Prediction of Drug Effectiveness based on RCT Efficacy Data & Real-World Evidence

- A CASE STUDY ON RHEUMATOID ARTHRITIS -

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Eva-Maria Didden, on behalf of GetReal
Institute of Social and Preventive Medicine (ISPM), University of Berne, Switzerland

Motivation

 Gap in treatment outcomes between RCT and real-world populations

- DAS28 – Disease Activity Score (28 examined joints)
- DMARD – Disease Modifying Anti-Rheumatic Drug

![Graph showing change in DAS28 after 6 months comparing RCT data and observational data for Conventional DMARD (cDMARD) and Biologic DMARD (bDMARD)]
Research Task

Predicting the effectiveness of a new bDMARD in patients with Rheumatoid Arthritis (RA) who are likely to receive this treatment in the real world of a healthcare system

Availability of individual participant data:
- RCT data on the new bDMARD
- no real-world data (RWD) on the new bDMARD
- RWD on an existing similar bDMARD

Definitions

- **Treatment predictor:** predictor of real-world treatment decision
- **Prognostic factor:** associated with the clinical outcome independent of treatment decision → measure of the natural course of the disease
- **Effect modifier:** associated with the clinical outcome in interaction with treatment decision → acts differently in different treatment arms
The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no. 115303, resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in-kind contribution. www.imi.europa.eu

### Suggested Framework

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Evidence used</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Identify a market-approved drug (S) which is similar to the new drug (N) you want to make predictions about.</td>
<td>Expert advice</td>
</tr>
<tr>
<td>b) Estimate the relative efficacy of drug N and account for any relevant effect modifiers. Identify the relevant prognostic factors and assess their impact on disease progression.</td>
<td>RCT data (on N), expert advice, RWD (on S), RCT data (on N), expert advice</td>
</tr>
<tr>
<td>c) Identify the relevant treatment predictors to determine the profile of patients who are likely to receive N.</td>
<td>RWD (on S), expert advice</td>
</tr>
<tr>
<td>d) Predict treatment outcome in patients who are likely to receive N.</td>
<td>RWD (on S), expert advice</td>
</tr>
</tbody>
</table>

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a) Identification of an existing similar bDMARD

Two drugs are assumed to be «similar» if they...

... are prescribed for the same purpose.

... are administered to the same types of patients, i.e. to patients

- with similar physical attributes,
- with comparable disease and treatment histories,
- with similar living conditions, etc.

We could identify a bDMARD (S) which is similar to the new bDMARD of interest (N)
b) Modelling of treatment effect

1. Selection of the relevant prognostic factors and effect modifiers
   i. Follow the clinical experts’ advice
   ii. Perform statistical variable selection

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prognostic factors</th>
<th>Effect modifiers</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-months change in DAS28</td>
<td>RF-positivity</td>
<td>RF-positivity</td>
</tr>
<tr>
<td>disease duration</td>
<td>baseline DAS28</td>
<td># [previous anti-TNF agents]</td>
</tr>
<tr>
<td>obesity/body-mass index</td>
<td>DAS: disease activity score</td>
<td>TFN: tumor necrosis factor</td>
</tr>
</tbody>
</table>

2. Estimation of...
   ...the efficacy of N, accounting for the selected effect modifiers \( \leftarrow \) RCT data
   ...the impact of the prognostic factors \( \leftarrow \) RCT data on N and RWD on S

c) Modelling of treatment assignment

1. Selection of the relevant treatment predictors
   i. Follow the clinical experts’ advice
   ii. Perform statistical variable selection

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selected treatment: bDMARD vs. cDMARDs</td>
<td>RF-positivity, disease duration</td>
</tr>
<tr>
<td>baseline ESR</td>
<td># [previous cDMARDs], # [previous anti-TNF agents]</td>
</tr>
<tr>
<td># [concomitant cDMARDs]</td>
<td>steroids (y/n)</td>
</tr>
</tbody>
</table>

2. Estimation of the effects of the treatment predictors on treatment choice \( \leftarrow \) RWD on S
d) Prediction of drug effectiveness in a simulated real-world patient population

i. Predict treatment decision «bDMARD N vs. cDMARDs»

ii. Predict treatment outcome in those patients who were assigned to receive N.

iii. Compare the predicted treatment outcome with the outcome observed in patients taking cDMARDs.

Retrospective Analysis

Change in DAS28 after 6 months
cDMARDs bDMARD N

Observed/RIVD
Predictions for a RW population

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**Discussion**

**Deliverable**

Comprehensive *inference framework* to connect information from various sources

- Prediction of real-world treatment effect
- Assessment of the efficacy-effectiveness gap

**Possible extensions:**
- Use of aggregate data as prior information
- Comparison of more than two treatment arms

**Internal model validity:** satisfied

**External model validity:** model transferability between countries not ensured
- different healthcare systems → different treatment receiving patterns → ...

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Didden et al. (2016/17), *Prediction of Real-World Treatment Effectiveness based on Trial and Registry Data*, in progress.