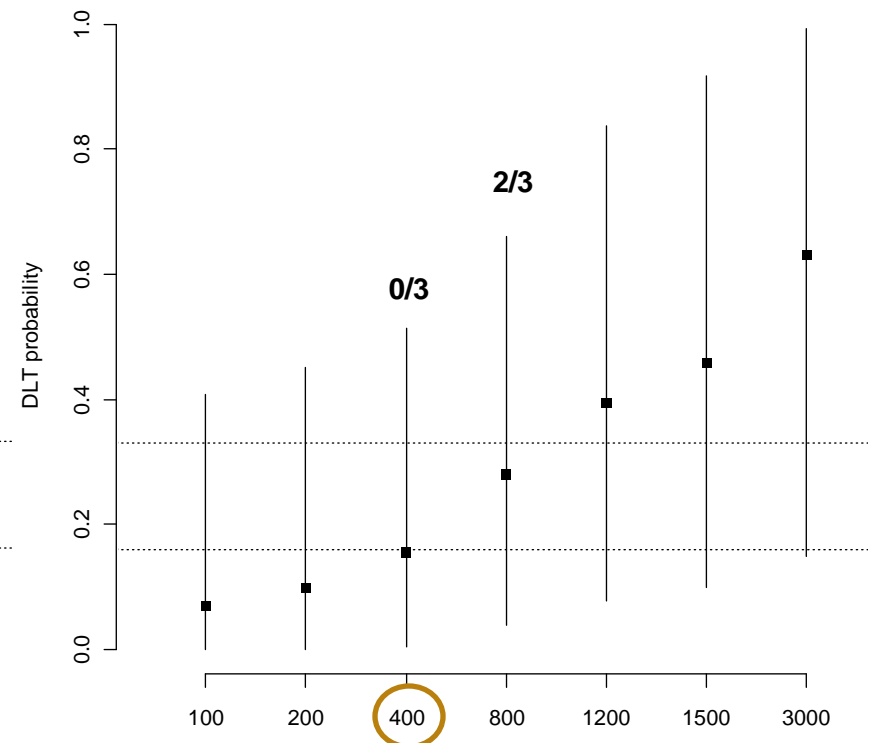
Similarity scenario

- Less uncertainty compared to prior
- Recommendation: **retest at 1500**
- Good borrowing from Western data



Dissimilarity scenario

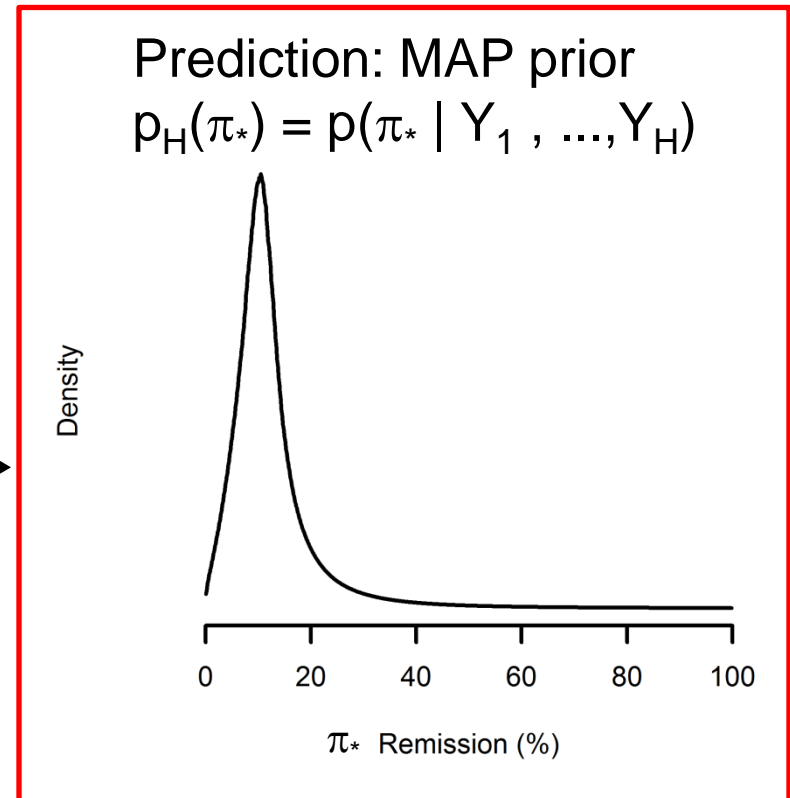
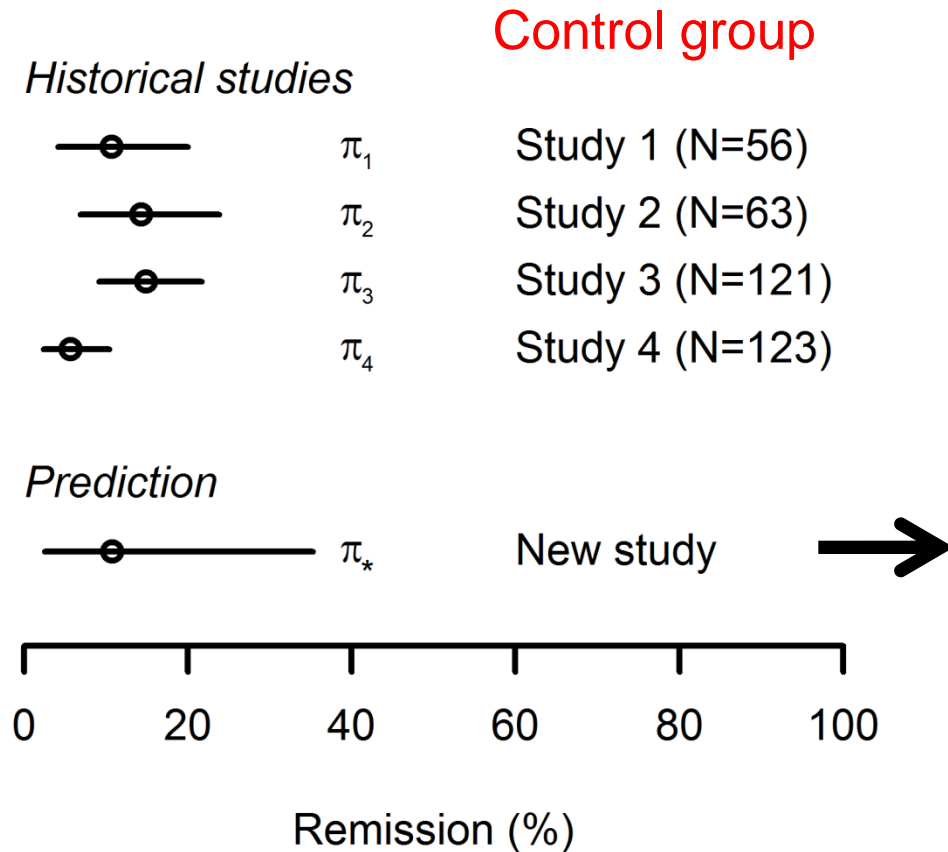
- **More uncertainty** compared to prior
- Recommendation: **de-escalate to 400**
- Good robustness



More on MAP Priors

4. More on MAP Priors

Example 2 Revisited



(density plot from MCMC sample)

4. More on MAP Priors

Approximating the MAP Prior

- MAP prior

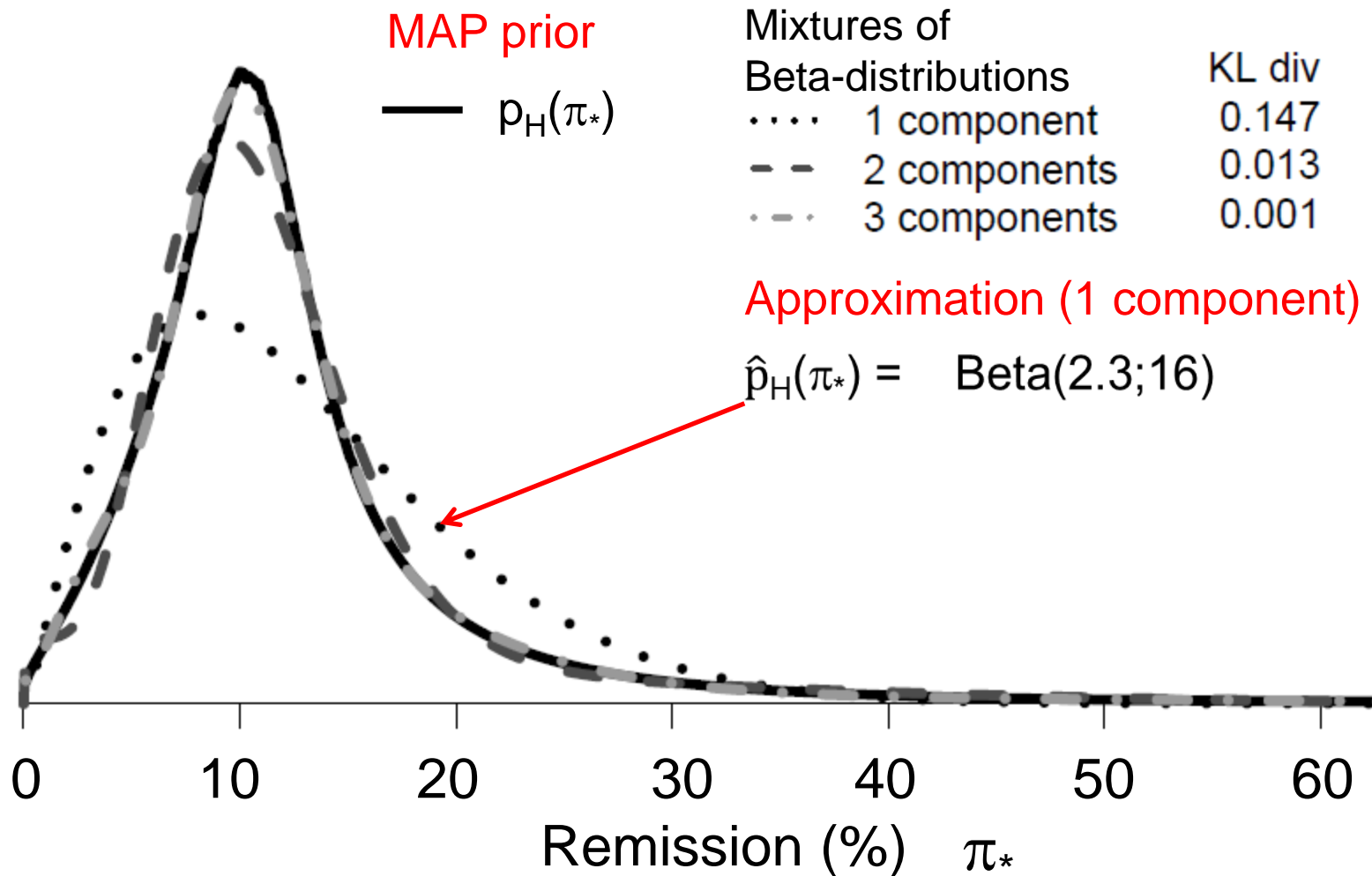
- Not available analytically (just MCMC sample), but can be well approximated by **mixture of conjugate priors**

Dallal and Hall (1983), Diaconis and Ylvisaker (1985)

- Mixture of conjugate priors. Advantages
 - *Easy communication:*
discussions with clinical trial team, health authorities, ethics committees, study protocols, publications
 - *Analytical posterior calculation*
→ fast operating characteristics

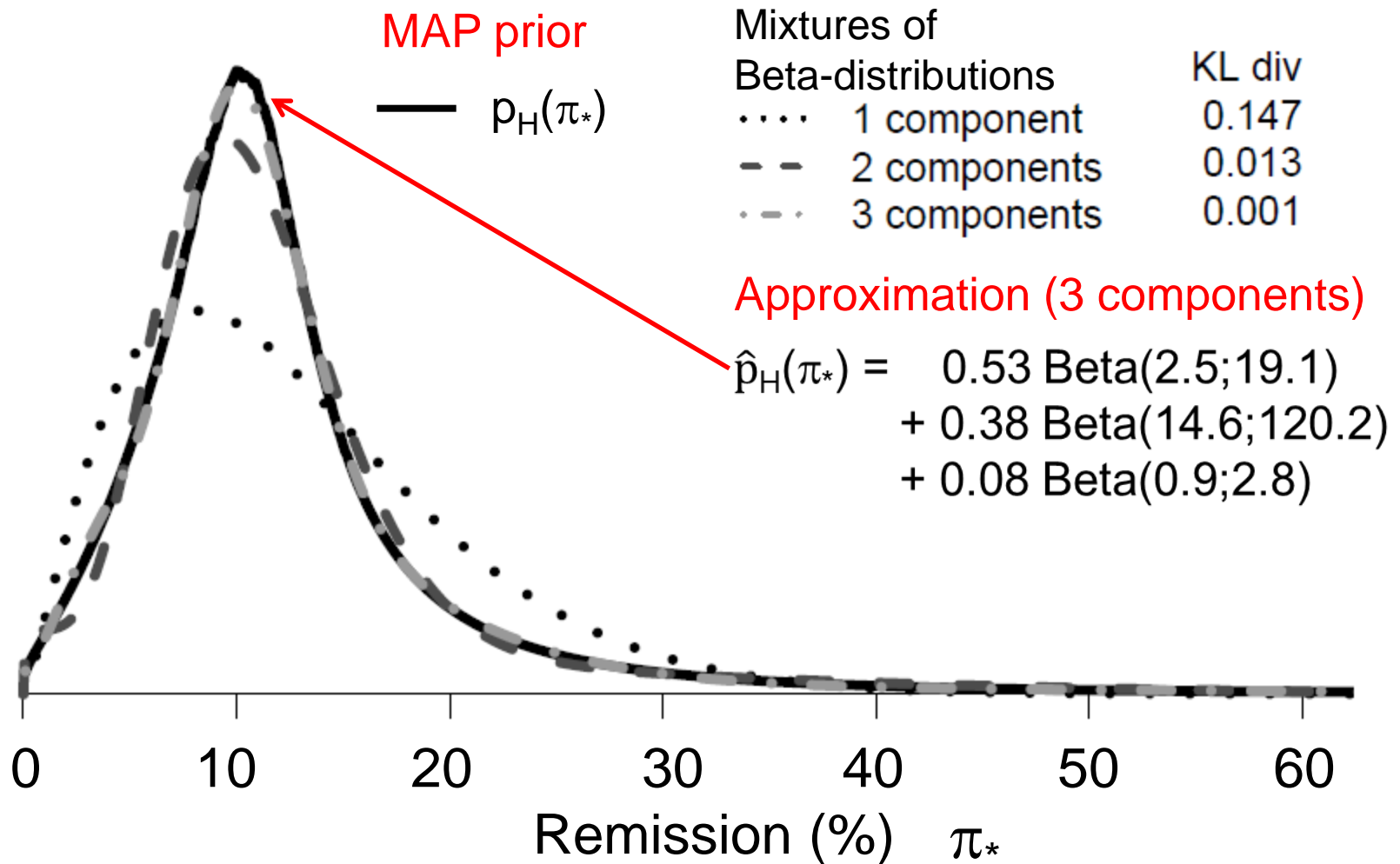
4. More on MAP Priors

Example 2: MAP Prior approximated by single Beta



4. More on MAP Priors

Example 2: MAP Prior approximated by 3-comp Beta Mixture



4. More on MAP Priors

Robustness

- Prior-data conflict

- *Conjugate priors*: fixed prior-data compromise
- *Heavy-tailed priors* : prior discarded under conflict

O'Hagan (1979), O'Hagan and Pericchi (2012)

- MAP priors

- Typically heavy-tailed, hence naturally robust
- Further robustness and more rapid adaptation to prior-data conflict by adding weakly-informative component:

$$w \times \text{MAP} + (1-w) \times \text{Uniform} \quad \text{e.g. } w = 0.9 \text{ or } 0.5$$

4. More on MAP Priors

Non-Robustness of Conjugate Prior

Conjugate prior

Beta(2.3,16)

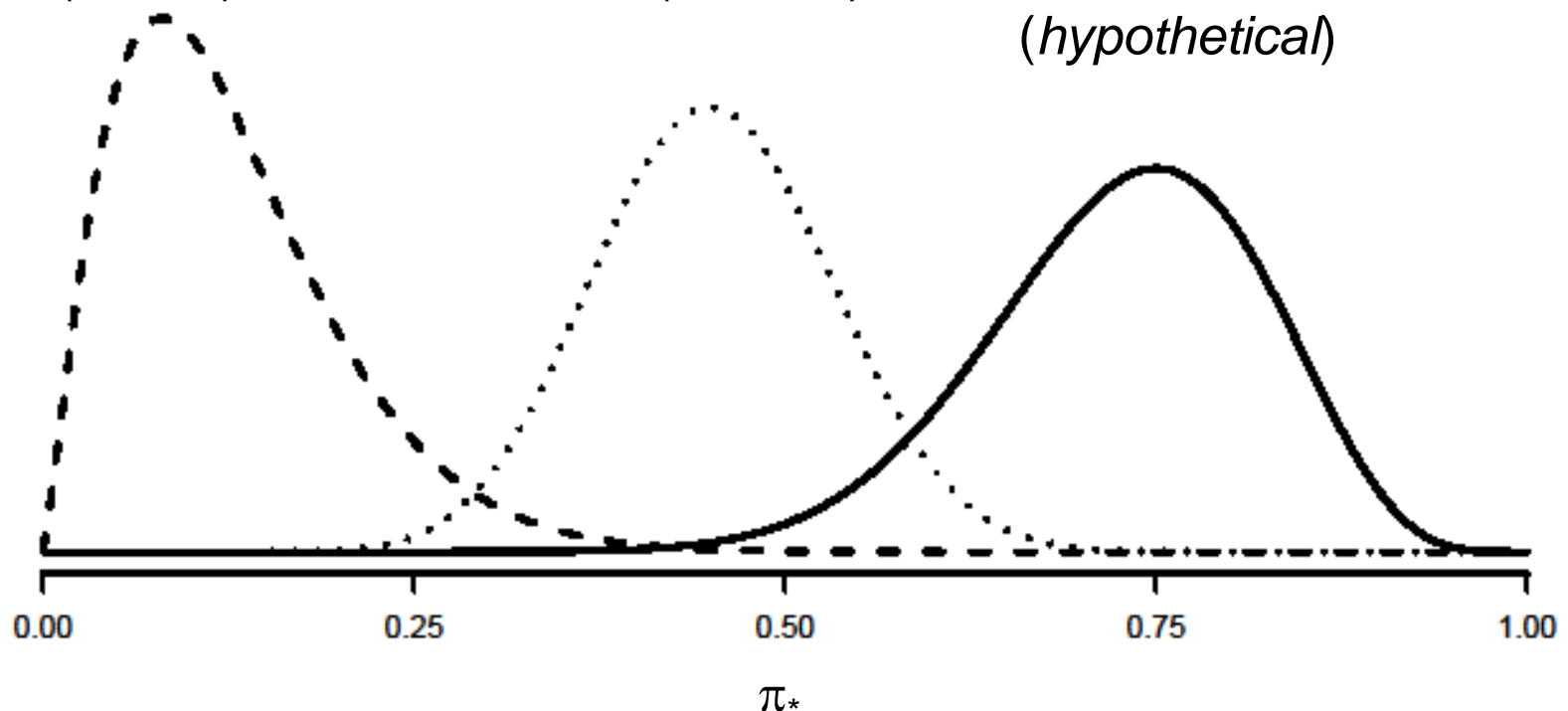
Posterior

Beta(17.3,21)

Likelihood

15 / 20

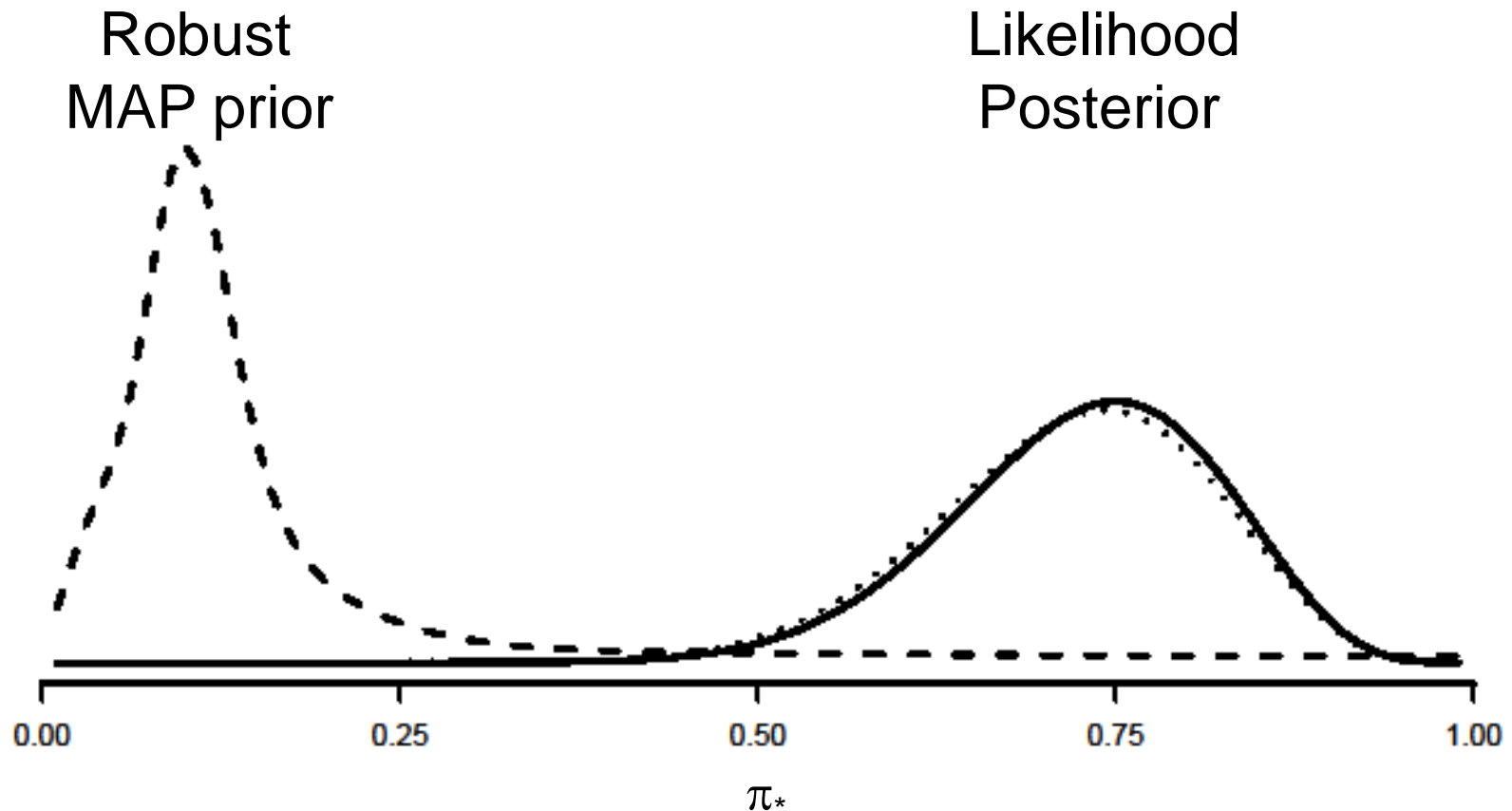
(hypothetical)



"Bayesian - One who, vaguely expecting a horse and catching a glimpse of a donkey, strongly concludes he has seen a mule". Stephen Senn

4. More on MAP Priors

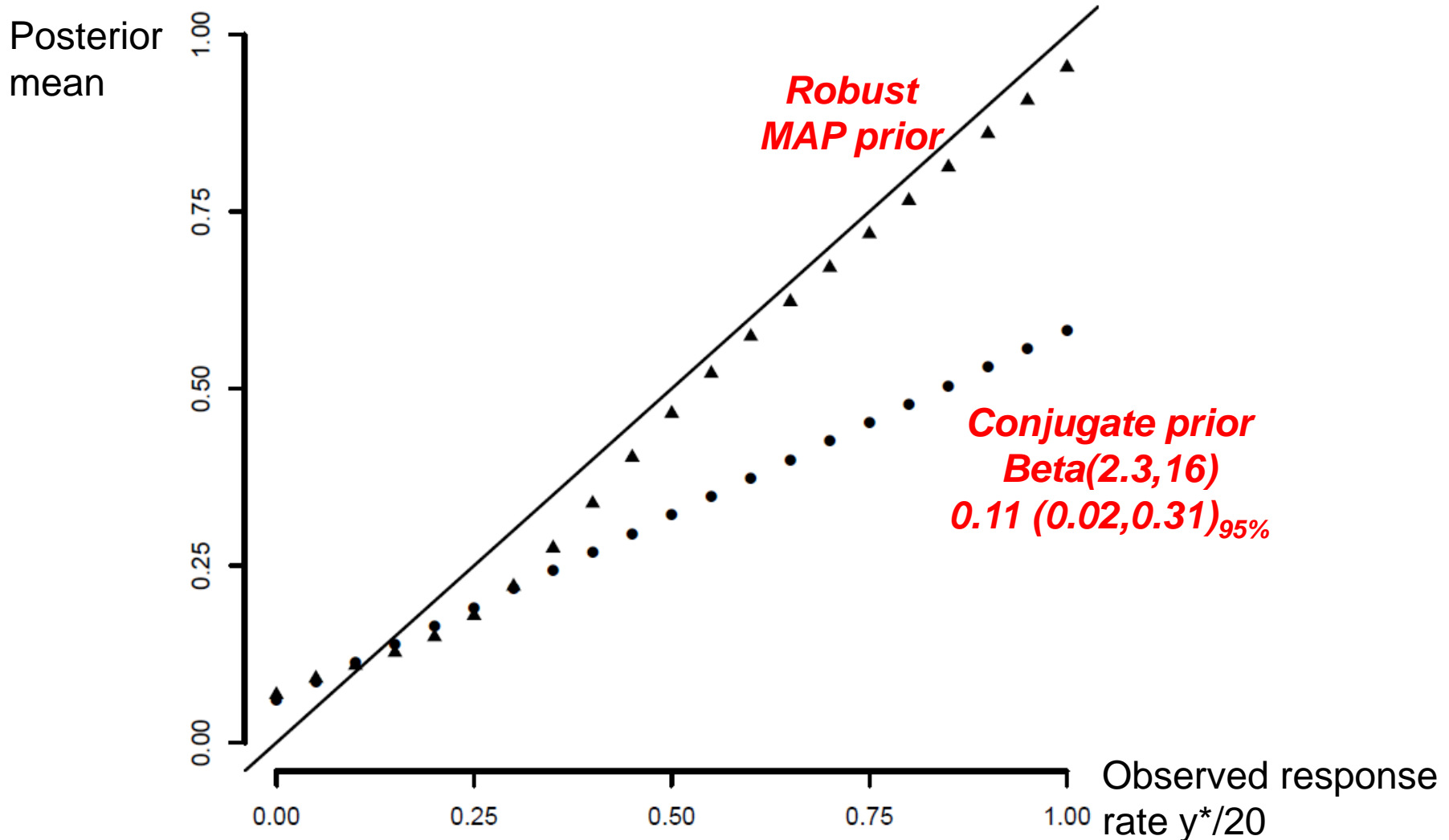
Robustness of MAP Prior



- $\text{MAP} = 0.53 \text{ Beta}(2.5, 19.1) + 0.38 \text{ Beta}(14.6, 120.2) + 0.08 \text{ Beta}(0.9, 2.8)$
- $\text{Robust MAP} = 0.9 \times \text{MAP} + 0.1 \times \text{Beta}(1, 1)$

4. More on MAP Priors

Estimates for Simple Conjugate and Robust MAP Prior



4. More on MAP Priors

Operating Characteristics (OC): Summary

- Frequentist properties (OC) for robust MAP priors
 - *Estimation:*
 - Bias well-controlled
 - MSE: better for MAP priors compared to weakly-informative priors if prior is well-specified
 - Testing
 - Success criterion = $1-\alpha$ posterior probability for $\delta = \theta_T - \theta_* > 0$
 - Type-I error: some inflation (or deflation), but fairly well controlled
 - Power: gain in power compared to weakly-informative prior

4. More on MAP Priors

Operating Characteristics (Estimation): Two Designs

■ Compare Control vs. Test

- Control vs. treatment effect: $\delta = \theta_T - \theta_*$
- Control prior worth n^* patients:

$$\theta_* \sim N(\theta_0, \sigma_0^2), \quad \sigma_0^2 = \sigma^2 / n^*$$

- Assume no information for test treatment (flat prior for θ_T)
- Two Designs
 - **Standard Balanced Design (B)**, with sample sizes n
 - **Historical Data Design (H)**: save n^* control patients

	C	C-prior	T
B: Balanced Design	n	-	n
H: Historical Data Design	$n-n^*$	n^*	n

4. More on MAP Priors

Operating Characteristics (Estimation): MSE

- Mean-squared error (MSE) for mean difference δ

$$\text{MSE}_{(H)} > \text{MSE}_{(B)} \quad \Leftrightarrow \quad |\theta - \theta_0|/\sigma_0 > 1$$

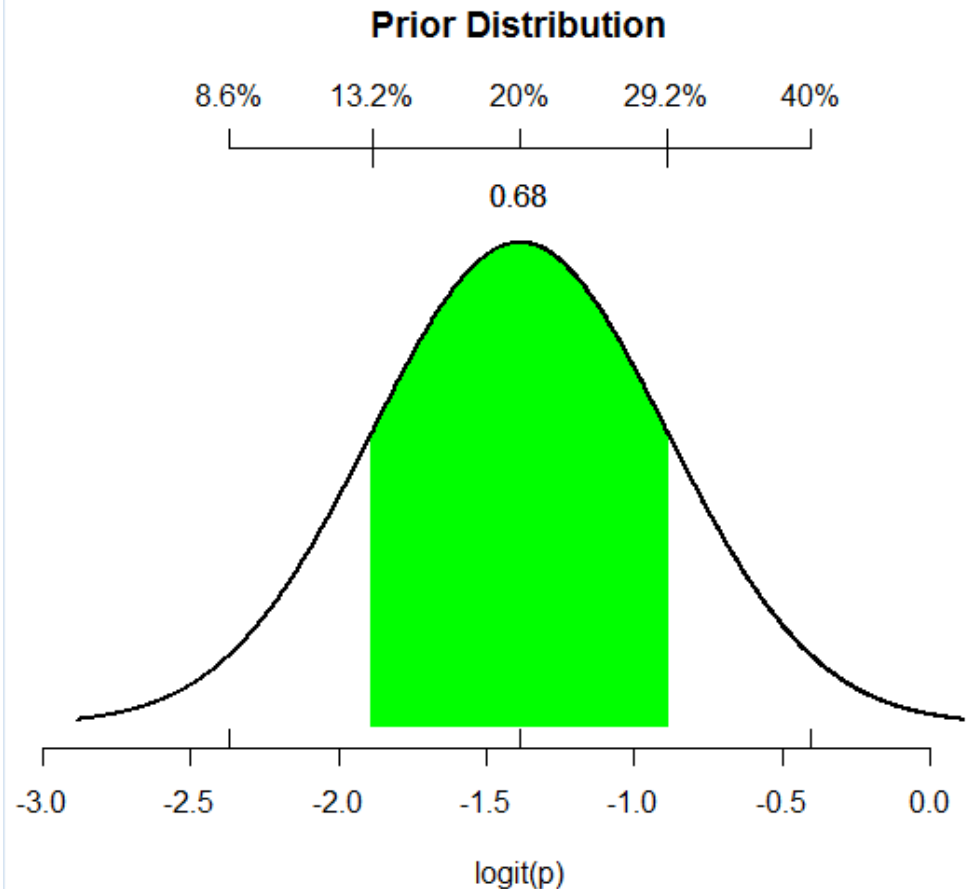
- **H**istorical data design better than **B**alanced design
 - if true parameter is less than one standard deviation away from the prior mean
 - i.e., if true parameter is in the 68% interval of the prior
- There is a benefit if prior is well-specified

4. More on MAP Priors

Operating Characteristics (Estimation): MSE - Example

Example: Binary data

- Control response rate
- Prior:
 - mean = 0.2, weight $n_* = 25$
- Normal approximation
 - $\text{logit}(0.2) = -1.386$
 - $(1/p+1/(1-p)) / n_* = 0.5^2$
- Prior:
 - $\text{logit}(p) \sim N(-1.386, 0.5^2)$
 - 95%-interval: **0.086 to 0.4**
- For MSE, H-design better than B-design if $p \in (0.13, 0.29)$



4. More on MAP Priors

Operating Characteristics (Testing): Comparison of Priors

- Test treatment vs. Control, binary endpoint
 - Vague prior for test treatment: $\text{Beta}(1,1)$
 - Informative prior for control, e.g.
ESS
 - i. **Beta:** simple conjugate $\text{Beta}(4,16)$ prior: 0.19 (0.06,0.40)_{95%}
 - ii. **Mix90:** $0.9 \times \text{Beta}(4,6) + 0.1 \times \text{Uniform}$
 - iii. **Mix50:** $0.5 \times \text{Beta}(4,16) + 0.5 \times \text{Uniform}$
 - iv. **Unif:** Uniform prior
 - Robust prior on control discarded in case of prior-data conflict – may lead to inconclusive results
 - An adaptive design can reduce this risk (Hobbs et al. 2013)

4. More on MAP Priors

Operating Characteristics (Testing): Adaptive Design

- Two-stage adaptive design
 - Target sample size at end of trial:
 - $n = 40$ for control, $m = 40$ for test
 - **Stage 1:**
 - $n_1 = 15$ for control
 - $m_1 = 20$ for test
 - **Interim analysis:** for control, get interim ESS_C
 - **Stage 2 of adaptive design:**
 - $40 - ESS_C$ for control
 - 20 for test

4. More on MAP Priors

Operating Characteristics (Testing): Type-I Error, Power

Control Rate					Expected Sample Size (Control Group)			
	Mix50	Mix90	Beta	Unif	Mix50	Mix90	Beta	Unif
Type-I Error ($\delta = 0$)								
0.1	0.6	0.1	0.0	1.8	28	20	20	40
0.2	2.5	1.5	1.6	2.3	26	20	20	40
0.3	3.9	5.5	6.1	2.4	29	21	20	40
0.5	3.4	12.3	26.0	2.8	37	27	20	40
Power ($\delta = 0.3$)								
0.1	92	81	82	90	28	20	20	40
0.2	88	86	88	82	26	20	20	40
0.3	83	88	93	80	29	21	20	40
0.5	78	85	99	82	37	27	20	40

Schmidli et al. (2014, submitted)

Conclusions

5. Conclusions

- Use of historical (trial-external) data is
 - attractive
 - ambitious
 - ambiguous
- *Attractive*
 - more information should lead to better inference, and, subsequently, to better decisions
 - various potential benefits: smaller control groups, more ethical trials, cost savings

5. Conclusions

■ *Ambitious*

- Requires upfront work: find relevant data
- Statistically more challenging
- MA approaches (various dialects) are useful
- Robust approaches look promising

■ *Ambiguous*

- Compromise between acceptable frequentist and Bayesian metrics is needed
- Clinical trials: the topic is important, and its importance will most likely grow in the near future

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