UNIVERSITÄTSMEDIZIN GÖTTINGEN UMG

IDENTIFYING SUBGROUPS OF TREATMENT RESPONDERS

A meta-analytic approach

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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; jointly with Meinhard Kieser (HD), Werner Brannath (HB)

GEFÖRDERT VOM Bundesministerium für Bildung und Forschung

BIMIT

  - Work package C: Tim Friede**,** Marius Placzek, Rolang Gera (Göttingen); Heinz Schmidli (Novartis)
- **“Innovative methodology for small populations research (InSPiRe)**”
  - funded by EC under FP7

InSPiRe Innovative methodology for small populations research

  - Work package 4: Tim Friede, Steffen Unkel, Christian Röver (Göttingen); Beat Neuenschwander, Simon Wandel (Novartis); Norbert Benda (BfArM); …

OUTLINE

- **Motivation**: 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

PERSONALISED MEDICINE

- Efficacy, safety and consequently benefit-risk might vary across patient population
- **Personalised medicine**
  - 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
- **Identification of subgroups** of patients responding particularly well to a particular treatment

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

STRATIFIED MEDICINE: SOME PROJECTS WE ARE INVOLVED IN

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- **Better treatments** (in terms of benefit-risk ratio) **through stratification of populations**
- **Clinical collaborations**
  - Individualize MS (KKNMS, BMBF)
  - Low back pain repository (Warwick, NIHR)
  - Stratification of ICD populations
    - EU-Trig-Treat
    - EU-CERT-ICD

Bundesministerium für Bildung und Forschung

NHS National Institute for Health Research

EUROPEAN COMMISSION
7th Framework Programme for Research, technological Development and Demonstration

EU-CERT-ICD

- **Methodological research**
  - **Designs for clinical research**: biomarker-driven designs, adaptive subgroup selection

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BIMIT

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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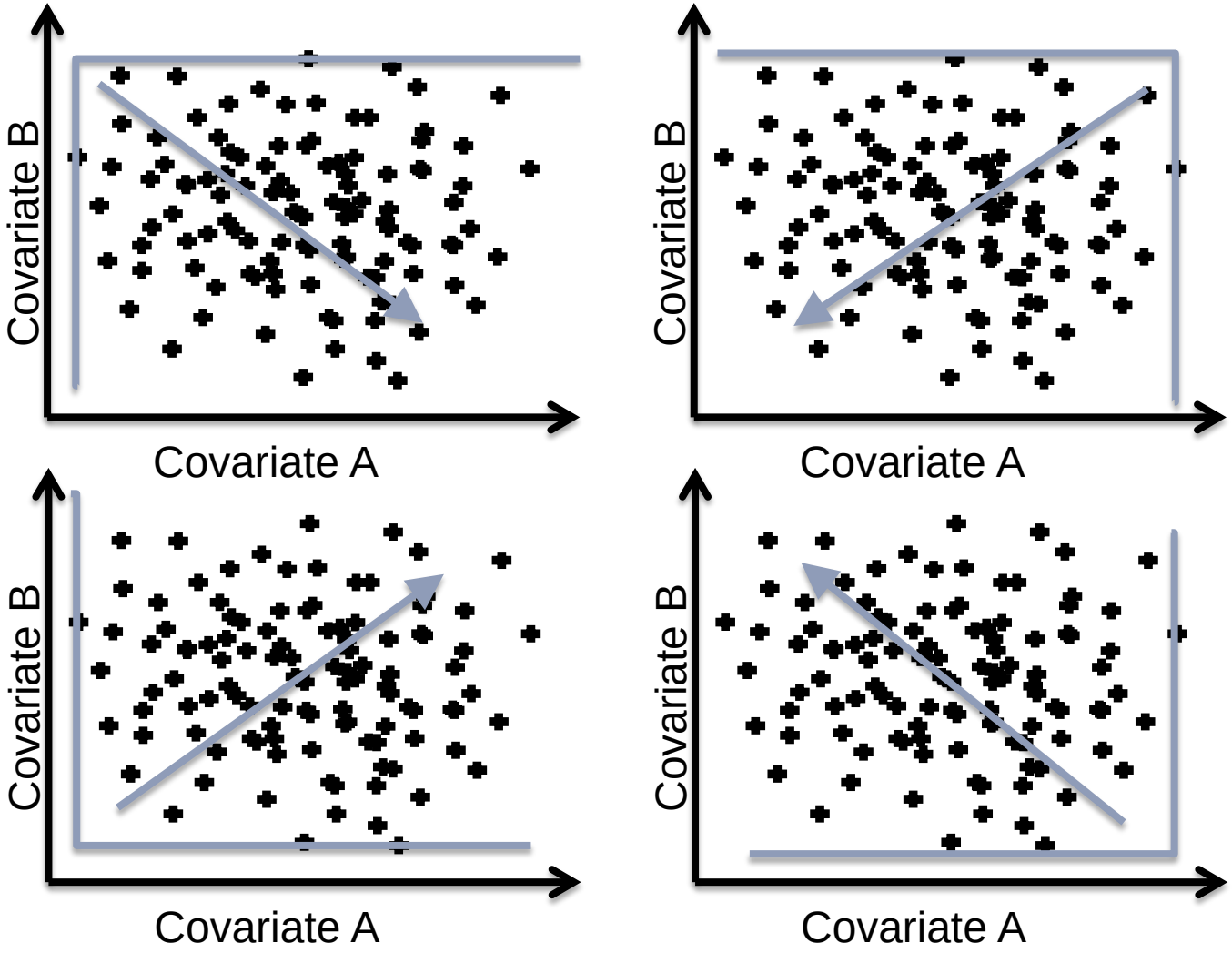
1. Investigating **interactions of covariates with treatment** determines covariates to be included and direction of peeling
2. Start with a “subgroup” B^0 that includes all observations.
3. For each variable we **peel a certain number of observations off** resulting in subgroups $B_j^m, j = 1, \dots, p$.
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)



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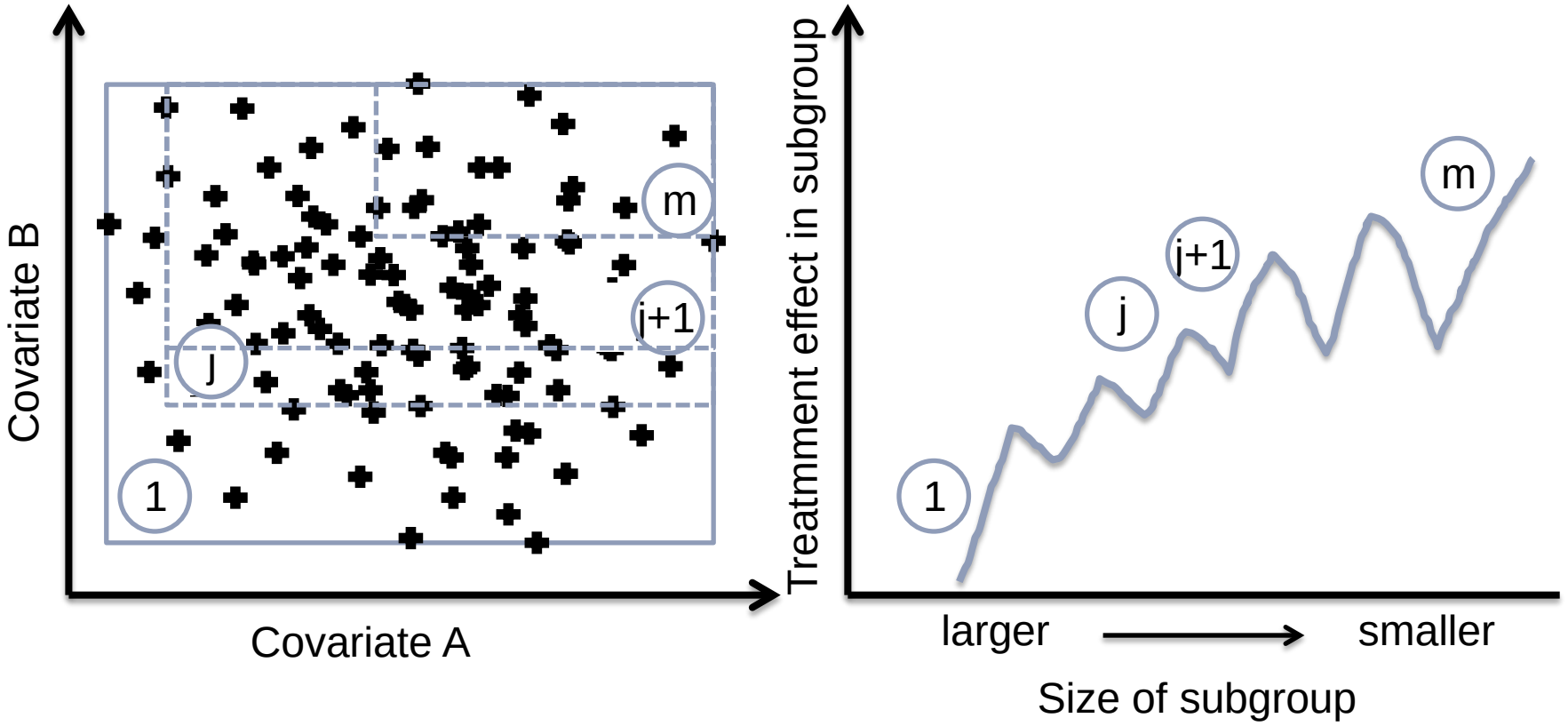

SUB-GROUP IDENTIFICATION: ADAPTIVE REFINEMENT BY DIRECTED PEELING (ARDP)

- **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 (as in random effects meta-analysis)
  - **Example with continuous outcome in SAS**

```
proc mixed data=&data;
   class &trt &trials;
   model &outcome = &trt &var &trt*&var / s ddfm=satterth;
   random intercept &trt / subject=&trials;
   repeated / group=&trials;
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

ESTIMATION OF BETWEEN-TRIAL HETEROGENEITY WITH FEW TRIALS

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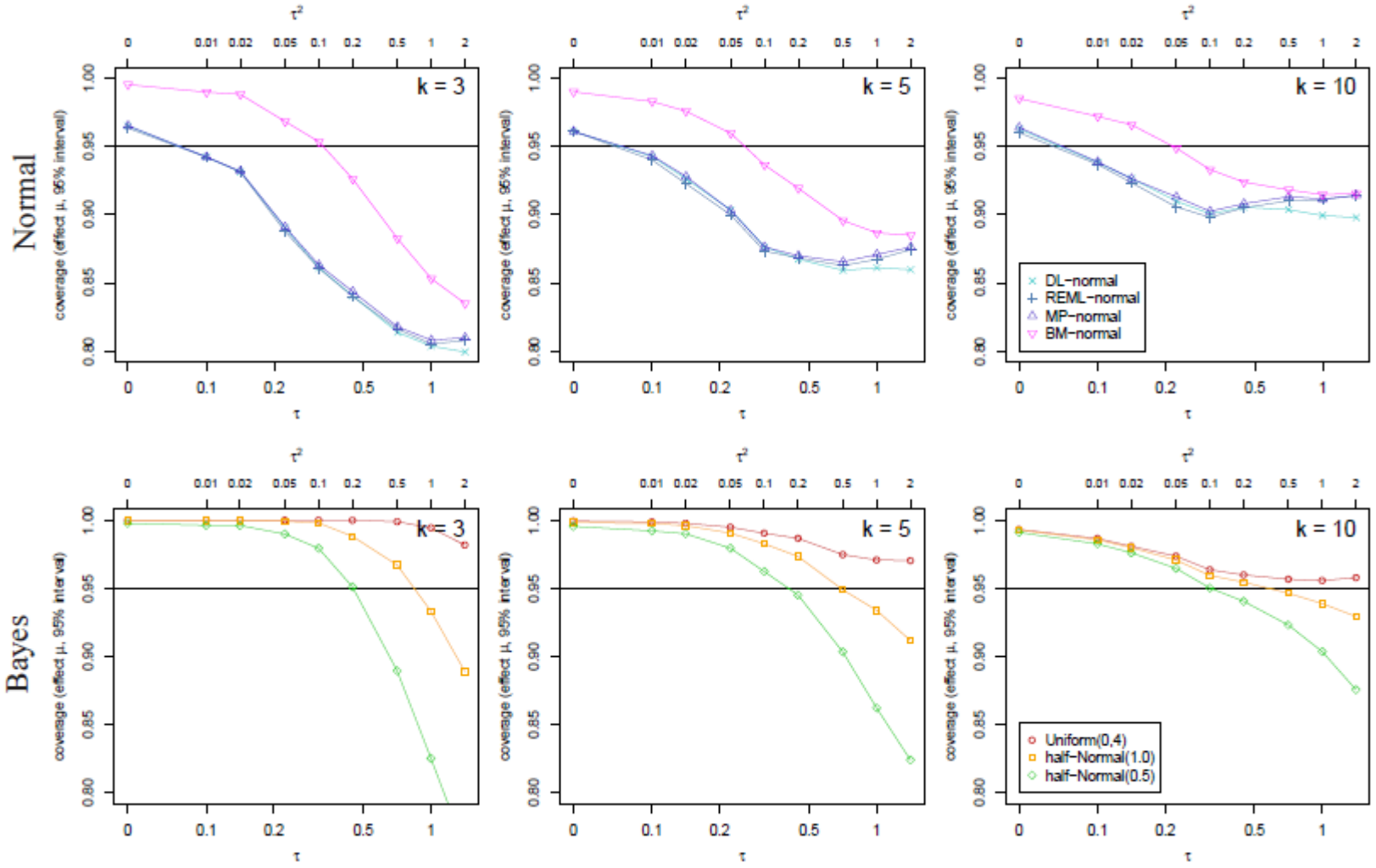

Friede et al. (2015)

META-ANALYSIS WITH FEW SMALL STUDIES

- If you want to learn more about this …

Evidence Synthesis and the Use of Co-Data (CEN Invited Session)

Invited session
Wednesday, 17 June 2015
09:00 - 10:30
Room: U6-A10
Session chair: Held, Leonhard; Friede, Tim

Röver, Christian : ***Meta-analysis of few small studies in small populations and rare diseases***
Author list: *Röver, Christian; Neuenschwander, Beat; Wandel, Simon; Friede, Tim*

The between-study heterogeneity plays a central role in random-effects meta-analysis. Especially when the analysis is based on few studies, which is a common problem not only for rare diseases, external a-priori information on heterogeneity may be helpful. In case of little information, the use of plausible weakly informative priors is recommended. Computational simplifications (using the bmeta R package) helped to speed up computations for Bayesian standard random-effects meta-analysis to explore the frequentist properties of Bayesian estimators for different priors. We investigated a range of scenarios (heterogeneities, numbers of studies), to compare bias, MSE and coverage of the Bayesian and classical estimators. The different approaches are illustrated using an application in pediatric transplantation.

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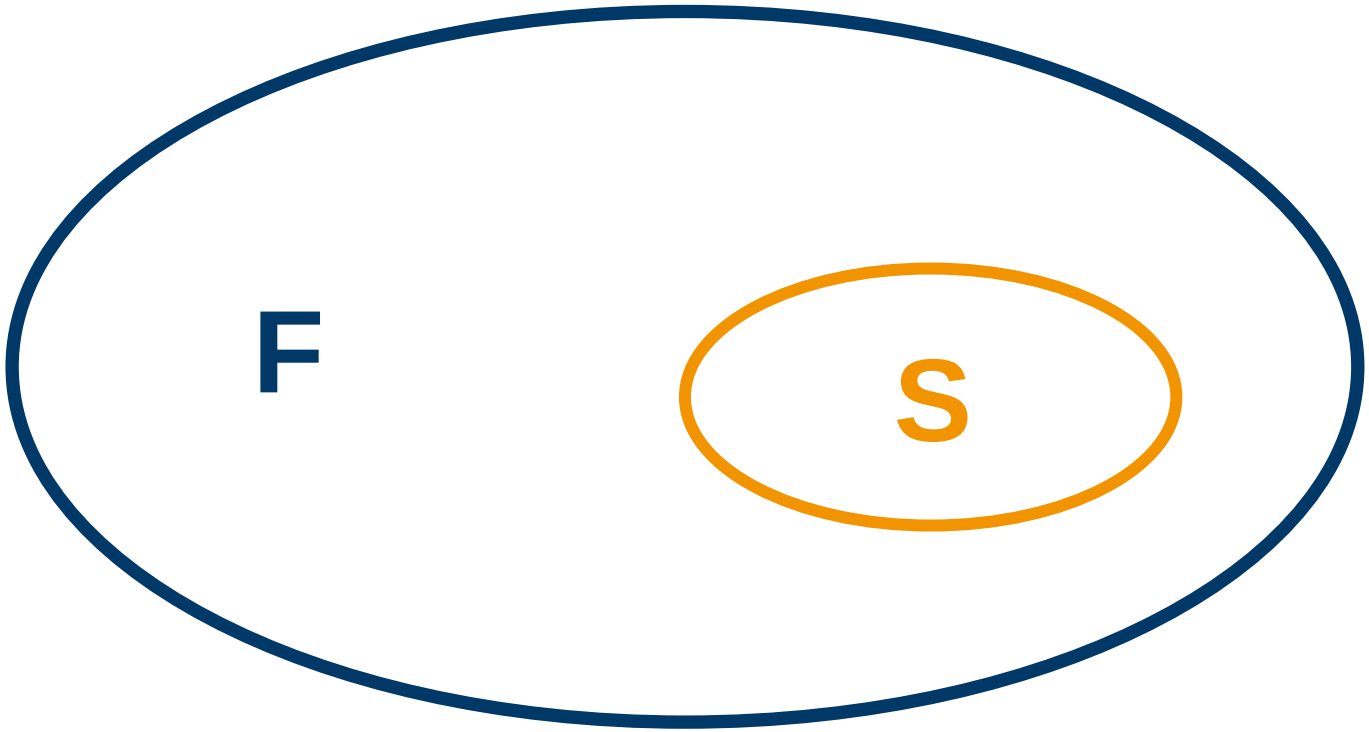
STRATIFIED MEDICINE



Full population

Sub-population

CLINICAL DEVELOPMENT PROGRAMME INCLUDING AN ADAPTIVE ENRICHMENT DESIGN

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

ADAPTIVE ENRICHMENT DESIGN

- Stage 1: Recruit patients from full population (F)
- **Interim analysis**: make the decisions on …
  - whether trial is stopped for futility
  - if trial is continued, decide whether recruitment is from full population (F) or subpopulation (S) (enrichment)
  - testing strategy in final analysis
- **Final analysis**: test for an effect in F and/ or S

ADAPTIVE ENRICHMENT DESIGN

- If you want to learn more about this topic …

Adaptive Clinical Trials with Subpopulation Selection

Invited session
Thursday, 18 June 2015
14:00 - 15:30
Room: Aula Martini
Session chair: Heinzmann, Dominik; Rufibach, Kaspar

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

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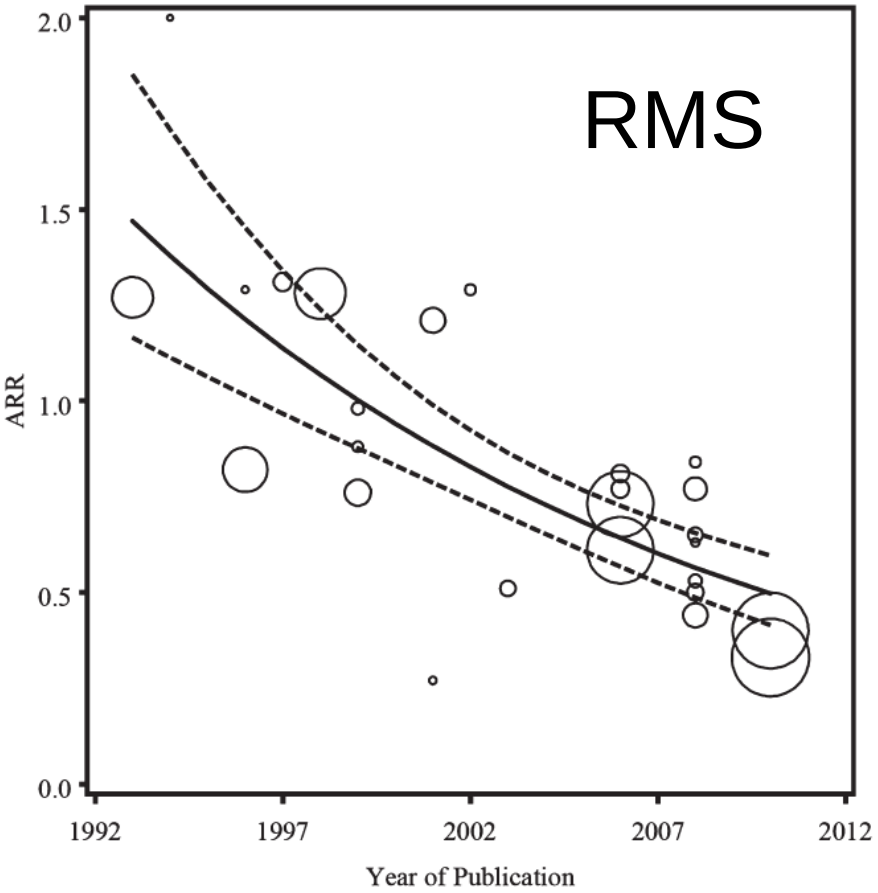
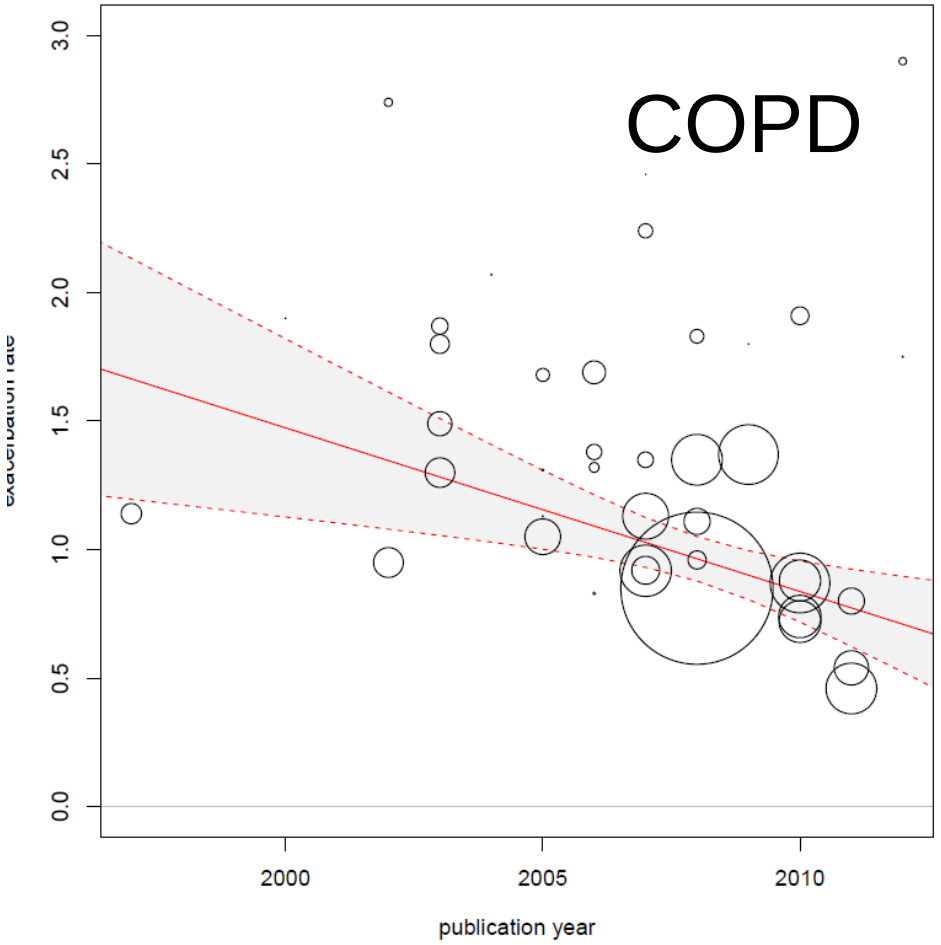
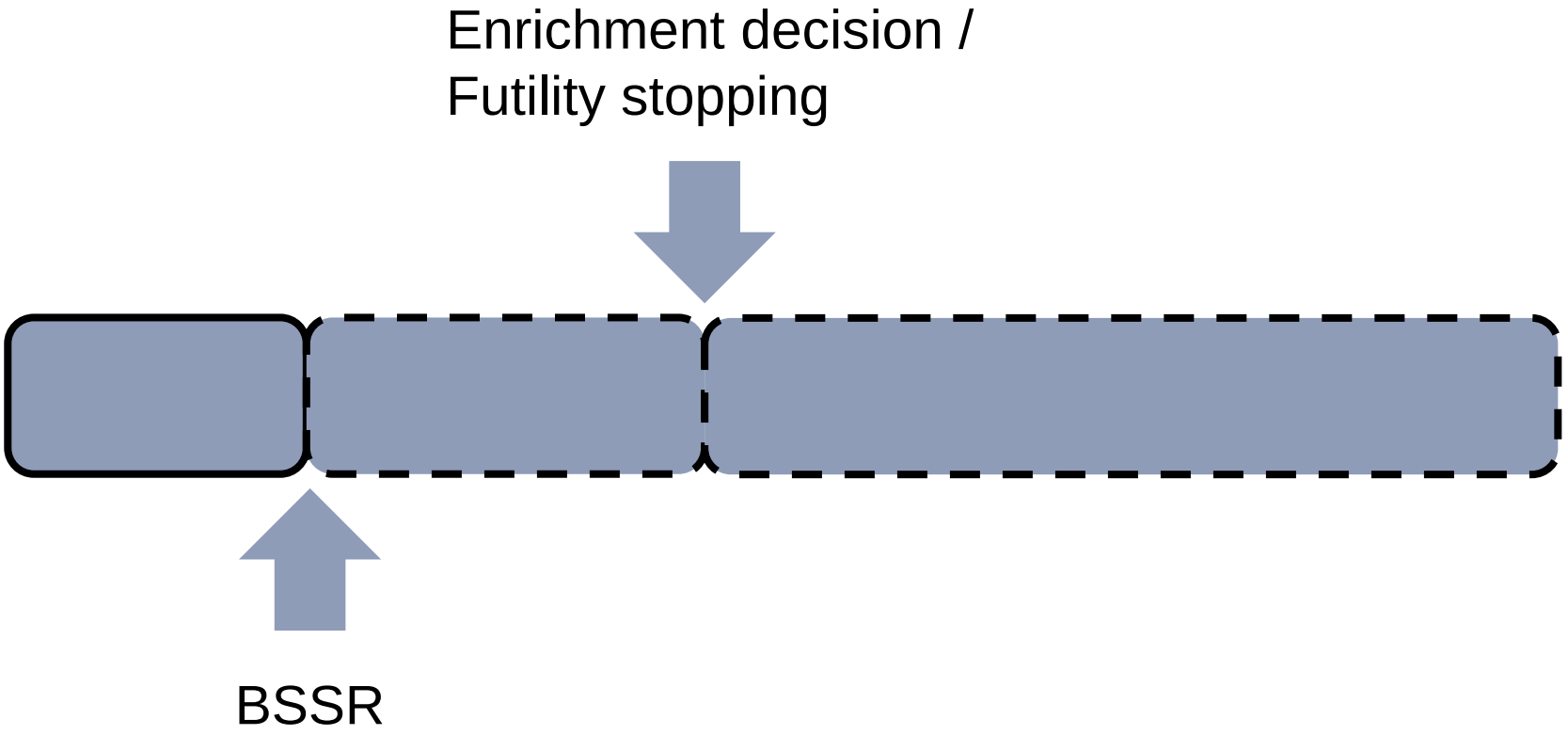




Nicholas et al. (2011) MSJ

Röver et al. (2015)

BLINDED SAMPLE SIZE REESTIMATION (BSSR) IN ADAPTIVE ENRICHMENT DESIGNS



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

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Clinical Scenario Evaluation (CSE)

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Framework for the Assessment of Competing Strategies

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

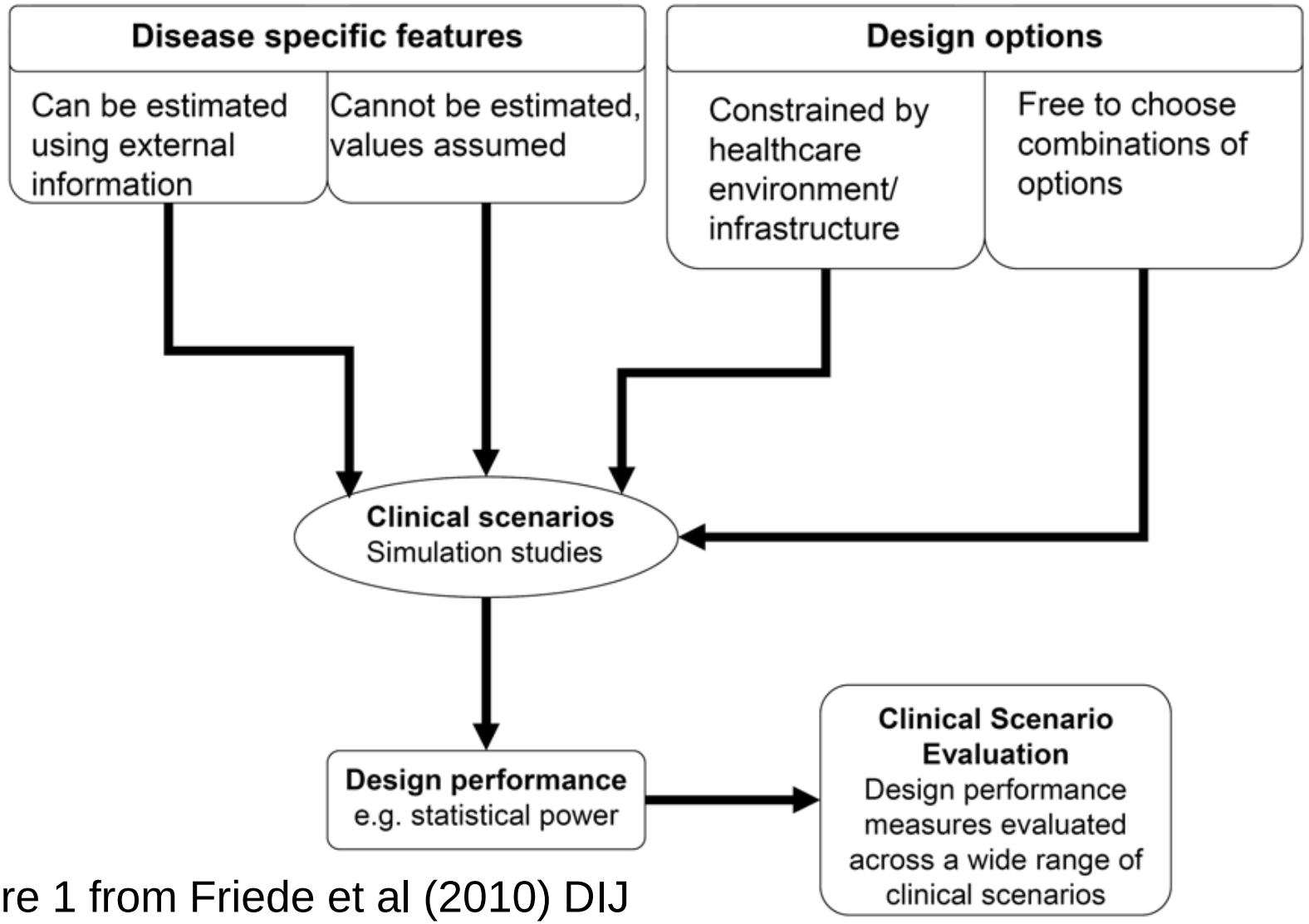

Figure 1 from Friede et al (2010) DIJ

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**