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A FRAMEWORK FOR SIMULATIONS IN CLINICAL RESEARCH

with applications in small populations and rare diseases

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InSPiRe
Innovative methodology for small populations research

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- The worked **examples** are joint work with
  - Frank Konietschke (Dallas), Markus Pauly (Ulm)
  - Christian Röver (Göttingen)

UNCERTAINTY IN PLANNING TRIALS: Trends in Placebo Event rates in Chronic Conditions

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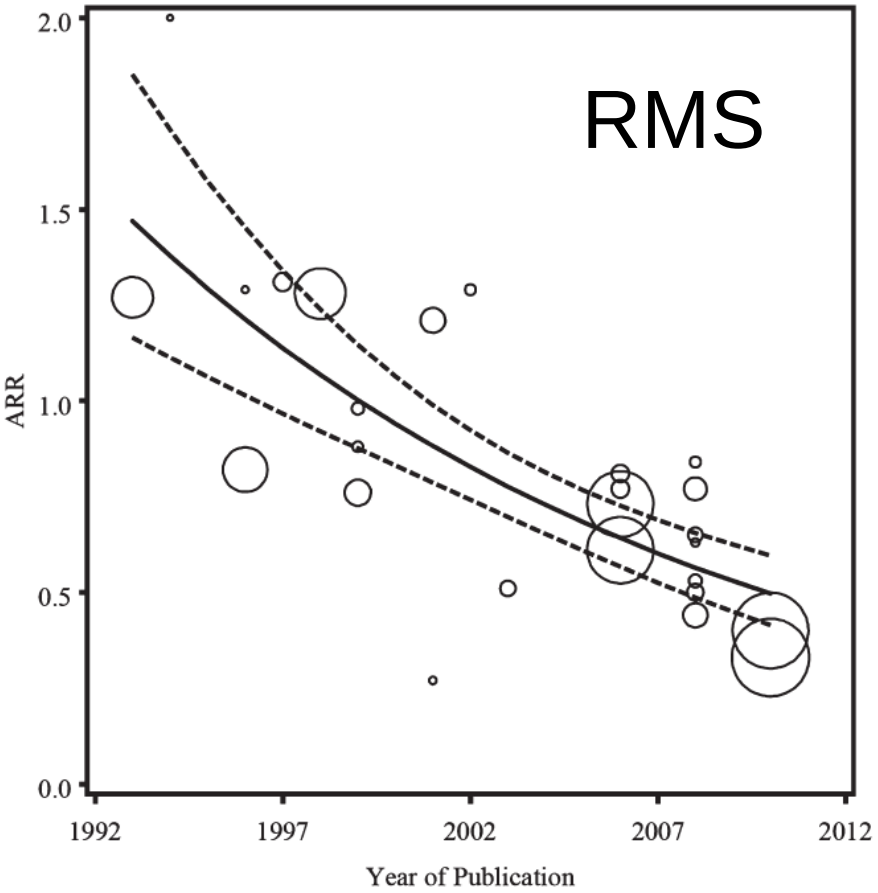

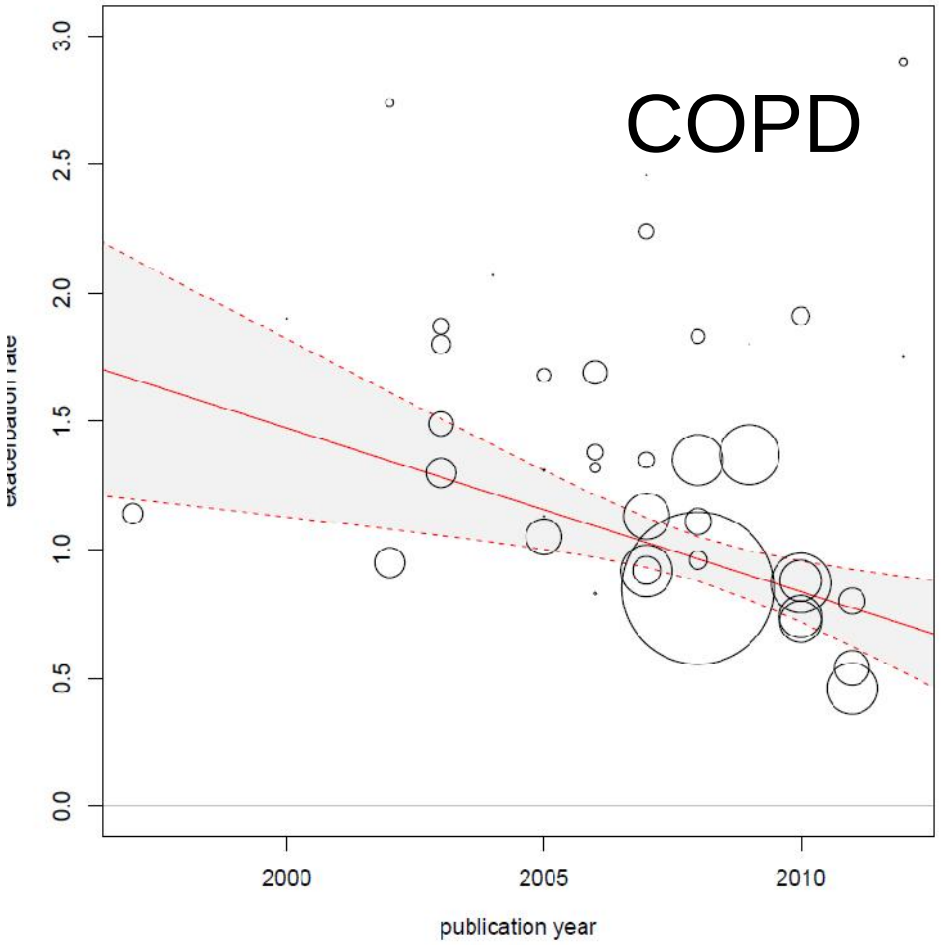

Nicholas et al. (2011) MSJ

Andreas et al. (2017)

SHIFTING PATIENT POPULATIONS: Example in relapsing multiple sclerosis

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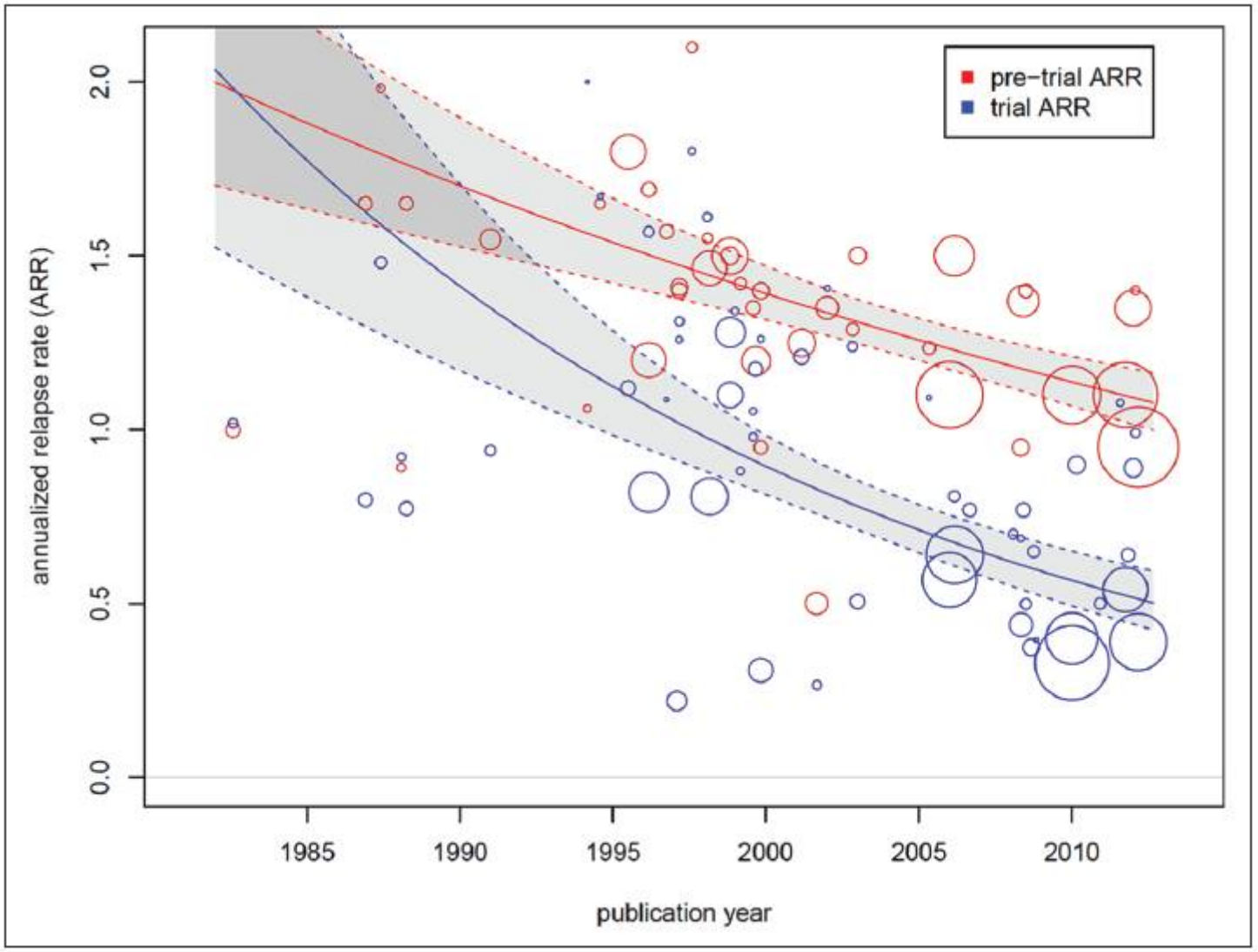


Steinvorth et al. (2013) MSJ

BACKGROUND

- With rising **pressure on resources** for clinical trials and **shifting patient populations** there is an increasing **demand for efficient and robust clinical trials**.
- As a consequence the way clinical trials are planned, conducted and analysed is changing with a move to **more complex designs and analysis methods**, which in turn leads to more frequent use of **Monte Carlo simulations** to plan individual clinical trials or entire clinical development programmes consisting of multiple clinical trials.

CLINICAL SCENARIO EVALUATION (CSE)

- **Purpose of the CSE framework**
  - Support structured and early planning
  - Exploration of efficient approaches
  - Assessment of robustness (e.g. reliance on assumptions)
- **Framework for the assessment of competing strategies**
  - Analysis level
  - Clinical trial level
  - Series / programme of clinical trials

COMPONENTS OF THE CSE FRAMEWORK

- **Assumption set** (underlying „truth“)
  - effect size, variability/correlation, distributions
  - structural models, dose-response shapes, etc.
  - missing value and dropout patterns
- **Set of options**
  - different designs, analysis strategies, endpoints, etc
- **Metrics**: Evaluation criteria / operational charecteristics
  - efficiency: success probability, time, cost
  - validity: type 1 error rate, bias, etc.

CSE FRAMEWORK

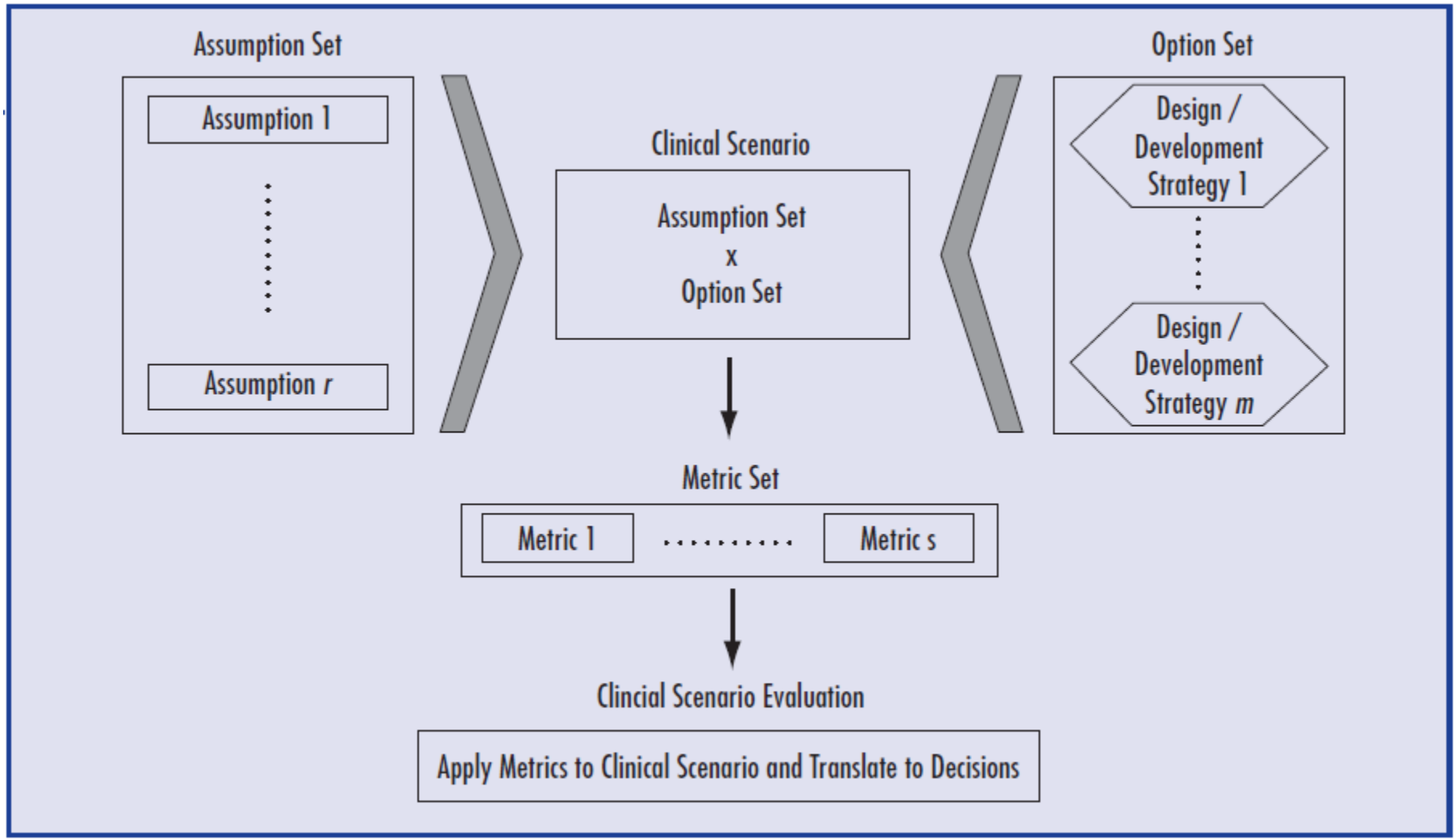


Figure 2 from Benda et al (2010) DIJ

REFINED CSE FRAMEWORK

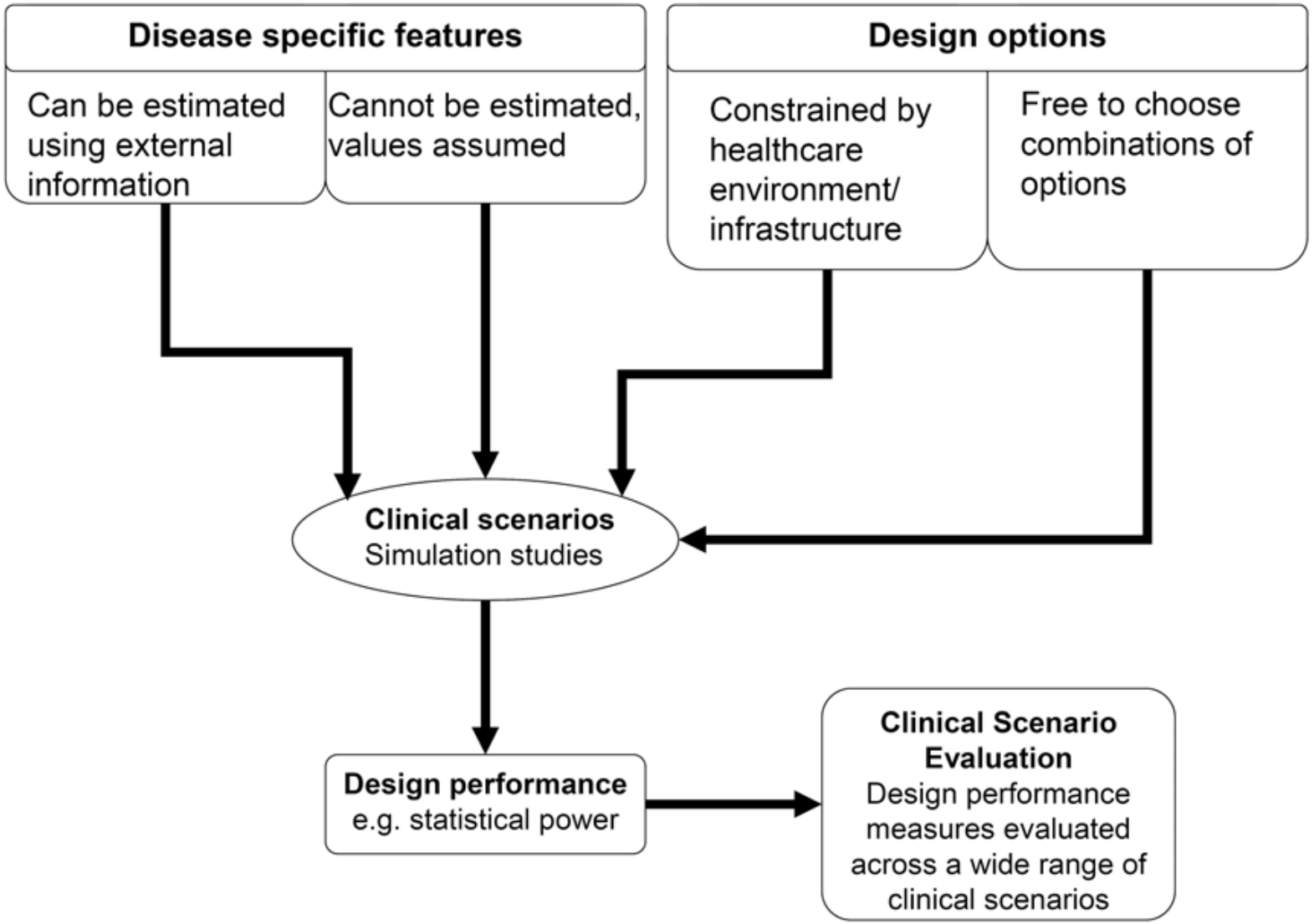


Figure 1 from Friede et al (2010) DIJ

EXAMPLE: MRI LESIONS IN RELAPSING MS

- **MRI lesion counts**: typical phase II endpoints in relapsing MS
- Total number of gadolinium enhancing lesions in monthly MRI scans over six months reported by Kappos et al. (2006)

Table 2. MRI and Clinical End Points at 6 Months in the Core Study.

End Point	Placebo	Fingolimod, 1.25 mg	Fingolimod, 5.0 mg	P Value	
				1.25 mg vs. Placebo	5.0 mg vs. Placebo
Primary MRI analysis population					
No. evaluated	81	83	77		
Total cumulative no. of gadolinium-enhanced lesions					
Mean ±SD	14.8±22.5	8.4±23.7	5.7±11.6	<0.001	0.006
Median (range)	5 (0–114)	1 (0–182)	3 (0–91)		

- **Overdispersion**: variance 24 - 67 times larger than mean
- **Negative binomial distribution** suggested to model MRI lesion counts (e.g. Sormani et al., 1999)

SMALL SAMPLES AND RARE DISEASES

- RCT in **paediatric multiple sclerosis** (Pakdamen et al, 2006)
  - assessing efficacy and safety of interferon beta-1a compared to no treatment
  - N=16 patients randomized
  - Endpoints: relapse rates and new T2 lesions
- Phase II trial of autologous mesenchymal **stem cells** in MS
  - relapsing-remitting MS patients not responding to at least a year of approved therapy
  - efficacy endpoint: cumulative number of gadolinium-enhancing lesions (GEL)
  - N=9 patients randomized (planned n=16)

EXAMPLE: CSE TO INFORM CHOICE OF ANALYSIS METHOD

- **Assumptions**
  - Distribution (e.g. NB), group-specific / common overdispersion parameter, size of treatment effect etc.
- **Options**
  - Analysis method: Test statistic and reference distribution
- **Metrics**
  - Type I error rate
  - Power / sample size

STATISTICAL MODEL AND HYPOTHESES

- **Statistical model:** $X_{ik} \sim NB(t_{ik}\lambda_i, \phi_i),\ i = 1, 2; k = 1, \ldots, n_i$
  - allowing for varying follow-up times, group-specific overdispersion parameters

- **Hypotheses:** $H_0 : h(\lambda_1, \lambda_2) = \theta \ \ versus \ \ H_1 : h(\lambda_1, \lambda_2) \neq \theta,\ \theta \in \mathbb{R}$

e.g. $h(\lambda_1, \lambda_2) = \lambda_1 - \lambda_2$ or $h(\lambda_1, \lambda_2) = \lambda_1/\lambda_2$

Konietschke et al (2017)

WALD-TYPE STATISTICS

- **Wald-type test statistics**

$$T_{(h)}^{\pi(c)} = f^{(c)} \frac{\left(h\left(\widehat{\lambda}_1^{\pi(c)}, \widehat{\lambda}_2^{\pi(c)} \right) - \theta \right)}{\widehat{\sigma}_{(c)}^{\pi}}$$

- **Variance estimators**
  - Moment estimator (simpler to compute; unbiased; more robust to model misspecifications)
  - Maximum-likelihood estimator (smaller variance under assumed model)

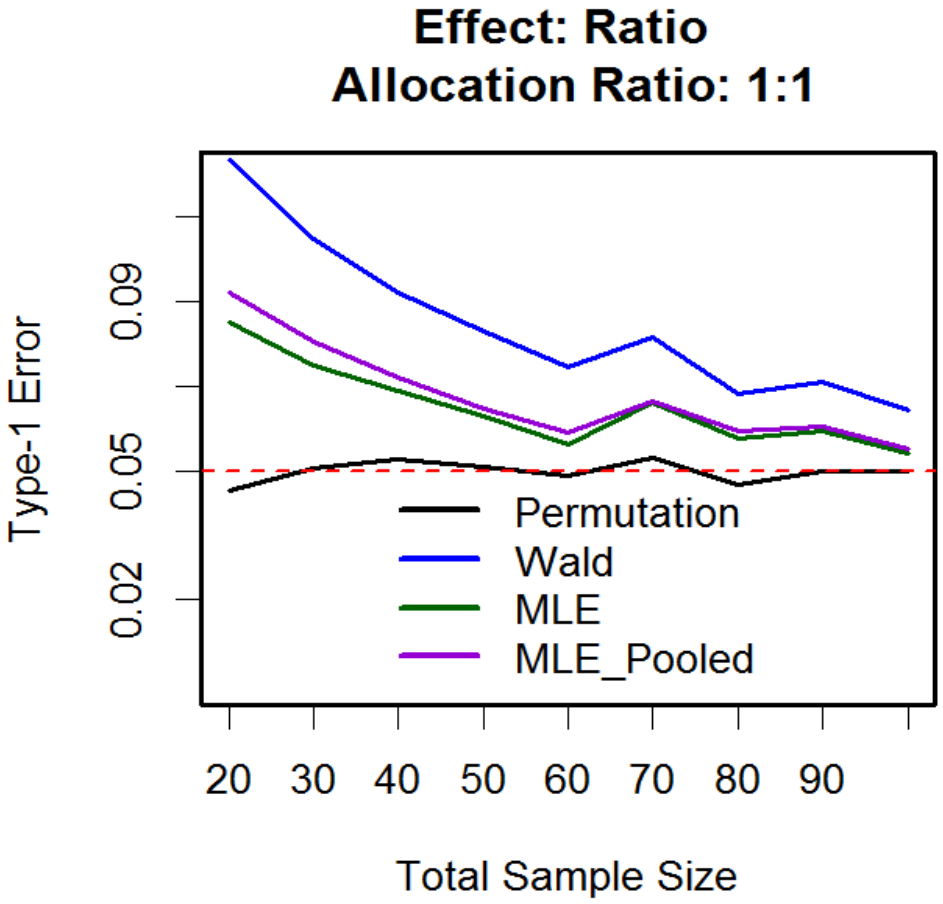
Konietschke et al (2017)

REFERENCE DISTRIBUTION

- **Normal approximation**
  - Use $(1 - {}^{\alpha}/_{2})$ – quantile $(z_{1-\alpha/2})$ of standard normal distribution as critical value
- **Resampling**
  - Permutations to estimate quantile
  - Due to overdispersion and varying follow-up times data are not exchangeable even under the null hypothesis
  - Idea: compute Wald-type statistic for each permutation and repeat procedure several times (e.g. 10,000 times)

Konietschke et al (2017)

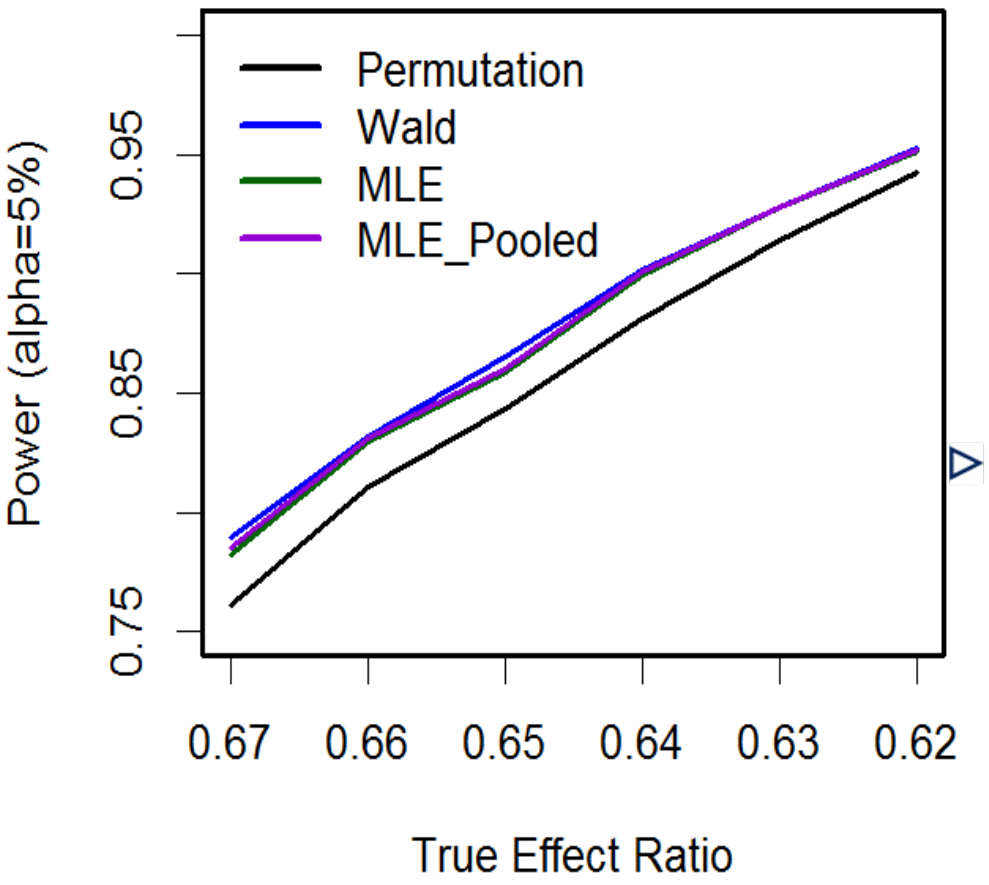
TYPE I ERROR RATE



- **Simulation study motivated by MRI lesion counts in MS**
  - Mean 10.0
  - Overdispersion parameter $\varphi_1 = \varphi_2 = 2.9$
  - Variance / mean $= 1 + 10 \times 2.9 = 30$
  - **Permutation test controls rate at nominal level**

Konietschke et al (2017)

POWER



- **Simulation study** motivated by MRI lesion counts in MS
  - Sample size: 100 patients per group
  - Type I error rate close to nominal level in this situation
- **Power of permutation test**
  - 1 -2 percentage points lower: Price to pay for robustness
  - Compensated by increase in sample sizes of about 5%

$$\frac{(z_{0.975}+z_{0.85})^2}{(z_{0.975}+z_{0.83})^2} \approx 1.05$$

Konietschke et al (2017)

EXAMPLES FOR EXTRAPOLATION IN RARE DISEASES AND SMALL POPULATIONS

- A small RCT and observational data
- Extrapolation from adults to children

EXAMPLE: DOXYCYCLINE IN EARLY CREUTZFELDT-JAKOB DISEASE (CJD)

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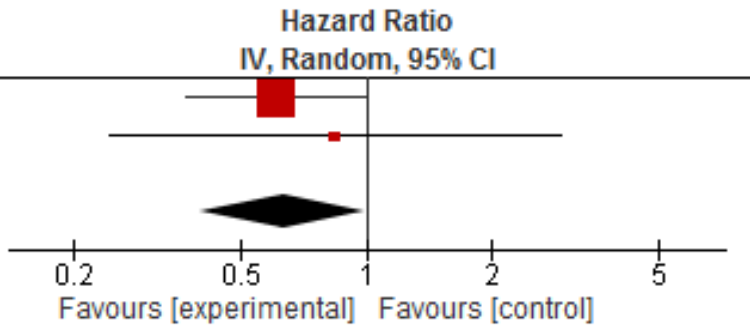
- **Creutzfeldt-Jakob disease**
  - prevalence of 1–9 cases per 1,000,000 people
  - qualifies as **rare disease** (EU: less than 5 in 10,000)
- **Varges et al (2016)** conducted:
  - double-blinded randomized phase II trial (n=12)
  - observational study (n=88) (Cox regression stratified by terciles of the propensity scores)
  - survival time as primary outcome

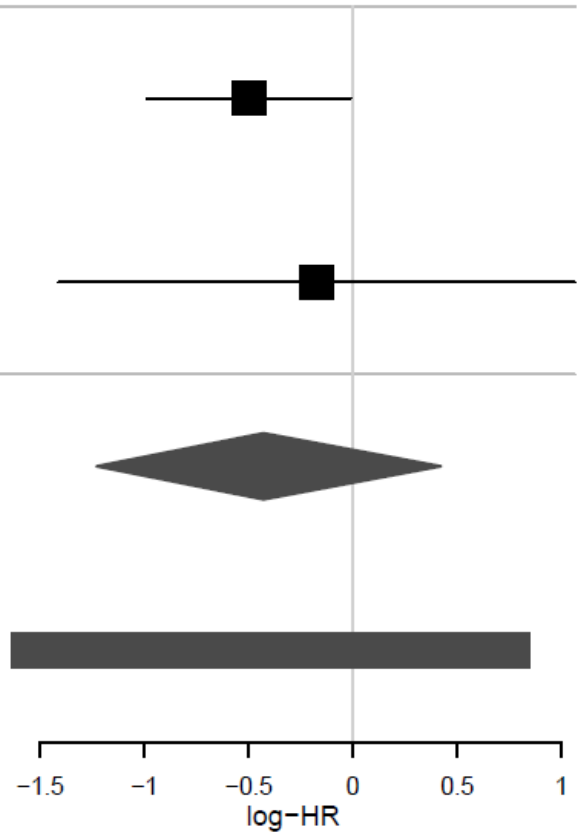
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Observational study	-0.49948	0.2493	86.5%	0.61 [0.37, 0.99]
RCT	-0.17344	0.6312	13.5%	0.84 [0.24, 2.90]
Total (95% CI)			**100.0%**	**0.63 [0.40, 1.00]**

Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 1.96 (P = 0.05)



EXAMPLE IN CJD: BAYESIAN RANDOM-EFFECTS META-ANALYSIS

study	estimate	95% CI
observational	−0.50	[−0.99, −0.01]
randomized	−0.17	[−1.41, 1.06]
mean	**−0.43**	**[−1.23, 0.42]**
prediction	**−0.43**	**[−1.64, 0.85]**



Röver & Friede (2017) in preparation

QUANTITIES OF INTEREST

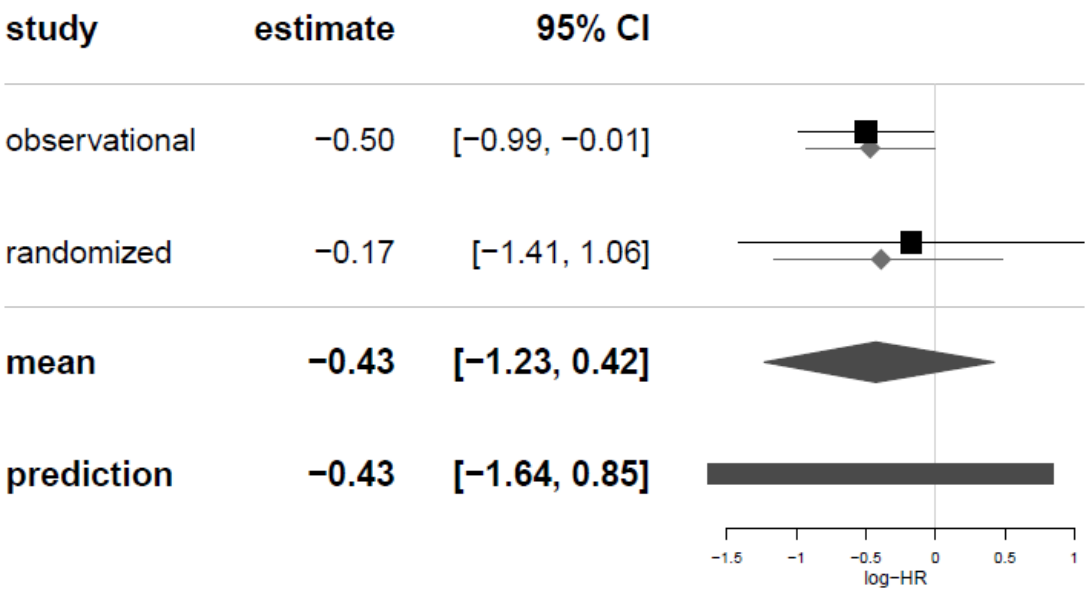
Different quantities of interest in hierarchical models

- **average effect** (μ) across studies
  - standard (pairwise) meta-analysis
- effect (θ_{k+1}) of a future study
  - **prediction / extrapolation**: adult to children; bridging
- effect (θ_i) of an individual study in the light of the other studies (**shrinkage estimator**)
  - small RCT with borrowing from registry

SHRINKAGE ESTIMATION

- **Approaches to compute shrinkage estimator**
  - **Meta-analytic-predictive (MAP) approach**: meta-analyze all but *ith* study; resulting posterior yields meta-analytic predictive (MAP) prior, use MAP prior and data y_i to infer θ_i
  - **Meta-analytic-combined (MAC) approach**: perform joint meta-analysis of all studies, determine *ith* shrinkage estimate
  - both approaches yield identical results (Schmidli et al (2014) Biometrics)

EXAMPLE IN CJD: SHRINKAGE ESTIMATOR



- **Gain in efficiency**
  - RCT shrinkage interval width: 66% of original CI width
  - Translates into 129% gain in sample size (about 27 instead of 12 patients)
- **Computations** carried out using R package `bayesmeta`

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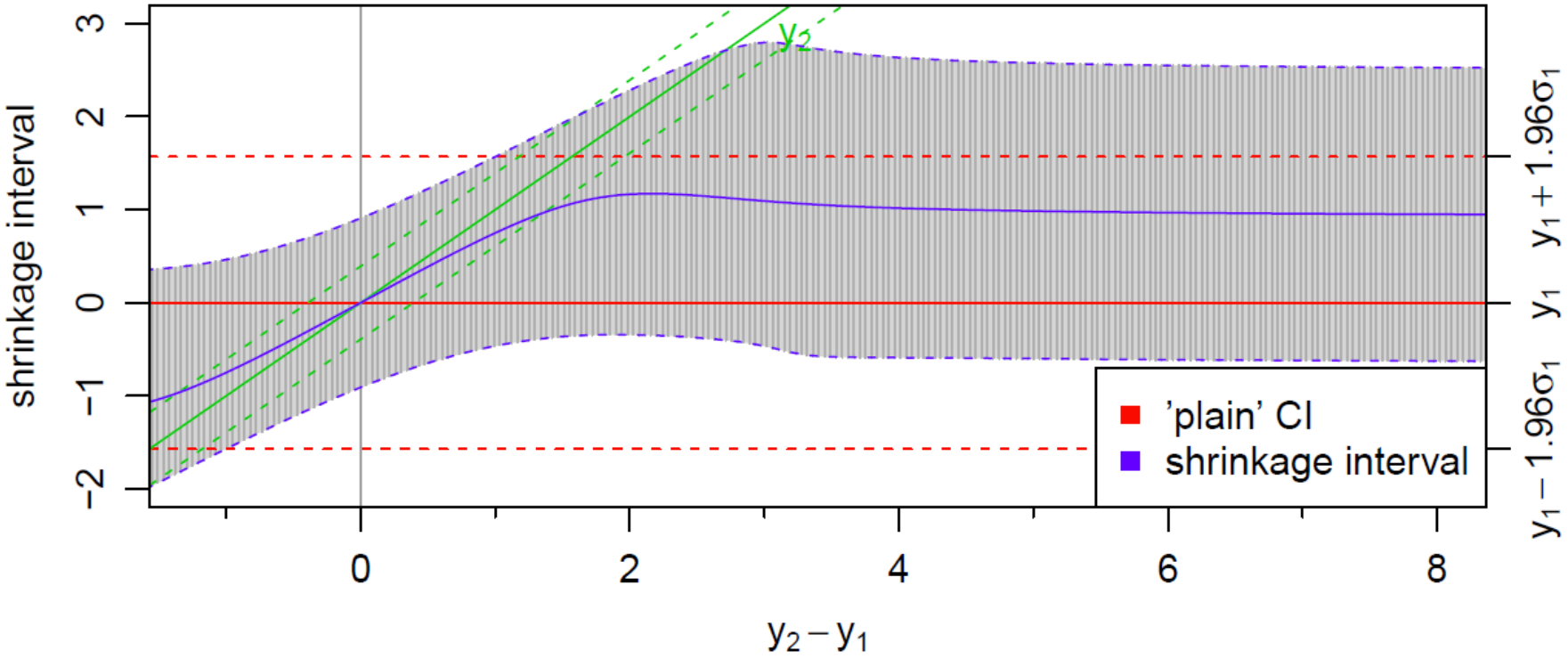
SHRINKAGE ESTIMATION: EXPLORING ROBUSTNESS IN CSE EXERCISE



- $n_1 = 25,\ n_2 = 400,\ p(\tau) = \text{HN}(0.5)$, interested in θ_1

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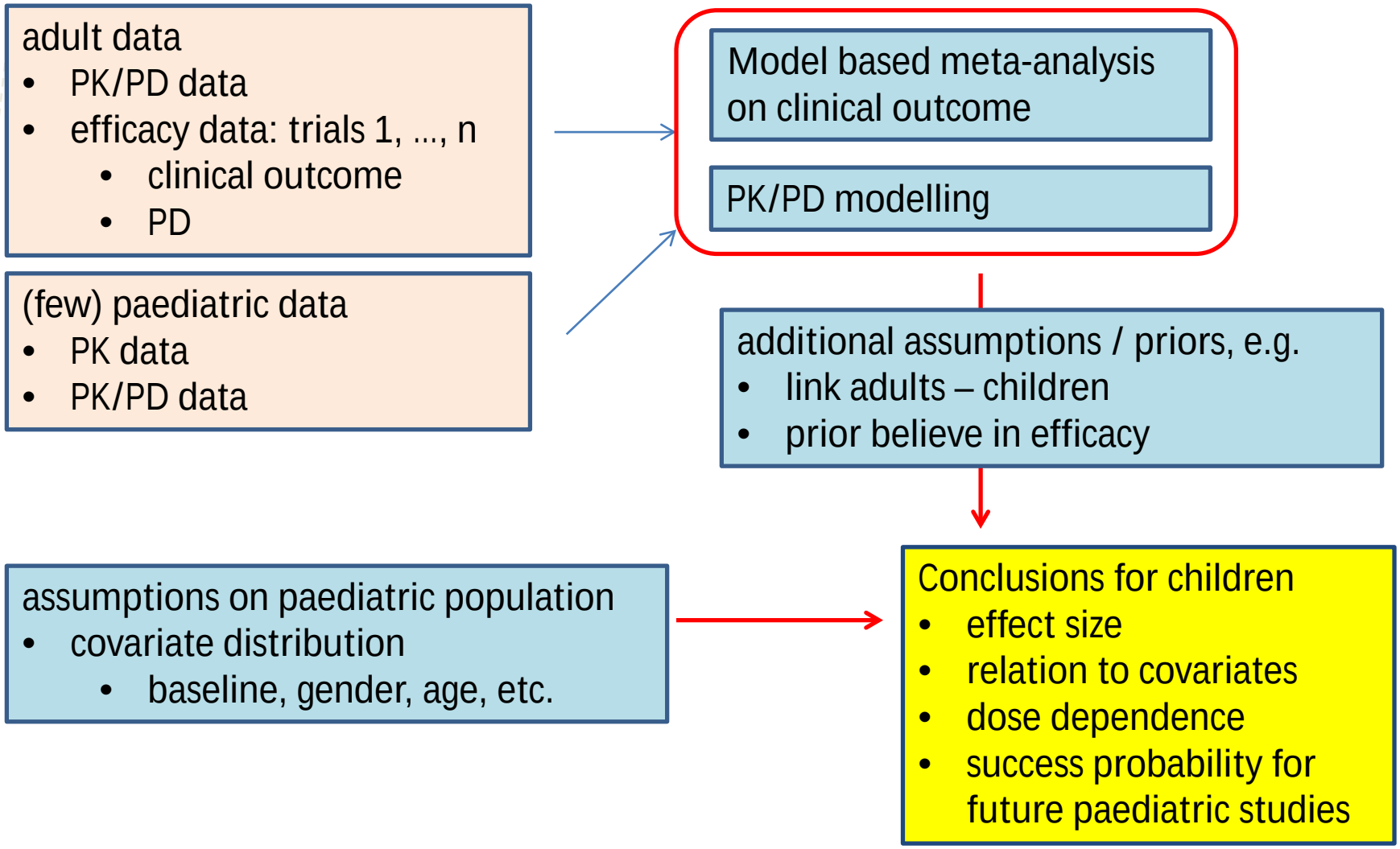
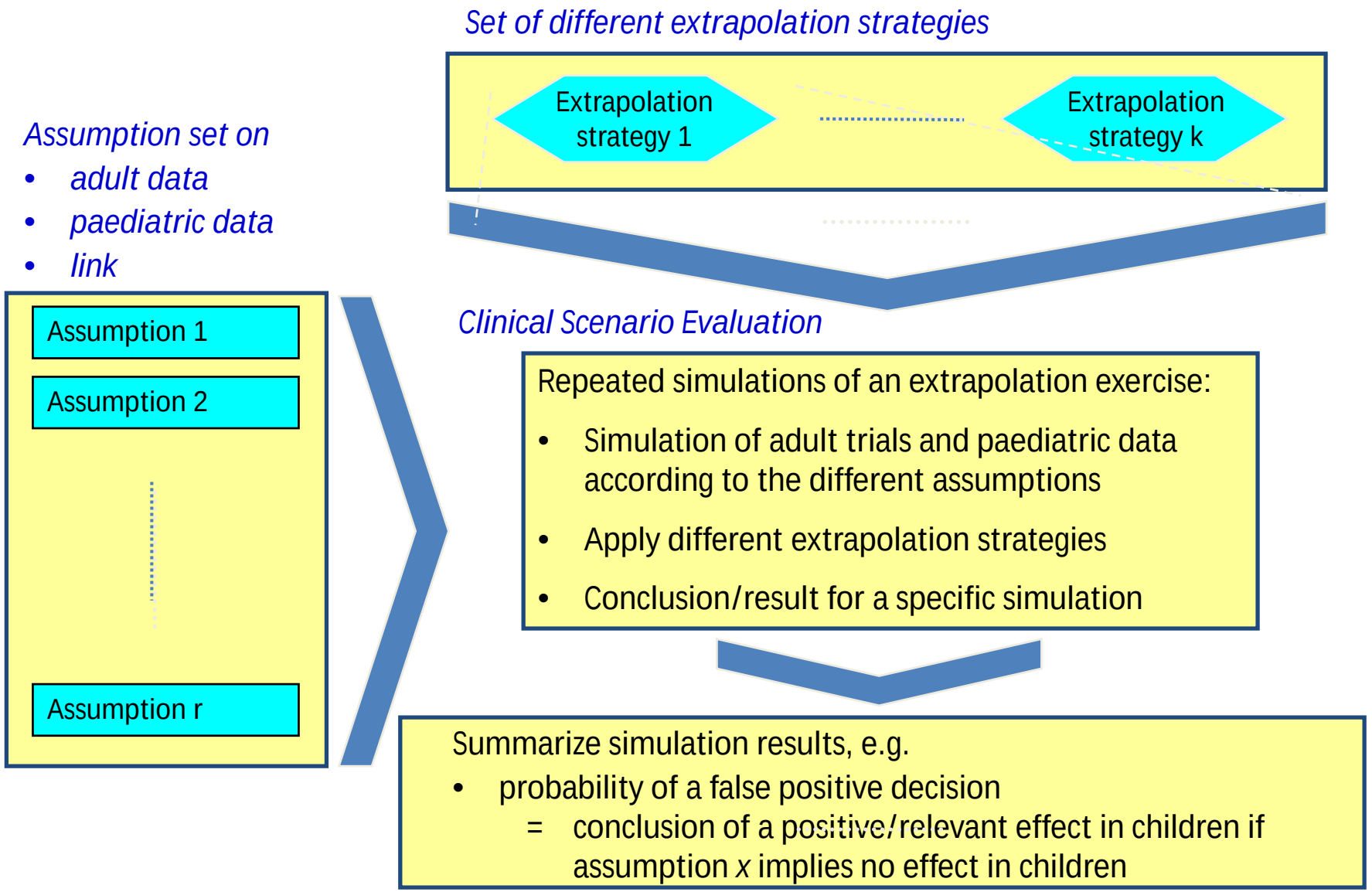
EXTRAPOLATION STRATEGY (EXAMPLE): ADULTS TO CHILDREN



CSE APPLIED TO EXTRAPOLATION



DISCUSSION AND CONCLUSIONS

- Rising **pressure on resources** for clinical trials and **shifting patient populations** lead to increasing **demand for efficient and robust clinical trials**
- **More complex designs and analysis methods** increase need for **Monte Carlo simulations**
- **Clinical scenario evaluation framework**
  - Support structured and early planning
  - Exploration of efficient approaches
  - Assessment of robustness
- **Challanges in small populations and rare diseases**

SOME REFERENCES

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