Combining RCT efficacy data and real-world evidence to predict drug effectiveness:

A case study in Rheumatoid Arthritis

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IMI-GetReal

- Consortium founded in 2013 by the Innovative Medicines Initiative (IMI)
- **Aims to show how robust new methods of RWE collection and synthesis could be adopted earlier in pharmaceutical R&D and the healthcare decision making process**
- Collaborative effort between pharma, academia, HTA agencies,…
- https://www.imi-getreal.eu/

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

Patient's organizations:

International Alliance of Patients' Organizations

IMI-GetReal

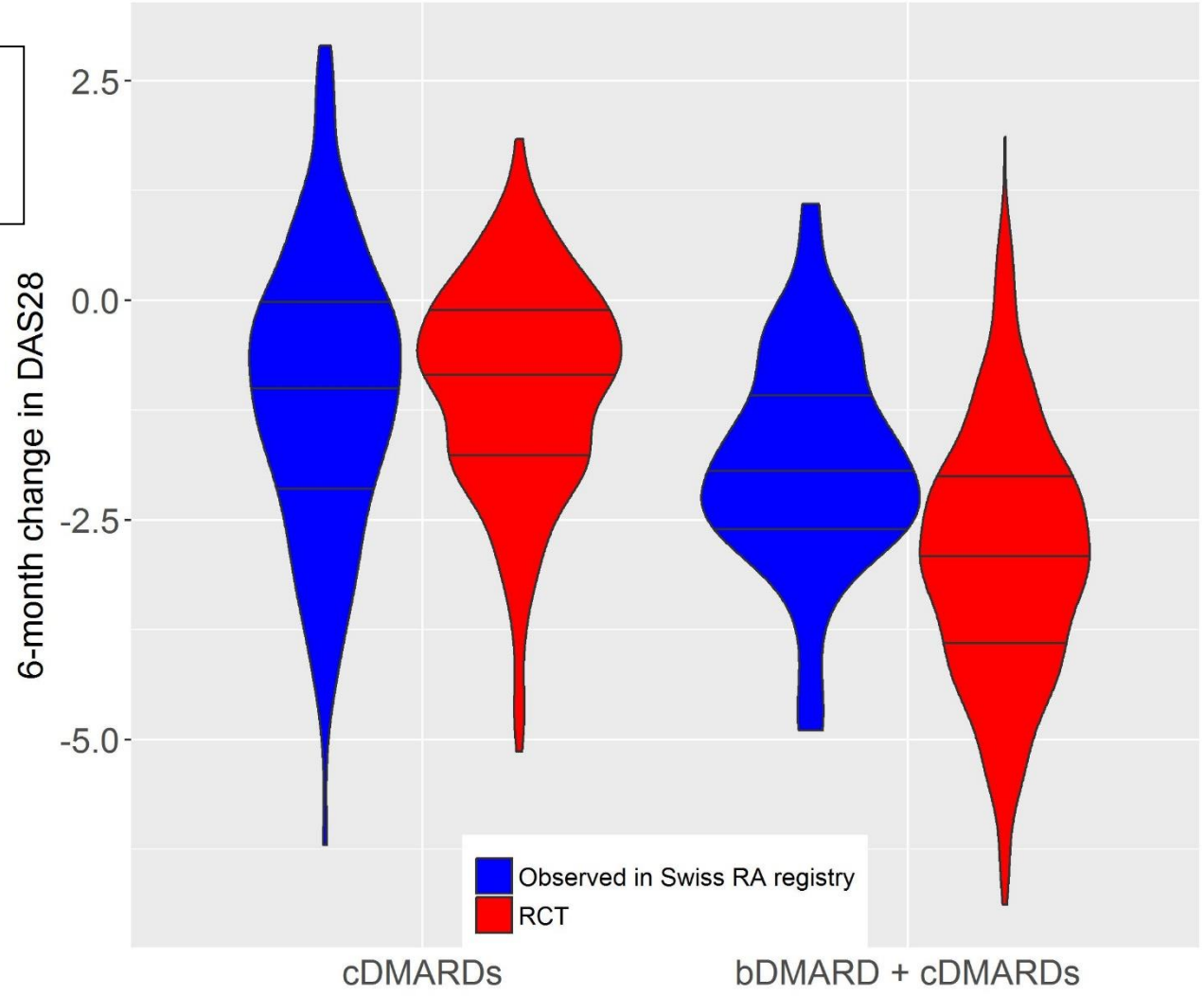
- Work Packages:
  - WP1 – Collaborating with a wide range of stakeholders in medicines development to assess the acceptability and usefulness of Real World Evidence (RWE) and approaches to the analyses of RWE, for the purpose of estimating the effectiveness of new medicines
  - WP2 – Study the scientific 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
  - WP4 – Identify and share best practice in evidence synthesis and predictive modelling of different types of data to estimate effectiveness
  - WP5 – Consortium Project Management
- Bern group (ISPM): Eva-Maria Didden, Noemi Hummel, Yann Ruffieux

RA case study, motivation

- RCT, two arms:
  - cDMARDs only
  - cDMARDs and the bDMARD
- 6-month change in DAS28 as measure of improvement (or worsening) of a patient's condition
- RWE from Swiss-based RA registry
- Suggests existence of an efficacy-effectiveness gap

DAS28 – **D**isease **A**ctivity **S**core (**28** examined joints)

DMARD – **D**isease **M**odifying **A**nti-**R**heumatic **D**rug



Context

- **Pre-launch**, RCT data on new drug available, but no (or insufficient) observational data on who the drug is prescribed to in routine practice
- Four-step approach

1. Identify *similar* drug for which observational data is available
2. Quantify the impact of treatment, prognostic factors, effect modifiers on clinical outcome
3. Determine characteristics of patients likely to receive new drug
4. Prediction of treatment prescriptions and outcomes in target population

Step 1

- Identify an approved drug already on the market, such that:
  - It is interchangeable with new drug in terms of characteristics of patients to whom it will be prescribed
  - It has the same function as the new drug
  - There is *observational* data providing information on profile of patients receiving (or not receiving) this drug in routine practice
- Requires advice from specialist(s) on the disease, drug, and health system, and from other sources if possible
- RA case study: we identified an approved, existing drug, also a bDMARD
  - ➢ expected to be prescribed to RA patients under similar conditions as the new drug

Step 2

- Aim: link disease progression to a patient's characteristics, with and without the new drug
- Prognostic factors (PF): variables which affect disease progression (outcome) regardless of treatment
- Effect modifiers (EM): variables which affect disease progression (outcome) differently depending on the treatment
- Chosen/identified with help from a specialist
- RA case study (outcome=change in DAS28 after 6 months)

  PF: *body mass index, baseline DAS28, disease duration*

  EM: *rheumatoid factor, number of previous anti-TNF agents*

Step 2

Generalized Linear Model (GLM), combining the two sources of data:

$$\mathrm{E}(Y_i) = \beta_0 + \boldsymbol{\beta^{PF} X_i^{PF}} + D_i\left(\mu_{\boldsymbol{N}} T_i + \boldsymbol{\beta_N^{EM} X_i^{EM}} T_i\right) + (1 - D_i)\left(\mu_{\boldsymbol{S}} T_i + \boldsymbol{\beta_S^{EM} X_i^{EM}} T_i\right)$$

- Obtain estimates $\left\{\hat{\beta}_0, \hat{\mu}_{\boldsymbol{N}}, \widehat{\boldsymbol{\beta}}^{\boldsymbol{PF}}, \widehat{\boldsymbol{\beta}}_{\boldsymbol{N}}^{\boldsymbol{EM}}\right\}$, and associated covariance matrix
- RA case study: linear (Gaussian) model, with Y_i = 6-month change in DAS28

$T_i \coloneqq \begin{cases} 1, \text{if treated with bDMARD} \\ 0, \text{otherwise} \end{cases}$ i: patient index	• $E(Y)$: expected treatment outcome • $\boldsymbol{X^{PF}}$: covariates considered as PFs • $\boldsymbol{X^{EM}}$: covariates considered as EMs • D $\coloneqq \begin{cases} 1 \Rightarrow \text{RCT participant} \\ 0 \Rightarrow \text{RW patient} \end{cases}$	• β_0: intercept • μ_j: relative treatment effect of j vs. control • $\boldsymbol{\beta^{PF}}$: effects of the PFs • $\boldsymbol{\beta_j^{EM}}$: effects of the EMs (j vs. control)

Step 3

- Aim: establish link between a patient's characteristics and treatment selection
- Treatment predictors (TP): patient characteristics that determine whether patient receives the similar drug rather than a comparator treatment
- Assumed to be 'transposable' from the similar drug to the new drug
- Chosen/identified with help from a specialist
- RA case study- TPs are: *rheumatoid factor, disease duration, concomitant steroid usage, number of concomitant cDMARDs, number of previous anti-TNF agents, number of previous cDMARDs, baseline DAS28*

Step 3

- Logistic regression model to capture the treatment selection

$$\boldsymbol{logit\{prob(T_i = 1)\} = \gamma_0 + \gamma^{TP} X_i^{TP}}$$

- Based on observational data from *similar* drug only
- Obtain estimates $\{\hat{\gamma}_0, \hat{\boldsymbol{\gamma}}^{\boldsymbol{TP}}\}$ and associated covariance matrix

$\boldsymbol{T} \coloneqq \begin{cases} 1, \text{if treatment} = \text{bDMARD} \\ 0, \text{if treatment} = \text{control} \end{cases}$	• $\boldsymbol{X^{TP}}$: covariates considered as TPs • i: patient index	• γ_0: intercept • $\boldsymbol{\gamma^{TP}}$: effects of the TPs

Step 4

- Extract or generate a 'target population' that is representative of patients liable to receive the new drug
- We will predict the treatment and outcome for each patient in the target population, based on the estimates obtained in Steps 2 and 3
- For each new patient, simulate a set of parameters $\{\tilde{\gamma}_0, \tilde{\boldsymbol{\gamma}}^{\boldsymbol{TP}}, \tilde{\beta}_0, \tilde{\mu}_N, \tilde{\boldsymbol{\beta}}^{\boldsymbol{PF}}, \tilde{\boldsymbol{\beta}}_{\boldsymbol{N}}^{\boldsymbol{EM}}\}$ from the previously generated parameter estimates and their (co-)variances

- For each patient i in target population, set $\tilde{T}_i = 1$ with probability

$$prob(T_i = 1) = \frac{\exp\{\tilde{\gamma}_0 + \tilde{\boldsymbol{\gamma}}^{\boldsymbol{TP}} \boldsymbol{X}_{\boldsymbol{i}}^{\boldsymbol{TP}}\}}{1 + \exp\{\tilde{\gamma}_0 + \tilde{\boldsymbol{\gamma}}^{\boldsymbol{TP}} \boldsymbol{X}_{\boldsymbol{i}}^{\boldsymbol{TP}}\}}$$

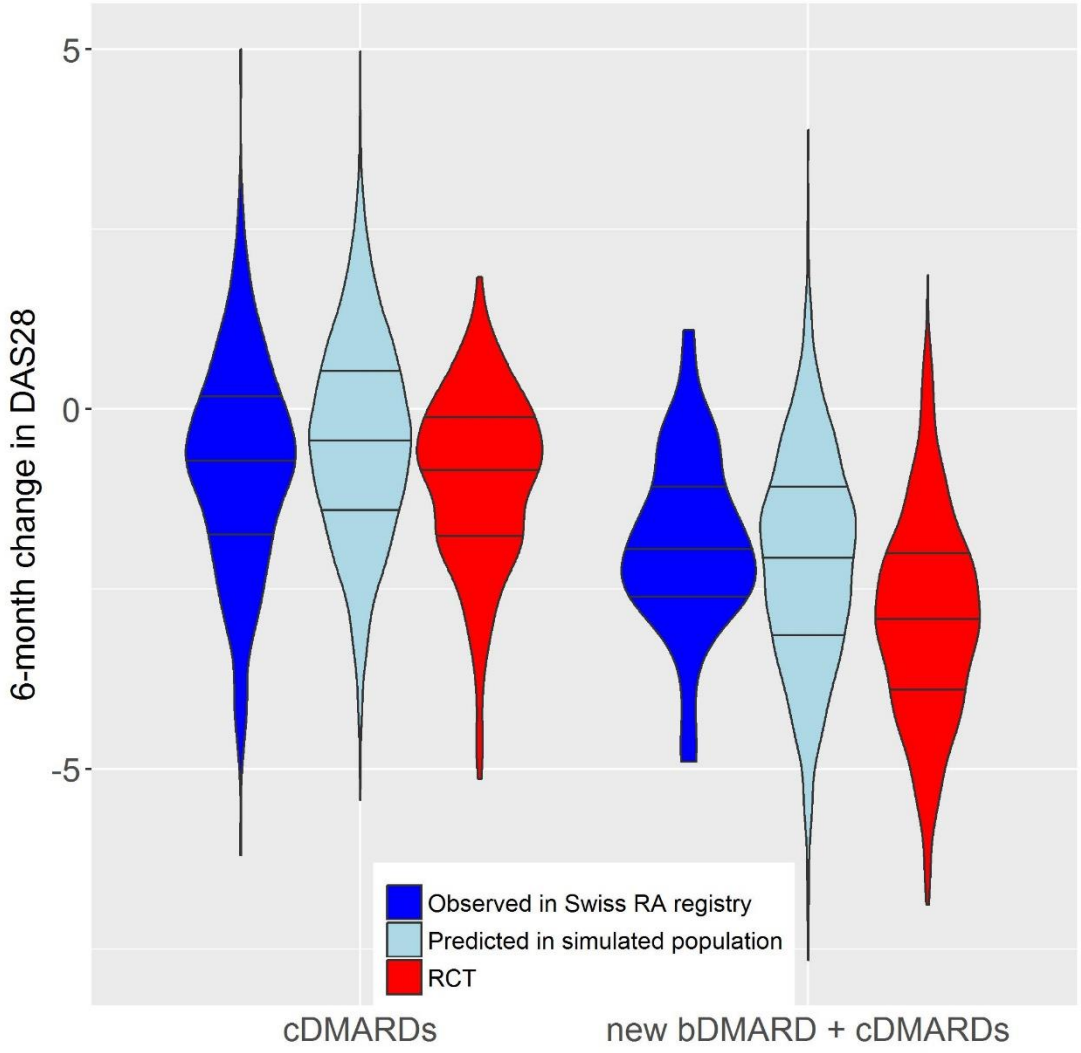
- Finally, predict outcome for patient i:

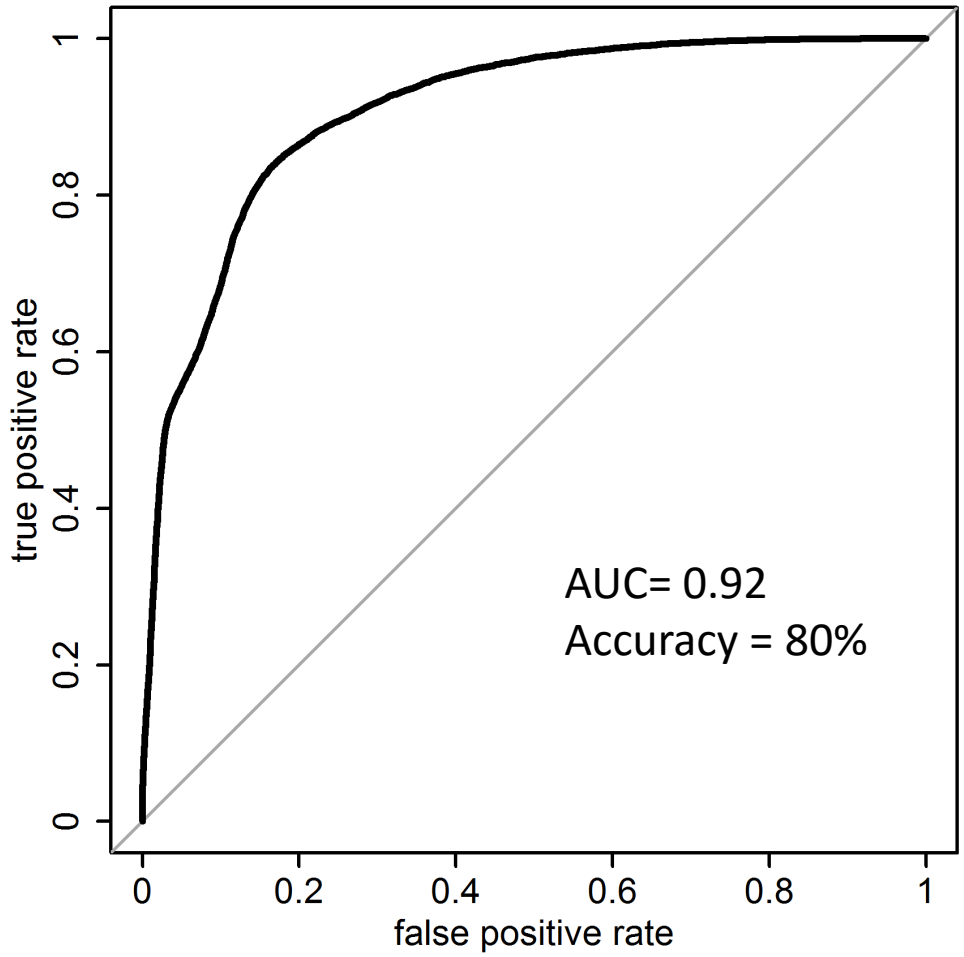
$$\tilde{Y}_i = \tilde{\beta}_0 + \tilde{T}_i \tilde{\mu}_N + \tilde{\boldsymbol{\beta}}^{\boldsymbol{PF}} \boldsymbol{X}_{\boldsymbol{i}}^{\boldsymbol{PF}} + \tilde{T}_i \tilde{\boldsymbol{\beta}}_{\boldsymbol{N}}^{\boldsymbol{EM}} \boldsymbol{X}_{\boldsymbol{i}}^{\boldsymbol{EM}} + \tilde{\varepsilon}_i$$

Step 4, RA predictions for new bDMARD

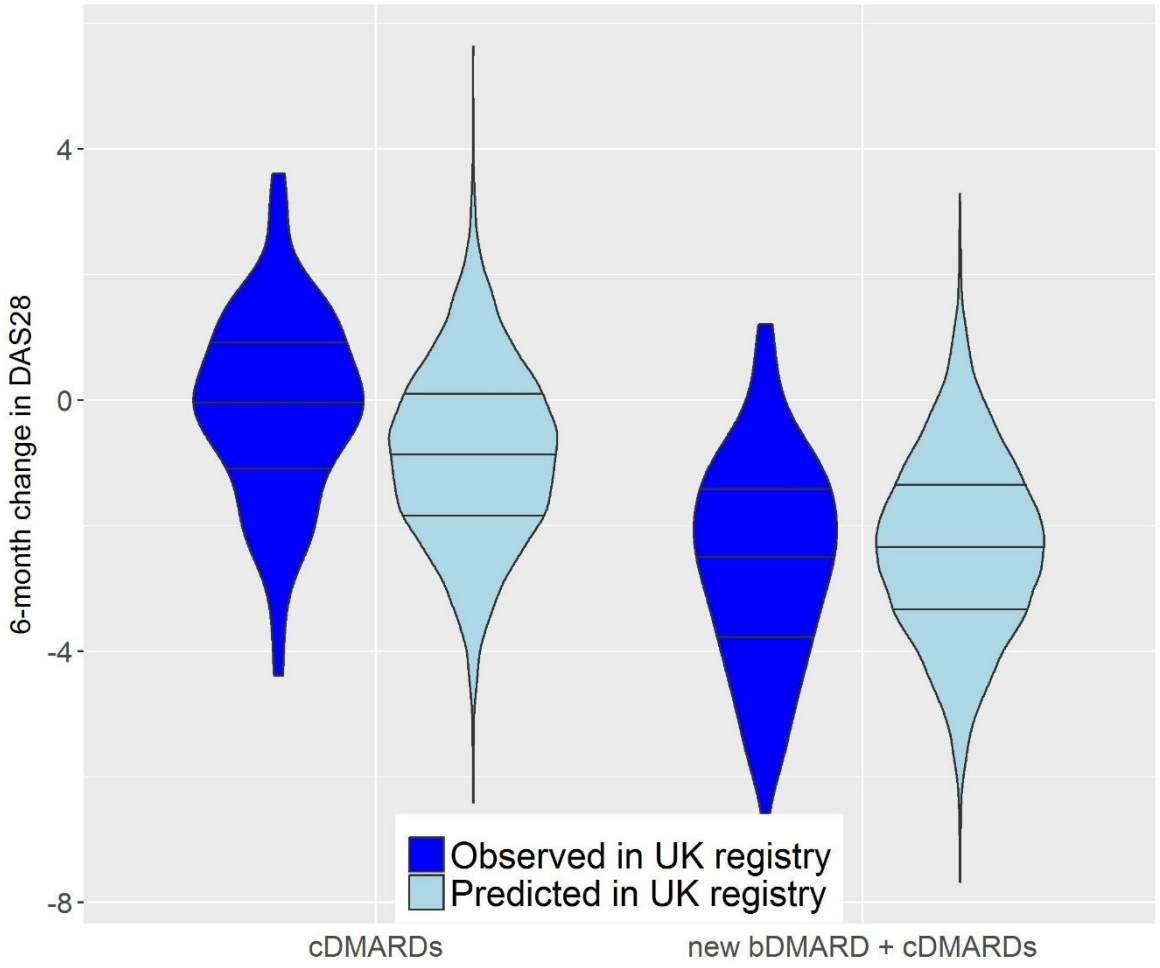
- Target population simulated (N=10000) based on Swiss RA registry
- Patients first assigned a treatment, then outcome is predicted
- **38 %** of patients predicted to receive the new drug
- Median of predicted 6-month change in DAS28,
  - in patients predicted to receive only cDMARDs: **-0.42, IQR [-1.38; 0.53]**
  - in patients predicted to also receive the new bDMARD: **-2.10, IQR [-3.13; -1.08]**

Retrospective evaluation





Transferability to UK health system?



Conclusion

- Flexible framework for predicting effectiveness of a drug pre-launch
- Fairly simple parts, not difficult implement
- The different parts of the approach can be adapted to suit the situation
- Not necessarily transposable between health systems or countries
- Worked very well in the RA example. Need more case studies!

Conclusion

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- Didden et al. (2018), Prediction of Real-World Drug Effectiveness Pre-Launch: Case Study in Rheumatoid Arthritis. *Med Decis Mak.* 2018

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