Statistical Methodology
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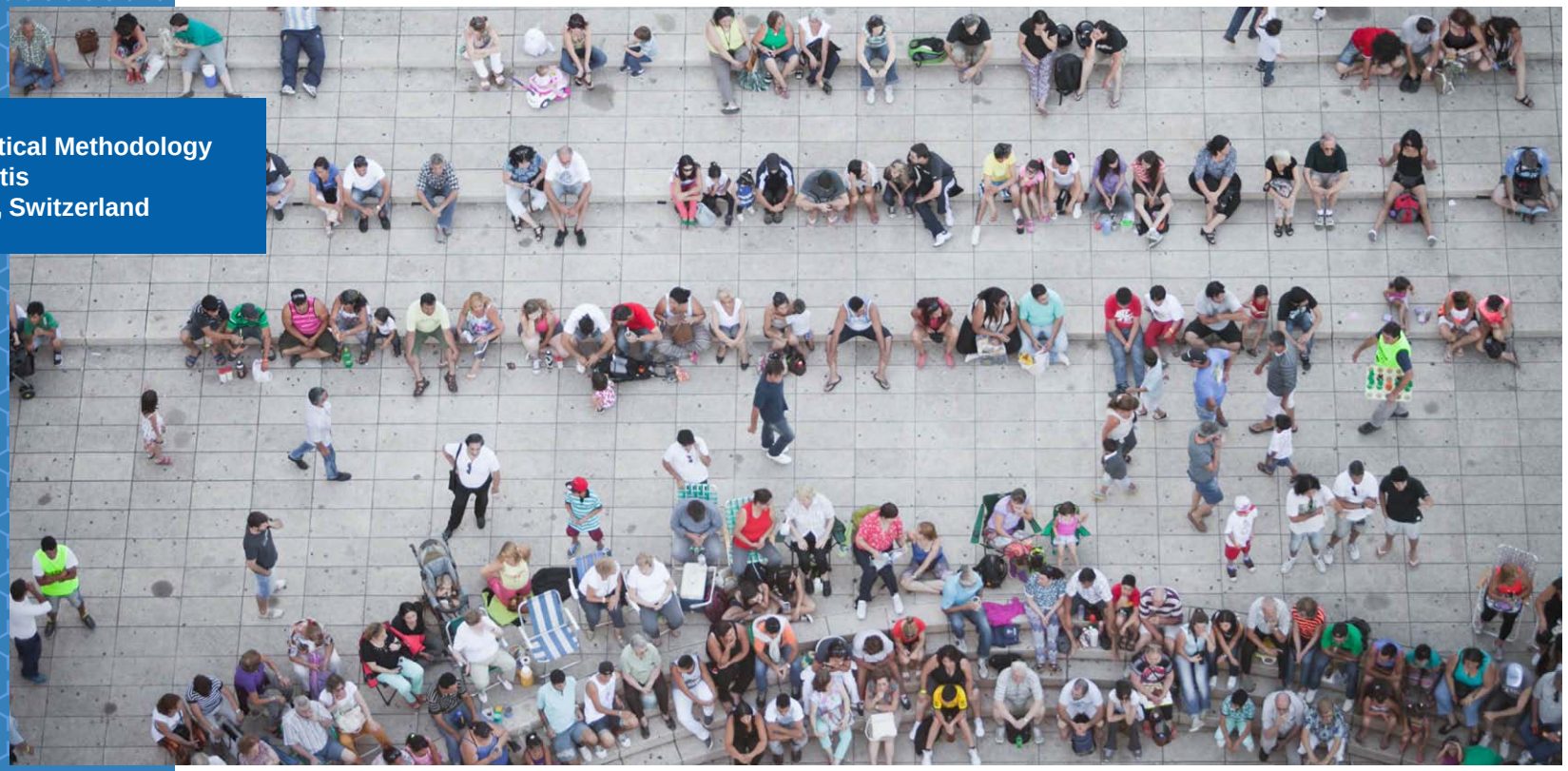

Bayesian approaches to extrapolation in clinical research

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Outline

- Introduction
- Extrapolation
- Robustness
- Applications
- Discussion

Acknowledgements

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David Spiegelhalter, Anthony O'Hagan

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Introduction

Extrapolation in clinical research

- Extrapolation

  Prediction, Bridging, Borrowing Strength, ...

- Very common in clinical research

  From source to target

  – From adults to children
  – From Caucasians to Japanese
  – From one disease subtype to another
  – From one drug to another

- Clinical trials as main source of information

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

Introduction

Extrapolation in clinical research – 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.*

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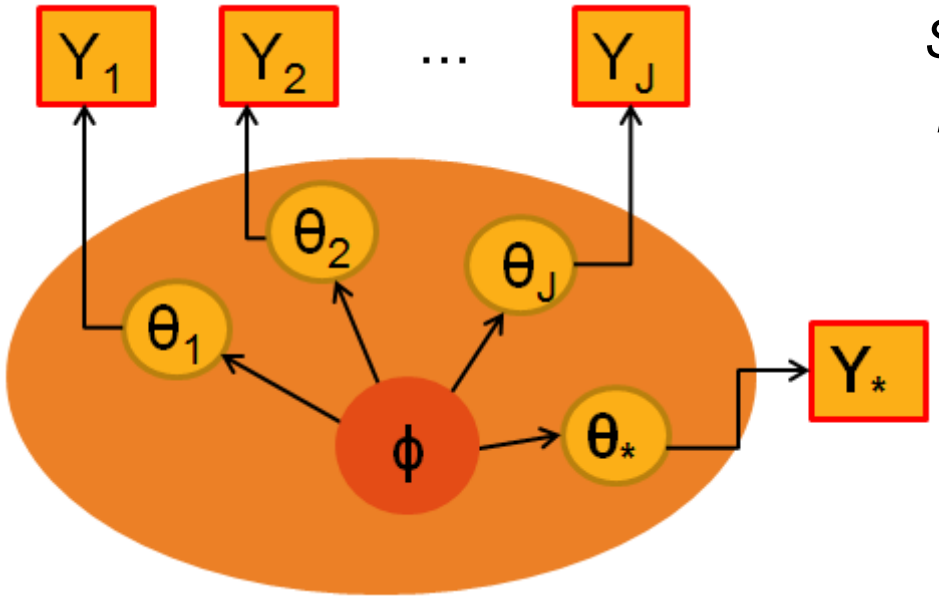
Introduction

Framework for evidence synthesis and extrapolation



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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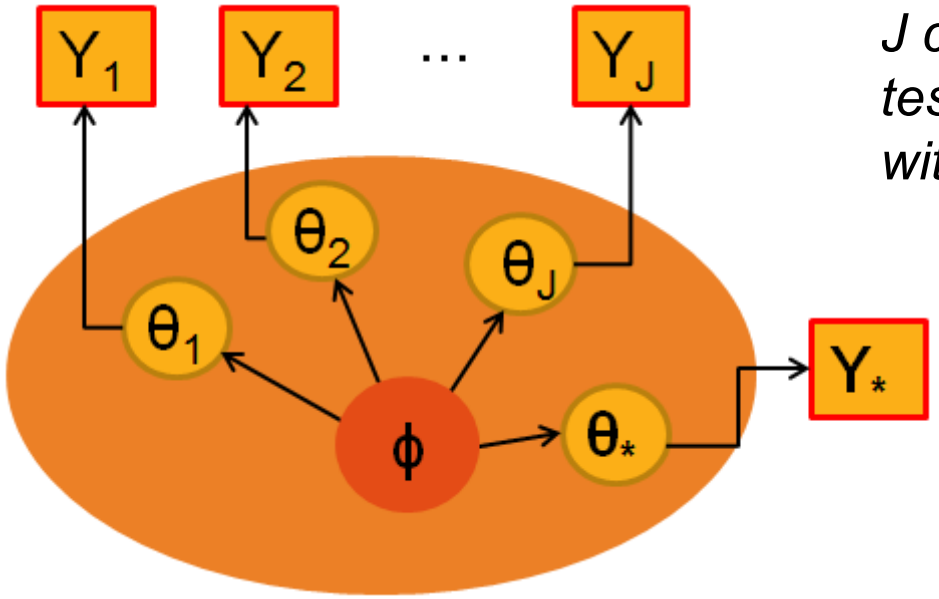
Extrapolation from adults to children

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 vs control, with treatment effect θ_**

Simplest hierarchical model to link parameters

$\theta_*, \theta_1, \ldots, \theta_J \mid \mu, \tau \sim N(\mu, \tau^2)$ *meta-analytic-predictive (MAP)*

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

Spiegelhalter et al. (2004)
Higgins et al. (2009)
Neuenschwander et al. (2010,2016)
Schmidli et al. (2013, 2014)

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Extrapolation from adults to children

Treatment of venous thromboembolic events (VTE)

- 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

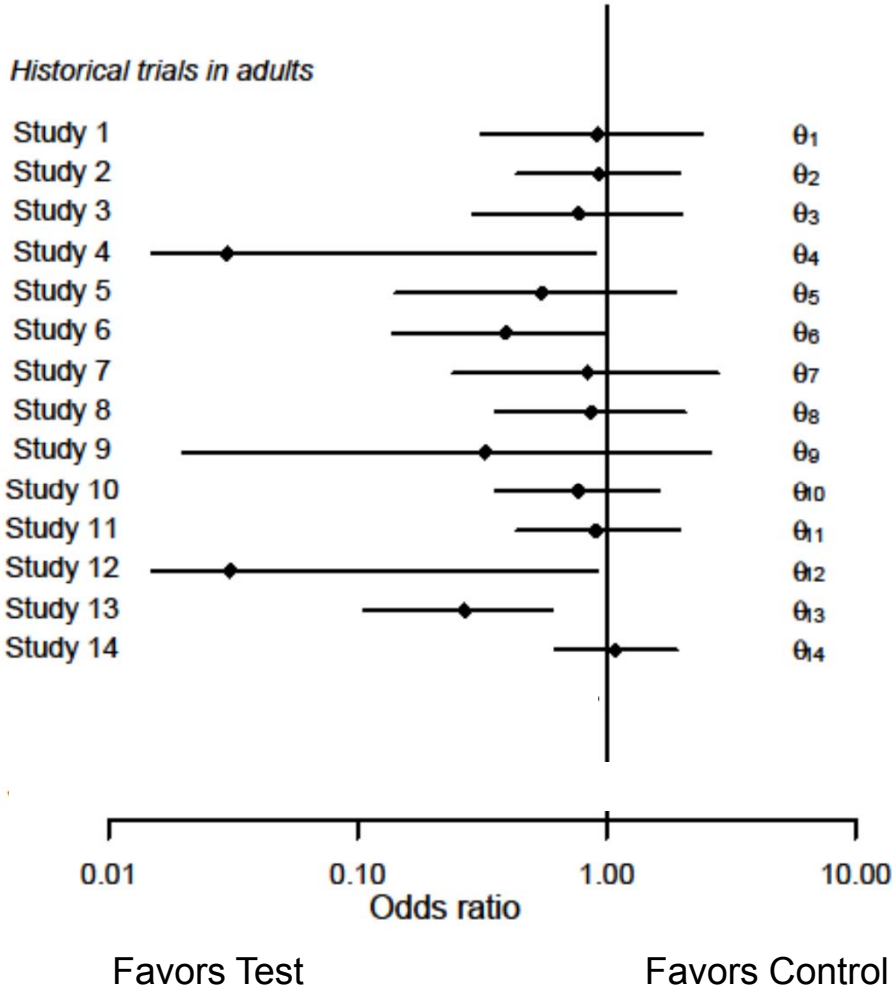
  Test vs Control, recurrent VTE (3 months) available

  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
  - Mode of action

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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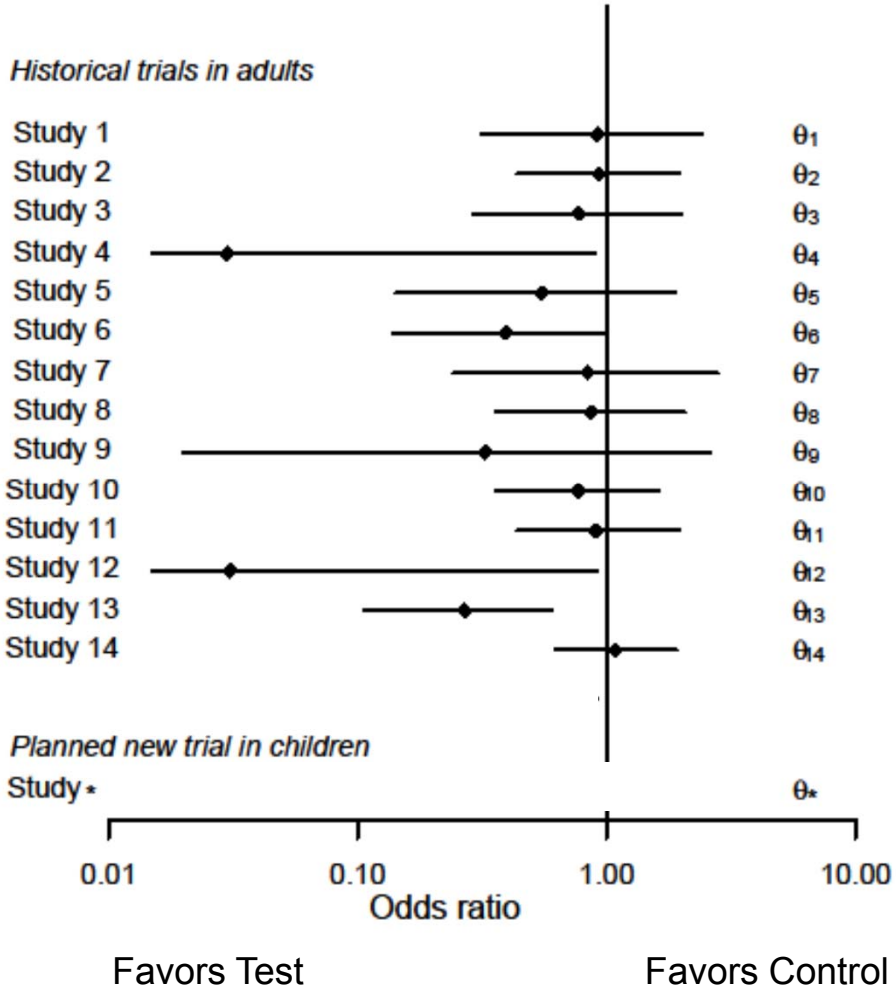
Extrapolation from adults to children

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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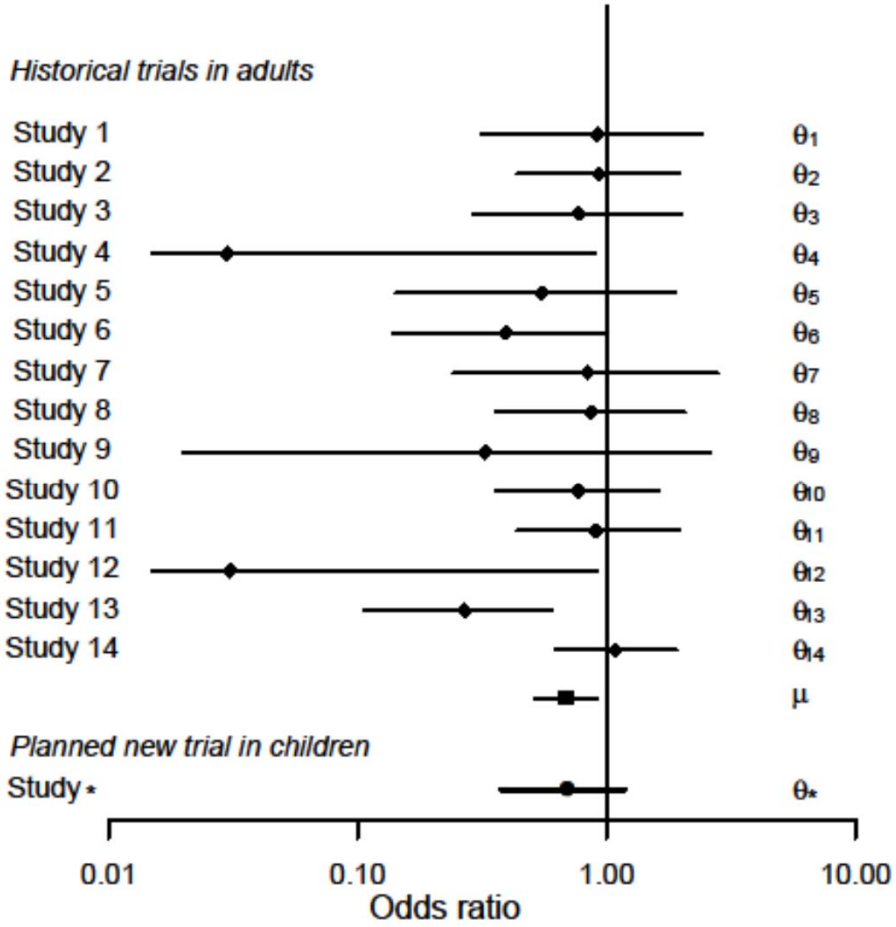
Extrapolation from adults to children

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

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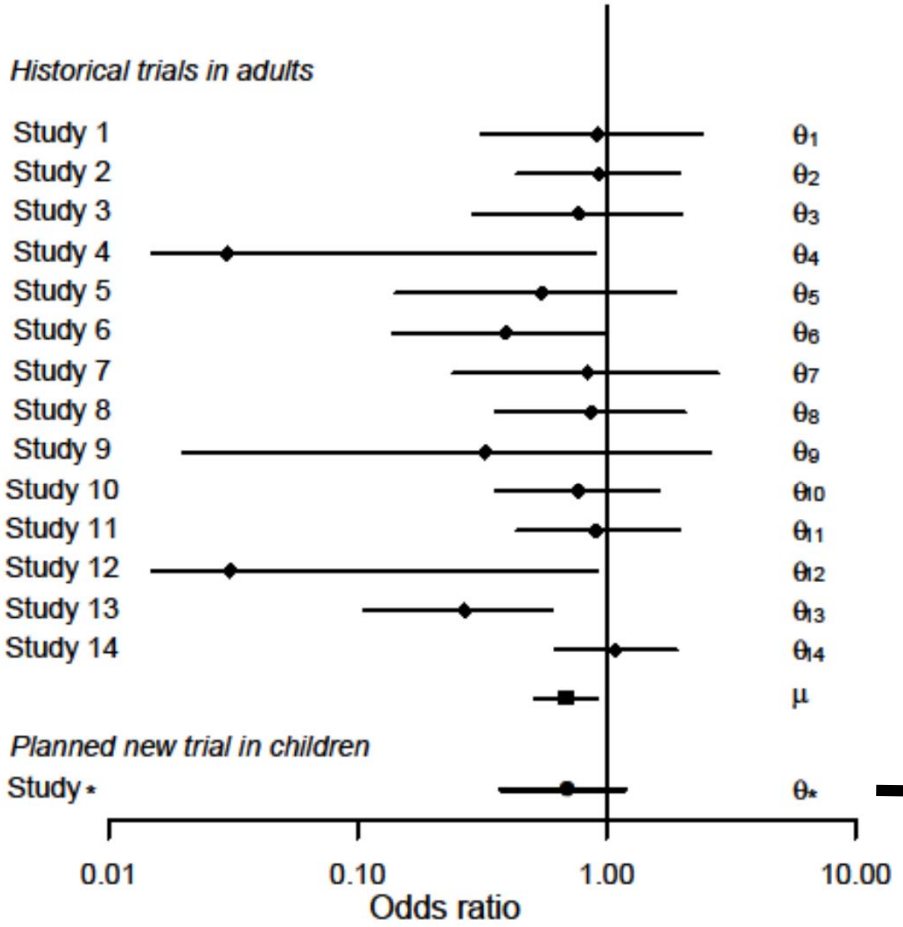
Extrapolation from adults to children

Treatment of venous thromboembolic events (VTE)

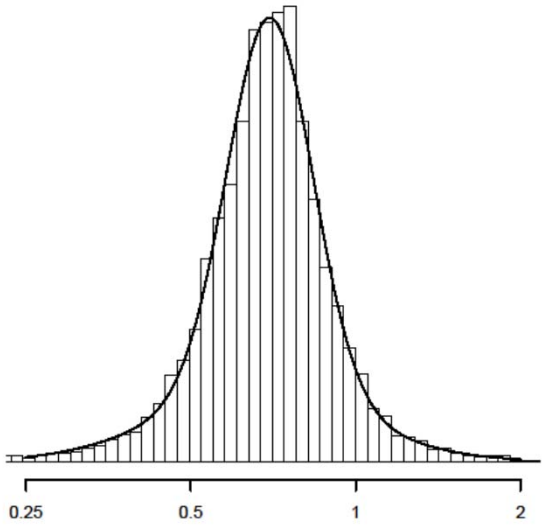


MAP prior

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

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

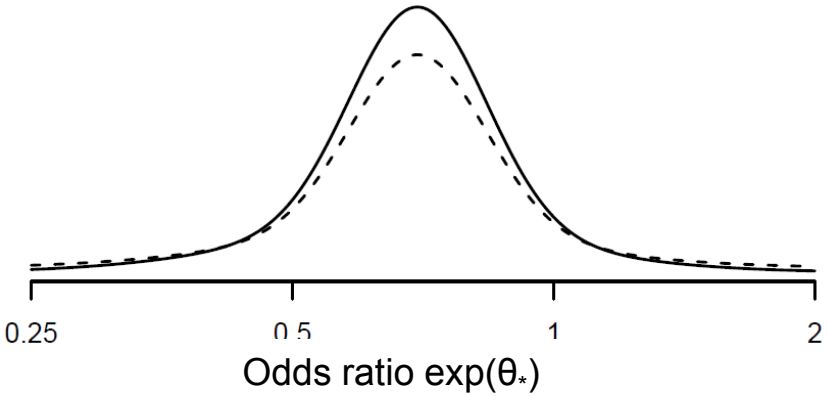
Robustness

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 $p_{Robust}(\theta_*) = (1-\varepsilon)\, p(\theta_*) + \varepsilon\, p_{Vague}(\theta_*)$
  - 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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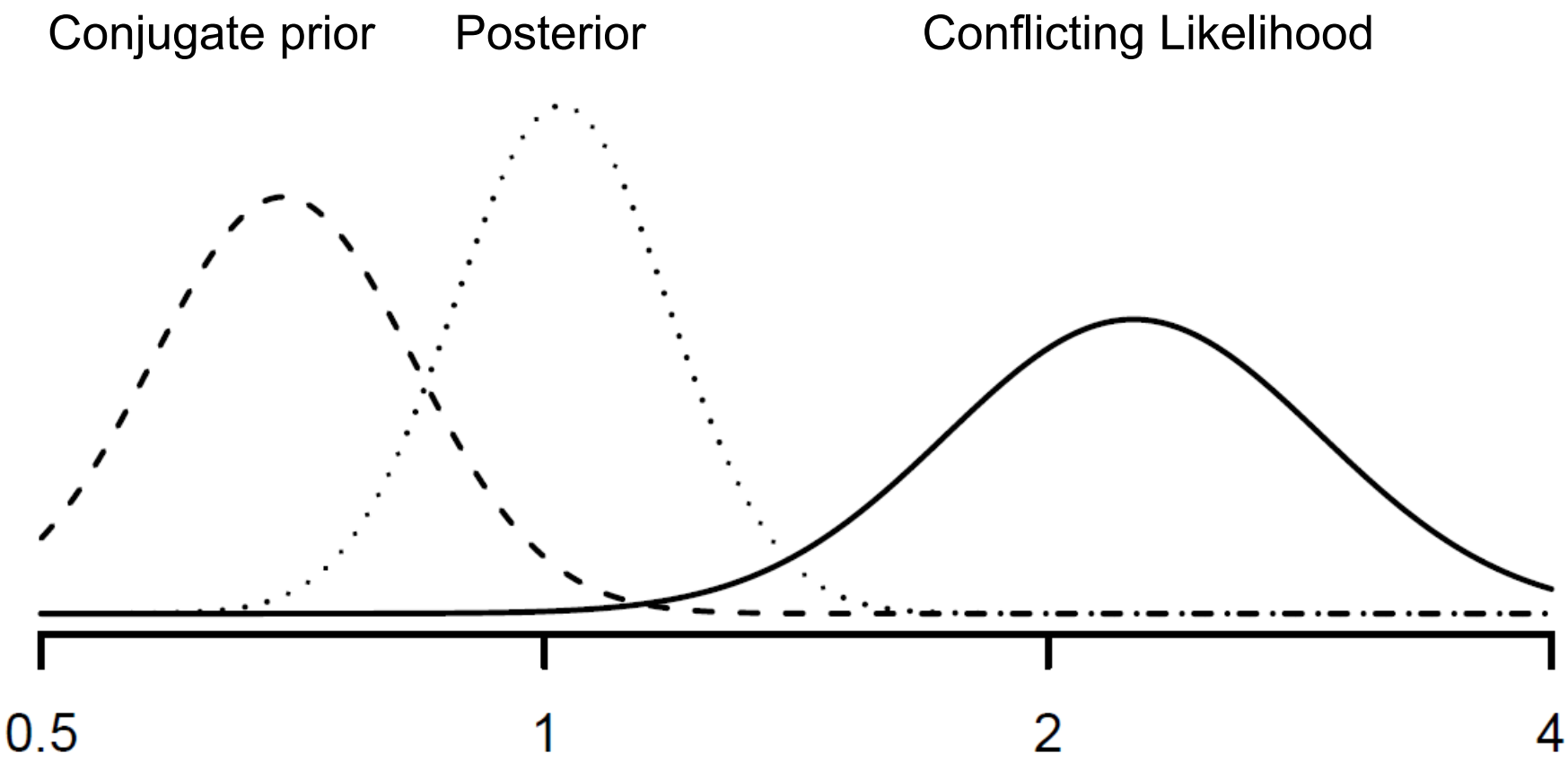
Robustness

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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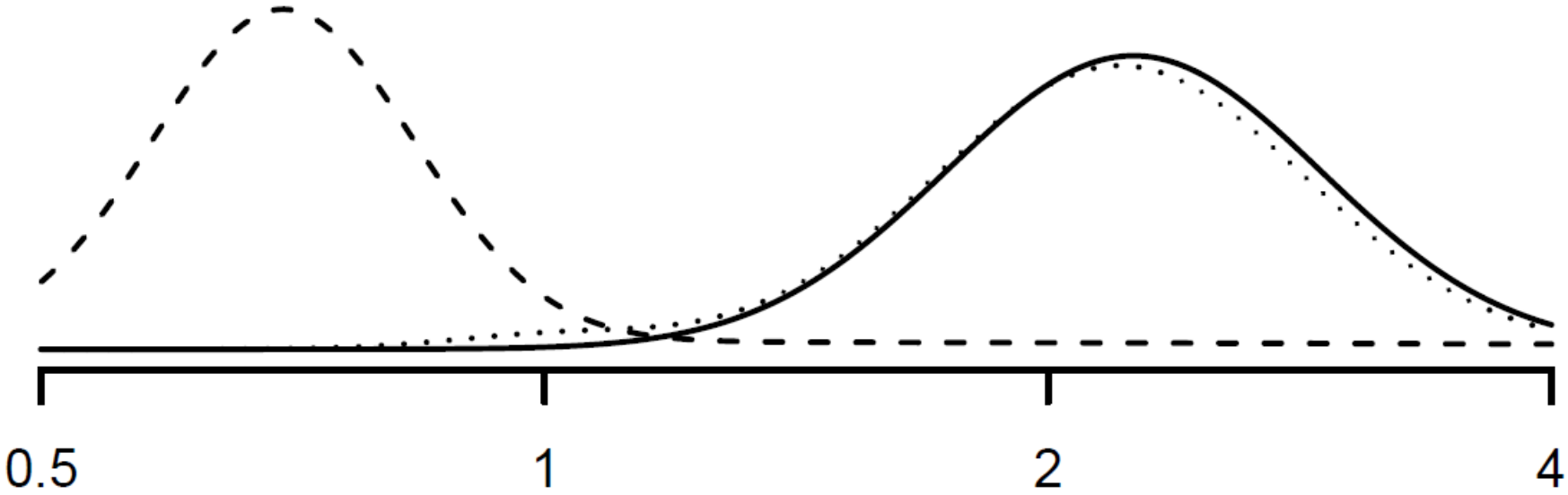
Robustness

Prior-data conflict - hypothetical

Robust prior

Posterior / Conflicting Likelihood



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

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Applications

Examples – hierarchical models

- Historical controls

  Extrapolate control effect in current trial based on historical trials

- Non-inferiority trials

  Extrapolate placebo vs active control effect to NI trial

- Comparative effectiveness

  Extrapolate effectiveness for treatments which have not be compared

- Disease subtypes/subgroups

  Extrapolate effect to specific subgroup

- Surrogate endpoints

  Extrapolate effect on clinical endpoint from effect on surrogate

Applications

Historical controls

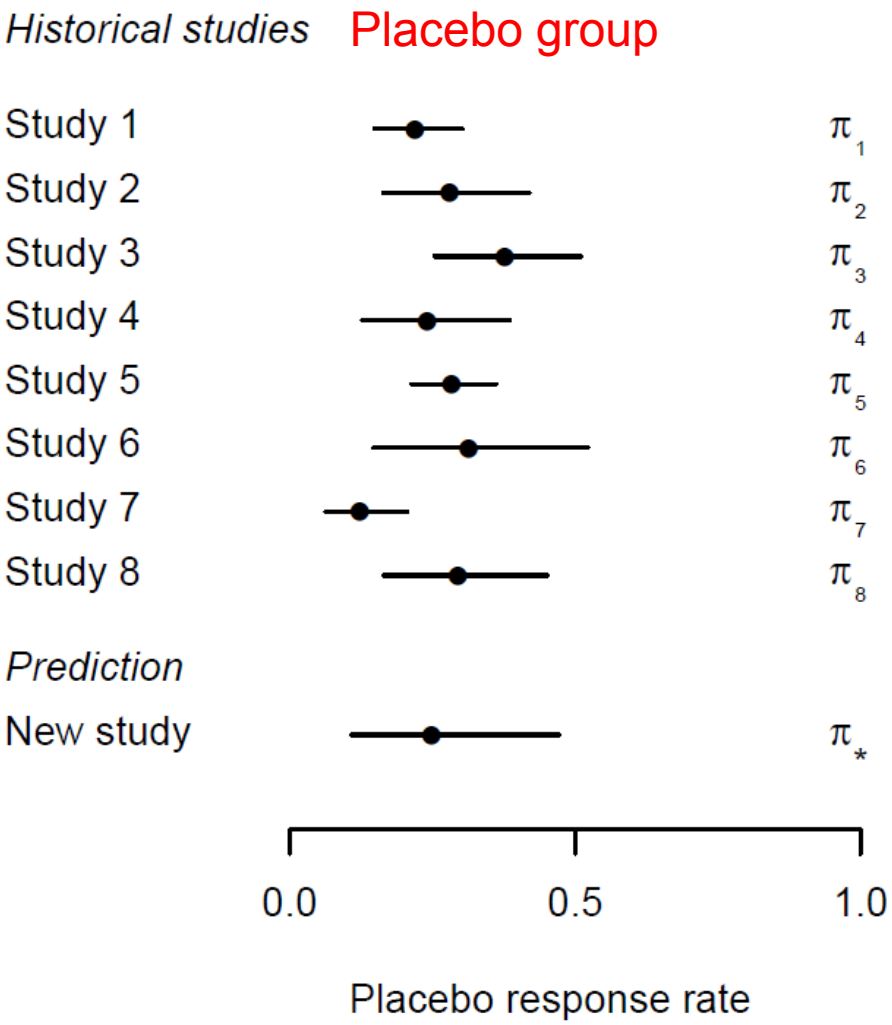
- *Disease*
  Ankylosing spondylitis
- *Experimental treatment*
  Secukinumab (monoclonal antibody)
- *Endpoint*
  Binary: response at week 6
- *Traditional clinical trial design*
  - Secukinumab (n=24) vs. Placebo (n=24)
  - Fisher's exact test

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

Could this historical placebo information be used?

Applications

Historical controls



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

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

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

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Applications

Historical controls

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

Baeten et al. (2013) *Lancet*

Applications

Non-inferiority trials

Minimal efficacy requirement for a new *test* treatment:

test (T) better than *placebo (P)*

1) Superiority trial: *test* (T) vs. *placebo* (P)

Direct evidence on whether T is better than P.

However, use of placebo may be unethical or not feasible:

- effective treatment is available
- disease is serious/life-threatening (cancer, HIV, transplantation,..)

2) Non-inferiority (NI) trial: *test* (T) vs. *active-control* (C)

No direct evidence on whether T is better than P.

External information needed to adress minimal efficacy requirement.

Temple and Ellenberg (2000), Ellenberg and Temple (2000)

Applications

Non-inferiority trials

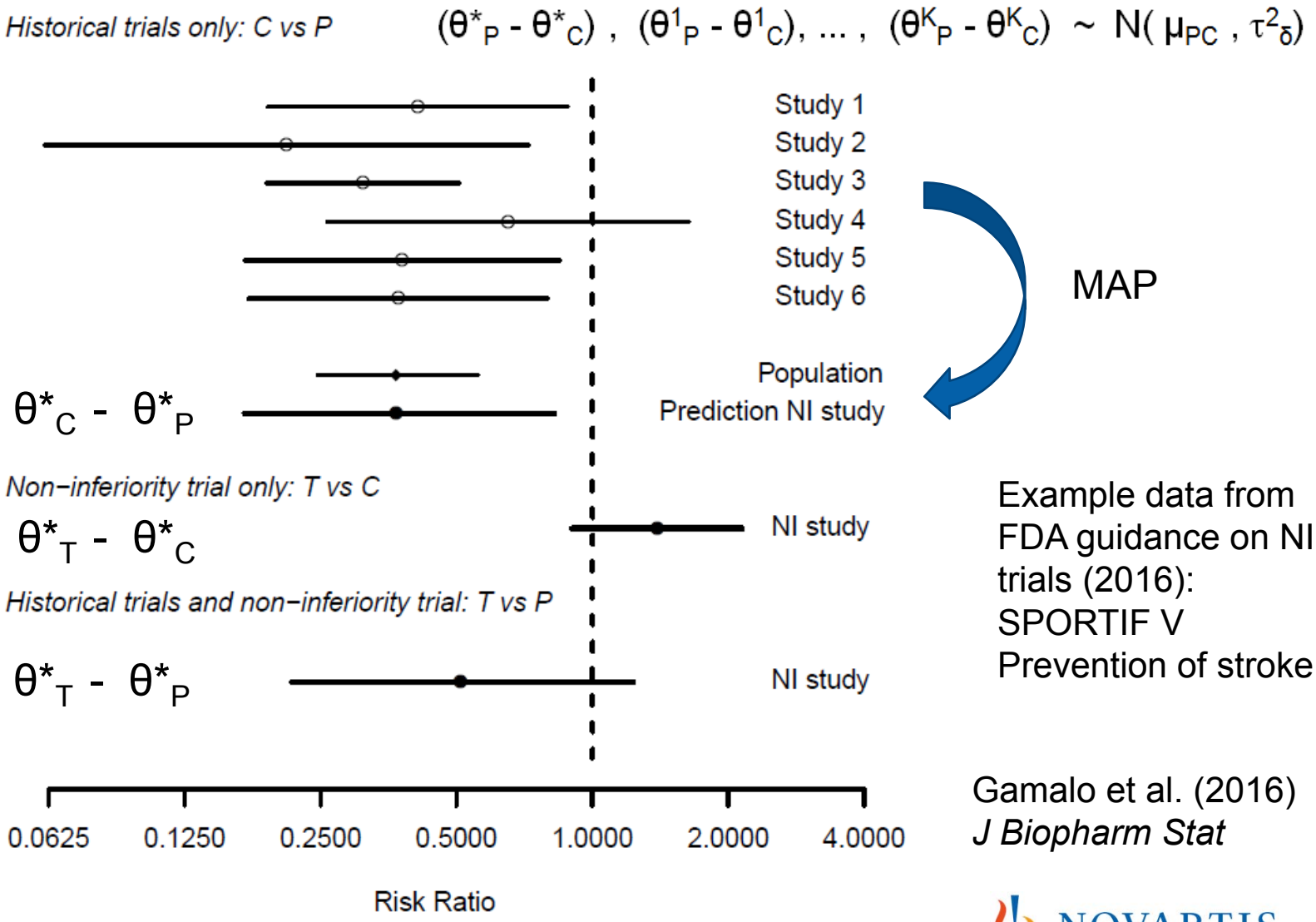
	Test (T)	Control (C)	Placebo (P)
*NI trial **	Y^*_T , θ^*_T	Y^*_C , θ^*_C	NA , θ^*_P
Historical trials			
Trial 1		Y^1_C , θ^1_C	Y^1_P , θ^1_P
Trial 2		Y^2_C , θ^2_C	Y^2_P , θ^2_P
...			
Trial K		Y^K_C , θ^K_C	Y^K_P , θ^K_P

Minimal efficacy requirement: θ^*_T vs. θ^*_P

- Model based: links parameters of NI and historical trials
- Predictive approach: no data directly related to θ^*_P

Applications

Non-inferiority trials



Example data from FDA guidance on NI trials (2016): SPORTIF V Prevention of stroke

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

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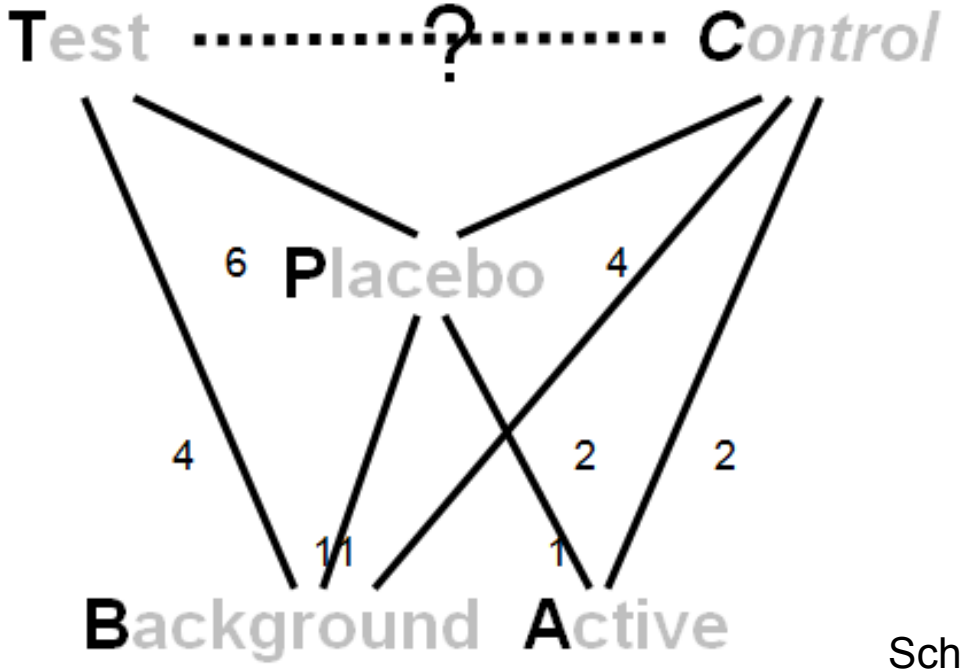
Applications

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*

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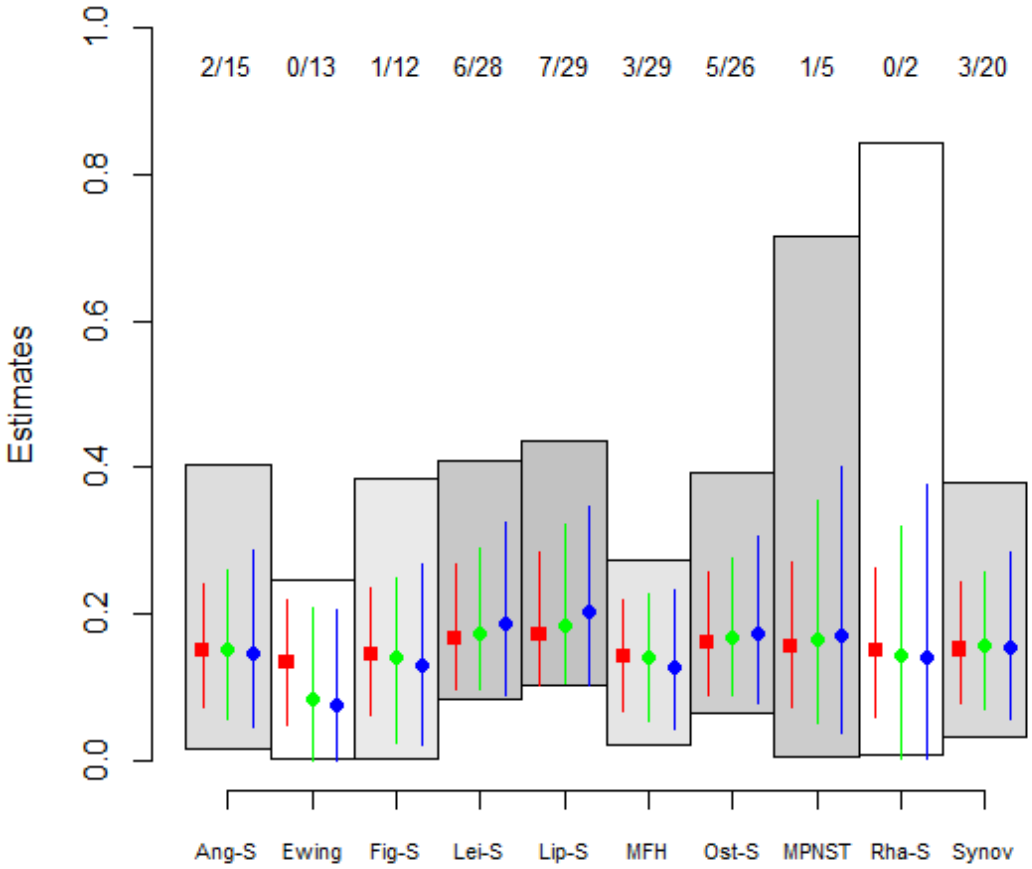
Applications

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*

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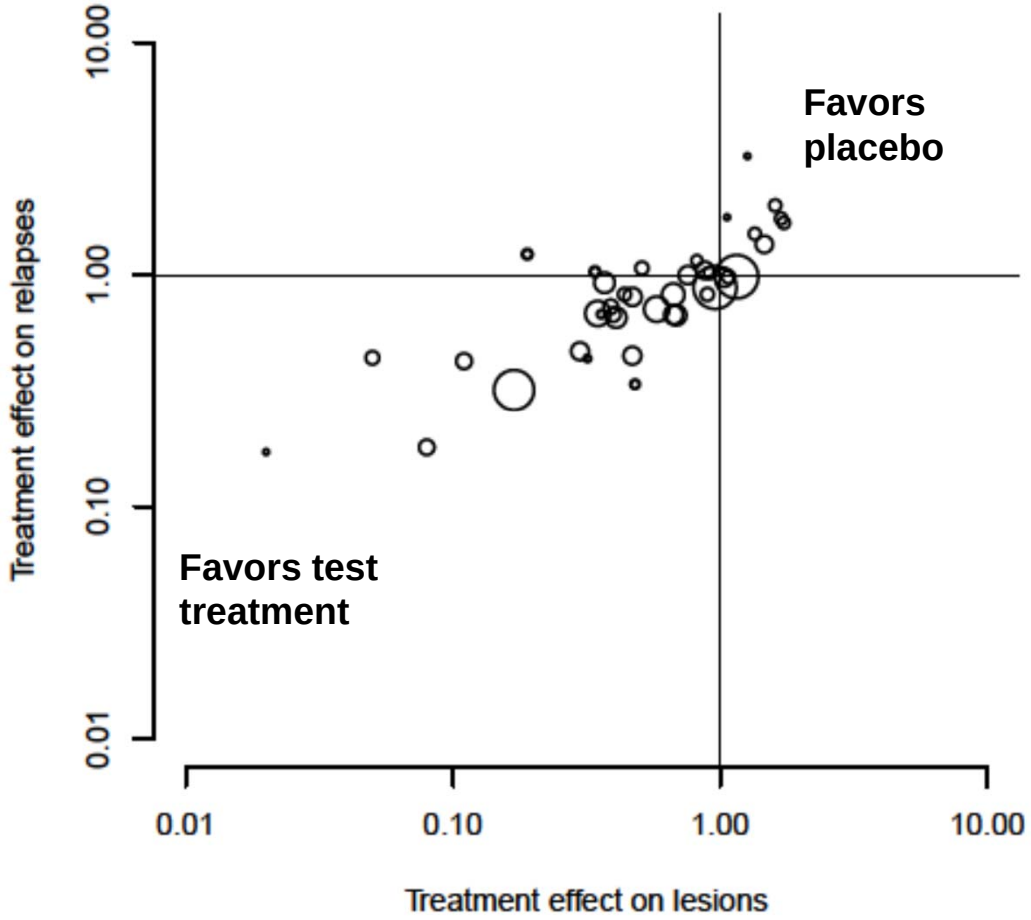
Applications

Surrogate endpoints

Treatment effects on

- Lesions
- Relapses

23 placebo-controlled studies (40 arms)



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

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Discussion

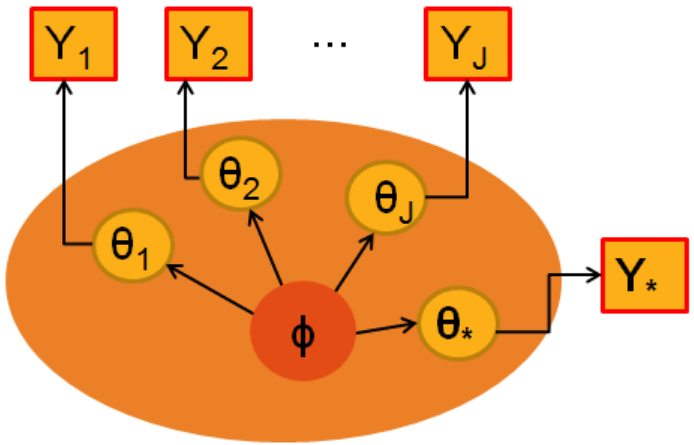
- Empirical hierarchical models to link parameters

  meta-analysis, network meta-analysis, meta-regression, multivariate meta-analysis, ...

- Mechanistic models to build on scientific understanding

  population pharmacokinetic/pharamacodynamic (Pop PK/PD) models, physiologically based pharmacokinetic (PBPK) models, dose-time-response/KPD models, ...

- Combined empirical and mechanistic models
  - Intrinsic/extrinsic factors
  - Biology and pharmacology



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Discussion

- 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

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