Use of Historical Controls Data (HCD) in Nonclinical

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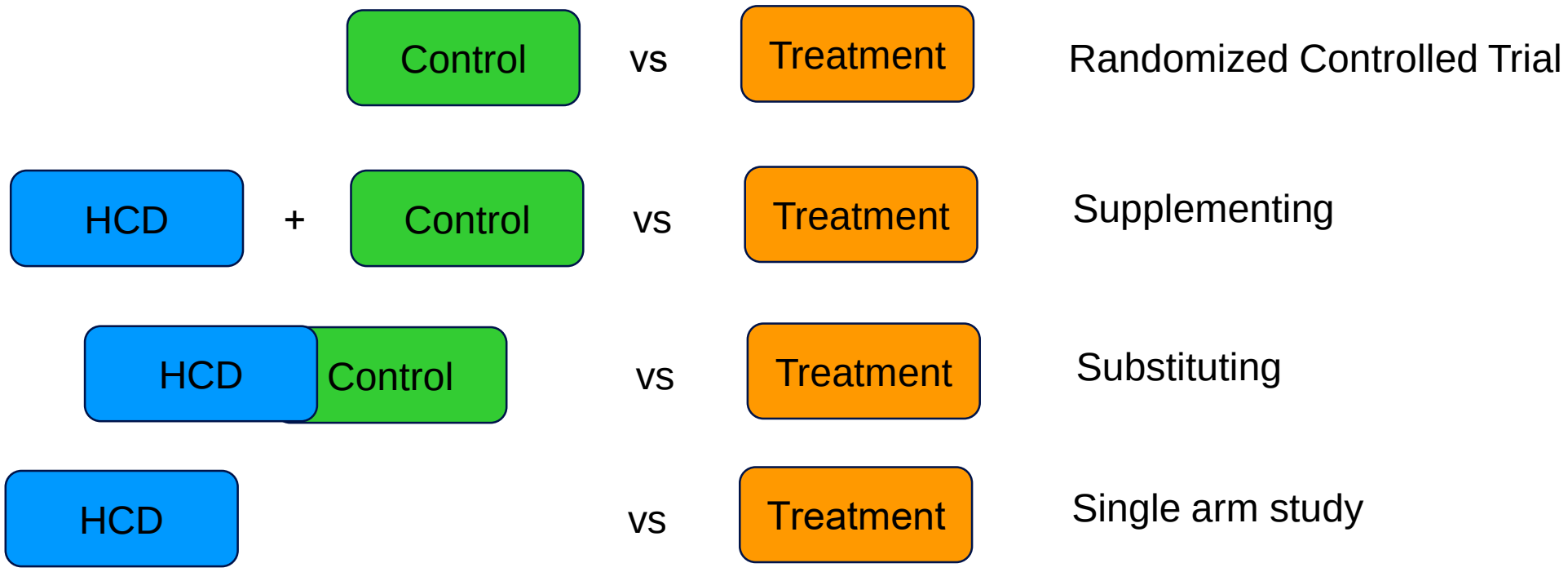
	Clinical	Pre-clinical / Non-clinical
HCD informal use	no	Yes
HCD formal use (e.g. MAP)	Yes	No
Virtual control groups	yes	no

How can Toxicology Learn from Clinical?

``HCD borrowing`` spectrum



Borrowing risk: What do we do if the Current control group and HCD groups conflict?

Pocock (1976) proposed guidelines of incorporating historical data and suggested a Bayesian approach

Historical data must be gathered by the *same research organization* (research team) that conducts or oversees the current study

Study protocol must remain *fixed* throughout the period covering historical and current studi

The historica *ble* with respect to potential imp

The historical control data should be *fairly recent* and recent data should be given larger weight in any analysis than older data

There must be *no detectable systematic differences* in response between the various control groups

50 years ago!!

Guidance for Industry

Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals

May 2001

The concurrent control group is always the most appropriate and important in testing drug related increases in tumor rates in a carcinogenicity experiment.

However, if used appropriately, historical control data can be very valuable in the final interpretation of the study results.

https://www.altex.org/index.php/altex/article/view/1728

Current (2020) use of historical control data in preclinical animal studies

The main purpose of this data collection is the performance control of the study and the assessment of outliers, which may occur in individual studies for various reasons.

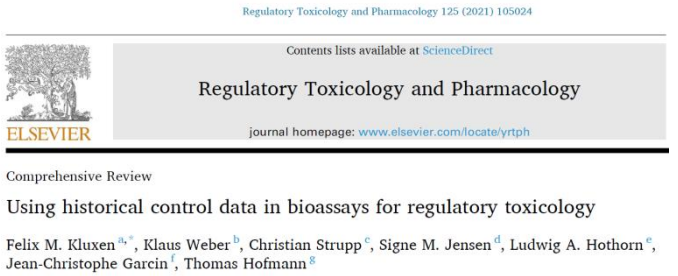
Legacy data from control animals are used to determine the range of parameters of untreated animals, its changes over time or the influences of changes in analytical methods.

If a statistically significant difference between a dose group and the control group is observed in a study for a specific parameter but the changes in the treated group lie within historical control ranges, then it is questionable whether the observation actually represents a compound-related effect.

Historical control data are of particular importance for the evaluation of carcinogenicity studies with respect to incidences of spontaneous tumors observed, which depend on the species and the strain used. In addition to the direct comparison with the control group, such a comparison with historical control data allows the assessment whether the occurrence of a rare tumor or a marginally increased tumor incidence is of biological relevance, i.e., caused by the chemical under investigation.

For the assessment of developmental toxicity studies, the situation regarding historical control data is similar compared to carcinogenicity studies.

HCD in regulatory toxicology are used mainly to: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Comprehensive Review

Using historical control data in bioassays for regulatory toxicology

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https://pubmed.ncbi.nlm.nih.gov/34364928/

- serve as quality assurance for the test system;
- identify abnormal controls;
- further represent background variation and help to distinguish true responses from chance findings;
- similarly to the previous point, judge biological relevance by comparing apparent changes to natural background variability; and
- informally address the statistical multiple comparison problem when using statistical tests.

- The idea behind using HCD in a toxicological evaluation is to assess biological variability with increased power, as compared to the relatively small concurrent control group.

- The concurrent control group may also be too small to characterise the relevance of rare events, which is of specific importance when assessing the carcinogenic or developmental toxicity potential of substances.
- Another use of HCD is monitoring, e.g. background infections or systematic changes in experimental conduct or in the animal model (genetic drift events during breeding).

Historical controls in clinical trials: methods and RBesT tool

Meta-**A**nalytic-**P**redictive Approach

Historical control information

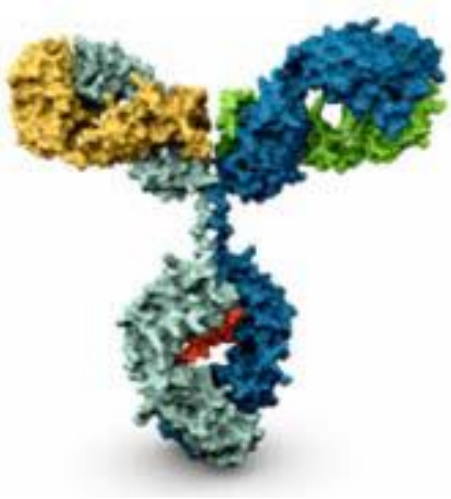
Motivating example - traditional clinical trial design

Disease

Ankylosing spondylitis

Experimental treatment

Secukinumab (monoclonal antibody)



Endpoint

Binary: response at week 6

Traditional clinical trial design

Secukinumab (n=24) vs. Placebo (n=24)

Fisher's exact test

However: 8 similar historical placebo-controlled clinical trials with different experimental treatments available

Could this historical placebo information be used?

Historical control information

Motivating example - trial design and analysis with historical controls

Historical placebo information

Bayesian primary analysis

Prior Placebo Derived from 8 historical trials (N=533), using a Meta-Analytic-Predictive (MAP) approach

Beta(11,32) worth 43=11+32 patients

Prior Experimental Weakly informative

Beta(0.5,1) worth 1.5=0.5+1 patients

Design:

Secukinumab (n=24) vs. Placebo (n=6)

Results:

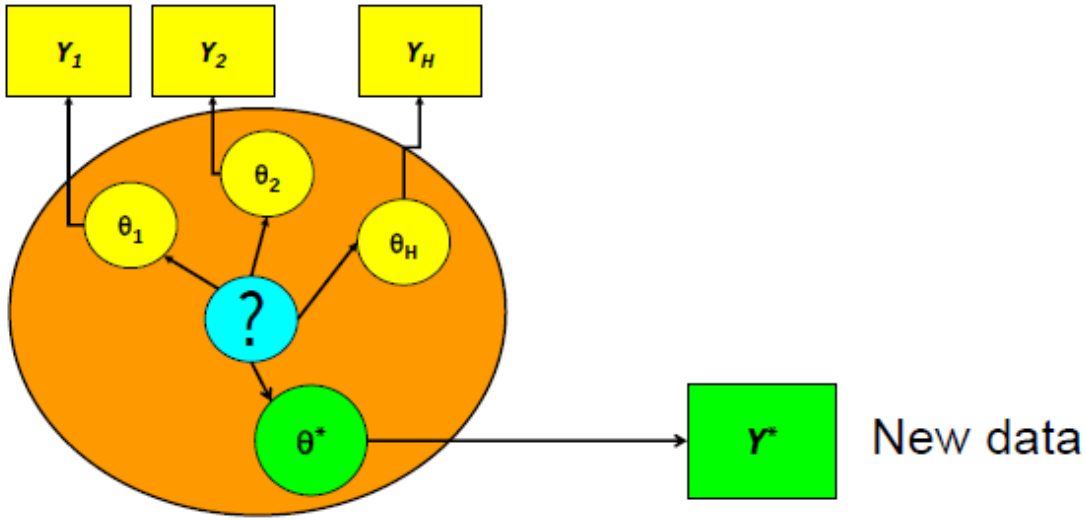
14/23 Secukinumab vs. 1/6 Placebo, p(δ >0 | data) > 99.8%

Positive result now confirmed in two phase 3 trials

Historical control information

Borrowing strength

Historical data



Meta-analytic approach

Model for all quantities involved, in particular for parameters

Infers the parameter of interest θ*

- At the design stage (without Y*), using MAP
- At the end of the new trial (with Y*)

Meta-analytic-predictive (MAP) approach

Hierarchical model

Control group data – number of responders Y

new study: $Y_* \sim \text{Binomial}(\pi_*, n_*)$ $\theta_* = \text{logit}(\pi_*)$

historical studies: $Y_h \sim \text{Binomial}(\pi_h, n_h)$ $\theta_h = \text{logit}(\pi_h)$ h=1,...,H

Exchangeability assumption

$\theta_*, \theta_1, \ldots, \theta_H \sim \text{Normal}(\mu, \tau^2)$

population mean μ, between-trial standard deviation τ

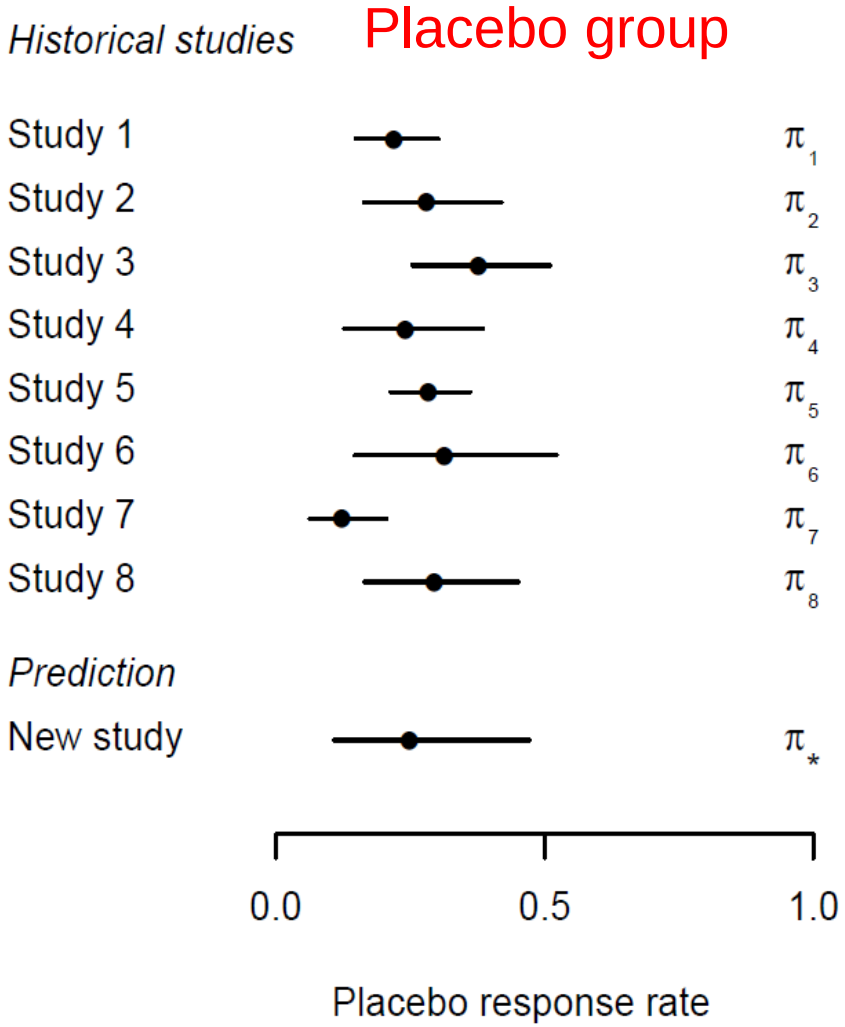
weakly informative priors for μ and τ

e.g. $\mu \sim \text{Normal}(0, 10^2)$, $\tau \sim \text{Half-Normal}(0, 1^2)$

Spiegelhalter et al. (2004), Neuenschwander et al. (2010), Schmidli et al. (2014)

Meta-analytic-predictive (MAP) approach

Clinical trial in ankylosing spondylitis:



$$\theta_* = \text{logit}(\pi_*)$$

$$\theta_h = \text{logit}(\pi_h)$$

$$\theta_*, \theta_1, \ldots, \theta_H \sim \text{Normal}(\mu, \tau^2)$$

No data for new study at design stage!

```
> AS
     study   n  r
1 Study 1 107 23
2 Study 2  44 12
3 Study 3  51 19
4 Study 4  39  9
5 Study 5 139 39
6 Study 6  20  6
7 Study 7  78  9
8 Study 8  35 10
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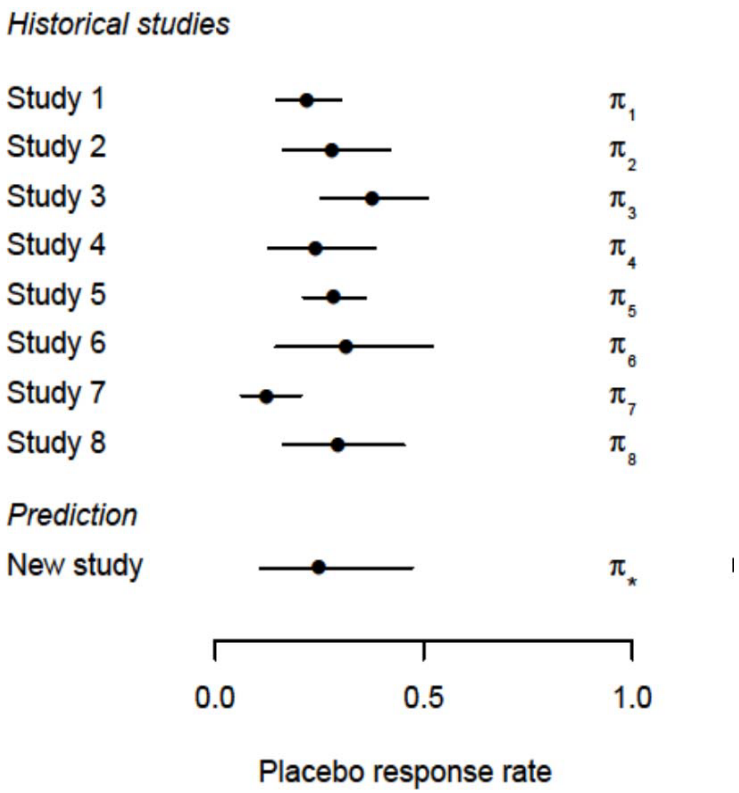
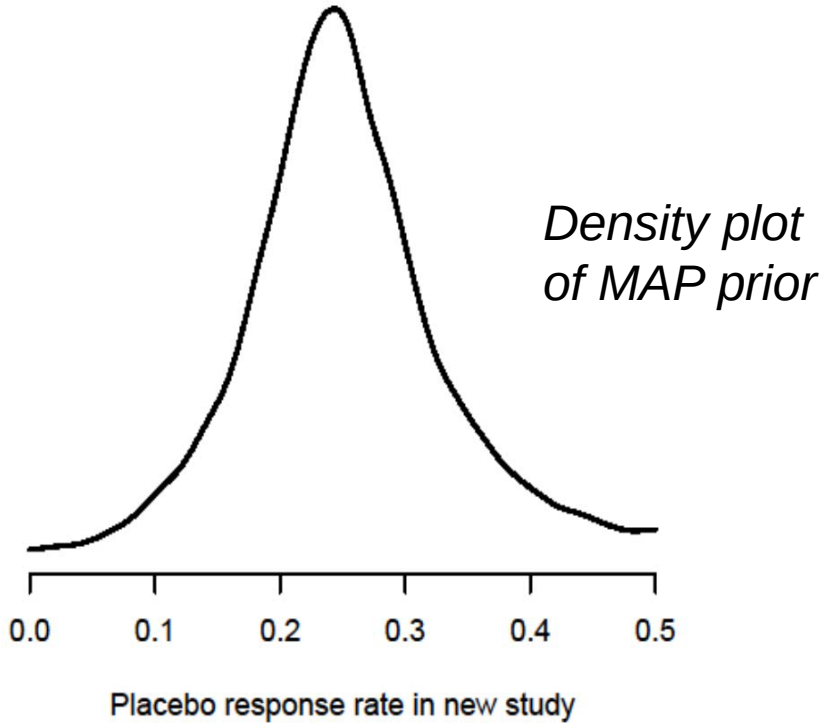
Meta-analytic-predictive (MAP) approach

MAP prior



MAP prior to be used as prior information in new study



Density plot of MAP prior

Meta-analytic-predictive (MAP) approach
Approximating the MAP prior

MAP prior not available analytically, just a very large sample from this distribution using Markov chain Monte Carlo (MCMC)

Approximating the MAP prior by a standard distribution has many advantages

Communication: discussions with clinical trial team, health authorities, ethics committees; clinical trial protocols; publications

Computation: priors can be easily specified in software; analytical evaluation of the posterior possible in conjugate settings

Conjugate distributions are convenient, as posteriors have same form as priors.

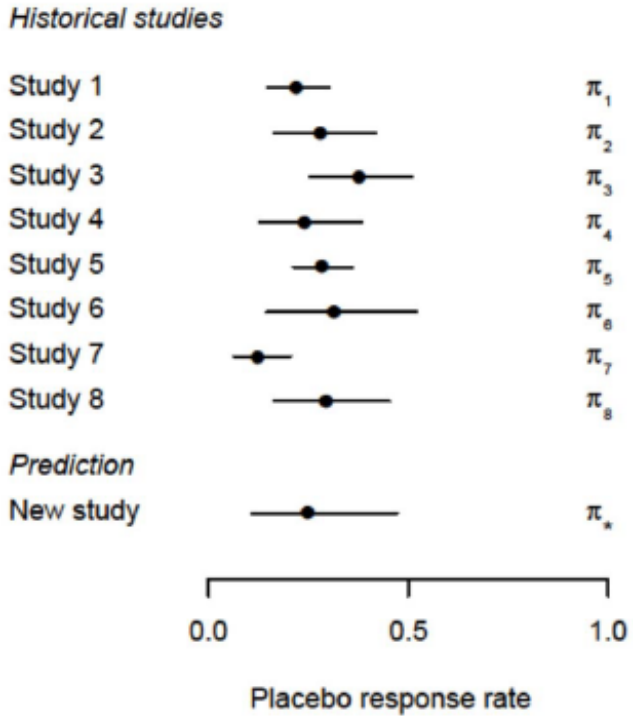
Binomial data: Beta prior distribution

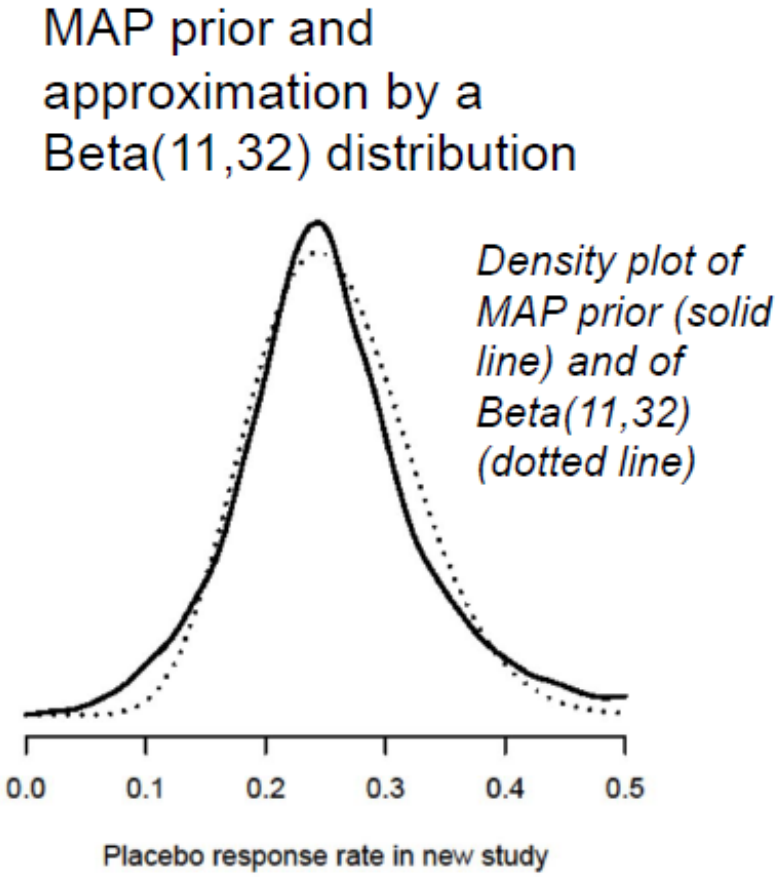
Normal data: Normal prior distribution

Poisson data, exponential data: Gamma prior distribution

Meta-analytic-predictive (MAP) approach

Approximating the MAP prior





Meta-analytic-predictive (MAP) approach

Analysis with the MAP prior

Clinical trial in ankylosing spondylitis

	Placebo	Experimental
Prior	Beta(11,32)	Beta(0.5,1)
Data	1/6 responders	14/23 responders
Posterior	Beta(11+1, 32+5)	Beta(0.5+14,1+9)

Difference in response rates δ

Posterior median (95% probability interval) for δ 0.35 (0.12,0.56)

$P(\delta > 0 \mid \text{data}) = 99.8\%$

***Note*: Using the exact MAP prior, rather than the approximate Beta(11,32) prior, one obtains $P(\delta > 0 \mid \text{data}) = 99.7\%$**

Meta-analytic-predictive (MAP) approach

Robustness to prior-data conflict

Prior-data conflict

Conjugate priors: always a fixed compromise between prior and data

Priors with heavy tails: prior information discarded with increasing conflict, which is appropriate in clinical trial settings

Robustification of a prior $p(\pi_*)$

Adding weakly-informative mixture component

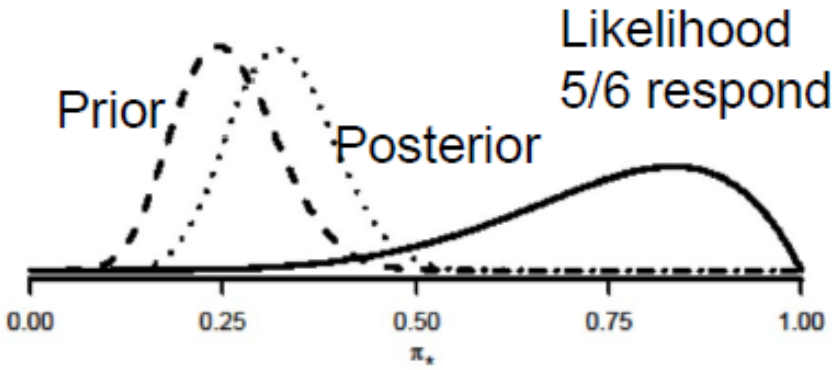
Robust prior: (1- *w*) $p(\pi_*)$ + *w* Beta(1,1)

Beta(1,1) is uniform distribution
Choice of *w* depends on mistrust in historical data
Typical values for *w* in the range of 0.1 to 0.5

Meta-analytic-predictive (MAP) approach

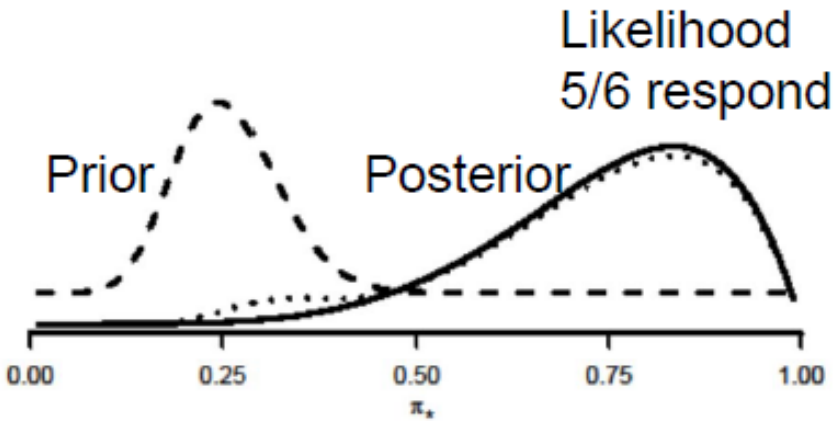
Robustness to prior-data conflict

Placebo prior – hypothetical case of conflict



Conjugate prior

Beta(11,32)



Robust prior

0.5 Beta(11,32) + 0.5 Beta(1,1)

Conclusions

Use of historical control information is attractive

Ethics, recruitment speed, trial costs, trial duration

Meta-analytic-predictive (MAP) approach

Historical data down-weighted due to between-trial heterogeneity

Easy communication through approximation of the MAP prior

Robustness to prior-data conflict achieved through adding a weakly informative mixture component

In rare case of prior-data conflict

Inference with robust prior still valid

May lead to inconclusive trial results

References

Baeten D et al. (2013) Anti-interleukin-17A monoclonal antibody secukinumab in treatment of ankylosing spondylitis: a randomised, double-blind, placebo-controlled trial. *Lancet* 382(9906):1705-1713.

Gelman A (2006) Prior distributions for variance parameters in hierarchical models. *Bayesian Analysis* 1, 515-533.

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

Schmidli H, Gsteiger S, Roychoudhury S, O'Hagan A, Spiegelhalter D, Neuenschwander B (2014) Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics* 70(4):1023-1032.

Spiegelhalter DJ, Abrams KR, Myles JP (2004) *Bayesian Approaches to Clinical trials and Health-Care Evaluation*. Chichester: John Wiley and Sons.

All R-code for the AS example is can be found here

[Weber, S., Li, Y., Seaman III, J. W., Kakizume, T., & Schmidli, H. (2021). Applying Meta-Analytic-Predictive Priors with the R Bayesian Evidence Synthesis Tools. Journal of Statistical Software, 100(19), 1–32. https://doi.org/10.18637/jss.v100.i19]

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Applying Meta-Analytic-Predictive Priors with the R Bayesian Evidence Synthesis Tools

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Thank you