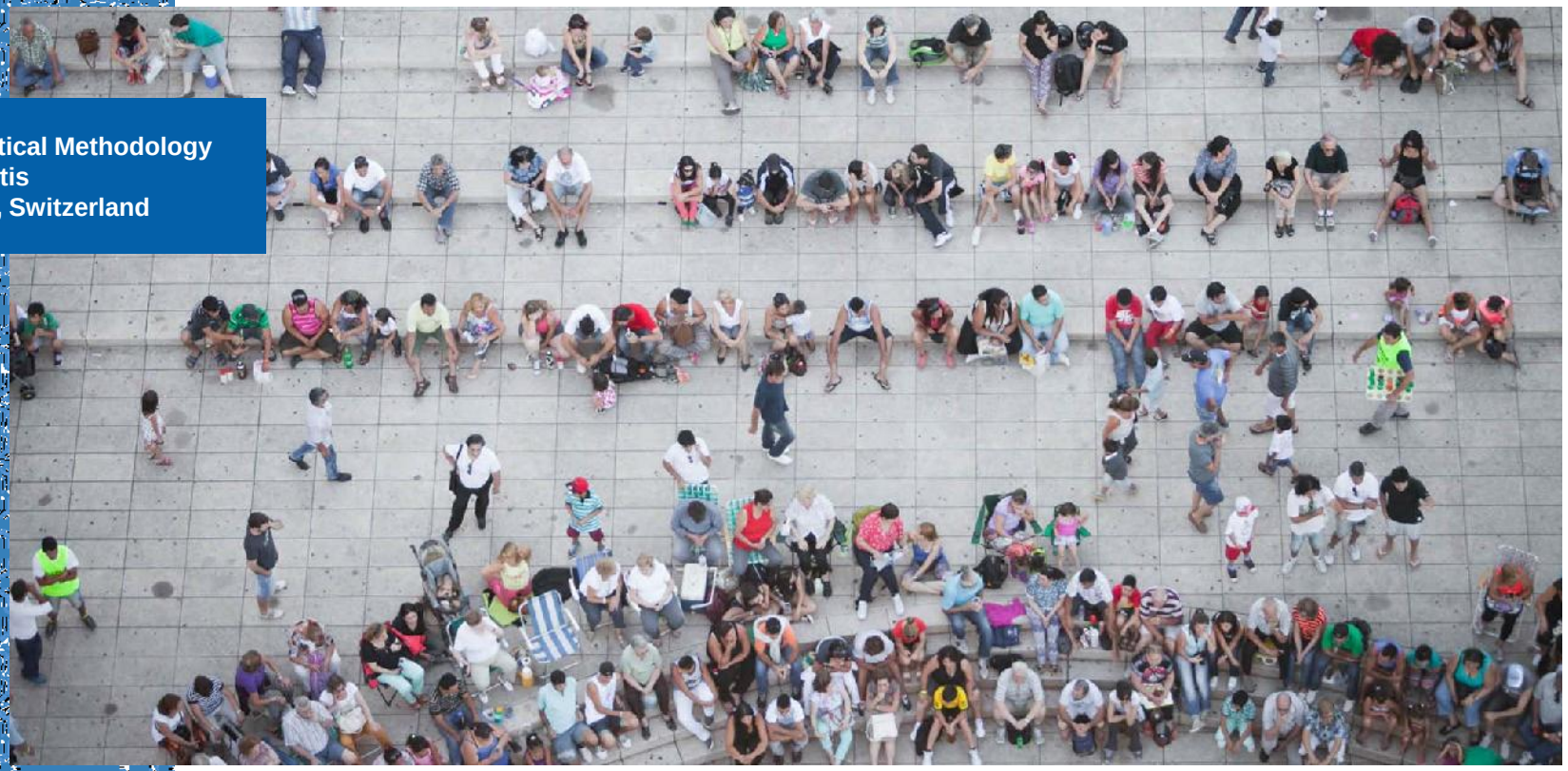
Statistical Methodology
Novartis
Basel, Switzerland



# Bayesian Evidence Synthesis for Extrapolation in Clinical Research

**Heinz Schmidli**

***38th Annual Conference of the ISCB***
***9-13 July 2017, Vigo***

NOVARTIS

# Outline

- Extrapolation/Prediction
  - Use of historical controls
  - Extrapolation from adults to children
- Robustness
- Type I error
- Further applications
- Conclusions

*Acknowledgements*

*Beat Neuenschwander, Simon Wandel*

*David Spiegelhalter, Anthony O'Hagan*



NOVARTIS

# Extrapolation/Prediction

*Introduction*

- Extrapolation/Prediction common in clinical research

  *From source to target*

  – From historical control to concurrent control
  – From adults to children
  – From biomarker to clinical endpoint
  – From one drug to another

  ...

- Clinical trials as main source of information

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

# Extrapolation/Prediction

*Bayesian approaches*

## Regulators open to Bayesian approaches

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.

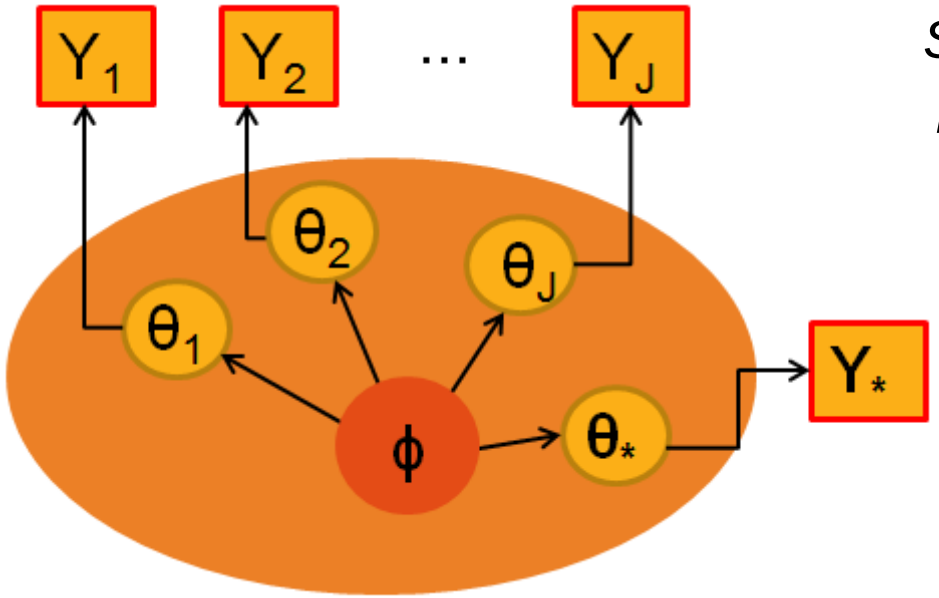
*While **Bayesian methods** are described in this document, non-Bayesian methods can also be **used for borrowing strength**.*



NOVARTIS

# Extrapolation/Prediction

*Framework for evidence synthesis and extrapolation*




*Source data*

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

*Target data*

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

*Hierarchical model to link parameters (hyper-parameter $\phi$)*

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

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

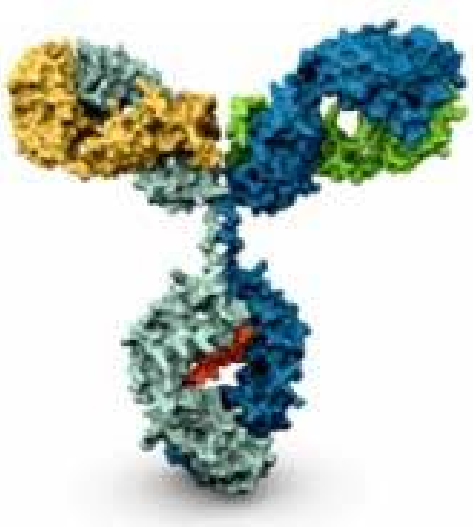


NOVARTIS

# 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

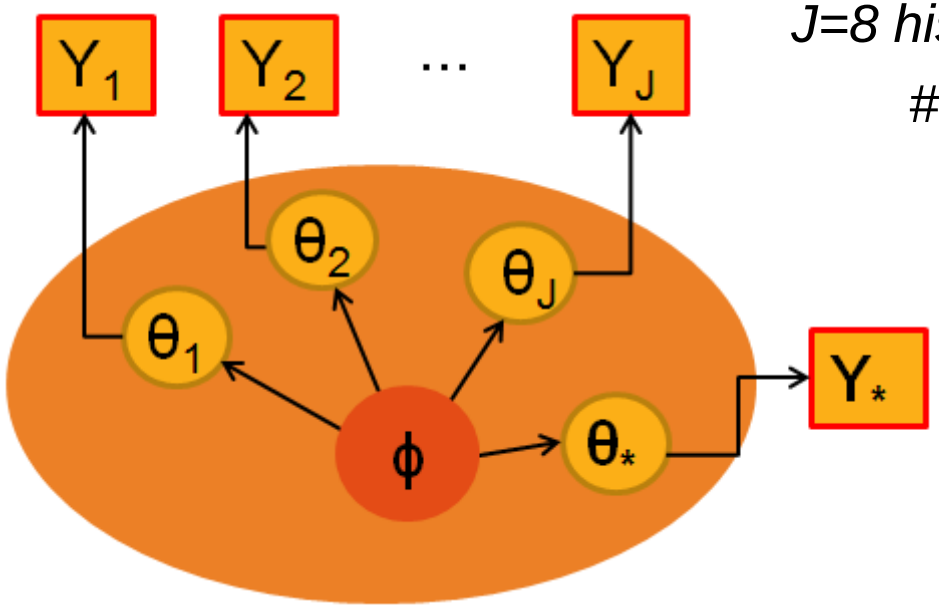


However: 8 similar historical placebo-controlled clinical trials with different test treatments

*Could this historical placebo information be used?*

# Use of historical controls

*Case study*




*J=8 historical placebo-controlled trials*

*# responders on placebo*

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

$\theta_j = logit(\ _j)$

*Planned clinical trial*

*# responders on placebo*

$Y_* \sim Binomial(\ _*, n_j)$

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

*Simplest hierarchical model to link parameters*

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

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

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

*Mean μ*

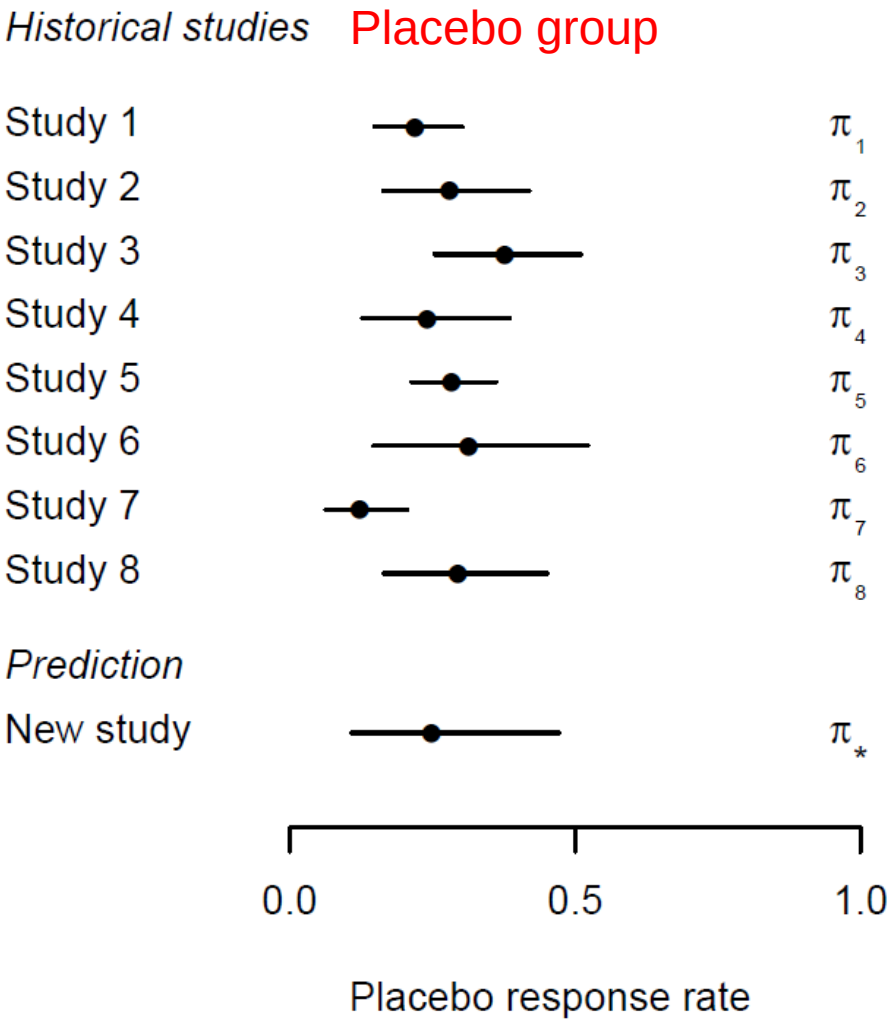
*Between-trial standard deviation*



NOVARTIS

# Use of historical controls

*Case study*




*Meta-analytic-predictive (MAP)*

$\theta_j = logit(\ _j)$

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

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

*Prior information for Placebo in new study*



NOVARTIS

# 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, $p(\ \ >0 \mid \text{data}) > 99.8\%$

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

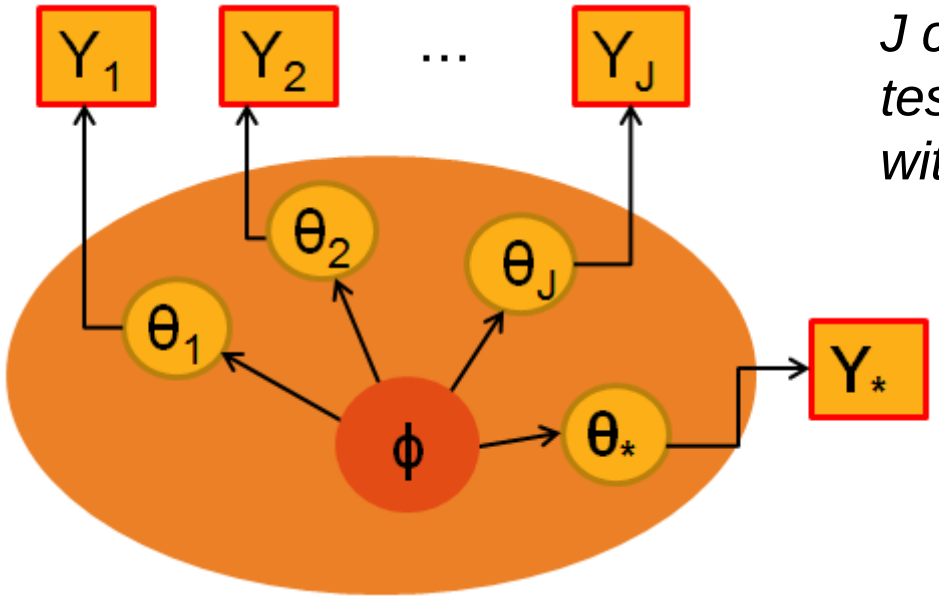
  – Prior-data conflict

  – 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 $\theta_j$*

*Clinical trial in **children** of test treatment vs control, with treatment effect $\theta_*$*

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*

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

*?*

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



NOVARTIS

# 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

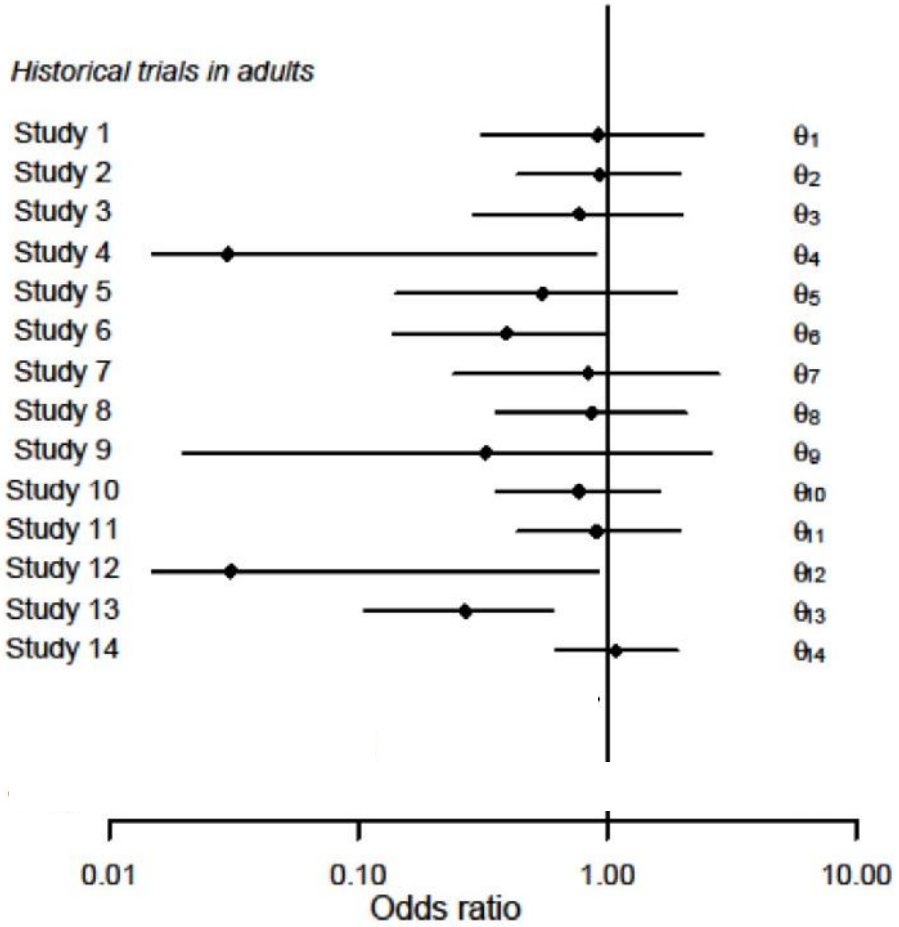
  Erkens and Prins (2010) Cochrane Database of Systematic Reviews
- Similar efficacy in children and adults seems plausible
  - Individualized dosing based on biomarkers and body weight
  - Same mode of action

  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)

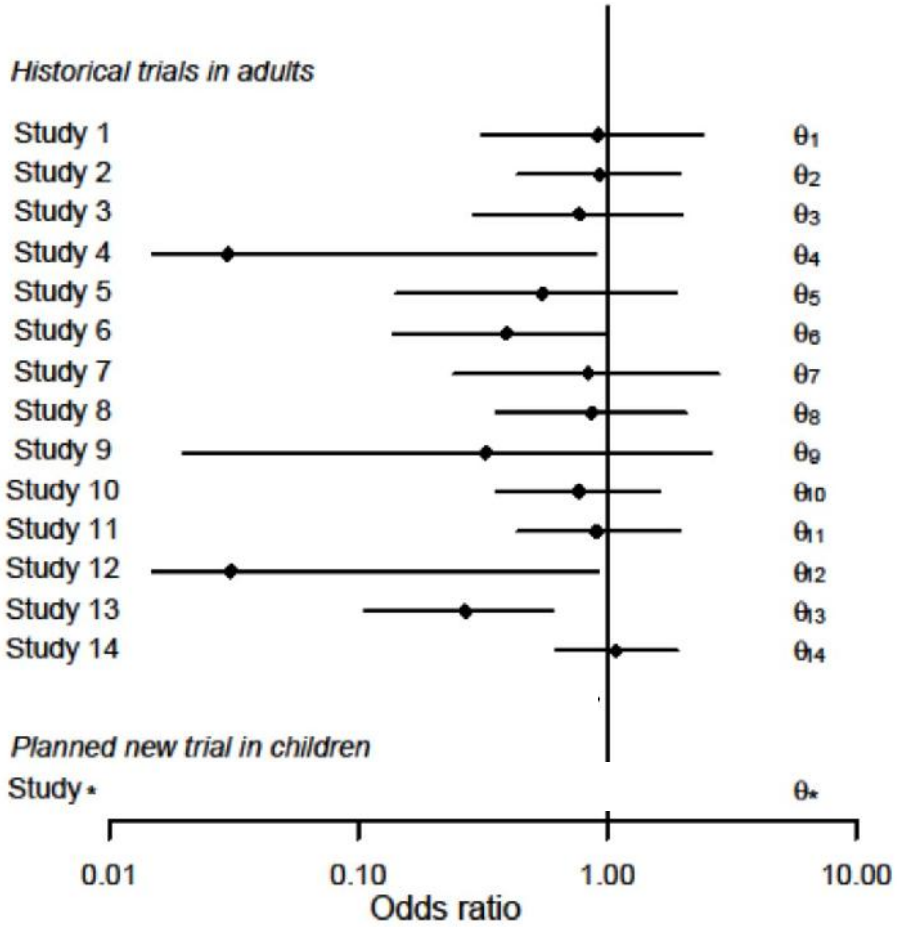
Test vs Control:
Log(odds ratio) $\theta_j$



NOVARTIS

# Extrapolation from adults to children

*Treatment of venous thromboembolic events (VTE)*




Recurrent VTE (3 months)

Test vs Control:
Log(odds ratio) $\theta_j$

Meta-Analytic-Predictive (MAP) model

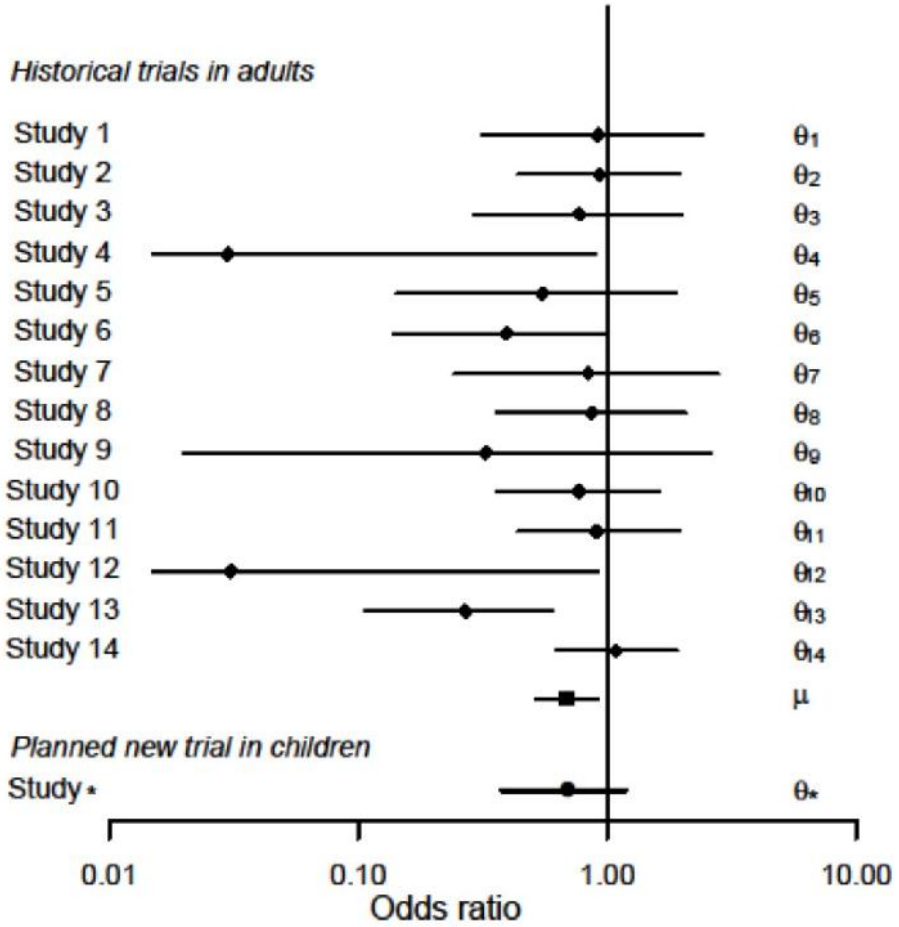
$\theta_*, \theta_1, \ldots, \theta_J \mid \mu, \quad \sim N(\mu, \ ^2)$



NOVARTIS

# Extrapolation from adults to children

*Treatment of venous thromboembolic events (VTE)*




Recurrent VTE (3 months)

Test vs Control:
Log(odds ratio) $\theta_j$

Meta-Analytic-Predictive (MAP) model

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

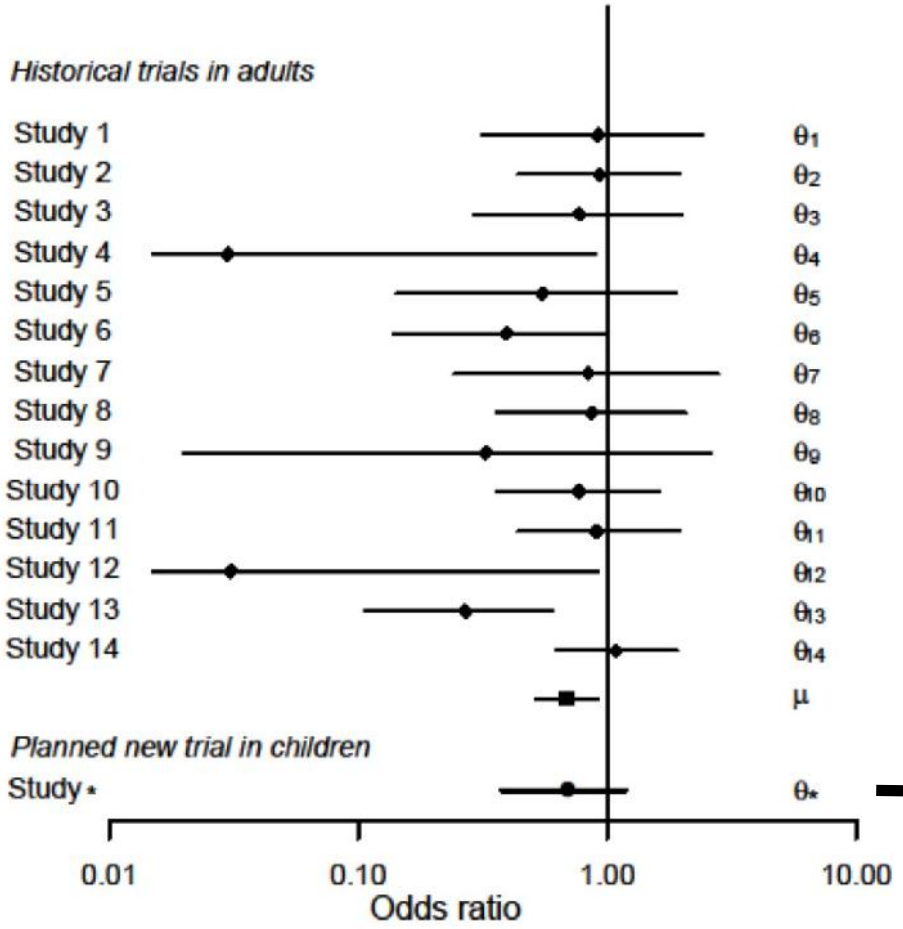
MAP prior $p_{MAP}(\theta_*)=p(\theta_*|Y_1,\ldots,Y_J)$



NOVARTIS

# Extrapolation from adults to children

*Treatment of venous thromboembolic events (VTE)*

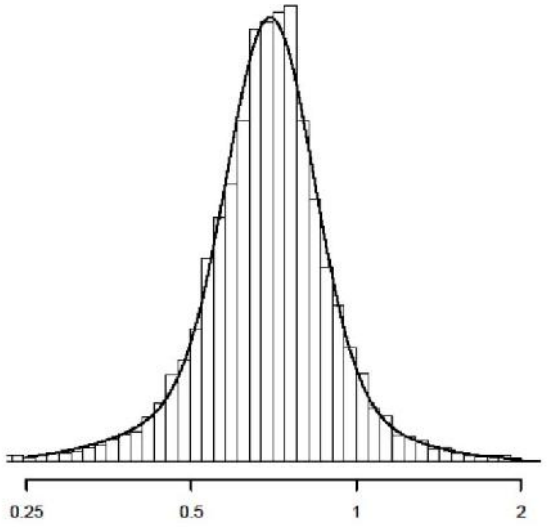



MAP prior

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

Approximated by mixture of normal distributions (solid line)

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






NOVARTIS

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

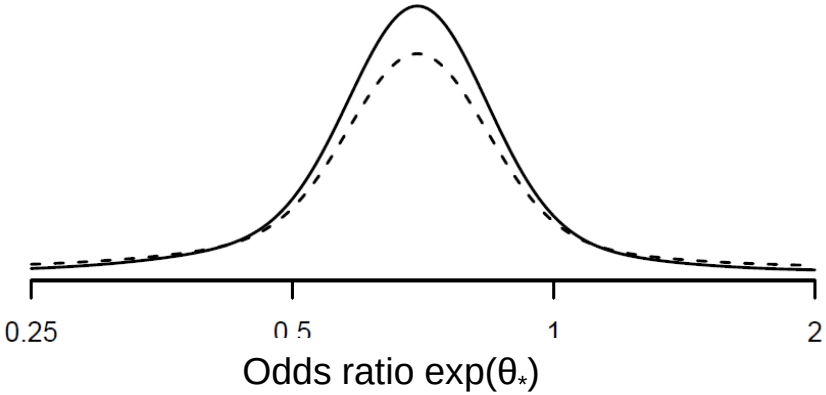
# Robustness

*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)



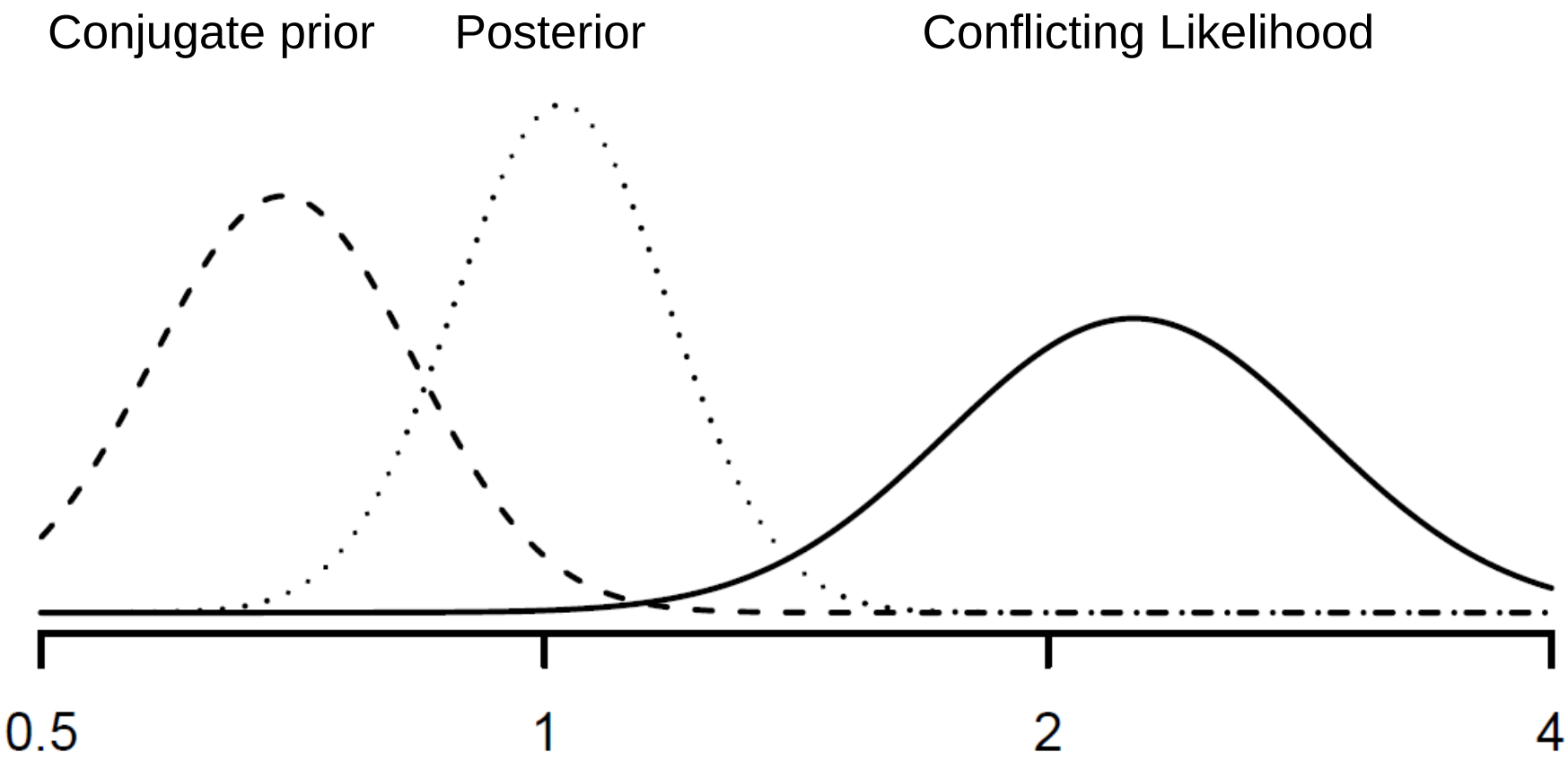

Solid line: $p(\theta_*)$
Dashed line: $p_{Robust}(\theta_*)$ with ε=0.2



NOVARTIS

# 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*



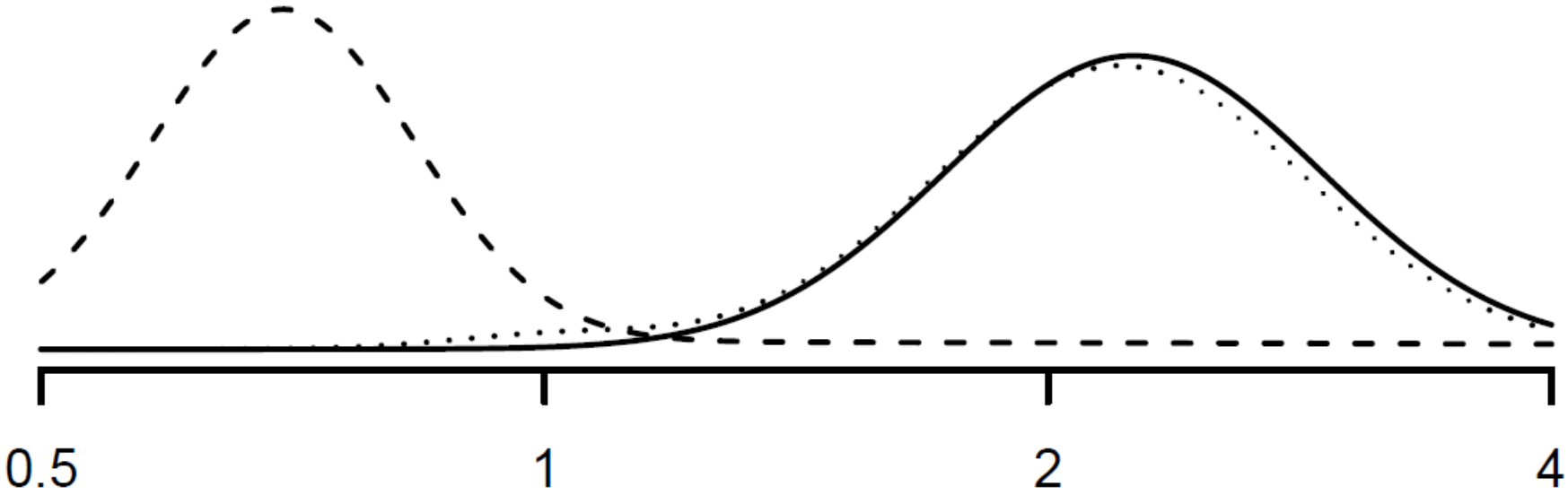
NOVARTIS

# Robustness

*Prior-data conflict - hypothetical*

Robust prior

Posterior / Conflicting Likelihood




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



NOVARTIS

# 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

  } Faster decisions

  – Decreases cost

- Risks

  – Prior-data conflict

  – Excessive type I error inflation

  Mitigated by using robust priors, adaptive designs

# Type I error

*Scientific judgement*

- Incompatible - can't have both!

  **Strict type I error control** vs. **Borrowing strength from external data**

- Strict type I error control not always required
  - Early phase trials (phase I, IIa, IIb)
  - Some phase III settings – two examples

    *Monotherapy treatment for epilepsy*: FDA requires single arm phase III trial with historical control

    French et al. (2010) *Epilepsia*

    *Non-inferiority trials*: superiority to placebo indirectly established based on historical trials

    FDA Guidance (2016) "In the absence of a placebo arm, knowing whether the trial had assay sensitivity **relies heavily on external (not within-study) information, giving NI studies some of the characteristics of a historically controlled trial**."

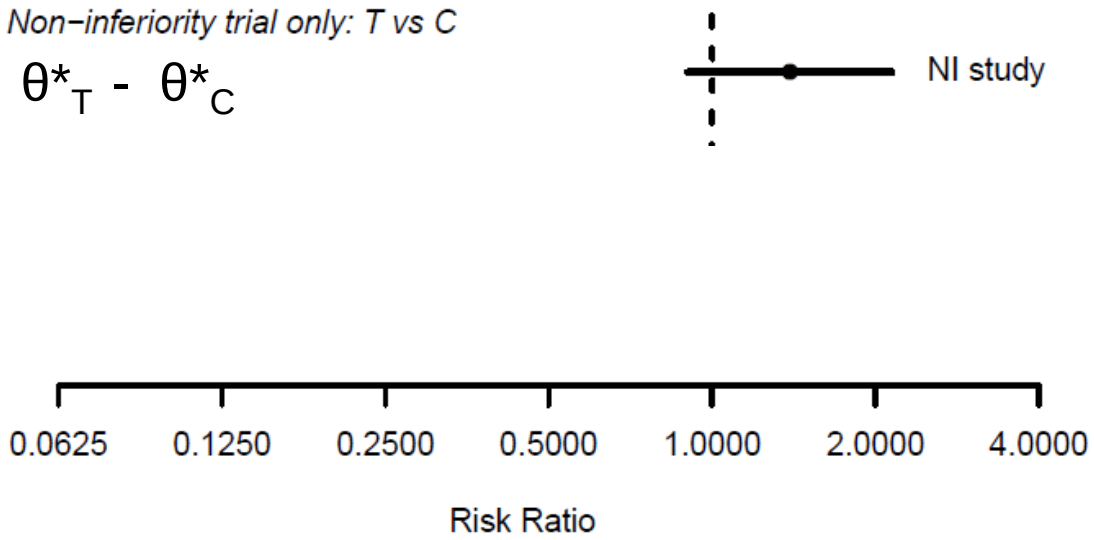
# Further applications

*Non-inferiority trials*

Example data from FDA guidance on NI trials (2016)

NI trial SPORTIF V for prevention of stroke T vs C

T test treatment C active control P placebo



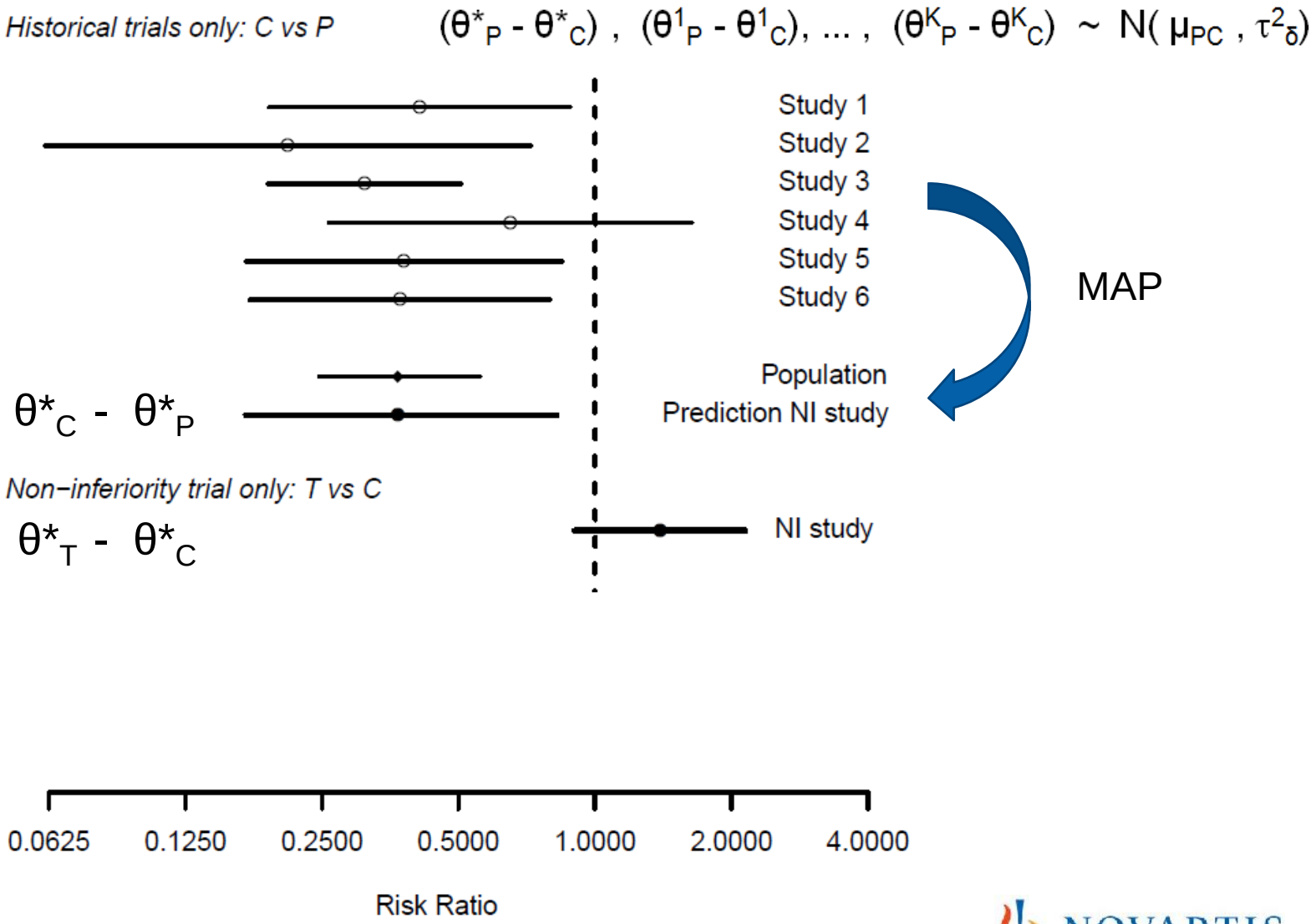

T vs P ?



NOVARTIS

# Further applications

*Non-inferiority trials*

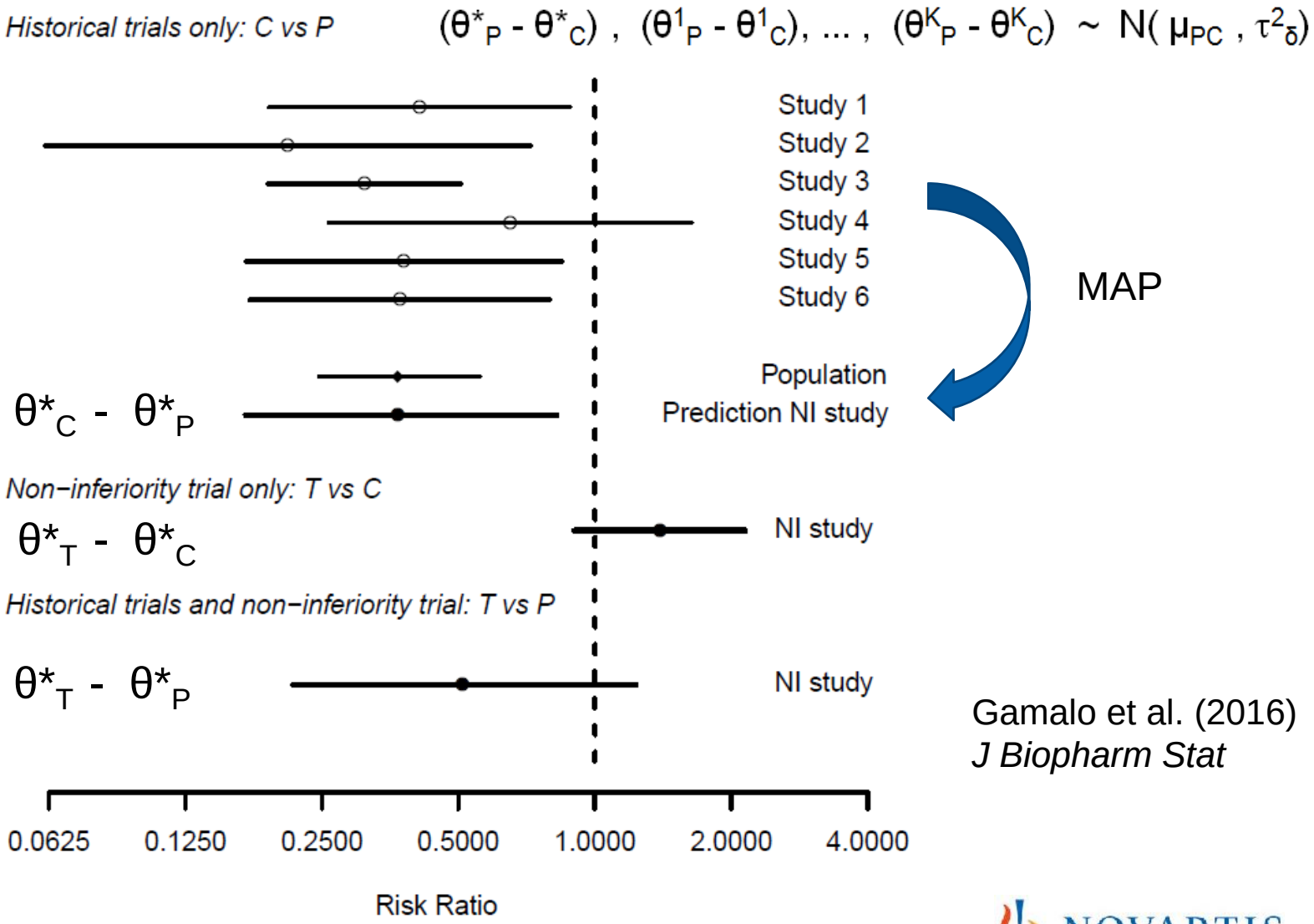





NOVARTIS

# Further applications

*Non-inferiority trials*




Gamalo et al. (2016)
*J Biopharm Stat*



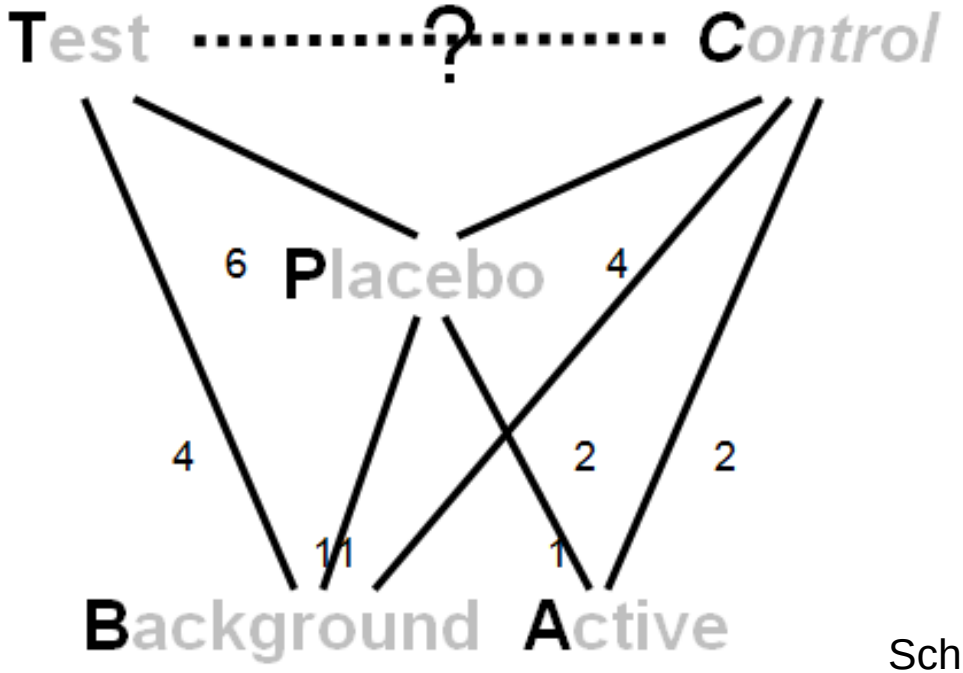
NOVARTIS

# Further applications

*Comparative effectiveness*

Prevention of serious vascular events (stroke, myocardial infarction, death from vascular causes)

Antiplatelet regimens: T (aspirin+dipyridamole), C (thienopyridine), P (aspirin), A (aspirin+thienopyridine), B (background therapy)




Network meta-analysis:
24 historical trials to predict
C vs T OR 1.19 (0.98, 1.43)

PRoFESS trial C vs T
C 1333/10181
T 1333/10151

Pr(observed OR<1 | hist) = 4.5%

Schmidli et al. (2013) *Stat Meth Med Res*

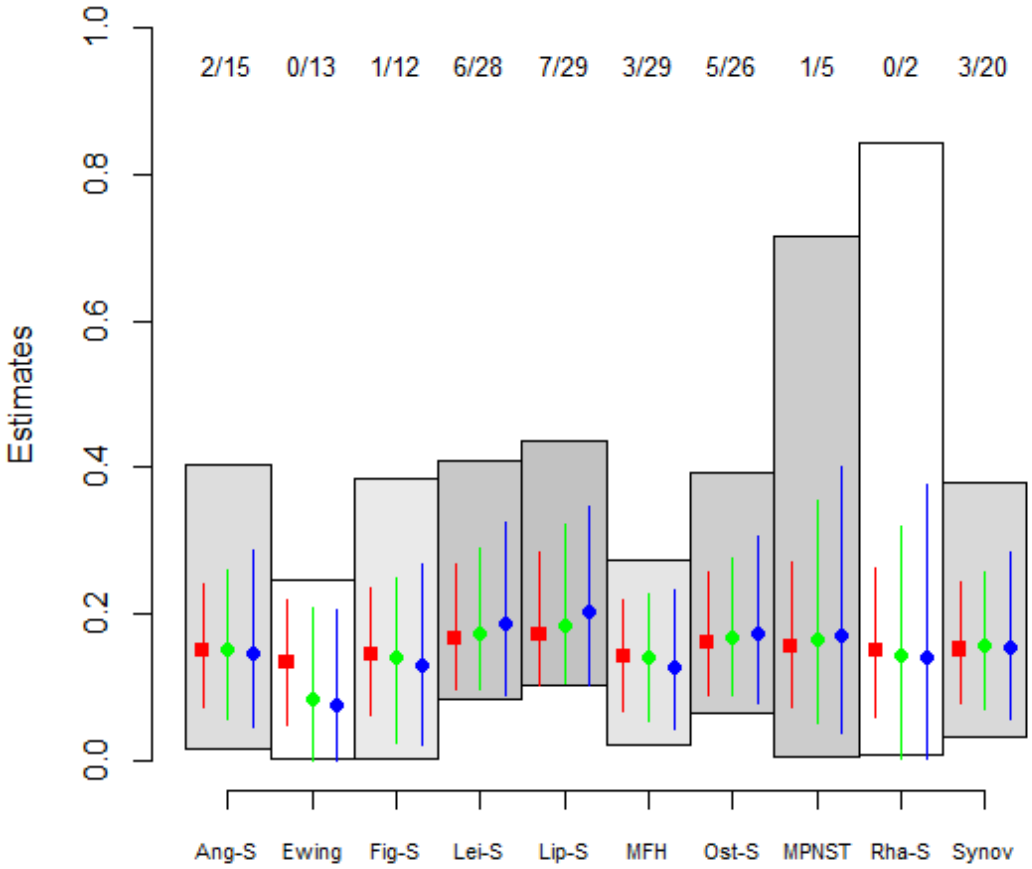


NOVARTIS

# Further applications

*Disease subtypes/subgroups*

Phase II cancer trial: Assess efficacy of imatinib in patients with one of **10 different subtypes of advanced sarcoma**




exact 95%-CI

- Considerable borrowing across all subgroups for **EX**, **EXNEX-1**, **EXNEX-2**
- Substantial precision gains

Neuenschwander et al. (2016) *Pharm Stat*



NOVARTIS

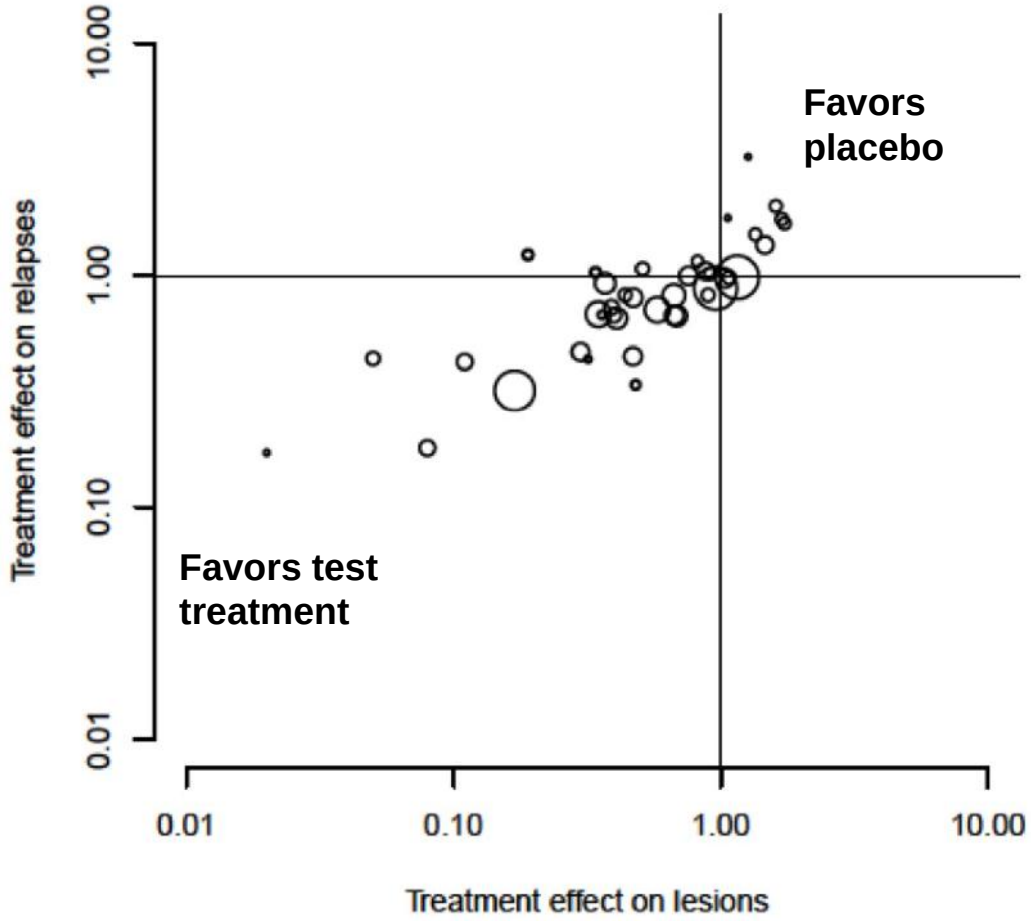
# Further applications

*Surrogate endpoints*

Treatment effects on

- Lesions (biomarker)
- Relapses (clinical)

23 placebo-controlled studies (40 arms)




Sormani et al. (2009) *Annals Neurology*, Pozzi et al. (2016) *Pharmaceutical Statistics*



NOVARTIS

# 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

# References


- Hampson LV, Whitehead J, Eleftheriou D, Brogan P (2016) Bayesian methods for the design and interpretation of clinical trials in very rare diseases. *Stat Med* 33:4186-4201.
- Neuenschwander B, Capkun-Niggli G, Branson M, Spiegelhalter DJ (2010) Summarizing historical information on controls in clinical trials. *Clin Trials* 7(1):5-18.
- Neuenschwander B, Wandel S, Roychoudhury S, Bailey S (2016) Robust exchangeability designs for early phase clinical trials with multiple strata. *Pharm Stat* 15(2):123-34.
- O'Hagan A, Pericchi L (2012) Bayesian heavy-tailed models and conflict resolution: a review. *Braz J Prob Stat* 26, 372-401.
- Schmidli H, Wandel S, Neuenschwander B (2013) The network meta-analytic-predictive approach to non-inferiority trials. *Stat Methods Med Res* 22(2):219-240.
- Schmidli H, Gsteiger S, Roychoudhury S, O'Hagan A, Spiegelhalter DJ, 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.
- Wadsworth I, Hampson LV, Jaki TF (2017) Extrapolation of efficacy and other data to support the development of new medicines for children: a systematic review of methods. *Stat Methods Med Res*
- Wandel S, Neuenschwander B, Röver C, Friede T (2017*)* Using phase II data for the analysis of phase III studies: An application in rare diseases. *Clin Trials* 14(3):277-285.




NOVARTIS