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EXPLORATORY AND CONFIRMATORY SUBGROUP ANALYSES IN CLINICAL TRIALS

EFSPI Biomarkers and Subgroups Meeting

Leiden, 24 June 2016

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ACKNOWLEDGEMENTS

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- **“Improving outcomes from the treatment of low back pain”** funded by UK NIHR (RP-PG-0608-10076); PI Martin Underwood (Warwick)
- **“BI**ostatistische **M**ethoden zur effizienten Evaluation von **I**ndividualisierten **T**herapien **(BIMIT)”** funded by BMBF
  - Coordinated by Meinhard Kieser (Heidelberg)
  - WP C: Tim Friede**,** Marius Placzek, Roland Gera (Göttingen); Heinz Schmidli (Novartis)

GEFÖRDERT VOM Bundesministerium für Bildung und Forschung

BIMIT

- **“Identification und confirmation of biomarker-defined populations in the personalized pharmacotherapy”** co-funded by BfArM
  - PIs Tim Friede, Jürgen Brockmöller (UMG), Norbert Benda Julia Stingl (BfArM)
- **"Innovative methodology for small populations research" (InSPiRe)** funded by EU's FP7 (HEALTH 2013 – 602144)
  - Coordinated by Nigel Stallard (Warwick)
  - WP4: Tim Friede, Christian Röver, Steffen Unkel (Göttingen); Beat Neuenschwander, Simon Wandel (Novartis); …

InSPiRe
Innovative methodology for small populations research

OUTLINE

- **Motivation**: Biomarkers, Personalised medicine
- **Identifying subgroups** in a single trial
- Extension to several trials: **Meta-analytic framework**
- **Clinical development plans**: Integration of subgroup identification and confirmation
- **Concluding remarks**

WHAT ARE BIOMARKERS?

- Definition by the **Biomarkers Definitions Working Group** (2001)
  - „A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.“
  - Very general definition
- **Sometimes more restrictive use of the term „biomarker“** relating only to measurements in blood, urine, CSF, …
- Excluding e.g. imaging markers

WHAT ARE BIOMARKERS USED FOR?

- Biomarkers are used …
  - to **diagnose** diseases (or certain subtypes)
  - to **predict** disease course or response to treatment
  - to **stratify** populations
  - to **monitor** patients
  - as **endpoints** in clinical trials

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PROGNOSTIC VS. PREDICTIVE BIOMARKERS

- **prognostic** biomarkers
  - markers affecting disease course

- **predictive** biomarkers
  - markers affecting treatment effect
  - technically: interactions with treatment effect, also known as moderators

- **Not necessarily the same biomarkers!**

PREDICTIVE BIOMARKERS

- **Personalised medicine**
  - Efficacy, safety and consequently benefit-risk might vary across patient population
  - Stratification of patient populations
  - Drive towards targeted treatments

- **Enrichment** of clinical study populations (Temple, 2010)
  - “to identify a population of patients in whom a drug effect, if present, is more likely to be demonstrable”
  - (a) practical, (b) prognostic, and (c) predictive enrichment

STRATIFIED MEDICINE: EXAMPLES OF TARGETED THERAPIES

Table I. Oncology products approved in the USA for selected populations.

Compound	Target	Indication
Crizotinib (Xalkori®)	ALK	ALK-rearranged non-small cell lung cancer
Vemurafenib (Zelboraf®)	BRAF	BRAF mutant advanced melanoma
Trametinib (Mekinist®)	MEK	BRAF mutant advanced melanoma
Trastuzumab (Herceptin®)	Her 2	Her 2 expressing breast cancer
Lapatinib (Tykerb®)	Her 2	Her 2 expressing metastatic gastric cancer
Rituximab (Rituxan®)	CD20	CD20(+) B-cell lymphomas
Cetuximab (Erbitux®)	EGFR	$KRAS^{wt}$, EGFR(+) metastatic colorectal cancer
Panitumumab (Vectibix®)	EGFR	$KRAS^{wt}$, EGFR(+) metastatic colorectal cancer

Table I from Mehta et al. (2014) Stat Med

EXAMPLE: IMPROVING OUTCOMES FROM THE TREATMENT OF LOW BACK PAIN

- NIHR funded project lead by Martin Underwood (Warwick, UK)
- **Project aim**
  - „… to improve the clinical and cost-effectiveness of low back pain treatment by providing patients, their clinical advisors, and health service purchasers with better **information about which participants are most likely to benefit from which treatment choices.**"
- **Repository**
  - Individual patient data of 19 randomised controlled trials
  - Total of 9,328 patients

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MODERATORS OF TREATMENT EFFECT

- Baseline variables affecting treatment effect; sometimes also referred to as **“predictive” factors** (not to be confused with prognostic factors)
- Technically **interaction effects** between baseline variable and treatment effect
- For instance, analysis of covariance (ANCOVA) with treatment, baseline covariables and treatment-by-baseline covariable interactions
- **More sophisticated**: Fractional polynomials (Royston & Sauerbrei, 2004)

SUBGROUP IDENTIFICATION

- For an overview refer to recent systematic literature **review by Ondra et al. (2015) on methods for subgroup identification and confirmation** in clinical trials
- **Exploratory subgroup identification**
  - attracted a lot of attention over the past years
  - several methods proposed
- Here we describe one we adopted when working on the back pain repository …

ADAPTIVE REFINEMENT BY DIRECTED PEELING (ARDP) ALGORITHM

- Proposed by LeBlanc et al. (2005) to identify risk groups (**prognostic factors**)
- Risk groups defined by (half open) **“boxes”** resulting in simple rules
- Here modified to identify subgroups responding particularly well to treatment (**predictive factors**)

SUB-GROUP IDENTIFICATION: ADAPTIVE REFINEMENT BY DIRECTED PEELING

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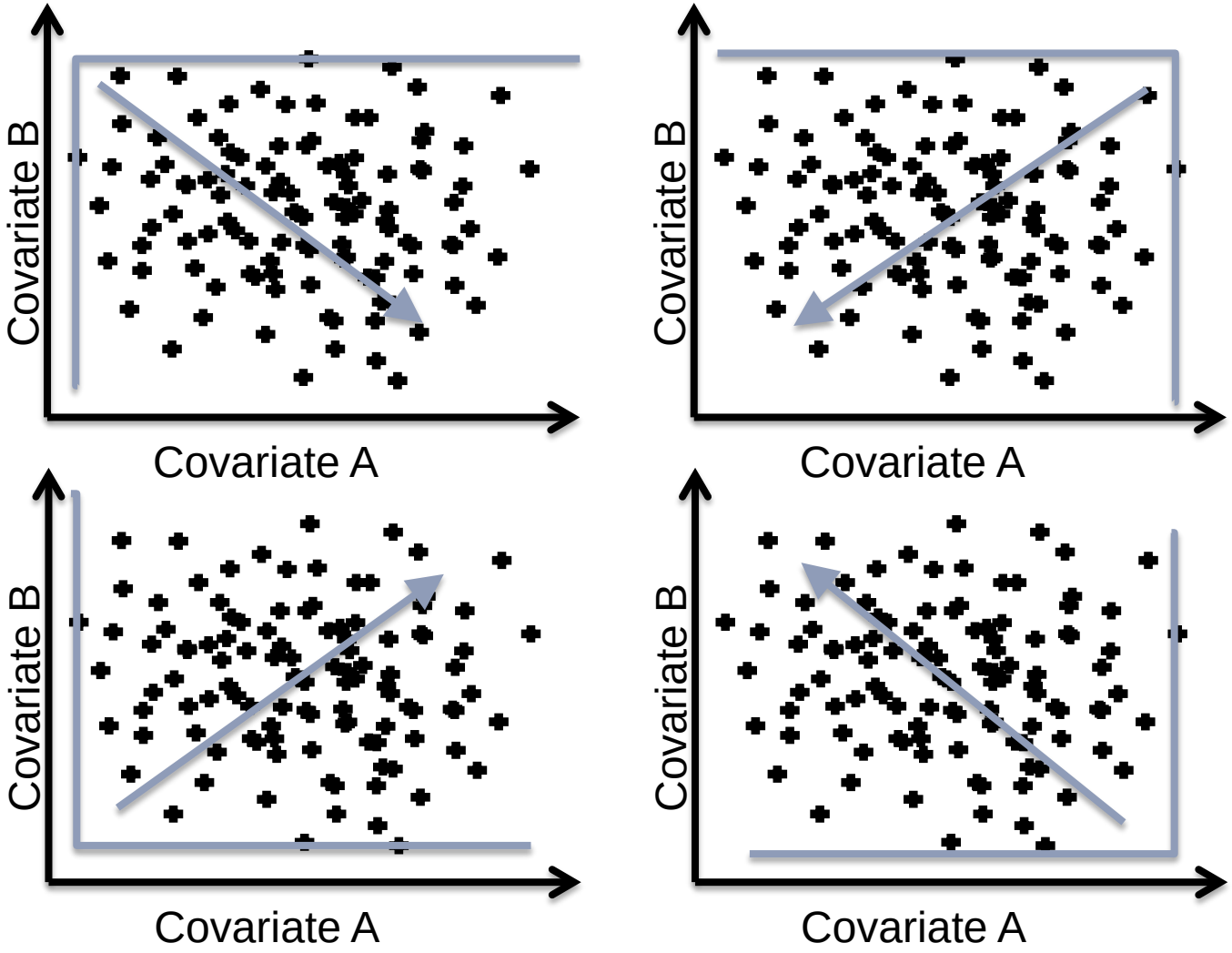
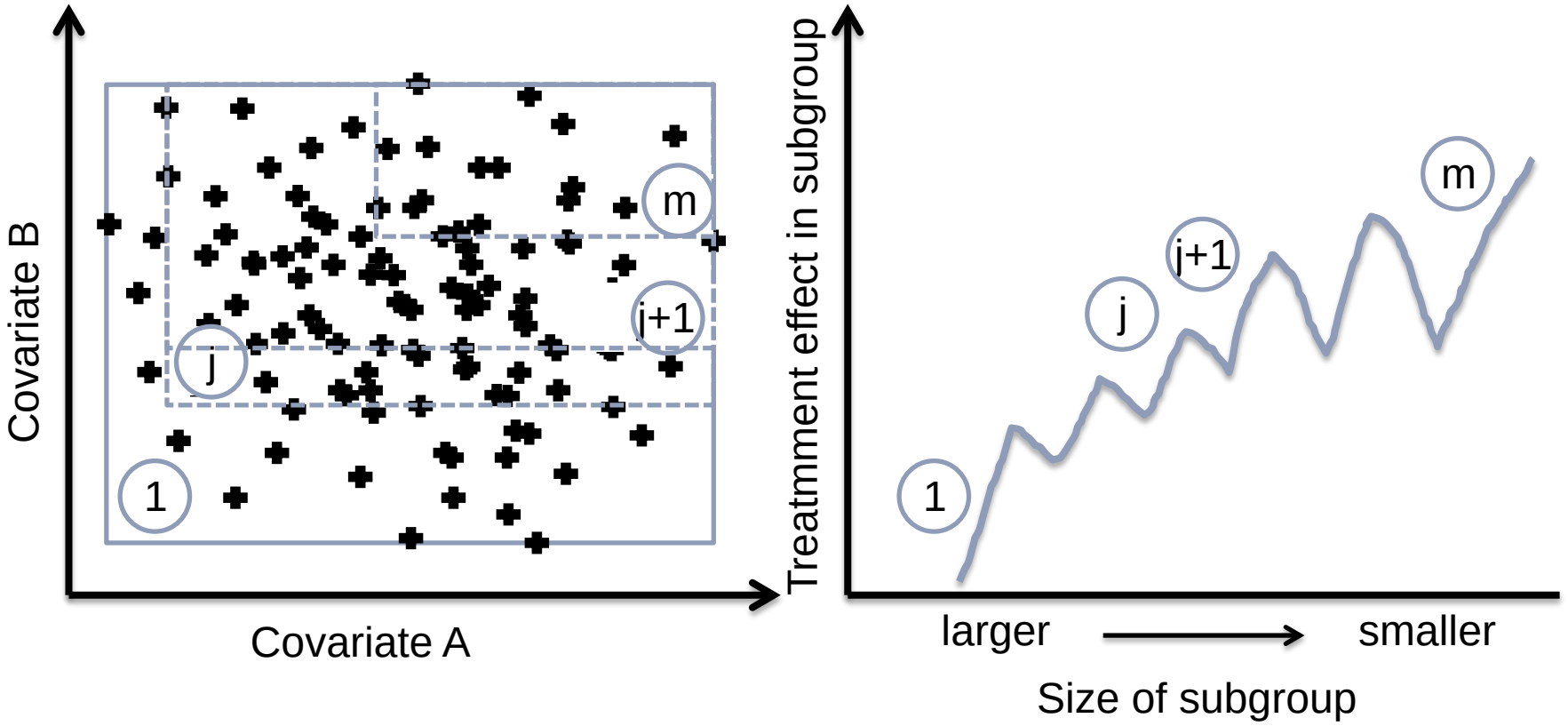
1. Investigating **interactions of covariates with treatment** determines covariates to be included and direction of peeling
2. Start with a “subgroup” B^0 that includes all observations.
3. For each variable we **peel a certain number of observations off** resulting in subgroups $B_j^m, j = 1, \dots, p$.
4. For each subgroup B_j^m calculate the **treatment-by-subgroup interaction** and select the B_j^m which gives the largest improvement on the interaction effect in comparison to the previous iteration. The selected subgroup is then called B^{m+1}.
5. Estimate the treatment effects for the outcome of interest for subgroup B^{m+1}.
6. Repeat steps 3 to 5 until the size of the remaining region is not smaller than *r*.

SUB-GROUP IDENTIFICATION: ADAPTIVE REFINEMENT BY DIRECTED PEELING (ARDP)



SUB-GROUP IDENTIFICATION: ADAPTIVE REFINEMENT BY DIRECTED PEELING (ARDP)



SUB-GROUP IDENTIFICATION: ADAPTIVE REFINEMENT BY DIRECTED PEELING (ARDP)

- **Algorithm can be applied to various kinds of endpoints**
  - Continuous: Gaussian linear models
  - Binary: logistic regression
  - Time-to-event: Cox proportional hazard models
- **No distributional assumption regarding the covariates** required, but they should be ordinal with sufficient number of possible outcomes
- If covariable not ordinal, then order could be imposed: order the categories by the regression coefficients estimated in Step 1 of the algorithm (LeBlanc et al., 2005).

SUB-GROUP IDENTIFICATION: ADAPTIVE REFINEMENT BY DIRECTED PEELING (ARDP)

- „Experience with simulated data with low signal shows that there can be **substantial estimation bias due to peeling** if there are a moderate number of predictors (p>5).“ (LeBlanc et al., 2005)
- LeBlanc et al. (2005) suggested **resampling methods** to reduce selection bias and for inference
- **K-fold crossvalidation** to reduce bias in estimation
- **Permutation test** to test whether the prognostic subgroups are associated with outcome

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MODERATORS OF TREATMENT EFFECT

- Modelling **between-study heterogeneity**
- **Hierarchical (mixed-effects) model**
  - Fixed effects: treatment, covariables, treatment-by-covariable interactions
  - Random effects: trial and trial-by-treatment interaction (a model similar to standard random-effects meta-analysis)
  - **Example with continuous outcome in SAS**

```
1 proc mixed data=&data;
2    class &trt &trials;
3    model &outcome = &trt &var &trt*&var / s ddfm=satterth;
4    random intercept &trt / subject=&trials;
5    repeated / group=&trials;
6 run;
```

SUB-GROUP IDENTIFICATION: ADAPTIVE REFINEMENT BY DIRECTED PEELING (ARDP)

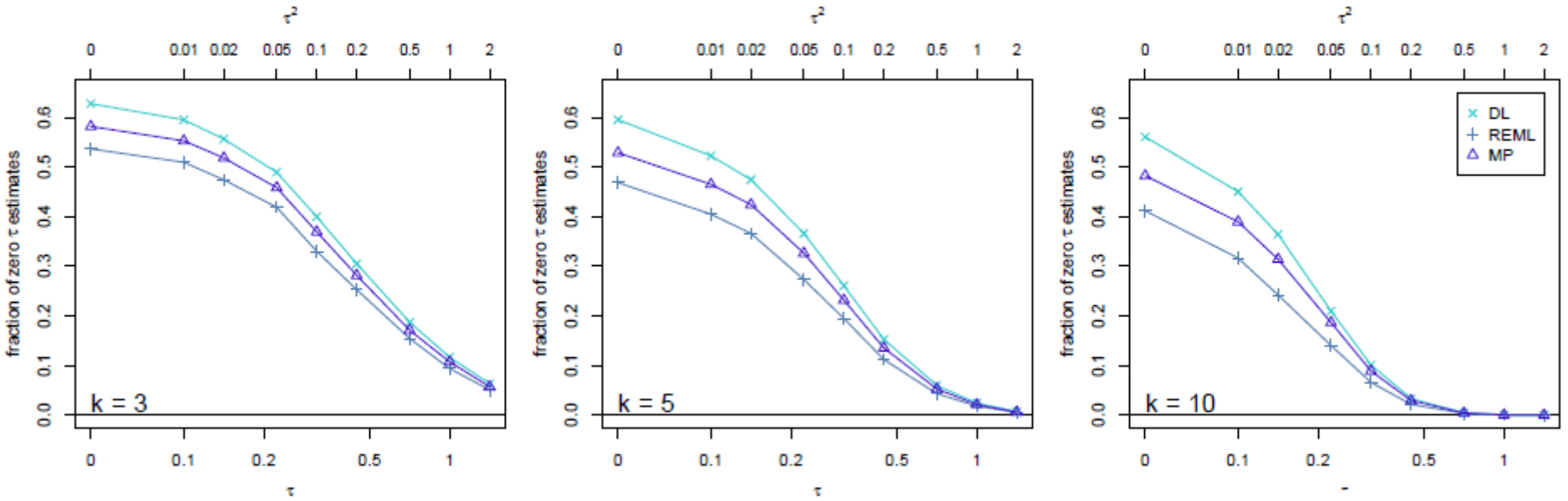
- Extension to multiple trials by including terms for between-trial heterogeneity in the model
- **Random effects meta-analyses of interaction effects**
  - Two-step procedure: interaction effects estimated from individual trials are combined in random-effects meta-analyses
  - One-step procedure: hierarchical model

BETWEEN-TRIAL HETEROGENEITY

- Likely to be present due to some differences in e.g. trial populations (see e.g. Higgins et al, 2009)
- Variety of estimators proposed including REML, MoM / DL, PM, … (see Veronicki et al, 2015)
- Estimation particularly challenging with only few studies (a situation frequently encountered)
- In the following: some results for pairwise meta-analysis with few small studies motivated by rare disease setting (InSPiRe)

ESTIMATION OF BETWEEN-TRIAL HETEROGENEITY

- Proportion of between-trial heterogeneity estimates being 0
- Estimators: DerSimonian-Laird (DL), restricted maximum likelihood (REML), Mandel-Paule (MP)



Friede et al. (2016) RSM

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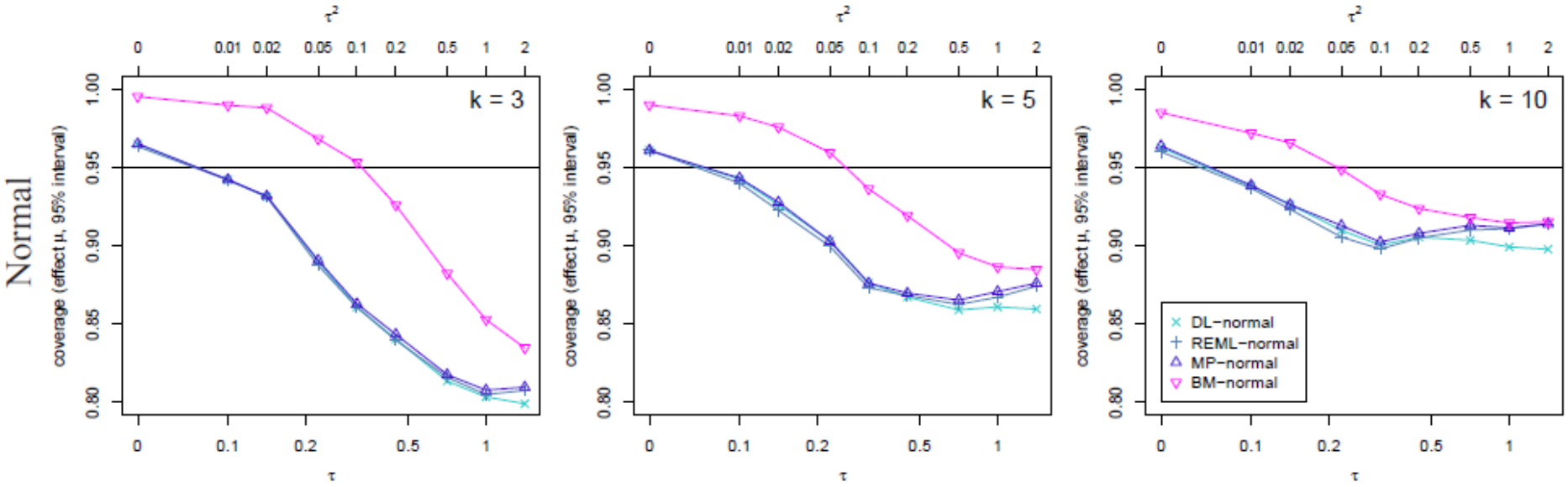
ESTIMATION OF BETWEEN-TRIAL HETEROGENEITY

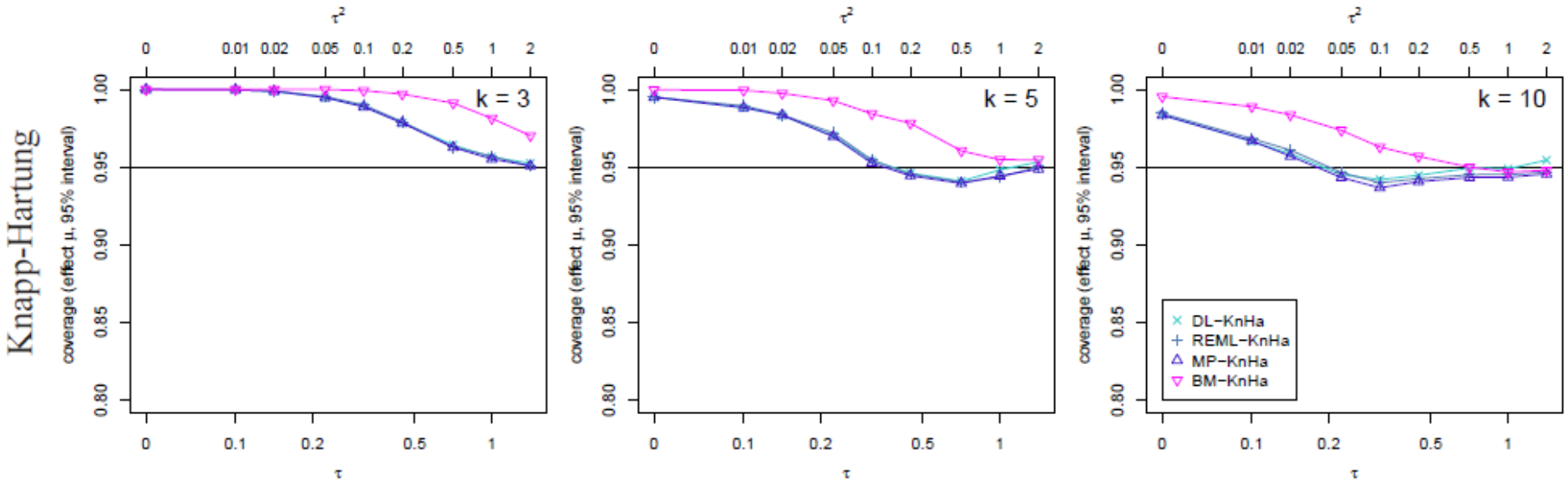
- Coverage probability for confidence intervals of combined effect
- Construction of confidence intervals using normal quantiles
- Estimators: DerSimonian-Laird (DL), restricted maximum likelihood (REML), Mandel-Paule (MP), **Bayes-modal** (BM)



Friede et al. (2016) RSM

ESTIMATION OF BETWEEN-TRIAL HETEROGENEITY

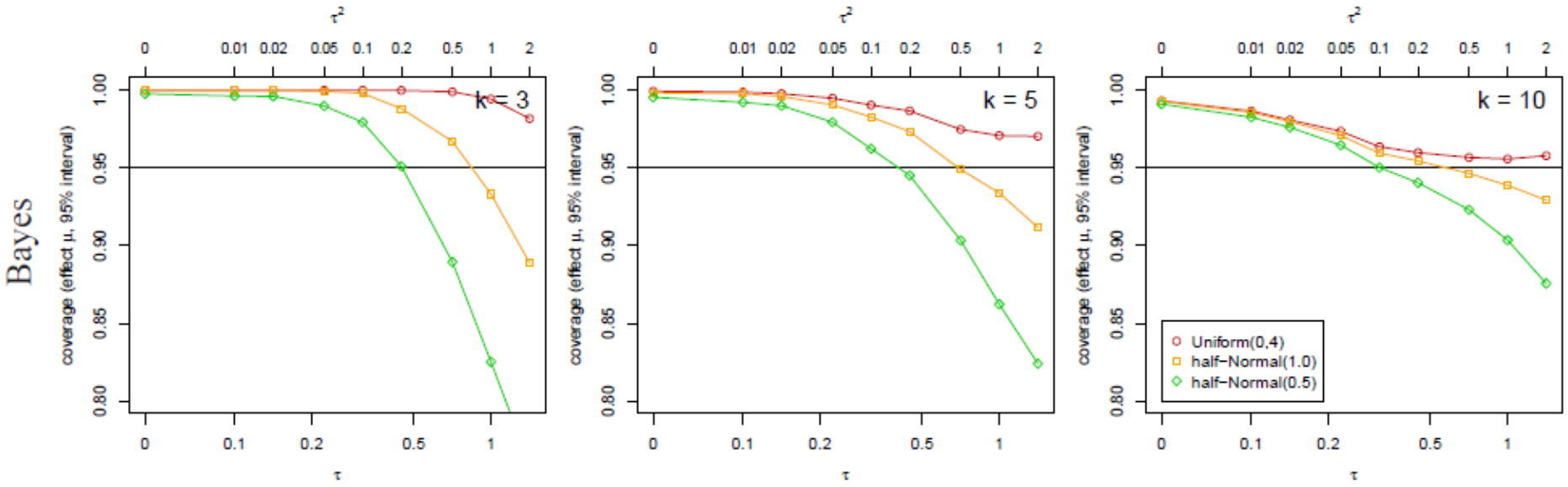
- Coverage probability for confidence intervals of combined effect
- Construction of confidence intervals using **Knapp-Hartung method** (using t-quantiles and scaling of standard error)



Friede et al. (2016) RSM

ESTIMATION OF BETWEEN-TRIAL HETEROGENEITY

- Coverage probability for credibility intervals of combined effect
- Bayes with “weakly informative” priors for tau
- R package **`bayesmeta`** available on CRAN (Christian Röver)



Friede et al. (2016) RSM

BETWEEN-TRIAL HETEROGENEITY

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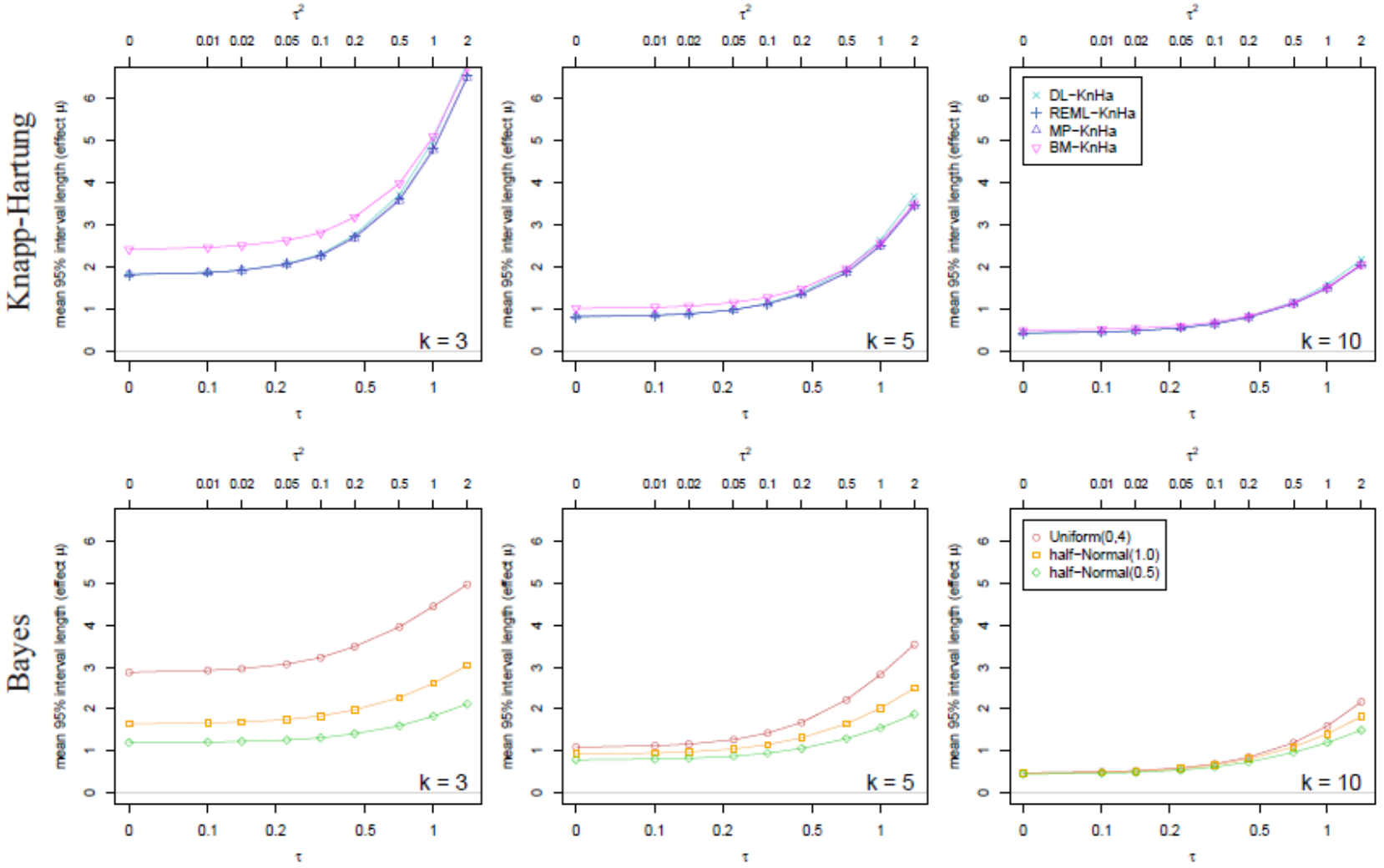
- Mean length of confidence / credibility intervals



Friede et al. (2016) RSM

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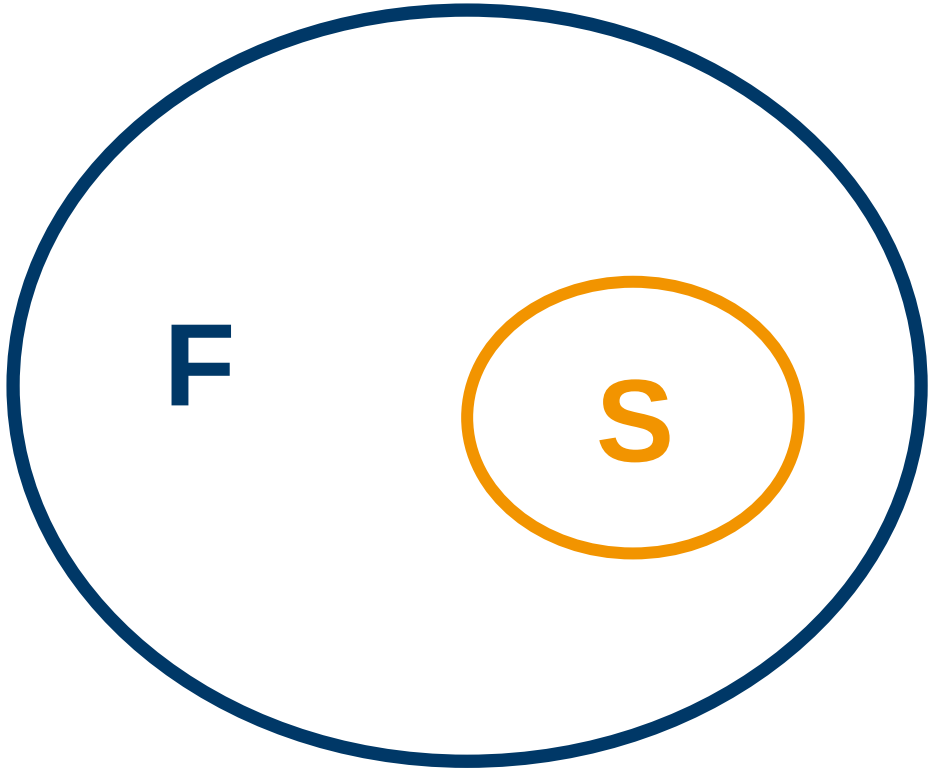
STRATIFIED MEDICINE

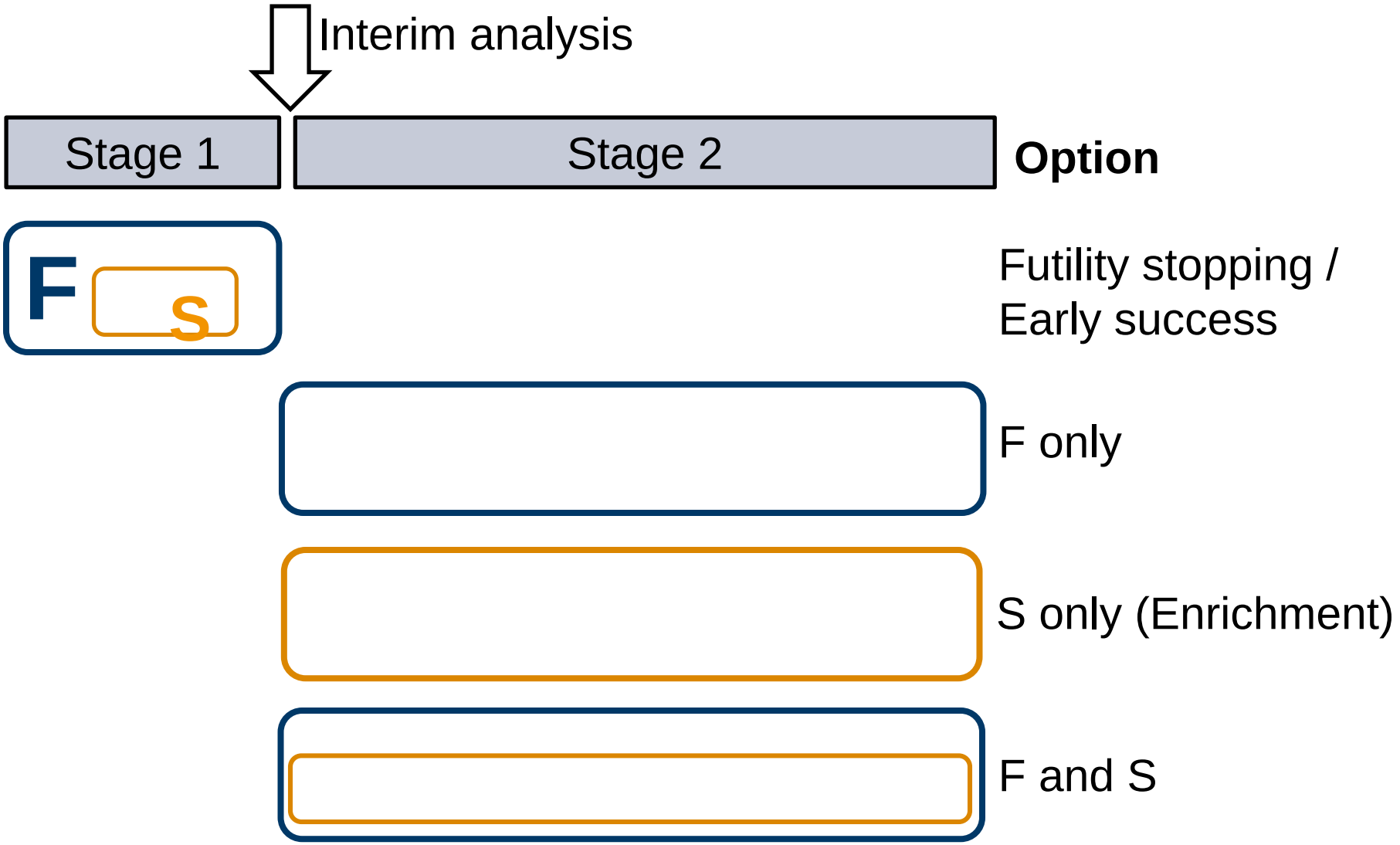


Situation considered

- Biomarker-defined subgroup identified in exploratory study
- Subgroup to be confirmed by independent data
- Confirmation of treatment effect in selected population

Full population **S**ub-population

ADAPTIVE ENRICHMENT DESIGN



STATISTICAL METHODOLOGY

- **repeated testing**
  - classical group sequential designs (e.g. Jennison & Turnbull 1999)
- **combining pre/ post adaptation data**
  - (recursive) combination test (Brannath et al, 2002), conditional error function approach (Müller & Schäfer, 2001)
- **multiple hypotheses**
  - closed test principle (Marcus et al, 1976), Bonferroni, . . .
- **combinations of these approaches in ASDs:** e.g. weighted inverse normal method and closed test principle

$$C(p_{S,1}, p_{S,2}) = 1 - \Phi(w_1 \Phi^{-1}(1 - p_{S,1}) + w_2 \Phi^{-1}(1 - p_{S,2}))$$

ENRICHMENT DESIGNS MORE POWERFUL

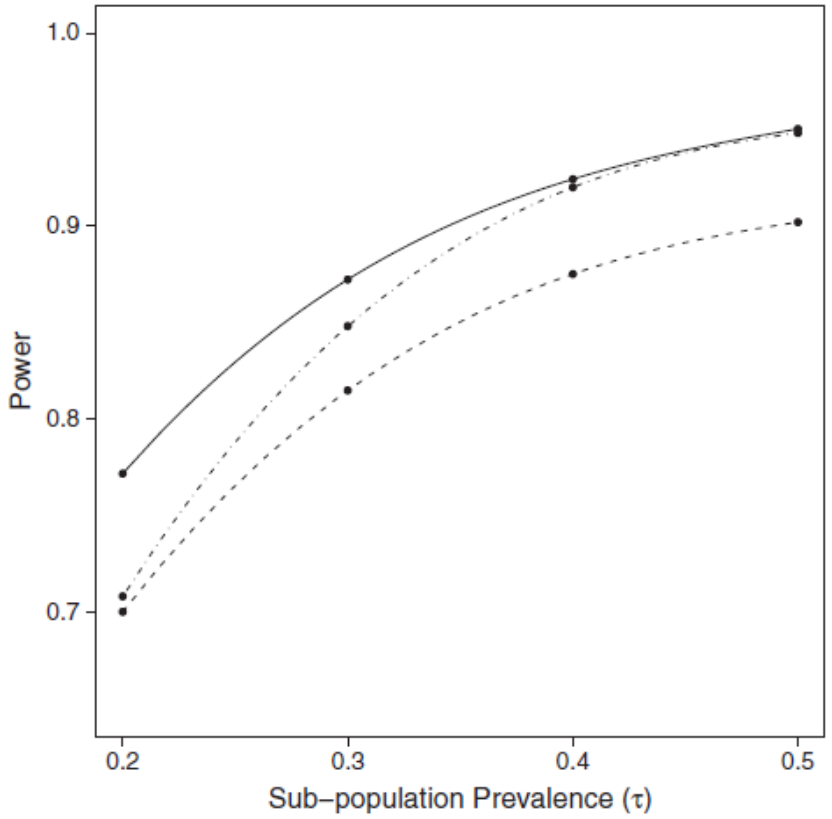


Figure 3. Power of rejecting at least one hypothesis of the adaptive conditional error function approach (——), separate designs (– – –) and the fixed design (– · –) for hazard ratios 0.77 in the subpopulation and 1 in the complement to the subpopulation (10 000 simulation replications per scenario).

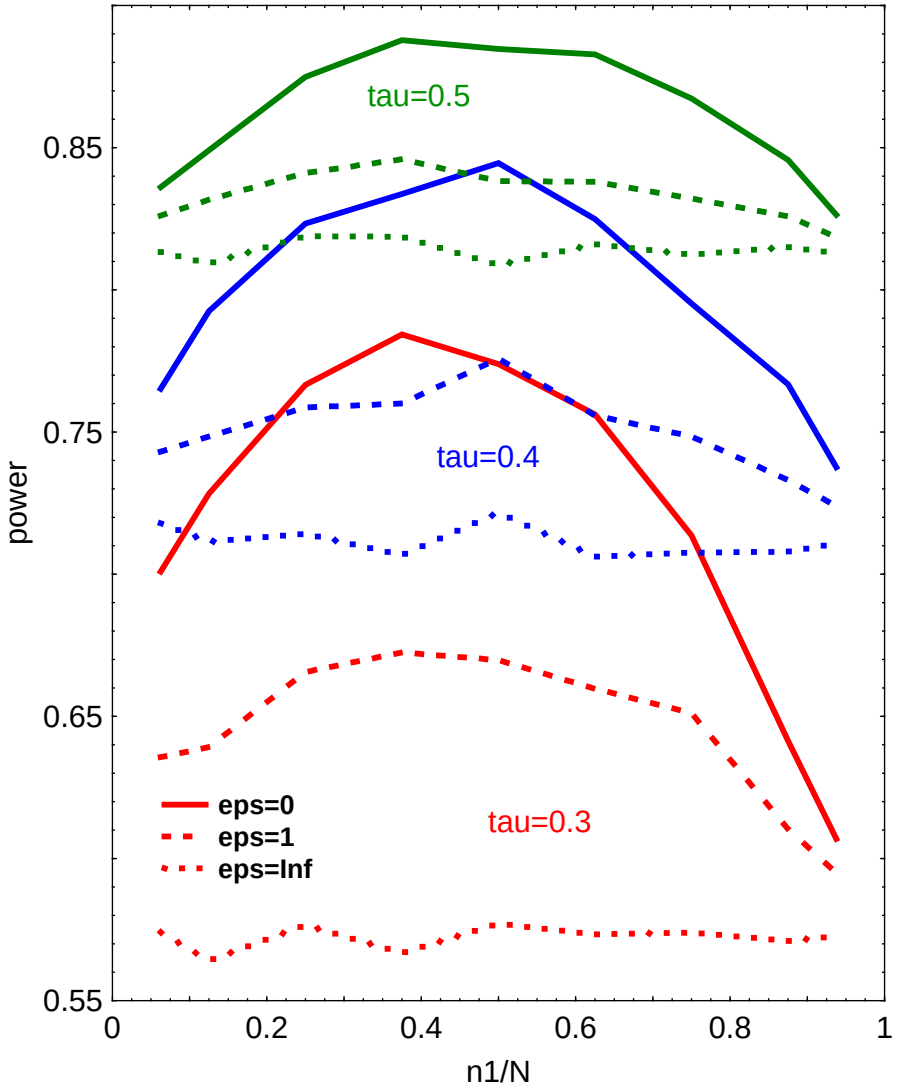
Friede et al. (2012) Stat Med

OPTIMAL TIME POINT FOR INTERIM ANALYSIS

- Adaptive enrichment design with CEF approach
- Simulation results for n_{sim}=10,000 replications
- n=400 subjects per group (treatment/placebo)
- Under the alternative

$$\Delta_{F \setminus S} = 0, \ \Delta_S = 0.3$$

- Maximum in power after 40-50% of the subjects



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

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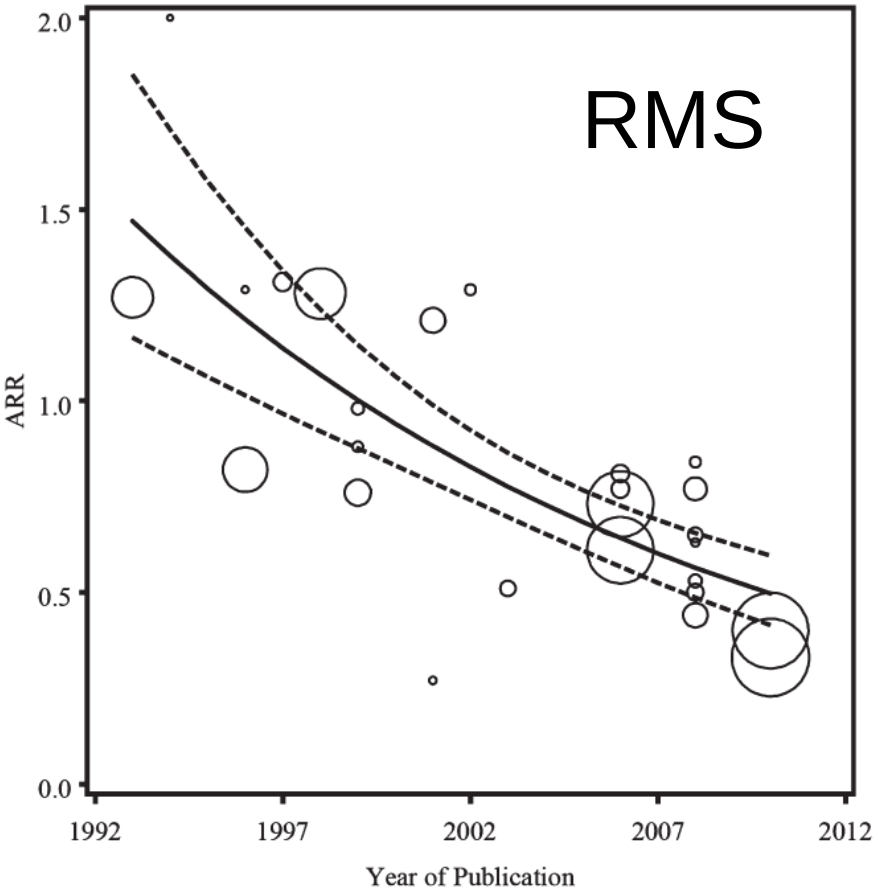
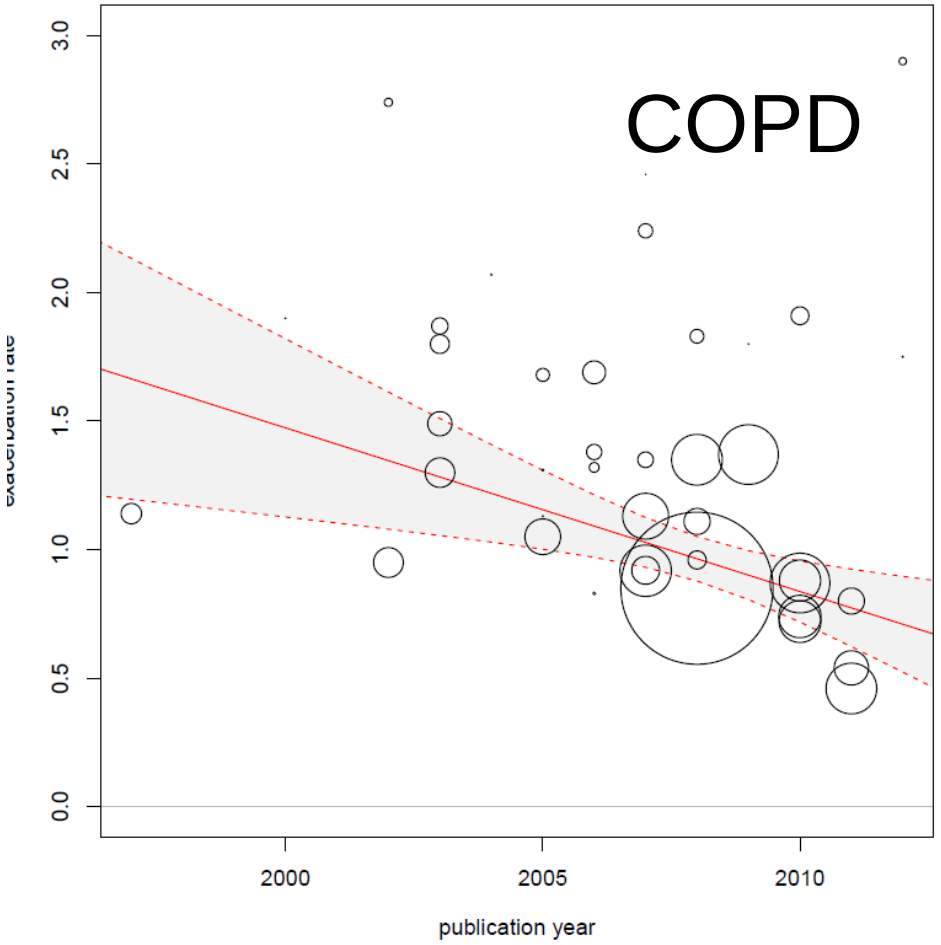
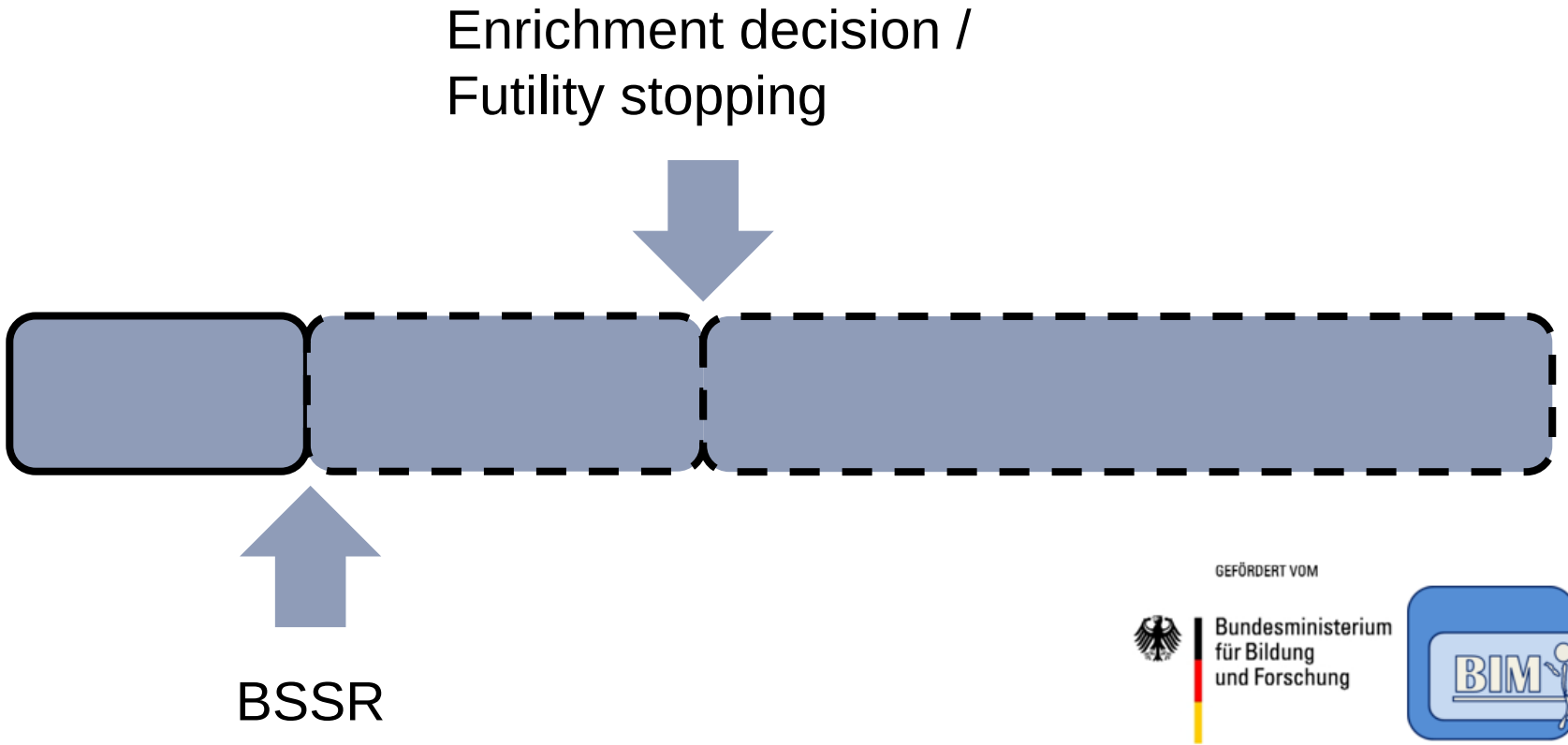




Nicholas et al. (2011) MSJ

Andreas, Röver et al. (2016)

BLINDED SAMPLE SIZE REESTIMATION (BSSR) IN ADAPTIVE ENRICHMENT DESIGNS



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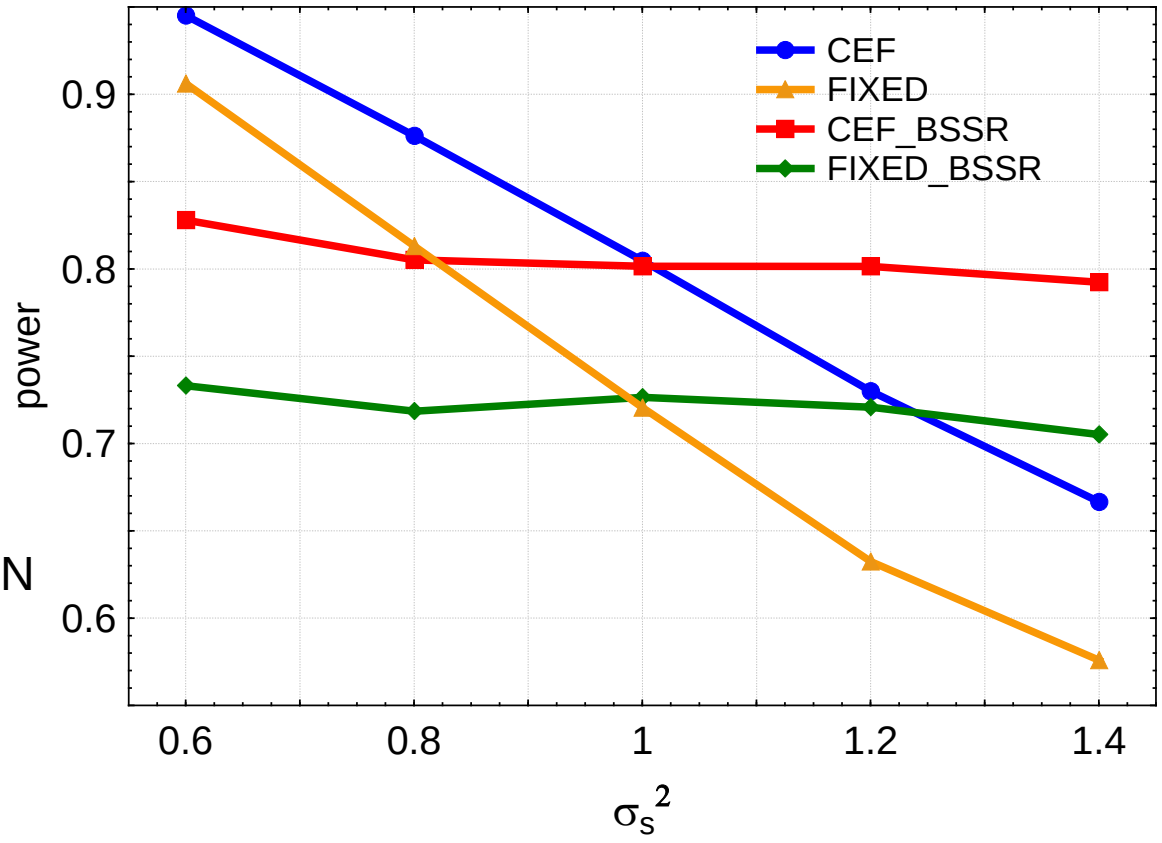
- Early IA for **blinded** sample size reestimation
- Later IA for enrichment decision / futility stopping (**unblinding**)

BSSR IN ADAPTIVE ENRICHMENT DESIGNS: SIMULATION STUDY

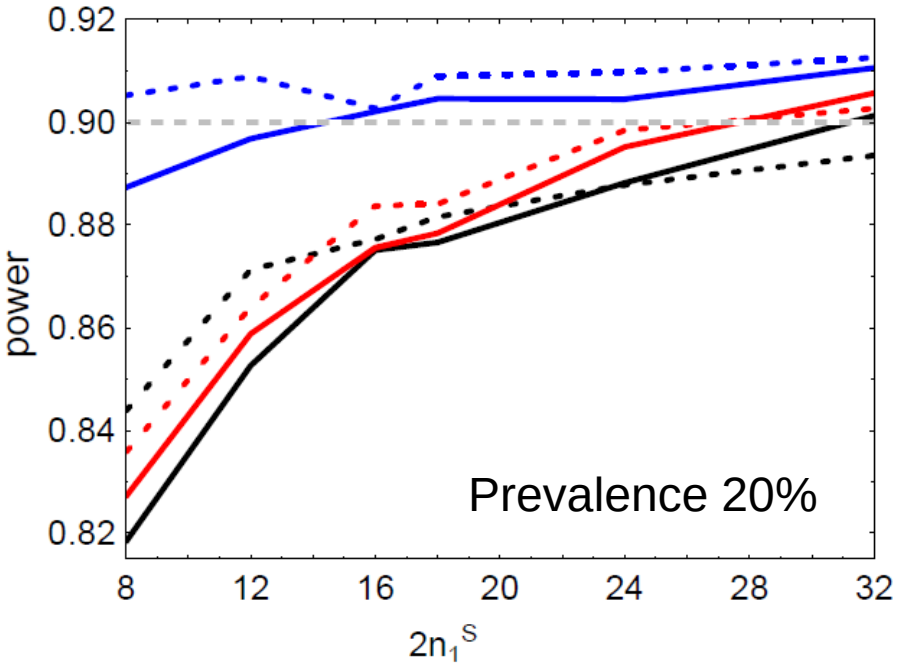
- n_{sim}=10,000, $\tau = 0.5$
- $\alpha = 0.025,\ 1-\beta = 0.8$
- $\Delta_{F\setminus S} = 0,\ \Delta_S = 0.5$
- $\sigma_F^{2*} = \sigma_F^2 = 1,\ \sigma_S^{2*} = 1$
- BSSR at 30% of N_0
- Interim Analysis at 50% of N ($\varepsilon = 1$)

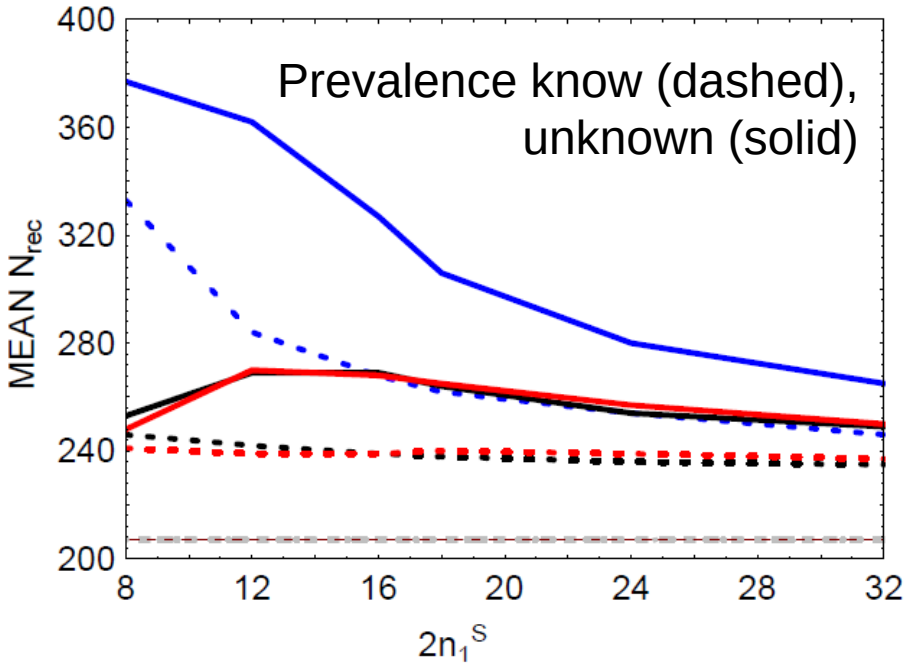


BSSR IN STUDY WITH SUBGROUP

- Simulated power and corresponding recalculated sample sizes depending on the number of subjects in the subgroup at the timepoint of the blinded review

$$1-\beta = 0.9 \quad \Delta_S = 1 \quad \sigma_S = 1.3 \quad n_{sim} = 10,000$$





- With small sample sizes / subgroups: uncertainty in estimation of nuisance parameters has to be accounted for leading to large average sample sizes

Placzek & Friede (2016)

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Clinical Scenario Evaluation (CSE)

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Framework for the Assessment of Competing Strategies

(Benda et al (2010) DIJ; Friede et al (2010) DIJ)

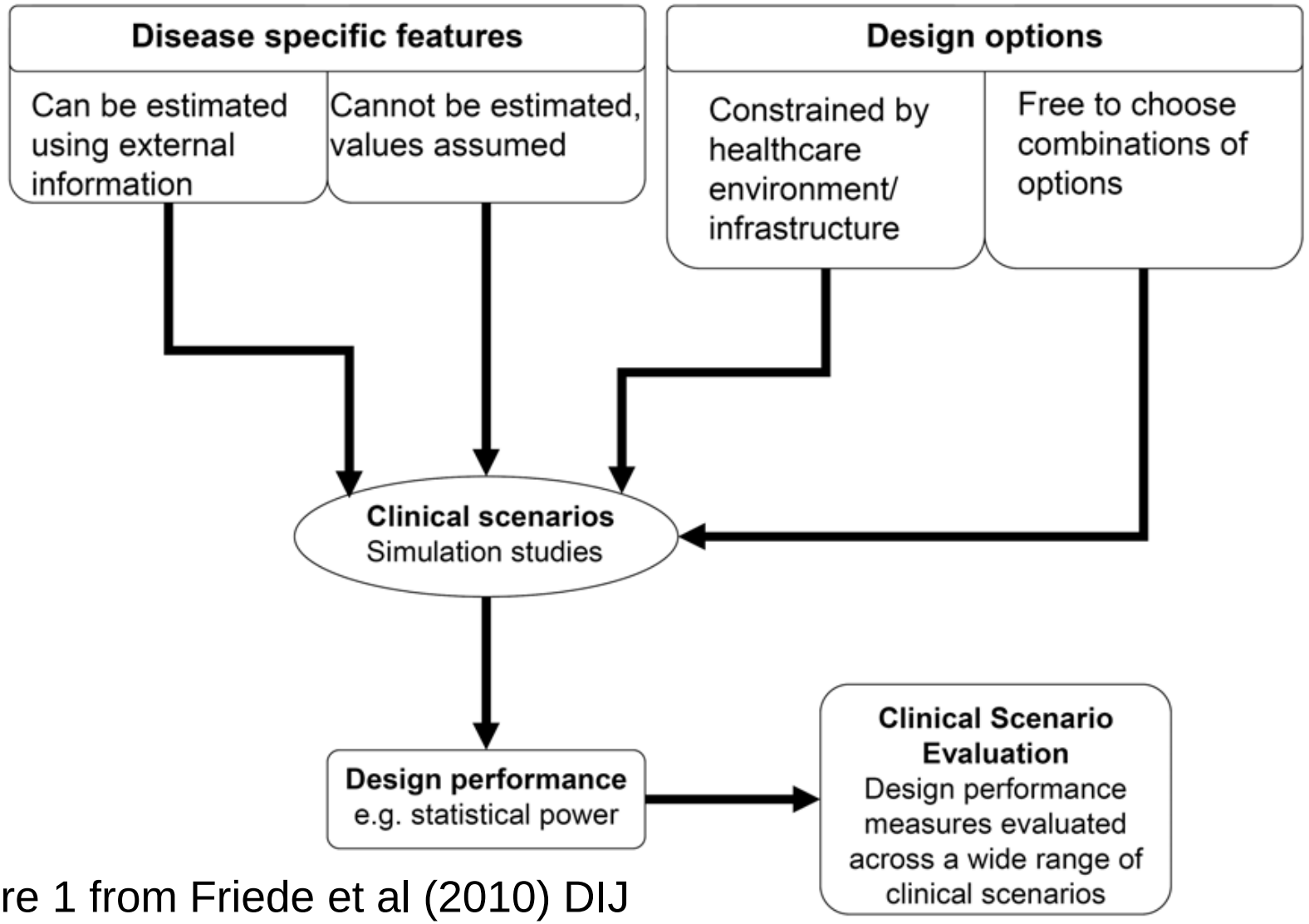

Figure 1 from Friede et al (2010) DIJ

CONCLUDING REMARKS

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- **Subgroup identification based on Adaptive Refinement by Directed Peeling (ARDP)**
  - Facilitates decision making on subgroup selection balancing size of subgroup with size of treatment effect
- **Subgroup identification from multiple trials**
  - Some level of between-trial heterogeneity expected and should be reflected in statistical model
  - Estimation difficult if only a small number of studies included in the analysis
- **Gain in power by adaptive enrichment design** compared to separate studies / fixed design can be substantial
- **Assessment of complex development plans usually requires extensive simulations**