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COMBINING RANDOMIZED CONTROLLED TRIALS AND REAL WORLD DATA

Hans van Houwelingen award ceremony and symposium

Utrecht, 15 June 2023

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ACKNOWLEDGEMENTS

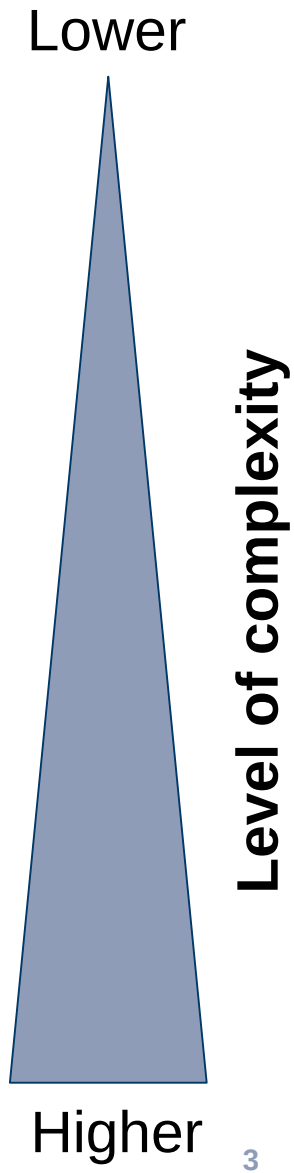
- The talk draws on **joint work** with a number of colleagues including
  - Christian Röver
  - Sarah Friedrich (Augsburg)
  - Tim Mathes

- Grateful for **funding** by DFG (German Research Foundation; FR 3070/3-1)

DFG Deutsche Forschungsgemeinschaft

EVIDENCE SYNTHESIS

- **Pairwise meta-analysis**
  - comparing two treatments
- **Meta-regression**
  - including study-level covariates
- **Network meta-analysis**
  - comparing multiple treatments indirectly
- **RCT with historical controls**
  - integrating control group data from previous trials
- **Generalized (or cross design) synthesis**
  - combining data from different types of studies

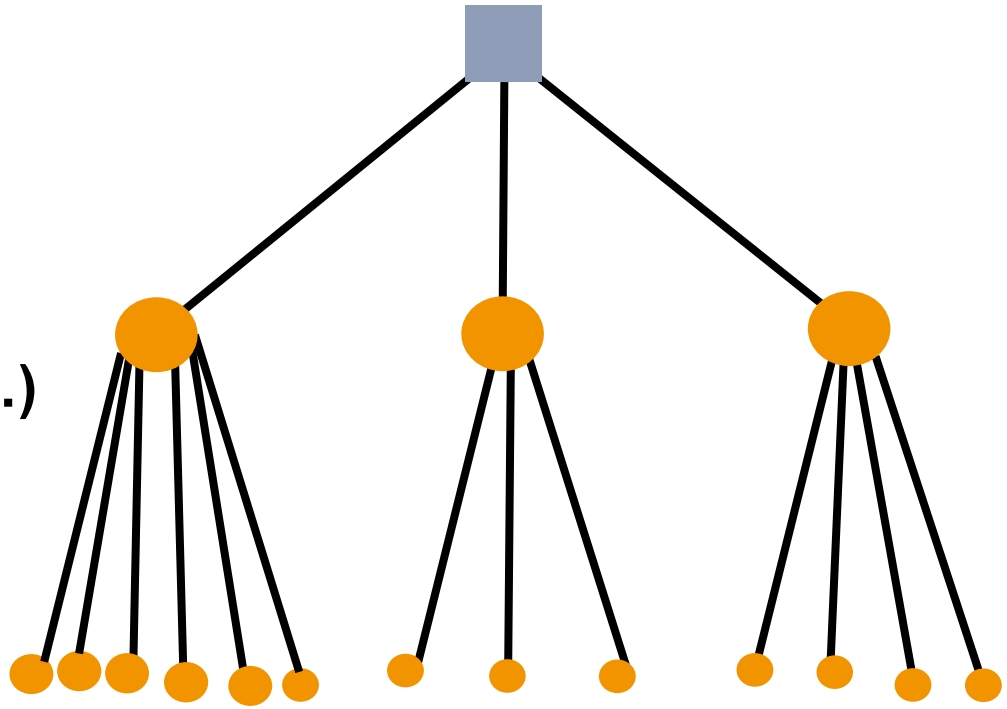


HIERARCHICAL MODELS

Meta-analysis

Studies (RCT, registry, …)

Patients



Example: **Normal-normal hierarchical model (NNHM)** for random-effects meta-analysis

$$y_i|\theta_i \sim \text{Normal}(\theta_i, s_i^2) \qquad \theta_i|\Theta, \tau \sim \text{Normal}(\Theta, \tau^2)$$

BAYESIAN META-ANALYSIS

- **Idea**: Weakly informative prior on between-trial heterogeneity for meta-analysis with few studies (Spiegelhalter et al, 2004), with uninformative prior on treatment effect
  - Avoids zero estimates of between-trial heterogeneity
  - Accounts for uncertainty in the estimation of the heterogeneity
- **Easy to compute**
  - Application of DIRECT algorithm (Röver & Friede, 2017) (which is faster than MCMC sampling and does not require inspection of convergence diagnostics)
  - R package **`bayesmeta`** by Christian Röver (available from CRAN)

"WHERE DOES THE PRIOR COME FROM?"

- Theoretical arguments, simulations, data

Received: 16 July 2020 | Revised: 13 January 2021 | Accepted: 16 January 2021
DOI: 10.1002/jrsm.1475

RESEARCH ARTICLE

Research Synthesis Methods WILEY

On weakly informative prior distributions for the heterogeneity parameter in Bayesian random-effects meta-analysis

Christian Röver[1] | Ralf Bender[2] | Sofia Dias[3] | Christopher H. Schmid[4] | Heinz Schmidli[5] | Sibylle Sturtz[2] | Sebastian Weber[6] | Tim Friede[1]

Received: 25 February 2022 | Revised: 16 November 2022 | Accepted: 18 March 2023
DOI: 10.1002/sim.9731

RESEARCH ARTICLE

Statistics in Medicine WILEY

Summarizing empirical information on between-study heterogeneity for Bayesian random-effects meta-analysis

Christian Röver[1] | Sibylle Sturtz[2] | Jona Lilienthal[2] | Ralf Bender[2] | Tim Friede[1]

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

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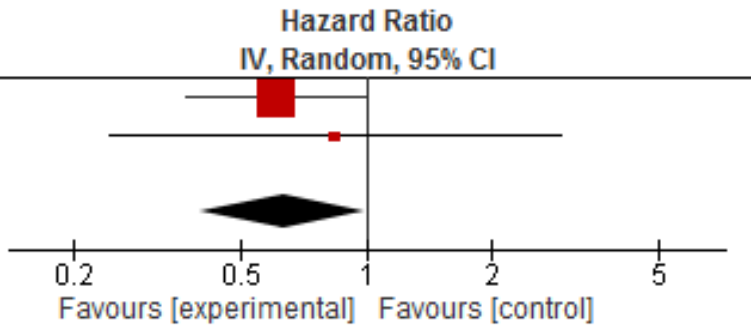
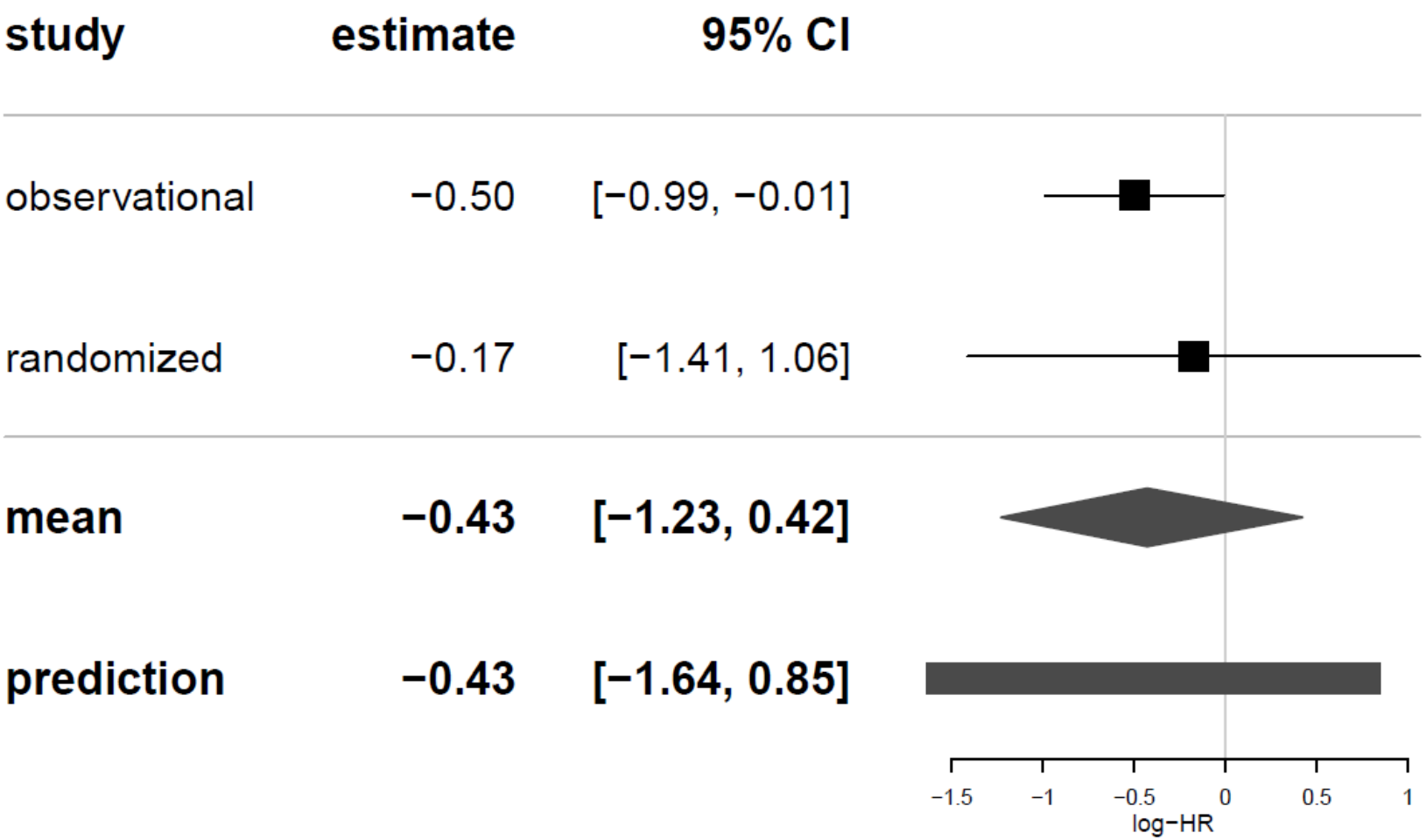
- **Creutzfeldt-Jakob disease**
  - prevalence of 1–9 cases per 1,000,000 people
  - qualifies as **rare disease** (EU: less than 5 in 10,000)
- **Varges et al (2017)** conducted:
  - double-blinded randomized phase II trial (n=12)
  - observational study (n=88) (Cox regression stratified by terciles 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



Computed with **`bayesmeta`**; HN(0.5) prior for τ

QUANTITIES OF INTEREST

Different quantities of interest in hierarchical models

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

EXAMPLE IN CJD: SHRINKAGE ESTIMATOR

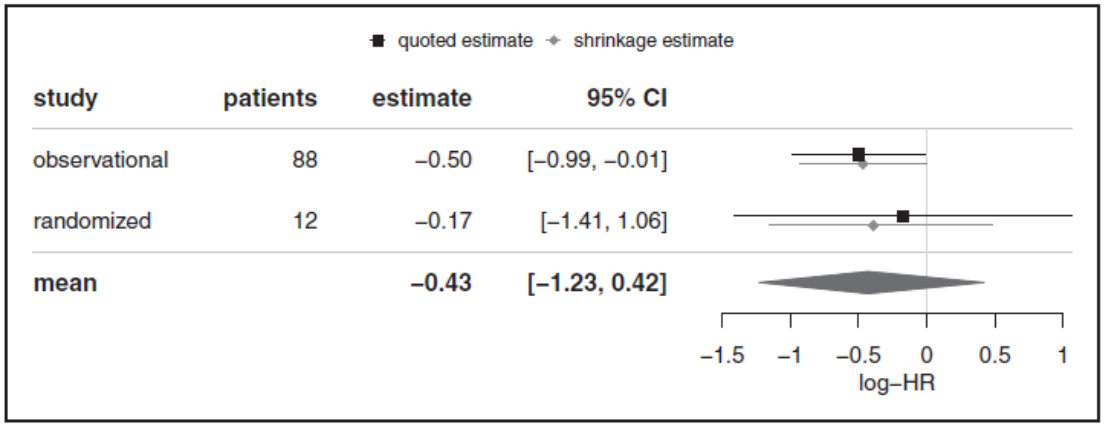
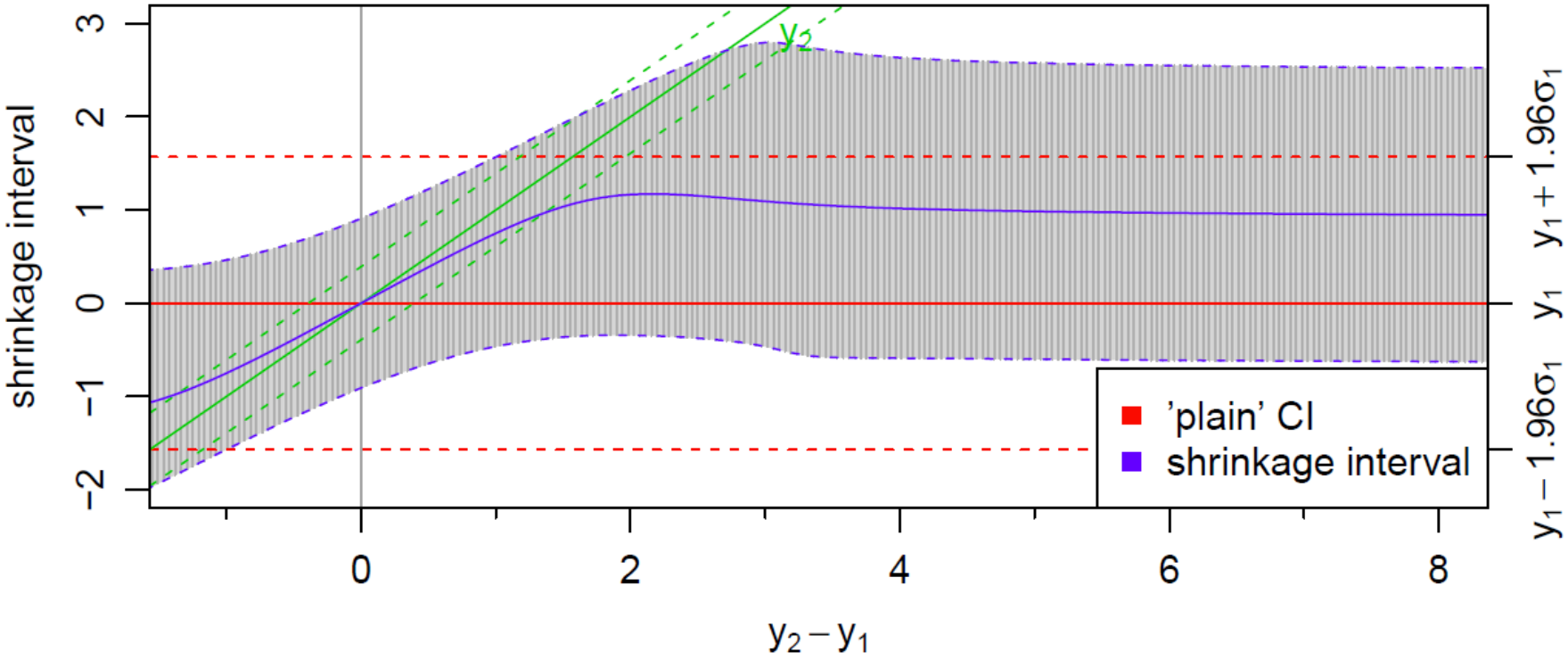


Figure 2. Forest plot for the CJD example (log-HR outcome). The shrinkage interval for the log-HR based on randomized evidence here is [−1.16, 0.48], spanning only two-thirds of the original confidence interval width.

- RCT shrinkage interval width: 66% of original CI width
- Translates into 129% gain in sample size (about 27 instead of 12 patients)

Röver & Friede (2020) SMMR

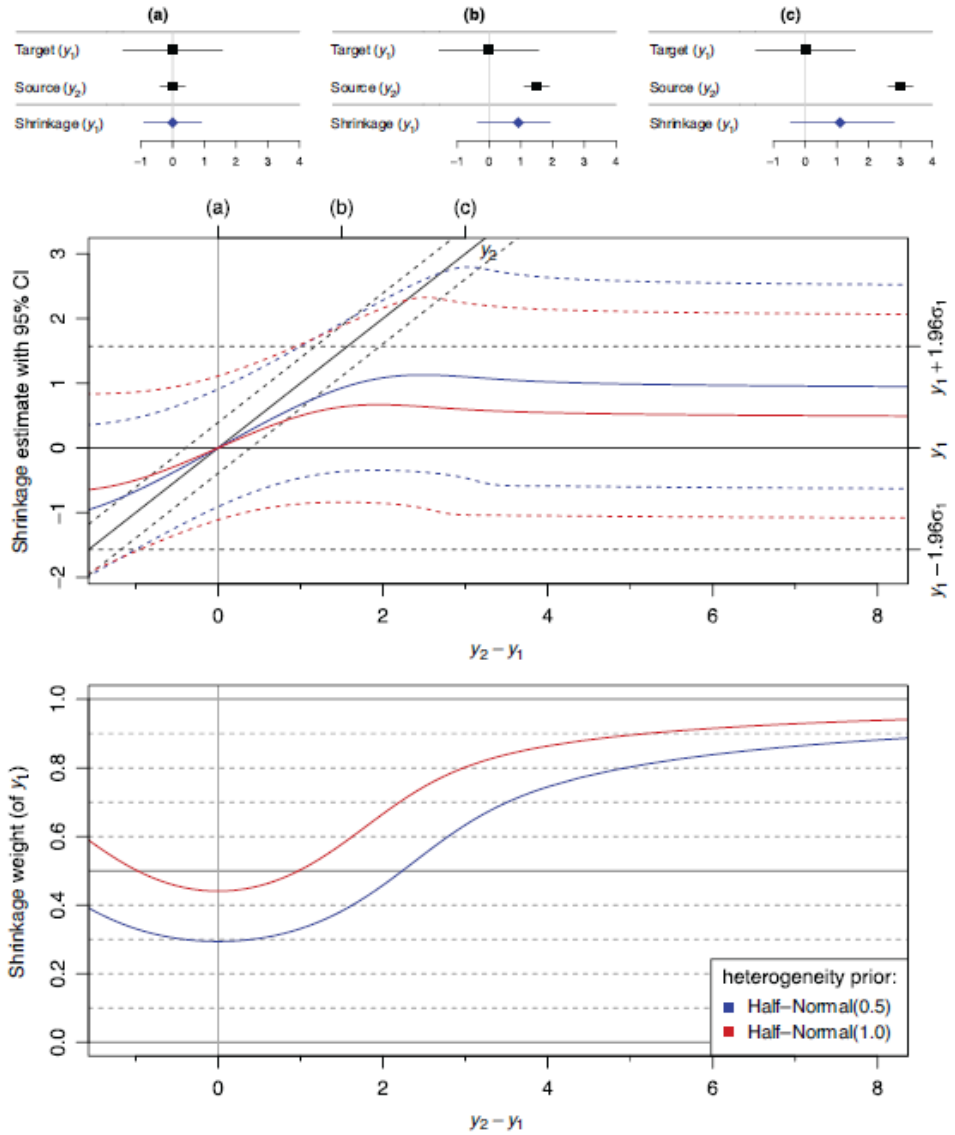
SHRINKAGE ESTIMATION WITH K=2 STUDIES



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

Röver & Friede (2020) SMMR

BOUNDS FOR THE WEIGHTS



- Lower bound on the target's weight for any data realization (y_1, y_2) or any heterogeneity prior given by common-effect (CE) weight $\sigma_2^{-2}/(\sigma_1^{-2} + \sigma_2^{-2})$
- In this example, $\sigma_1 = 0.8$ and $\sigma_2 = 0.2$ resulting in CE weight 1/17 (5.9%)
- Minimum where $y_1 = y_2$
- Min. weight 29% for HN(0.5)
- Larger weight for larger scale of heterogeneity prior

Röver & Friede (2021) Biom J

BOUNDS FOR THE WEIGHTS: CJD EXAMPLE

- Lower bound on the RCT's weight for any data realization (y_1, y_2) or any heterogeneity prior: $\sigma_2^{-2}/(\sigma_1^{-2}+\sigma_2^{-2})$=13.5%

TABLE 2 Data from Varges et al. (2017) on an observational and a randomized study investigating the effect of doxycycline on survival in CJD

		Patients		log(HR)	
i	Study	Treatment	Control	y_i	σ_i
1	Observational	55	33	−0.499	0.249
2	Randomized	7	5	−0.173	0.631

TABLE 3 Estimates for the CJD example

	Mean weight		Effect estimate θ_2	
τ prior	Minimum	Actual	Mean	95% CI
HN(0.5)	38.9%	39.5%	−0.370	[−1.157, 0.477]
HN(1.0)	52.1%	53.1%	−0.326	[−1.232, 0.664]
		(100.0%	−0.173	[−1.410, 1.064])

For different heterogeneity priors (HN(0.5) or HN(1.0)), the corresponding minimum (coincidence) weight is given, as well as the resulting weight for the actual data along with the corresponding shrinkage estimates. The very last line shows the estimate based only on y_2 and σ_2 for comparison.

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BAYESIAN BORROWING AND TYPE I ERROR RATE CONTROL

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- Type I error rate control (a frequentist property) cannot be guaranteed with Bayesian borrowing (Kopp-Schneider et al, 2019)
- Computer simulations used to explore impact of Bayesian borrowing on (frequentist) type I error rate

Table 1. Coverage (%) of shrinkage intervals for estimation of the first study's mean parameter (θ_1).

τ prior:		HN (0.5)							HN (1.0)						
n_1/n_2	τ:	0.0	0.1	0.2	0.5	1.0	2.0	*	0.0	0.1	0.2	0.5	1.0	2.0	*
25/400		99.7	99.6	98.9	93.4	84.0	79.0	94.7	99.3	99.3	99.0	96.7	92.5	90.5	95.1
25/100		98.7	98.7	98.1	93.9	86.1	80.0	95.1	98.4	98.6	98.5	96.5	93.2	90.8	94.4
100/400		98.7	98.2	97.1	93.2	90.9	90.4	94.9	98.1	97.7	97.2	94.8	93.7	93.5	95.3
25/25		96.6	96.7	96.1	94.5	90.5	84.6	95.0	97.0	97.2	96.6	95.7	94.0	92.1	94.9
100/100		96.7	96.5	96.3	94.0	91.1	90.7	95.7	96.7	96.4	96.6	95.3	93.7	93.6	94.9
400/400		96.7	96.6	95.0	94.0	94.0	93.9	95.0	96.4	96.4	95.0	94.9	94.9	94.8	95.0
100/25		96.0	95.6	95.3	94.8	93.8	92.3	94.7	96.0	95.8	95.6	95.2	94.7	94.3	94.8
400/100		95.5	95.6	95.4	94.7	93.7	93.8	95.1	95.6	95.5	95.5	94.9	94.3	94.5	95.1
400/25		95.1	95.1	95.2	94.7	94.9	94.5	95.3	95.0	95.2	95.2	94.8	95.0	95.0	95.2

Note: Sample sizes (n_1 and n_2) as well as settings for the heterogeneity prior ($p(\tau)$) and actual heterogeneity values (τ) are varied. The columns labelled by an asterisk (*) correspond to drawing the heterogeneity from its corresponding prior distribution.

Röver & Friede (2020) SMMR

EXAMPLE: EARLY PRO-TECT

www.kidney-international.org clinical trial

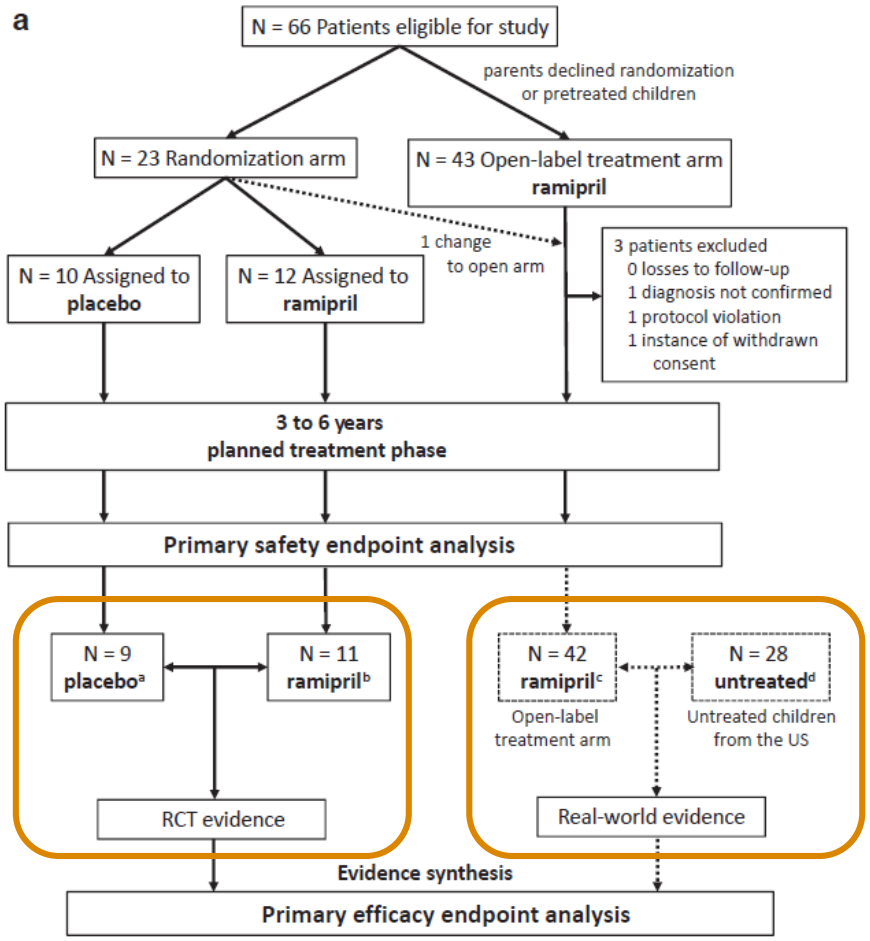
A multicenter, randomized, placebo-controlled, double-blind phase 3 trial with open-arm comparison indicates safety and efficacy of nephroprotective therapy with ramipril in children with Alport's syndrome

see commentary on page 1104

OPEN

Oliver Gross[1], Burkhard Tönshoff[2], Lutz T. Weber[3], Lars Pape[4], Kay Latta[5], Henry Fehrenbach[6], Baerbel Lange-Sperandio[7], Hildegard Zappel[8], Peter Hoyer[9], Hagen Staude[10], Sabine König[11], Ulrike John[12], Jutta Gellermann[13], Bernd Hoppe[14], Matthias Galiano[15], Britta Hoecker[2], Rasmus Ehren[3], Christian Lerch[4], Clifford E. Kashtan[16], Markus Harden[17], Jan Boeckhaus[1] and Tim Friede[17]; for the German Pediatric Nephrology (GPN) Study Group and EARLY PRO-TECT Alport Investigators[18,19]

EXAMPLE: EARLY PRO-TECT TRIAL

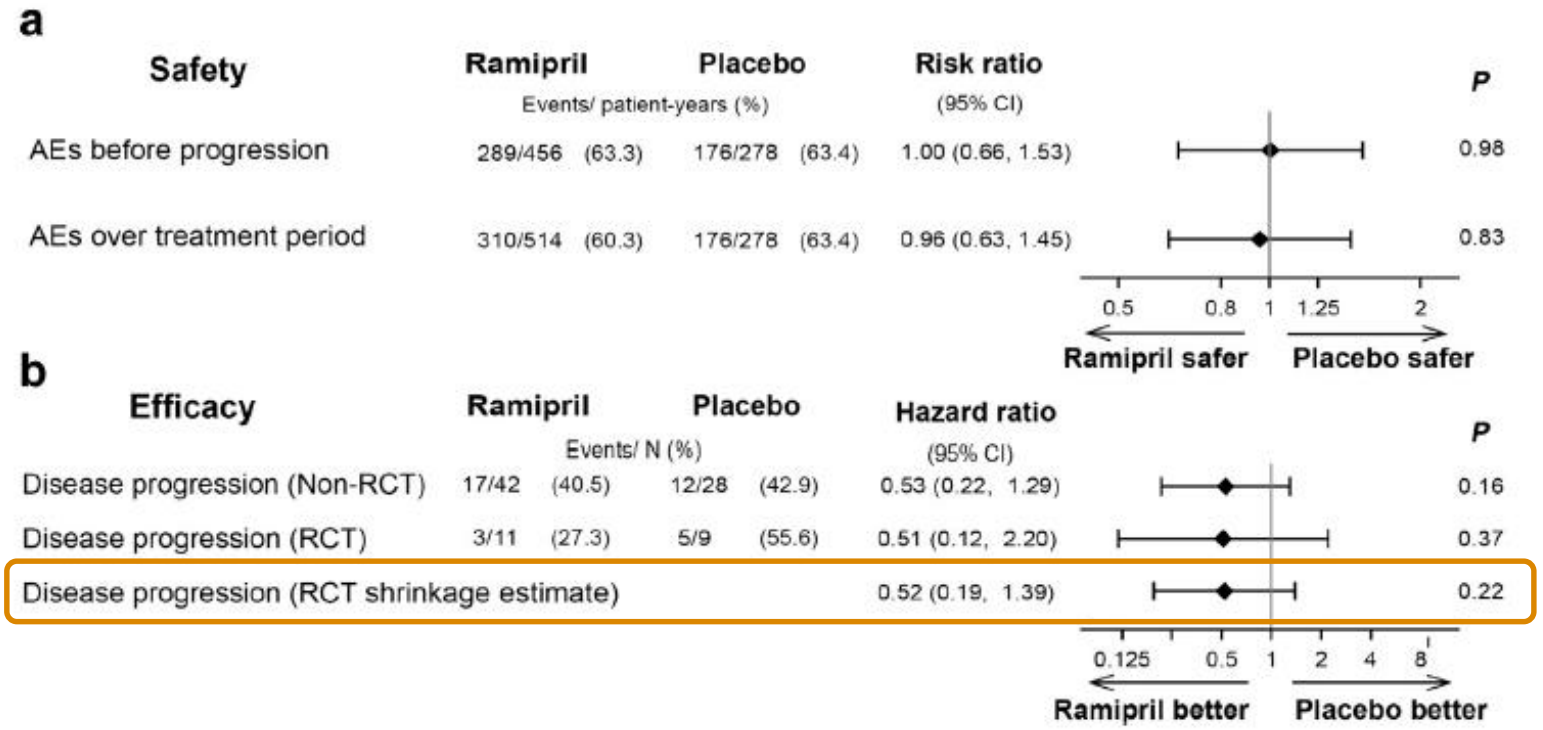


- **Randomised controlled trial in children with Alport's syndrome** (rare genetic disorder leading to end-stage kidney disease)
- **Observational data**
  - Open-label treatment arm
  - Natural disease cohort (registry)

Figure 1 in Gross et al (2020) Kidney International

EXAMPLE: EARLY PRO-TECT TRIAL

- Figure 2 in Gross et al (2020) Kidney International



- **Increased precision in estimating the treatment effect**: Interval shortened by 42%; equivalent to raising the sample size of the RCT from 20 to 43; i.e. 70 patients in RWE count as 23 RCT patients

COMPREHENSIVE COHORT STUDIES

- **Schmoor et al (1996) Stat Med**

STATISTICS IN MEDICINE, VOL. 15, 263–271 (1996)

RANDOMIZED AND NON-RANDOMIZED PATIENTS IN CLINICAL TRIALS: EXPERIENCES WITH COMPREHENSIVE COHORT STUDIES

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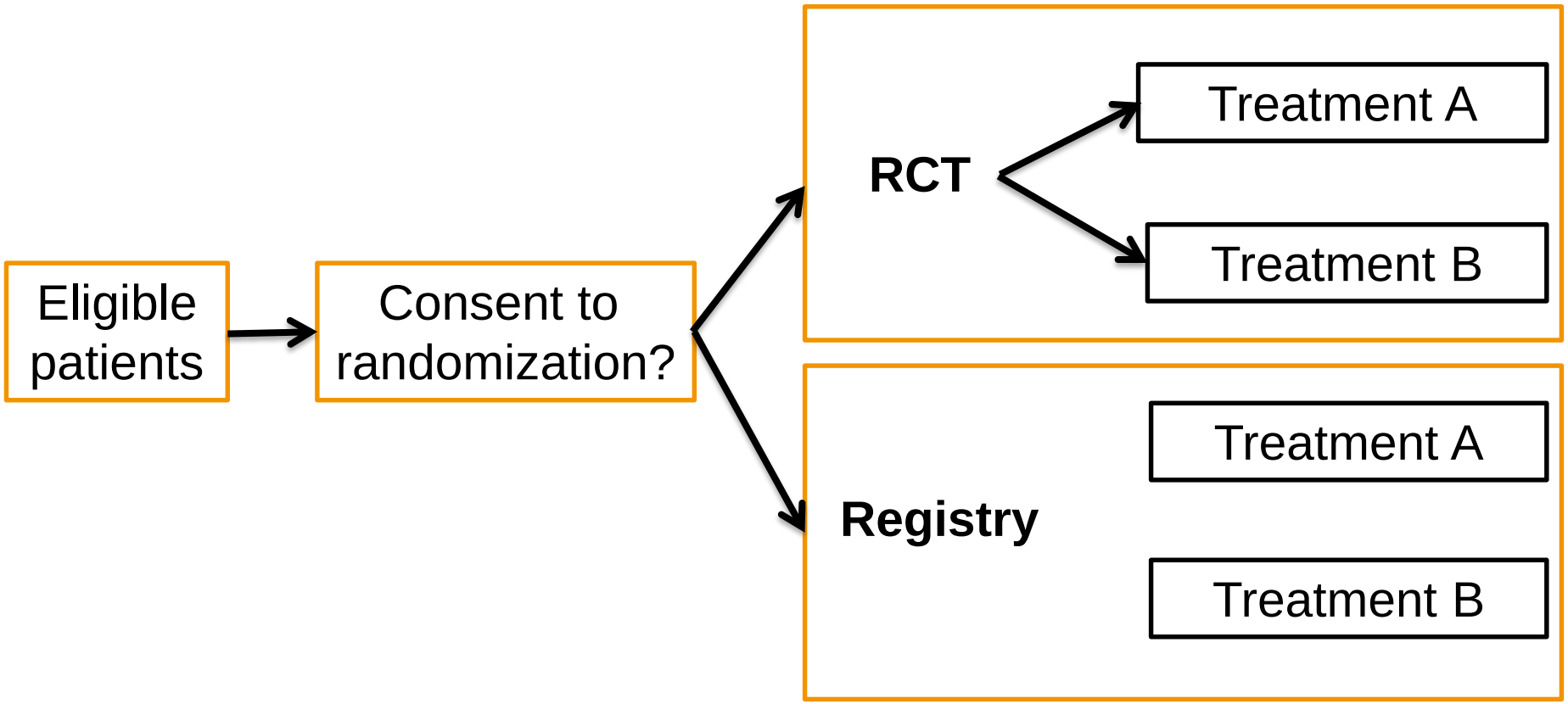
SUMMARY

In clinical research, randomized trials are widely accepted as the definitive method of evaluating the efficacy of therapies. Random assignment of patients to treatment ensures internal validity of the comparison of new treatments with controls. An assessment of external validity can best be achieved by comparing the randomized study sample to the population of patients who met the eligibility criteria but did not consent to randomization. The Comprehensive Cohort Study (CCS) is designed to recruit all patients fulfilling the clinical eligibility criteria regardless of their consent to randomization. The CCS concept was adopted in the major clinical trials of the German Breast Cancer Study Group (GBSG) conducted between 1983 and 1989. In this period 124 centres recruited 2084 patients in three clinical trials. 734 (35 per cent) of these patients accepted being randomized, while 1350 (65 per cent) chose one of the treatments under study; the randomization rates differed remarkably between trials. In this paper we examine the representativeness of the randomized patients in the three trials. Based on a median follow-up of about 5 years we present results on the external validity of the treatment effects estimated in the randomized patients by means of Cox's proportional hazards model and compare them between trials. We discuss advantages and disadvantages of the CCS design and conclude that its use is only justified under extraordinary circumstances.

COMPREHENSIVE COHORT DESIGN



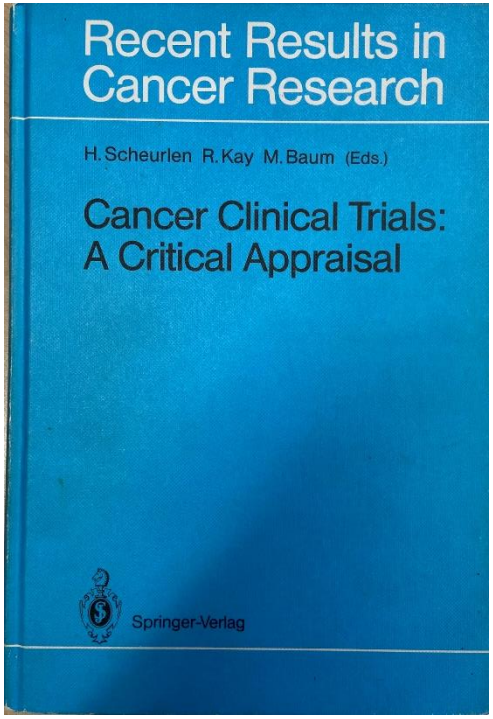
Adapted from Figure 1 in Schmoor et al (1996)

ORIGINS OF THE CCS DESIGN

Some references from Schmoor et al (1996)

REFERENCES

1. Olschewski, M. and Scheurlen, H. 'Comprehensive Cohort Study: An alternative to randomized consent design in a breast preservation trial', *Methods of Information in Medicine*, **24**, 131–134 (1985).
2. Principal Investigators of CASS and their Associates 'National Heart, Lung, and Blood Institute Coronary Artery Surgery Study', *Circulation*, **63 I**, 1–82 (1981).
3. Olschewski, M., Schumacher, M. and Davis, K. B. 'Analysis of randomized and non-randomized patients in clinical trials using the comprehensive cohort follow-up study design', *Controlled Clinical Trials*, **13**, 226–239 (1992).



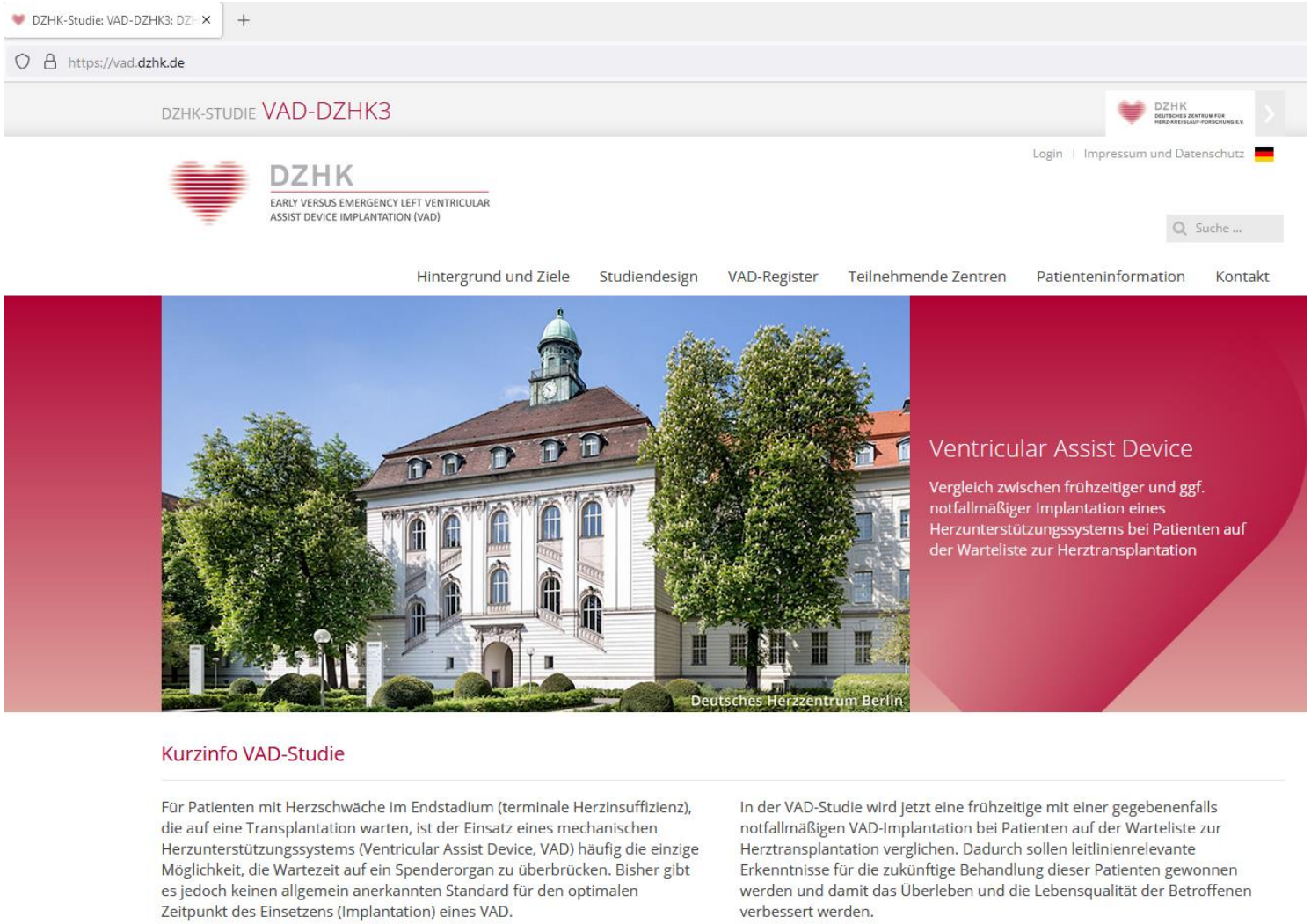
INTERNAL AND EXTERNAL VALIDITY

- **Randomized controlled trial**
  - Internal validity through randomisation
- **Assessment of external validity in comprehensive cohort studies** (Schmoor et al, 1996)
  - Comparisons of RCT and registry with regard to
    - baseline characteristics
    - follow-up / outcome
    - treatment effects

EXTENSION OF CCS APPROACH

- **Randomized controlled trial**
  - Internal validity through randomisation
- **Assessment of external validity in comprehensive cohort studies**
  - Comparisons of RCT and registry with regard to baseline characteristics and follow-up (Schmoor et al, 1996)
- **Data integration**
  - Meta-analytic framework to integrate data from RCT and registry (using appropriate causal inference approach) accounting for heterogeneity (Röver and Friede, 2020)

EXAMPLE: VAD-DZHK3



CAUSAL INFERENCE IN SMALL OBSERVATIONAL STUDIES

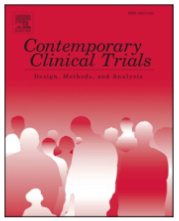
- **Data requirements**: characterization of patients, granularity of follow-up
- Do **causal inference methods** (e.g. propensity score based approach, g-computation) work with small sample sizes?

Contemporary Clinical Trials 99 (2020) 106213

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial



Causal inference methods for small non-randomized studies: Methods and an application in COVID-19

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RECOMMENDATIONS FOR THE ANALYSIS OF SMALL NON-RANDOMIZED STUDIES

Based on (limited) simulations with binary outcome, binary treatment and covariates (Friedrich & Friede, 2020)

1. Unmeasured confounder rendered the methods useless. Therefore, careful clinical characterization of patients important
2. Effect measure: risk difference preferred over odds ratio
3. For small sample sizes, the best performance observed for covariate adjustment, PS covariate and doubly robust g-computation (based on quintiles)
4. IPTW performed well regarding bias and RMSE, but coverage of confidence intervals very low (and therefore not recommended)
5. Conduct simulations to explore properties of the methods in scenarios similar to the one at hand (R code available)

CONCLUSIONS AND DISCUSSION

- **Hierarchical models**
  - flexible statistical framework for evidence synthesis
- **Bayesian inference**: advantages over traditional methods in the presence of heterogeneity and only (very) few studies
  - easy to apply using R package **`bayesmeta`**
- **Cross-design synthesis of available evidence**
  - Promising in rare diseases
  - more practical (and regulatory) experience needed
- **Bounds for weights:** concerns of evidence being easily overwhelmed by external data are largely unwarranted
- **Alternative approaches** including power prior model

ANY QUESTIONS?

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SOME REFERENCES

- Röver C, Friede T (2020) Dynamically borrowing strength from another study through shrinkage estimation. Statistical Methods in Medical Research 29: 293–308.
- Röver C, Friede T (2021) Bounds for the weight of external data in shrinkage estimation. Biometrical Journal 63: 1131–1143.
- Varges D, …, Friede T, Zerr I (2017) Doxycycline in early CJD – double-blinded randomized phase II and observational study. Journal of Neurology, Neurosurgery & Psychiatry 88: 119–125.
- Gross O, Tönshoff B, Weber LT, …, Friede T for the GPN Study Group and EARLY PROTECT Alport investigators (2020) A multicenter, randomized, placebo-controlled, double-blind phase 3 trial with open arm comparison indicates safety and efficacy of nephroprotective therapy with Ramipril in children with Alport's syndrome. Kidney International 97: 1275–1286.