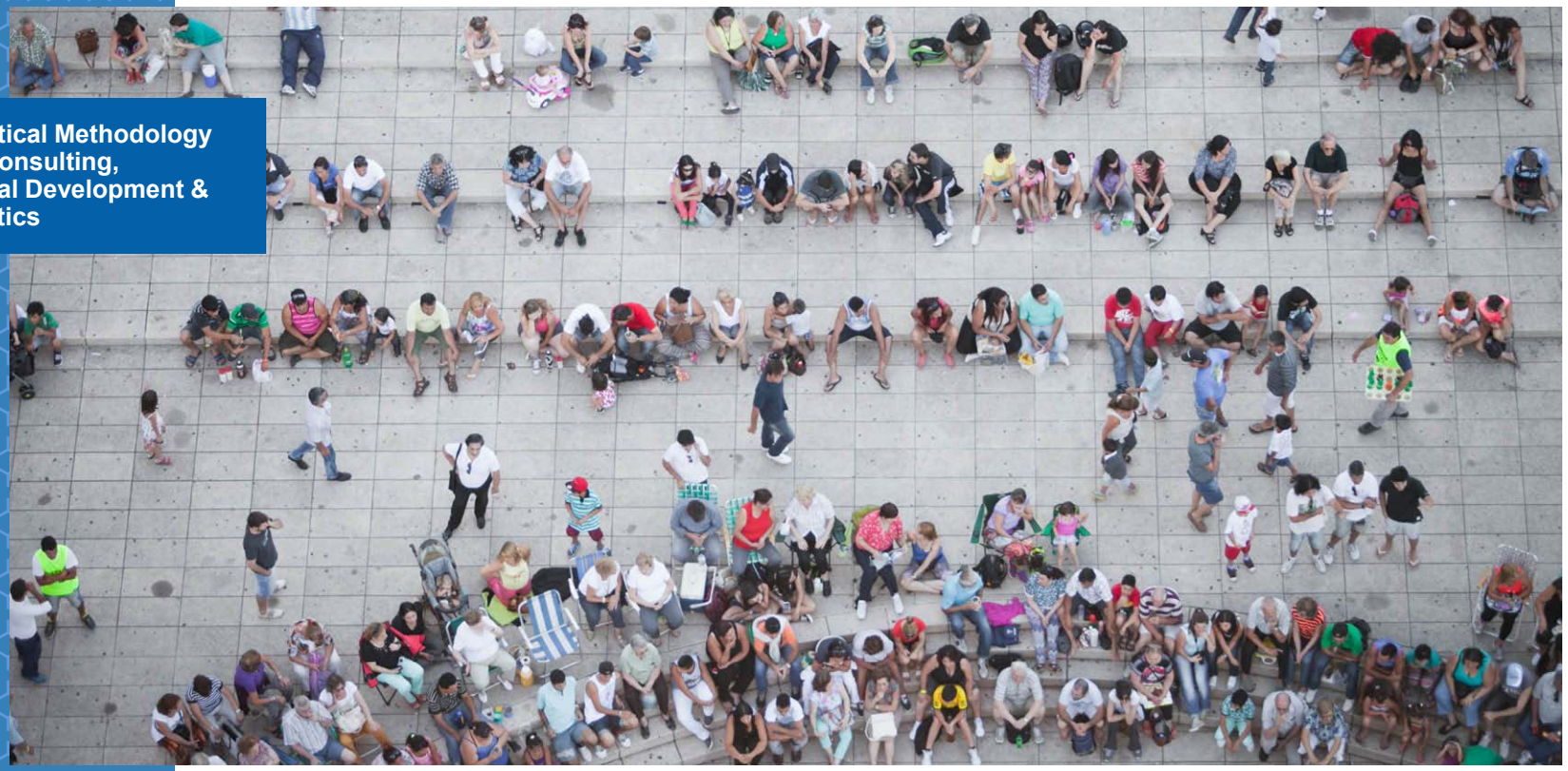
Statistical Methodology and Consulting, Clinical Development & Analytics



Use of historical data

Methods, applications and implementation with the R package RBesT

Heinz Schmidli and Sebastian Weber

Workshop of IBS-GR WG Bayes Methods
Göttingen, Germany, Dec 6-7 2018

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Outline - Methods

- Evidence synthesis and prediction
- Use of historical controls
- Extrapolation from adults to children
- Robustness
- Probability of Success
- Conclusions

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Evidence synthesis and prediction

Introduction

- Evidence synthesis and prediction/extrapolation

  From source to target

  – From historical control to concurrent control

  – From historical adult trials to trial in children

  – From historical trials on one drug to trial in a similar drug

  ...

- Historical clinical trials as main source of information

- Hierarchical models very natural for *evidence synthesis* and *prediction*

Evidence synthesis and prediction

Bayesian approaches

Regulators open to Bayesian approaches in some areas

EMA (2012) Concept paper on extrapolation of efficacy and safety in medicine development (draft).

*Some efficacy data are considered necessary in the target population the nature of which depending on the degree of extrapolation from the source population. Such a scenario could be supported by **'Bayesian' statistical approaches using prior information from the source population(s)**.*

EMA (2016) Reflection paper on extrapolation of efficacy and safety in paediatric medicine development (draft).

*... using **Bayesian methods** to either summarise the prior information for the extrapolation concept, or **to explicitly borrow information (from adult trials, from control groups, from other paediatric clinical trials**).*

FDA (2016) Leveraging existing clinical data for extrapolation to pediatric uses of medical devices.

*While **Bayesian methods** are described in this document, non-Bayesian methods can also be **used for borrowing strength**.*

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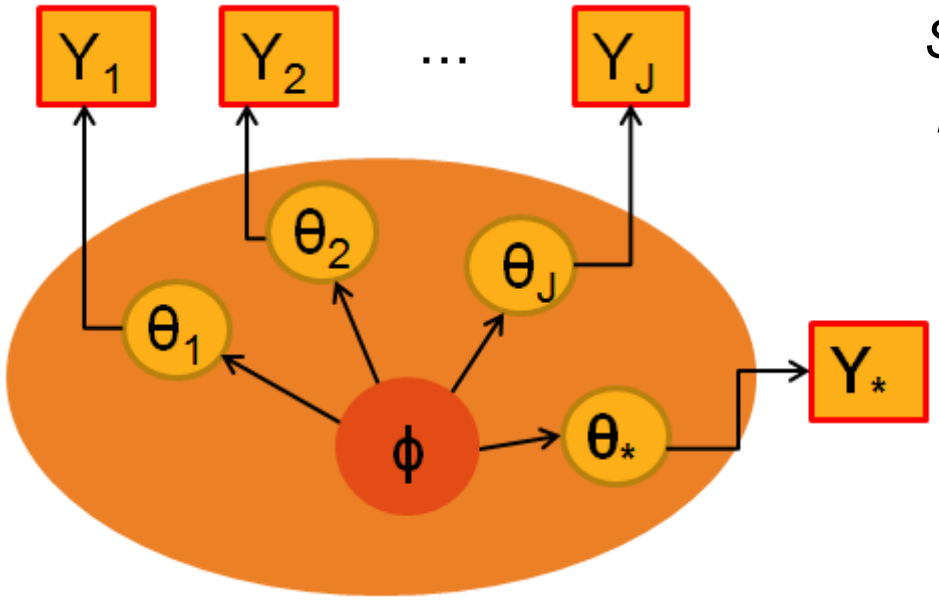
Evidence synthesis and prediction

Framework



Source data

$p(Y_j \mid \theta_j)$ $j=1,...,J$

Target data

$p(Y_* \mid \theta_*)$

Hierarchical model to link parameters (hyper-parameter ϕ)

$p(\theta_*, \theta_1, \ldots, \theta_J \mid \phi)$

Bayesian inference on unknowns $\boldsymbol{\theta}_*$ $(\theta_1, \ldots, \theta_J, \phi)$

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Use of historical controls

Case study

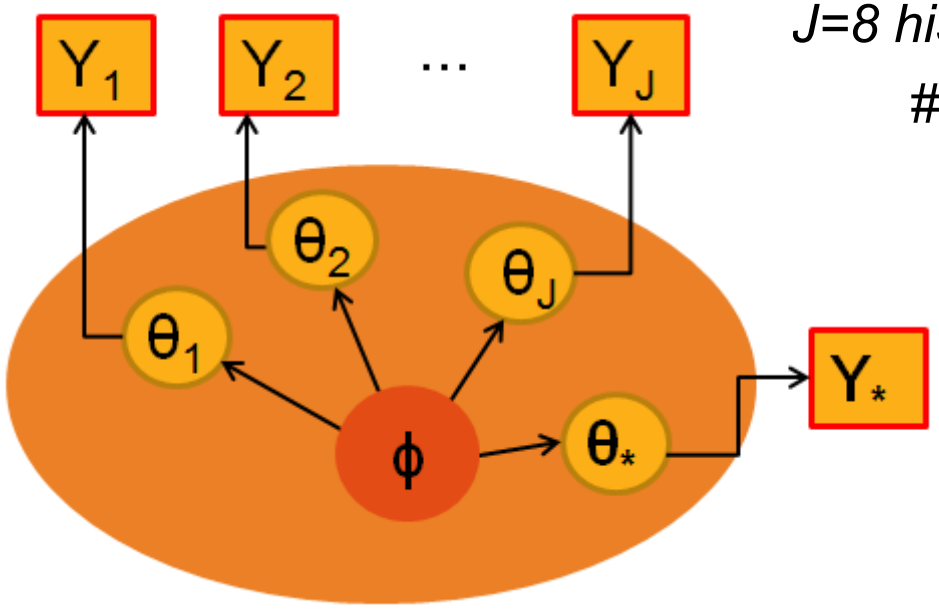
- *Disease*
  Ankylosing spondylitis
- *Test treatment*
  Secukinumab (monoclonal antibody)
- *Endpoint*
  Binary: response at week 6
- *Traditional clinical trial design*
  - Secukinumab (n=24) vs. Placebo (n=24)
  - Fisher's exact test

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

Could this historical placebo information be used?

Use of historical controls

Case study



J=8 historical placebo-controlled trials

 # responders on placebo

$Y_j \sim Binomial(\pi_j, n_j)$

$\theta_j = logit(\pi_j)$

Planned clinical trial

 # responders on placebo

$Y_* \sim Binomial(\pi_*, n_*)$

$\theta_* = logit(\pi_*)$

Simplest hierarchical model to link parameters

$\theta_*, \theta_1, \ldots, \theta_J \mid \mu, \tau \sim N(\mu, \tau^2)$

***M**eta-**A**nalytic-**P**redictive (MAP)*

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

Mean μ
Between-trial standard deviation τ
Hyper-parameter ϕ = (μ, τ)

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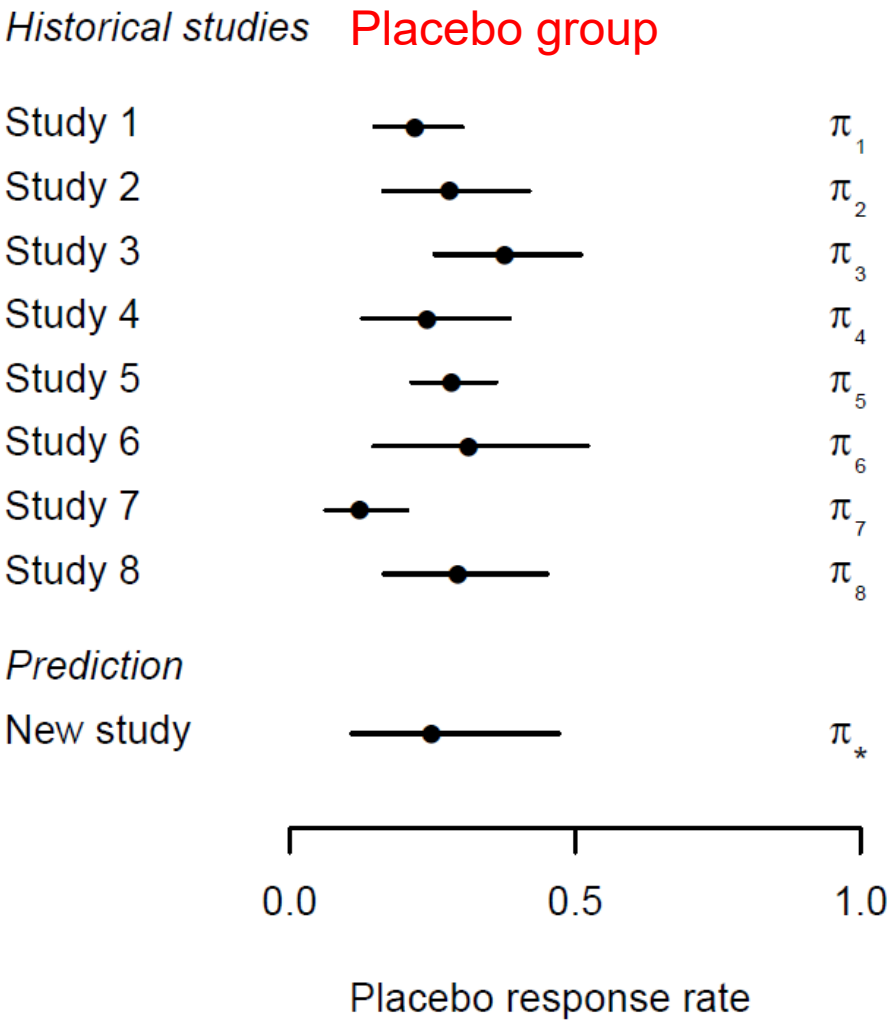
Use of historical controls

Case study



Meta-analytic-predictive (MAP)

$\theta_j = logit(\pi_j)$

$\theta_* = logit(\pi_*)$

$\theta_*, \theta_1, \ldots, \theta_J \mid \mu, \tau \sim N(\mu, \tau^2)$

Prior information for Placebo in new study

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Use of historical controls

Case study

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 Test Treatment* 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, $p(\delta > 0 \mid \text{data}) > 99.8\%$

Baeten et al. (2013) *Lancet*

Use of historical controls

Summary

- Benefits

  Allows to reduce number of placebo patients in new trial

  – Decreases cost

  – Shortens trial duration

  – Facilitates recruitment

  } Faster decisions

  – May be more ethical in some situations

- Risks

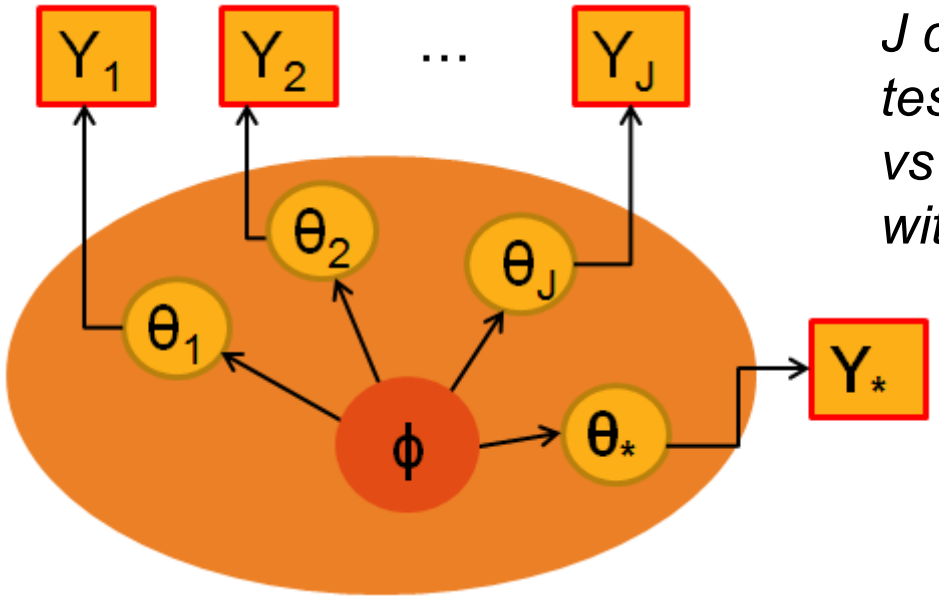
  – Prior-data conflict

  – Excessive type I error inflation

  Mitigated by using robust priors, adaptive designs

Extrapolation from adults to children

Example for evidence synthesis and extrapolation



*J clinical trials in **adults** of test treatment vs control, with treatment effect θ_j*

*Clinical trial in **children** of test treatment (children version) vs control, with treatment effect θ_**

- Full extrapolation: $p(\theta_* \mid Y_1, \ldots, Y_J)$
- Partial extrapolation: $p(\theta_* \mid Y_1, \ldots, Y_J, Y_*)$
- No extrapolation: $p(\theta_* \mid Y_*)$

Models to link parameters

$$\theta_*, \theta_1, \ldots, \theta_J \mid \mu, \tau \sim N(\mu, \tau^2)$$

?

$$\theta_* \mid \mu_*, \tau_* \sim N(\mu_*, \tau_*^2)$$

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Extrapolation from adults to children

Illustrative example - treatment of venous thromboembolic events (VTE)

- Considered clinical trial in children
  - *Test*: low molecular weight heparin
  - *Control*: unfractionated heparin, followed by oral anticoagulation

  Binary primary endpoint: recurrent VTE (3 months)
- 14 similar historical cinical trials in adults

  Test vs Control, recurrent VTE (3 months) available

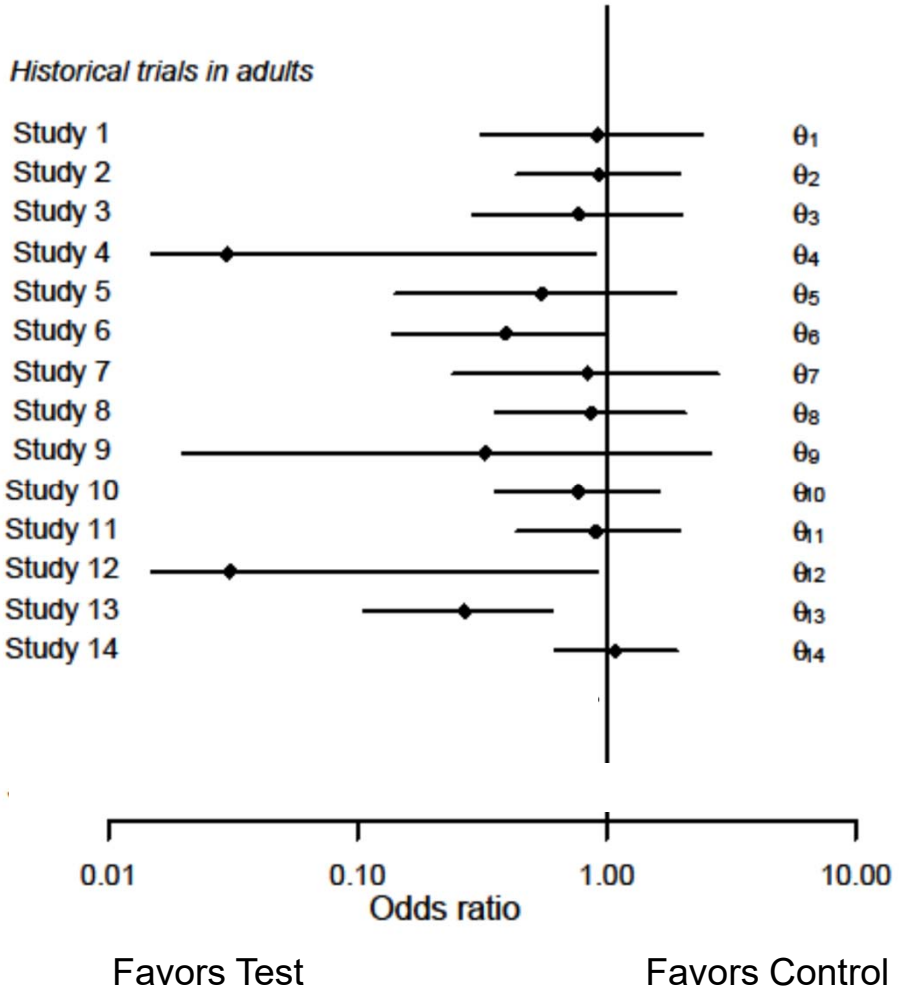
  Erkens and Prins (2010) Cochrane Database of Systematic Reviews
- Similar efficacy in children and adults seems plausible
  - Individualized dosing based on biomarkers and body weight
  - Same mode of action

  Full extrapolation?

Comparable setting discussed by Gerß et al. (2012)

Extrapolation from adults to children

Treatment of venous thromboembolic events (VTE)



Recurrent VTE (3 months)

Test vs Control:
Log(odds ratio) θ_j

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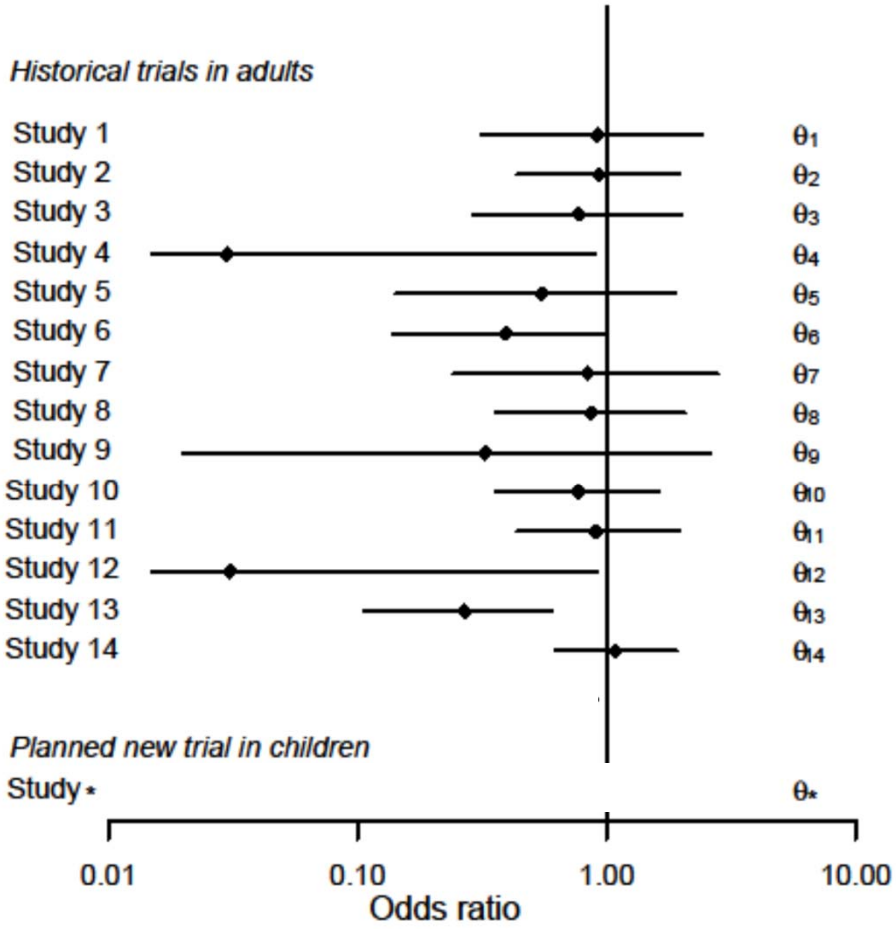
Extrapolation from adults to children

Treatment of venous thromboembolic events (VTE)



Recurrent VTE (3 months)

Test vs Control:
Log(odds ratio) θ_j

Meta-Analytic-Predictive (MAP) model

$\theta_*, \theta_1, \ldots, \theta_J \mid \mu, \tau \sim N(\mu, \tau^2)$

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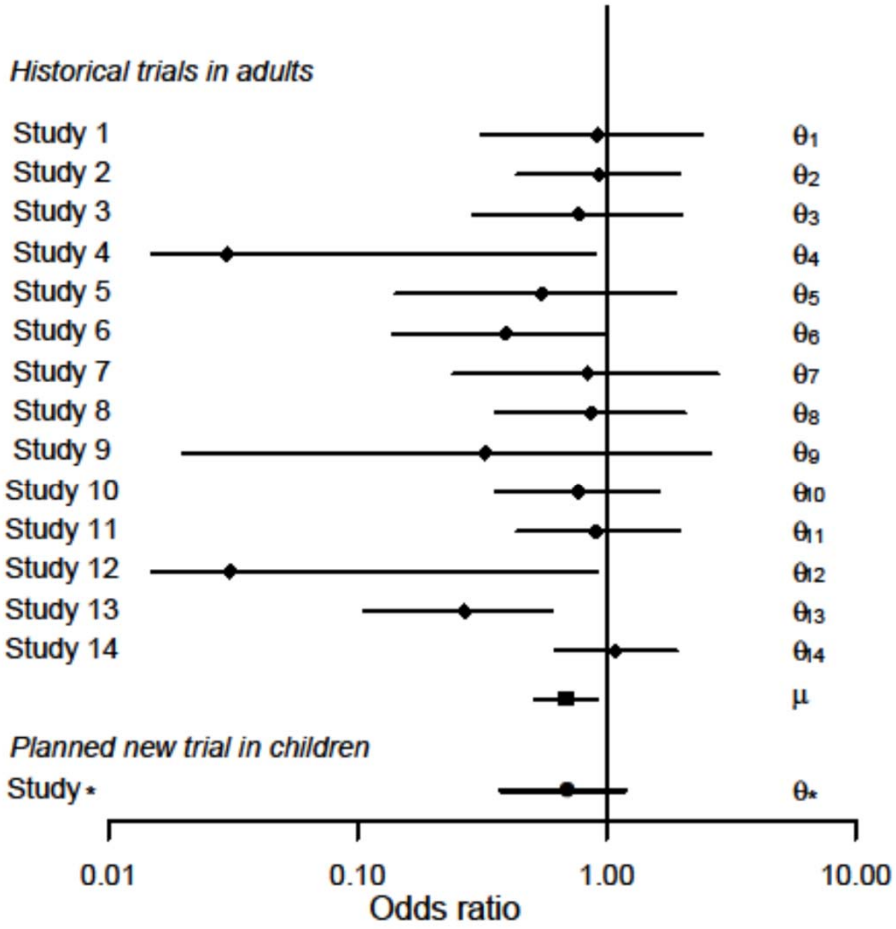
Extrapolation from adults to children

Treatment of venous thromboembolic events (VTE)



Recurrent VTE (3 months)

Test vs Control:
Log(odds ratio) θ_j

Meta-Analytic-Predictive (MAP) model

$\theta_*, \theta_1, \ldots, \theta_J \mid \mu,\tau \sim N(\mu,\tau^2)$

MAP prior $p_{MAP}(\theta_*)=p(\theta_*|Y_1,\ldots,Y_J)$

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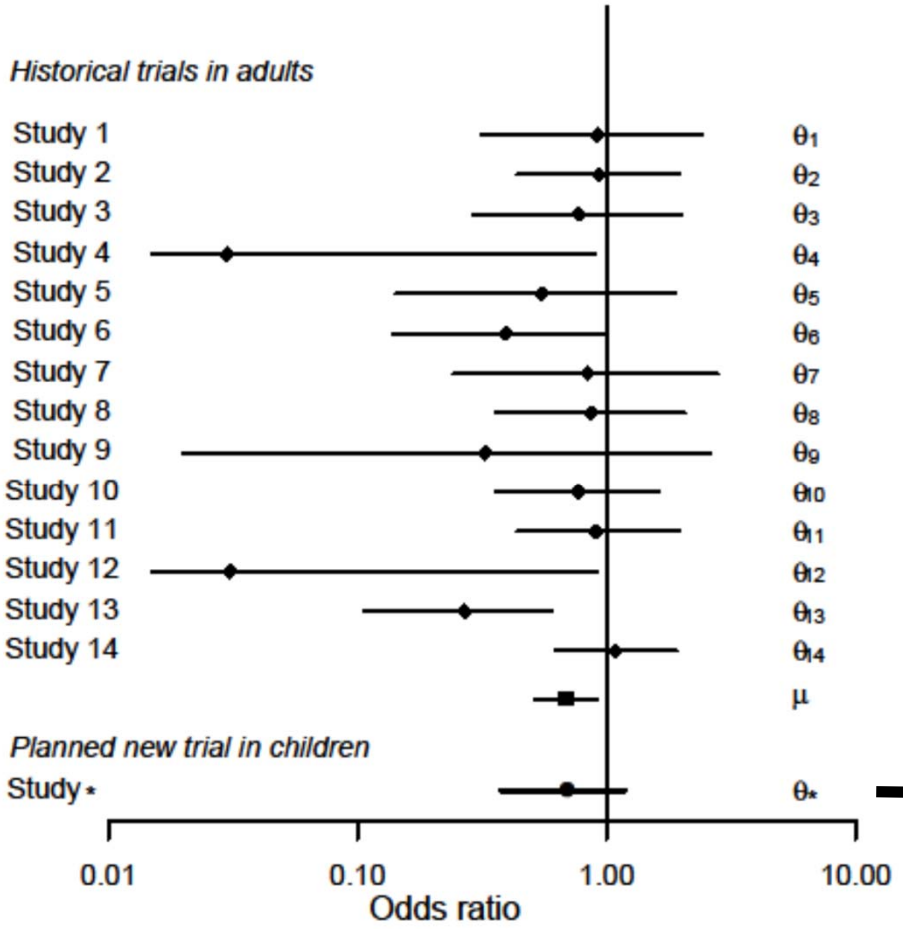
Extrapolation from adults to children

Treatment of venous thromboembolic events (VTE)

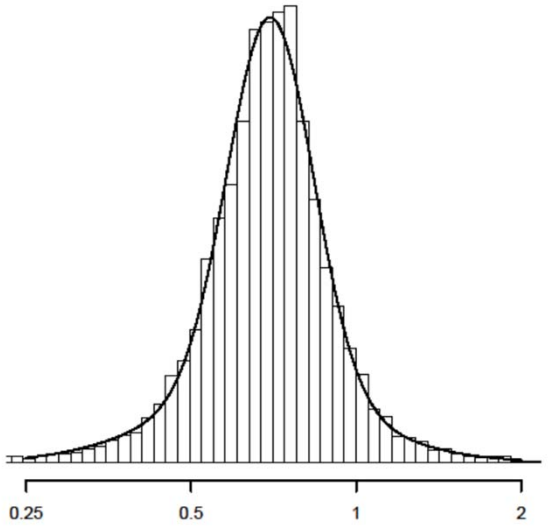


MAP prior

$p_{MAP}(\theta_*) = p(\theta_* \mid Y_1, ..., Y_J)$

Approximated by mixture of normal distributions (solid line)

$0.71\ N(-0.36, 0.18^2) + 0.29\ N(-0.41, 0.42^2)$



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Extrapolation from adults to children

Treatment of venous thromboembolic events (VTE)

- MAP approach to extrapolate from adults to children

  MAP prior $p_{MAP}(\theta_*)$ derived from total of 6551 adults (14 studies)

- Trial in children

  Recurrent VTE (3 months): *Test* 2/36 vs *Control* 4/40

  Massicotte et al. (2003) planned N=352, actual N=78

- Extrapolation from adults to children

	Odds ratio $\exp(\theta_*)$ median (95% prob. interval)	Prob OR<1	Effective sample size (ESS)
Full	0.69 (0.37, 1.19)	94%	1030
Partial*	0.68 (0.38, 1.09)	96%	1199
No	0.48 (0.06, 2.84)	78%	78

* Using $\theta_*, \theta_1, \ldots, \theta_J \mid \mu, \tau \sim N(\mu, \tau^2)$

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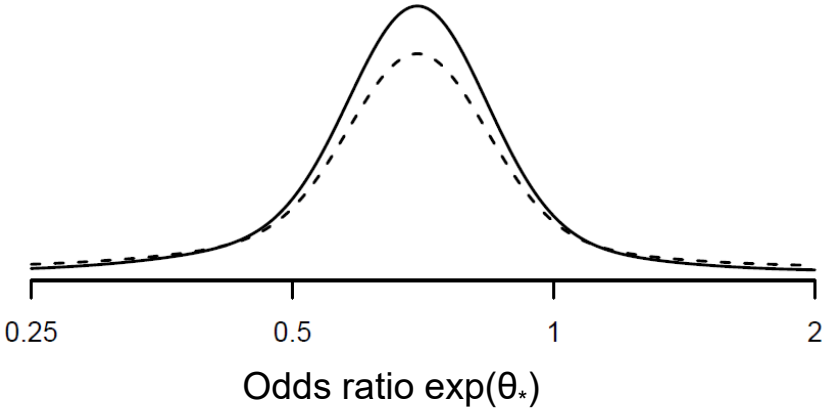
Robustness

Relevance of source data

- Prior $p(\theta_*)$ derived from adults considered to be relevant for children, however...

  "... think it possible that you may be mistaken." Cromwell

- Robust prior $p_{Robust}(\theta_*) = (1-\varepsilon)\, p_{MAP}(\theta_*) + \varepsilon\, p_{Vague}(\theta_*)$
  - Mixture of prior derived from adults and vague prior
  - Value ε chosen to reflect scepticism on relevance of adult data
  - Robust priors are heavy-tailed, and hence discarded in case of clear prior-data conflict O'Hagan and Pericchi (2012), Schmidli et al. (2014)



Solid line: $p(\theta_*)$
Dashed line: $p_{Robust}(\theta_*)$ with ε=0.2

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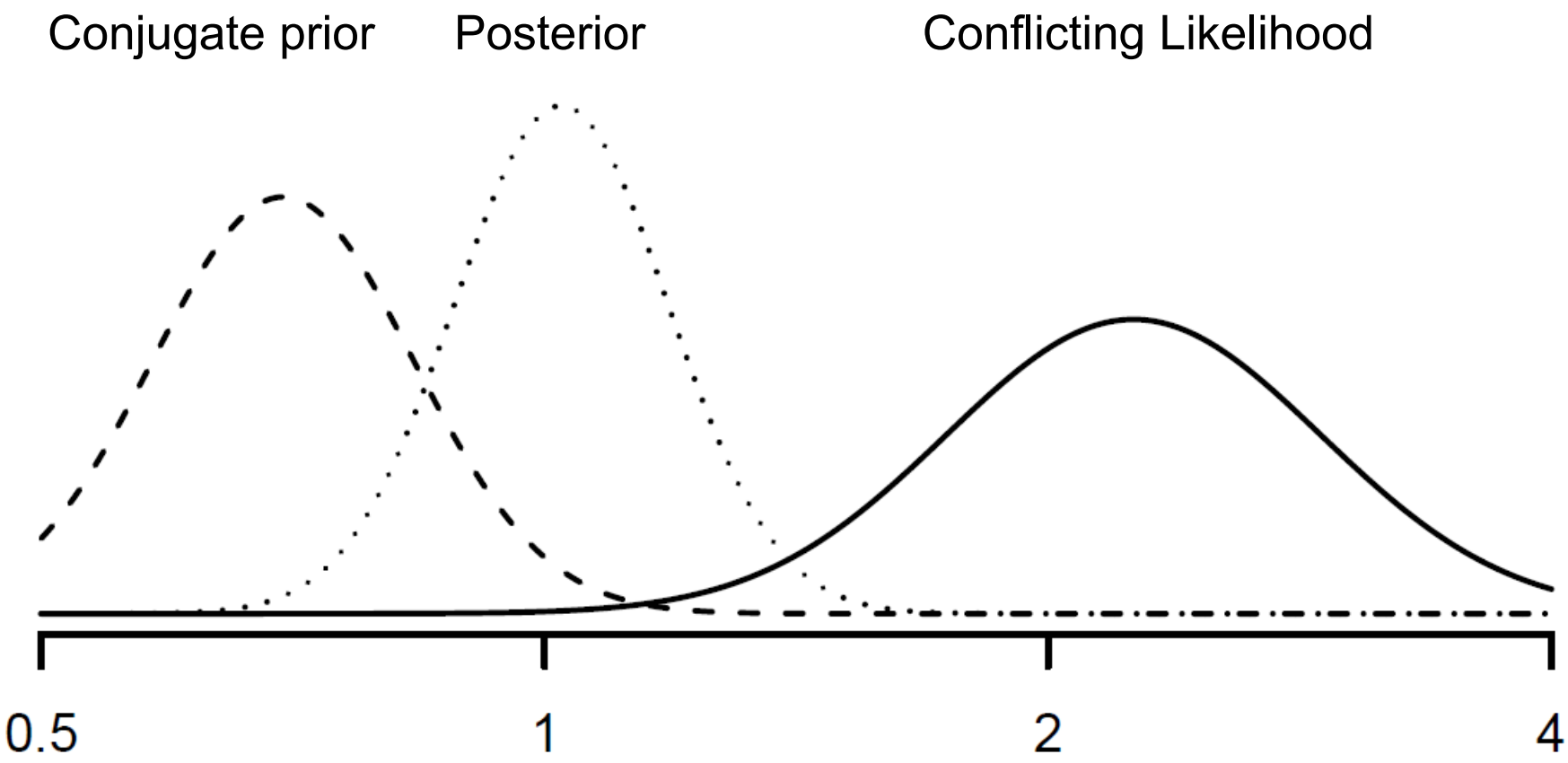
Robustness

Prior-data conflict - hypothetical



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

Stephen Senn

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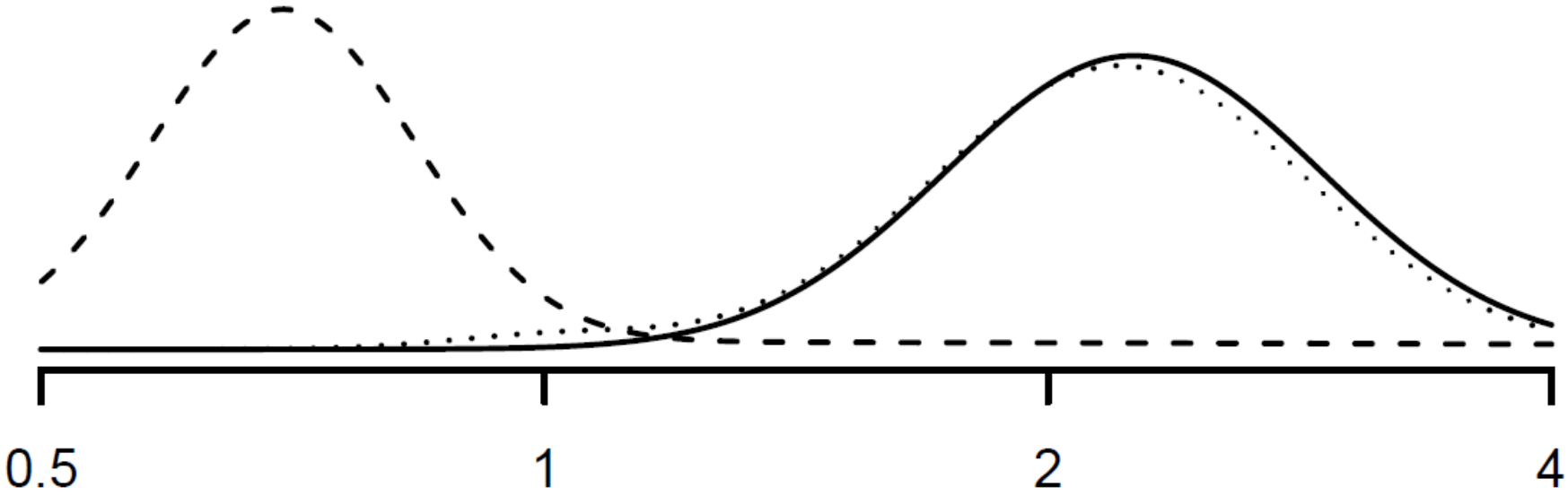
Robustness

Prior-data conflict - hypothetical

Robust prior

Posterior / Conflicting Likelihood



Robust prior essentially discarded in case of clear prior-data conflict

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Extrapolation from adults to children

Summary

- Benefits

  Allows to reduce number of children in new trial

  – More ethical in many situations
  – Facilitates recruitment
  – Shortens trial duration
  – Decreases cost

  } Faster decisions

- Risks

  – Prior-data conflict
  – Excessive type I error inflation

  Mitigated by using robust priors, adaptive designs

Probability of Success

Introduction

Success in a ...

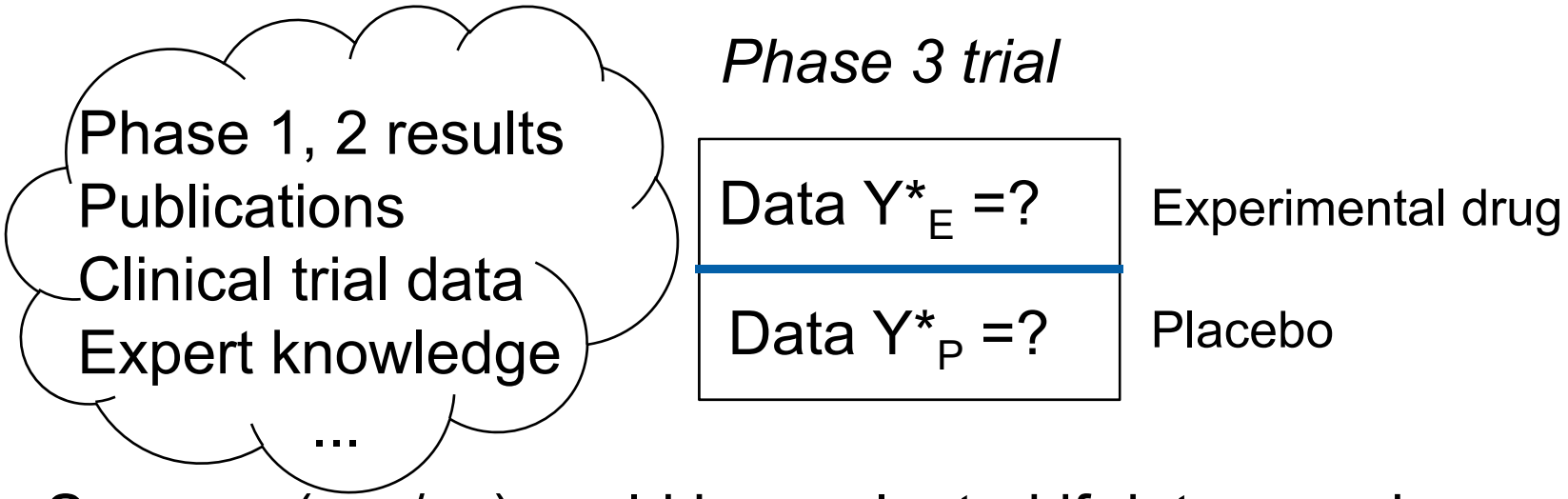
- Clinical trial
  - Statistically significant efficacy result
  - Observed response rate on drug > 60%
  - Less observed AE than in active control

  ...
- Clinical development program
  - Target product profile – meet “base“/“upside“ case
  - Drug approval
  - Drug reimbursement
  - ...

Probability of Success

Planning a Phase 3 trial

- Historical data/information available



- Success (yes/no) could be evaluated if data were known...

  E.g. success: p-value < 2.5% (one-sided)

- Uncertainty on data, hence uncertainty about success

Probability of success (PoS)	0-100%

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Probability of Success

Planning a Phase 3 trial: Evaluating PoS

Bayesian framework

Prediction: predictive distribution of future data $Y^* = (Y^*_E , Y^*_P)$

Y^*_E =?
Y^*_P =?

E.g.10’000 times:

- sample Y*(i) from predictive distribution
- Calculate success S(i) (1/0)
- Probability of Success PoS ≈ Σ S(i) / 10’000

In simple cases: analytical evaluation rather than simulation

Probability of Success

Example: interim analysis in Phase 3

- Two phase 3 trials A and B running in parallel
  - endpoint survival
  - 379 events (n): α=2.5%, 90% power for log-hazard ratio log(0.75)
  - interim analysis when at least 150 deaths occurred in each of the trials
- Two historical trials

  1) a small proof-of-concept trial, and 2) a randomized phase 2 trial
- Interim decisions
  - based on probability of success (PoS)
  - stop phase 3 trial if PoS < 10% (e.g.)
- Evaluating PoS without/with co-data
  - *Without*: e.g. for phase 3 trial A, use just interim data from trial A for PoS
  - *With*: e.g. for trial A, use also interim data from trial B and historical trials

Probability of Success

Example: interim analysis in Phase 3

Data available at interim analysis for HR θ

	Study	deaths	HR (95%-int)	
1.	Proof-of-concept	8	θ_1 0.70 (0.18,2.80)	Co-data
2.	Phase 2	85	θ_2 0.75 (0.49,1.15)	
3.	Phase 3 study A	162	θ_3 0.83 (0.61,1.13)	
4.	Phase 3 study B	150	θ_4 0.78 (0.57,1.07)	

- Success = statistical significance
  PoS = predictive power (Spiegelhalter et al., 1986)
- Evaluating PoS for Phase 3 study B
  - classical conditional power $CP(\theta_4) = p(\text{final p-value}<0.025 \mid \theta_4, \text{interim data})$
  - $PoS = \int CP(\theta_4)\, p(\theta_4 \mid \text{interim data})\, d\,\theta_4$
  - Posterior distribution $p(\theta_4 \mid \text{interim data})$ may be evaluated without or with co-data
  - With co-data: $\theta_1,\theta_2,\theta_3,\theta_4 \mid \mu,\tau \sim N(\mu,\tau^2)$

Probability of Success

Example: interim analysis in Phase 3

Study	deaths	HR (95%-int)	log(HR) (sd)	pr(HR<1)	PoS	ESS
stratified analyses						
1. Proof-of-concept	8	0.70 (0.18,2.80)	-0.36 (0.71)	0.69		8
2. Phase II	85	0.75 (0.49,1.15)	-0.29 (0.22)	0.91		85
3. Phase III study A	162	0.83 (0.61,1.13)	-0.19 (0.16)	0.88	0.45	162
4. Phase III study B	150	0.78 (0.57,1.07)	-0.25 (0.16)	0.94	0.64	150
co-data analysis						
3. Phase III study A	162	0.80 (0.63,1.04)	-0.22 (0.13)	0.95	0.51	254
4. Phase III study B	150	0.79 (0.61,1.01)	-0.24 (0.13)	0.97	0.65	252

ESS=effective sample size (number of events)

- PoS without co-data (stratified analyses) or with co-data
- Borrowing strength from co-data to support decision making

Neuenschwander et al. (2016)

Probability of Success

MAP or MAC?

Two approaches for evidence synthesis

- Meta-Analytic-Predictive (MAP) is *prospective*
  - At design stage of current trial, perform MA of co-data and obtain distribution of θ_* MAP Prior $p(\theta_* | Y_1,...,Y_J)$
  - For the analysis, combine MAP prior with current trial data Y*
- Meta-Analytic-Combined (MAC) is *retrospective*
  - Perform a meta-analysis of all co-data and current trial data
  - Parameter of interest is the parameter in the actual trial θ_* $p(\theta_* | Y_1 ,...,Y_J ,Y_*)$
- MAP and MAC give identical results!
- PoS evaluation
  - At design stage, MAP has to be used
  - At analysis stage, more convenient of MAP or MAC can be used

Conclusions

- Hierarchical models flexible and useful for
  - synthesis of evidence from various sources
  - extrapolation to target
- Bayesian framework natural for
  - Inclusion of prior information
  - Inference and prediction
- Scepticism on relevance of source data can be taken into account

heinz.schmidli@novartis.com

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