Get Real

Real-Life Data in Drug Development

Learning and Predicting Real-World Treatment Effect based on Randomized Controlled Trials and Registry Data: A CASE STUDY ON RHEUMATOID ARTHRITIS

BBS Seminar, Novartis Campus, Basel

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On behalf of GetReal Work Package WP4

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Outline

- **GetReal Project**
  - Overview
  - Work package 4

- **Rheumatoid Arthritis Case Study**
  - Research question
  - Predictive modelling framework
  - Discussion

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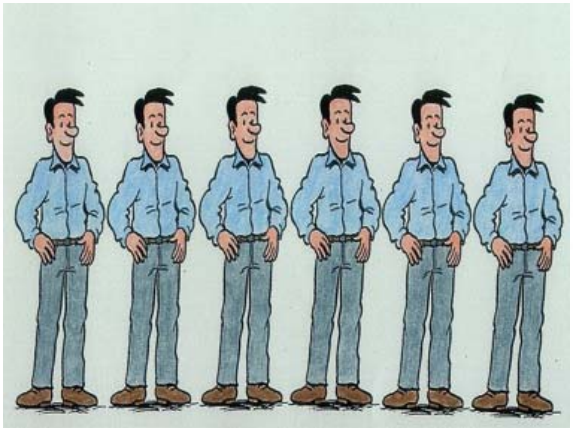
GetReal – Background

Efficacy-effectiveness gap:

Differences between treatment effect in a clinical trial population and in daily clinical practice



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GetReal – Objective

- Development of new methods for collecting and synthesizing real-world evidence (RWE)
- Presentation of a guideline on how to adopt these methods into the early process of pharmaceutical research and development (R&D) and of healthcare decision making

→ Close collaboration between companies, healthcare decision makers, academic institutions and other stakeholders

→ Generation of a consensus on best practice in the use of RWE in regulatory and reimbursement decision-making

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GetReal – Public-Private Partnership

11 Public partners:

- University Medical Center Utrecht, the Netherlands
- University Medical Center Groningen, the Netherlands
- University of Ioannina, Greece
- University of Bern, Switzerland
- University of Leicester, UK
- University of Manchester, UK
- European Organisation for Research and Treatment of Cancer, Belgium
- Zorginstituut Nederland, the Netherlands
- Haute Autorité de Santé, France
- National Institute for Health and Care Excellence, UK
- European Medicines Agency, UK

15 EFPIA companies:

- GlaxoSmithKline
- Amgen
- AstraZeneca
- Bayer
- Boehringer Ingelheim
- Bristol Myers Squibb
- Eli Lilly
- Janssen
- LASER
- Merck Serono
- MSD
- Novartis
- Novo Nordisk
- Roche
- Sanofi
- Takeda

Patients' organizations:

International Alliance of Patients' Organizations

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GetReal - Work Packages

WP1:

Collaborate with key stakeholders in medicine development to assess

- the acceptability and usefulness of RWE
- approaches to the analysis of RWE, i.e. the effectiveness of new therapies

WP2:

Study the scientific validity of RWE study designs and explore analytical approaches to better inform pharmaceutical R&D and healthcare policymakers

WP3:

- Identify the operational challenges of performing RWE studies early in the medicine development process
- Develop practical solutions to better inform the planning and delivery of RWE studies

WP5: Consortium Project Management

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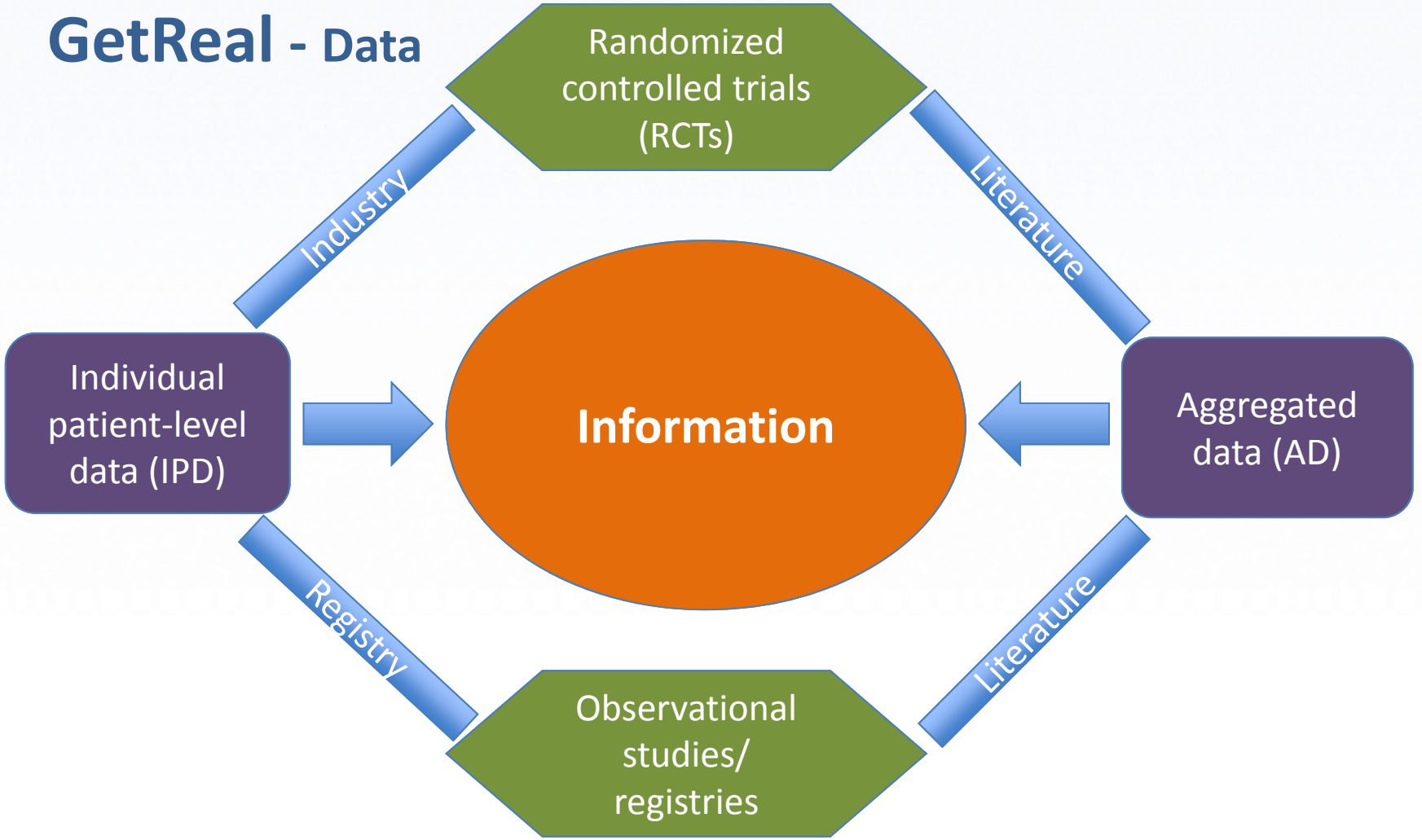
GetReal - Data



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WP4 - Tasks

- Develop best practices for evidence synthesis
  - Network meta-analysis based on AD
  - IPD meta-analysis
  - Mathematical modelling to predict relative effectiveness from RCT efficacy data

  } on RCTs and observational/registry data

  → 3 systematic reviews

- Develop and investigate methods using IPD

  → 4 case studies using IPD from RCTs and observational studies

- Develop a mathematical modelling framework to predict relative effectiveness from RCT efficacy → ***see below***

- Develop user-friendly evidence synthesis software and relevant training material to support best practice

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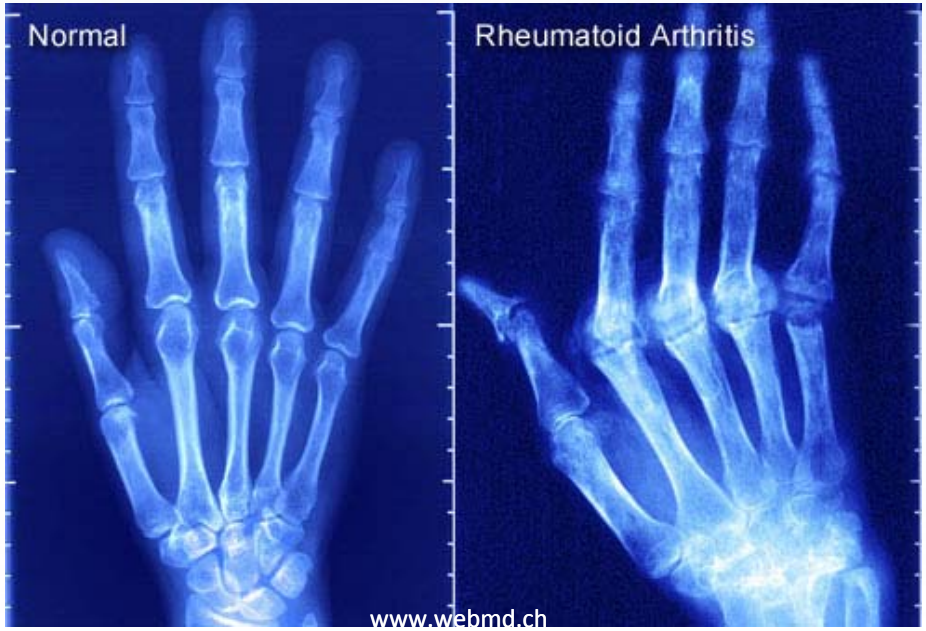
Case Study on Rheumatoid Arthritis (RA)

1. Research question
2. Predictive modelling framework
3. Results
4. Discussion



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Research Question

How can we - based on randomized controlled trial (RCT) and observational data - set up a mathematical model that allows us to predict treatment effect in patients with *Rheumatoid Arthritis* (RA)?

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Predictive Modelling - Procedure

1. Selection of a simple linear regression model for data from RCTs
2. Development of a *marginal structural model* (MSM) for observational data, to adjust for potential confounders
3. Incorporation of insights from both modelling approaches into a Bayesian inference framework
4. Prediction of treatment effect for a new real-world population, possibly under new study conditions

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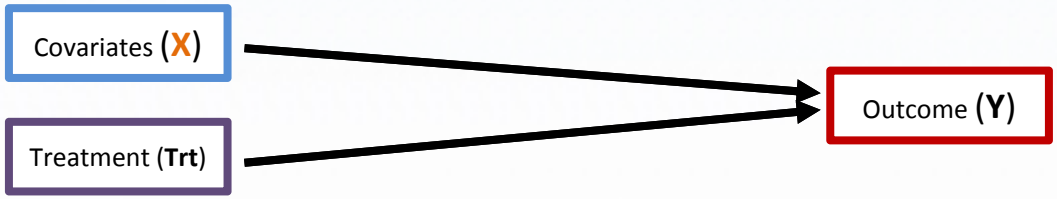
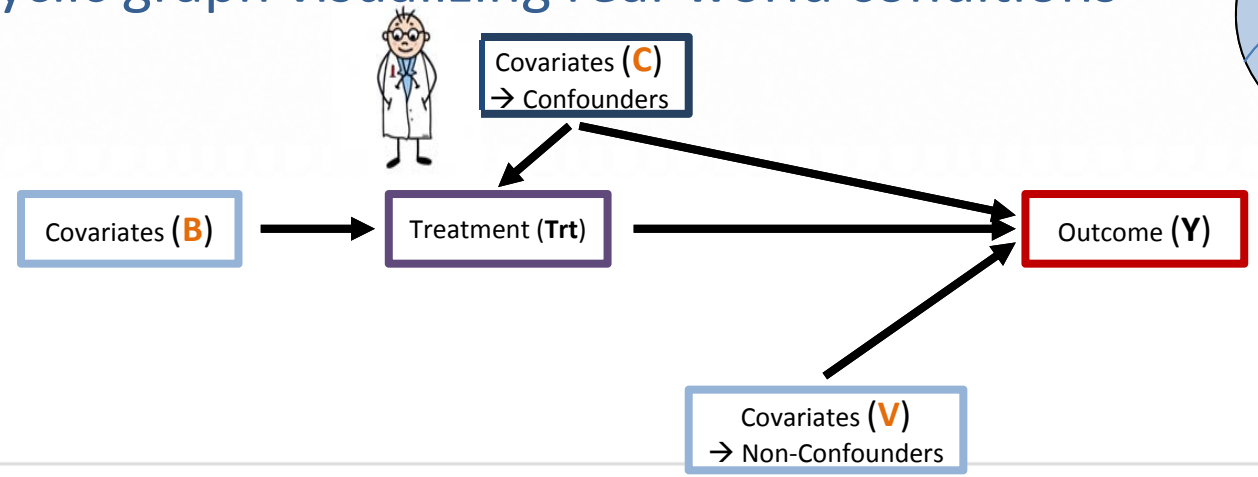
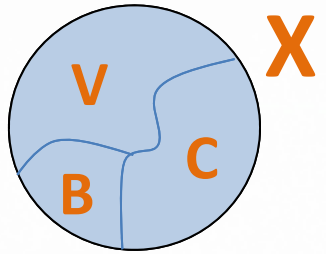
Predictive Modelling – Graphical model representation

- Acyclic graph visualizing RCT conditions



- Acyclic graph visualizing real-world conditions





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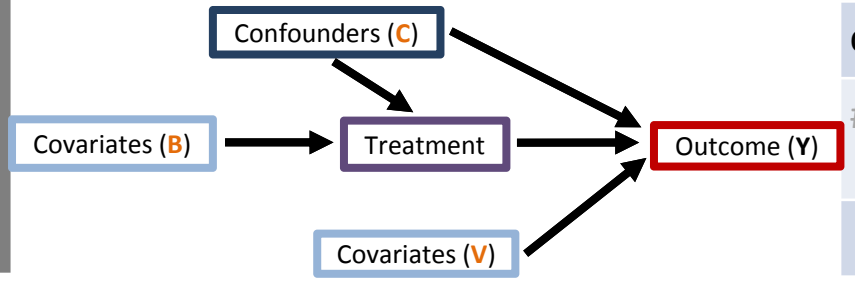
Predictive Modelling – Variable selection

Outcome: Change in	RCT DATA Covariates X	OBSERVATIONAL/REGISTRY DATA Covariates B	Covariates V	Confounders C	
DAS28	gender	calendar year	**BMI/obesity**	**age**	**Expert (RA)**
HAQ	seropositivity	hospital (y/n)	gender	**disease duration**	
EQ5D	baseline DAS28	socio-economics	steroid intake	**seropositivity**	
ACR	baseline HAQ-DI	……	# [concomitant DMARDs]	**smoking**	
CDAI	# [previous anti-TNF agents]		baseline HAQ-DI	# [previous anti-TNF agents]	
RADAI	…..		type of concomitant DMARDs	baseline DAS28	Stats
…..				comorbidities	
				# [previous DMARDs]	Not selected
				…..	



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Predictive Modelling – Formal model representation

- Linear model (LM) for RCT data:

α: Intercept, β: Treatment effect
γ: (non-confounding) Covariate effect

$$Y_{rct} \sim N(\alpha_{rct} + \beta_{rct} Trt + \gamma_{rct} X_{rct}, \sigma^2_{rct} I)$$

- MSM for the observational data:

$$Trt = \begin{cases} 1, & \text{biological agent} \\ 0, & \text{control treatment} \end{cases}$$

→ weighted linear regression model

$$Y_{ob} \sim N(\alpha_{ob} + \beta_{ob} Trt + \gamma_{ob} V_{ob}, \sigma^2_{ob} W_{ob}^{-1}), \quad W_{ob} \propto \frac{1}{f(Trt|C_{ob})}$$

«If both models are sufficiently well specified and further MSM assumptions hold, the estimated treatment effects should be similar.»

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Predictive Modelling – Formal model representation

Likelihood: Gaussian MSM of the form

$$Y|\Theta \sim N(\alpha + \beta Trt + \gamma V,\ \sigma^2\ W^{-1})\ ;\quad \Theta = \{\alpha, \beta, \gamma, \sigma^2, \Theta(W)\}$$

Priors:

- Set $\beta \sim N(\hat{\beta}_{rct}, \tau^2)$, where τ^2 must be carefully determined
- For the remaining parameters, choose suitable non- or weakly-informative priors

Predictions:

1. Take the previously selected MSM structure and variables as a modelling basis
2. Estimate the posterior distributions of all unknown parameters
3. For any new set of observational data Y, draw posterior realizations (predictions) $\hat{Y}_{BMSM} = \{\hat{Y}^{(1)}, \hat{Y}^{(2)}, \dots\}$ from the according posterior predictive distribution

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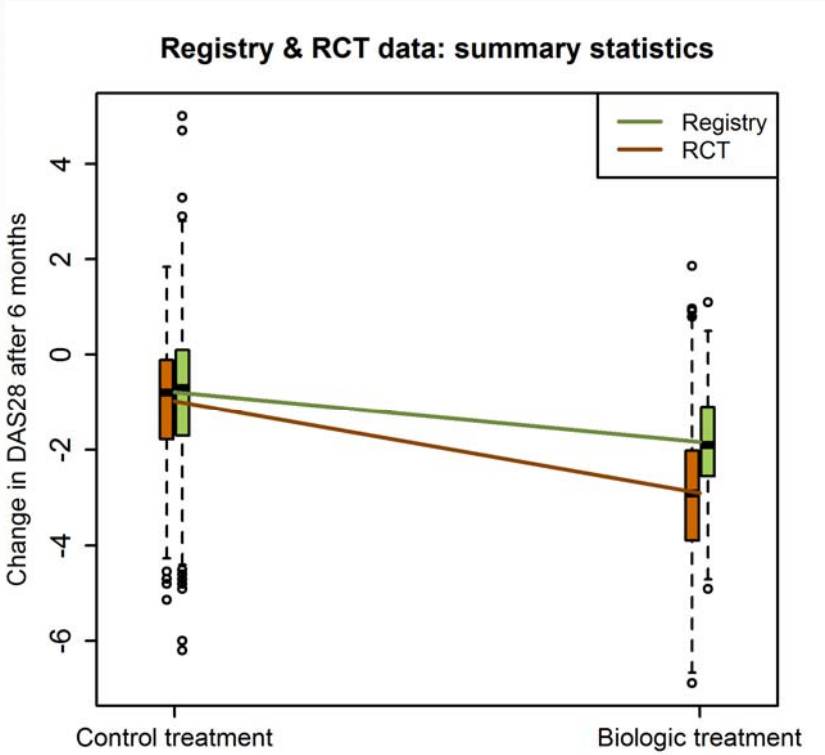
Results – Descriptive data analysis



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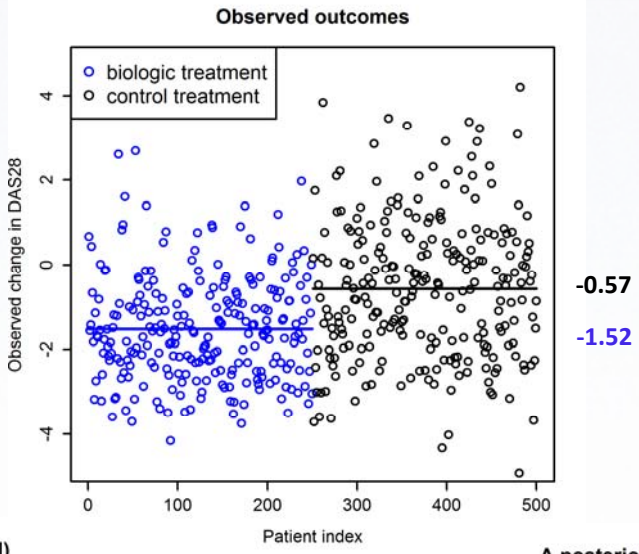
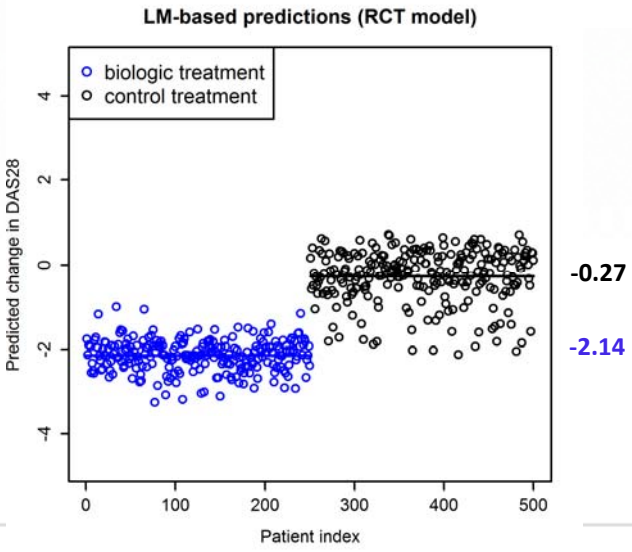
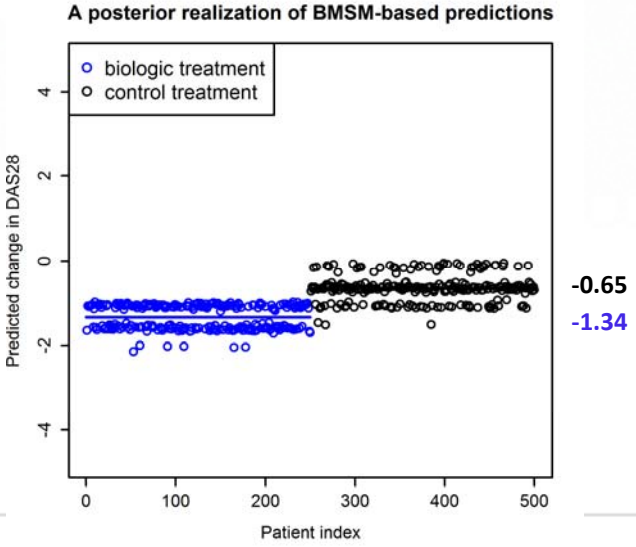
Results –
Predictions for a new real-world population







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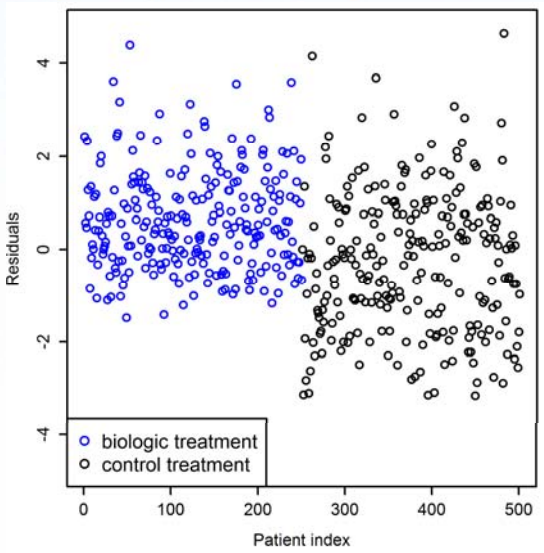
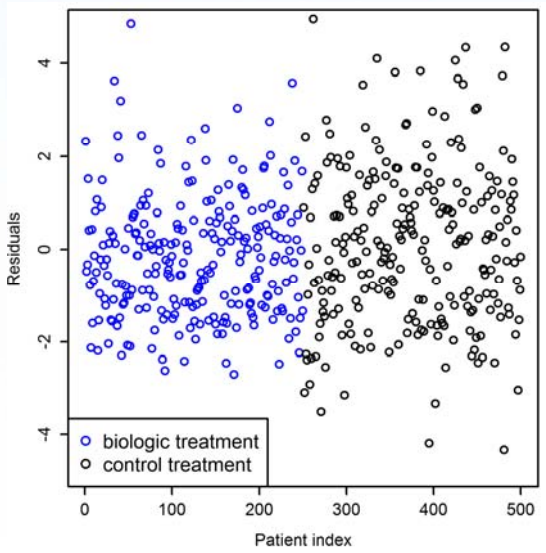
Results – Goodness-of-fit

Residuals $\hat{Y}_{lm} - Y$, under simple LM assumptions

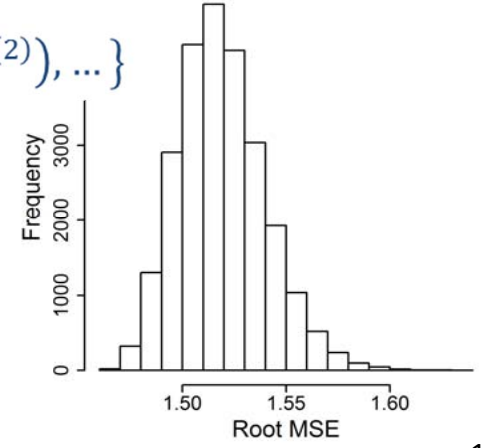


$rMSE(\hat{Y}_{lm}) = 1.59$

A posterior realiziation of residuals $\hat{Y}^{(\cdot)} - Y$, derived from our BMSM



Distribution of $\{rMSE(\hat{Y}^{(1)}), rMSE(\hat{Y}^{(2)}), \ldots\}$



$$rMSE(\hat{Y}) = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(\hat{Y}_i - Y_i)^2}$$

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Discussion – Summary

- **Why use an MSM to adjust for confounding?**
  - Flexibly applicable to different types of outcome and treatment data
  - Easily extendable to settings with time-varying treatment and confounding

Most critical assumption: assumption of no unmeasured confounding

- **Why work within a Bayesian inference and prediction framework?**
  - Inclusion of prior knowledge, possibly gained from multiple data sources
  - Estimation of posterior and posterior predictive distributions, and derivation of all measures of interest (e.g. posterior modus/mean of the parameters…)
  - Relaxation of the missing data problem

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Discussion – Work in progress

- Development of a framework to evaluate goodness-of-fit-and-prediction
- Consideration of dynamic treatment regimes with time-varying confounders and censoring
- Inclusion of covariate/confounder interactions
- Inclusion of additional patient records, e.g. from different countries
- Inclusion of AD from RCTs and observational studies
- Addressing the question whether and under which conditions the BMSM can be used to predict the real-world effect of a new drug, provided that only RCT data are available
- …

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