CLOSING THE EFFICACY TO EFFECTIVENESS GAP: GENERALIZING FROM RCTS TO REAL WORLD POPULATIONS

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Decision problem

- Following the regulatory approval of a new intervention, before that intervention can reach patients there is an additional requirement to provide evidence of added benefit and/or value.
- These decisions are often at a country level or even a regional level within a country.
- Reimbursement decisions are based on some of the following
  - Burden of disease
  - Cost effectiveness
  - Budget impact
  - Comparisons against active comparators
  - Clinical trial evidence.

Questions we often hear

- The RCT's that have been conducted are not relevant for our local population ?
- What is the impact of introducing this new indication into our population ?

These are two similar but different questions, and we explored these through the Innovation Medicines Initiative (IMI), GetReal.

In this presentation we will look at the first of these questions

IMI GetReal

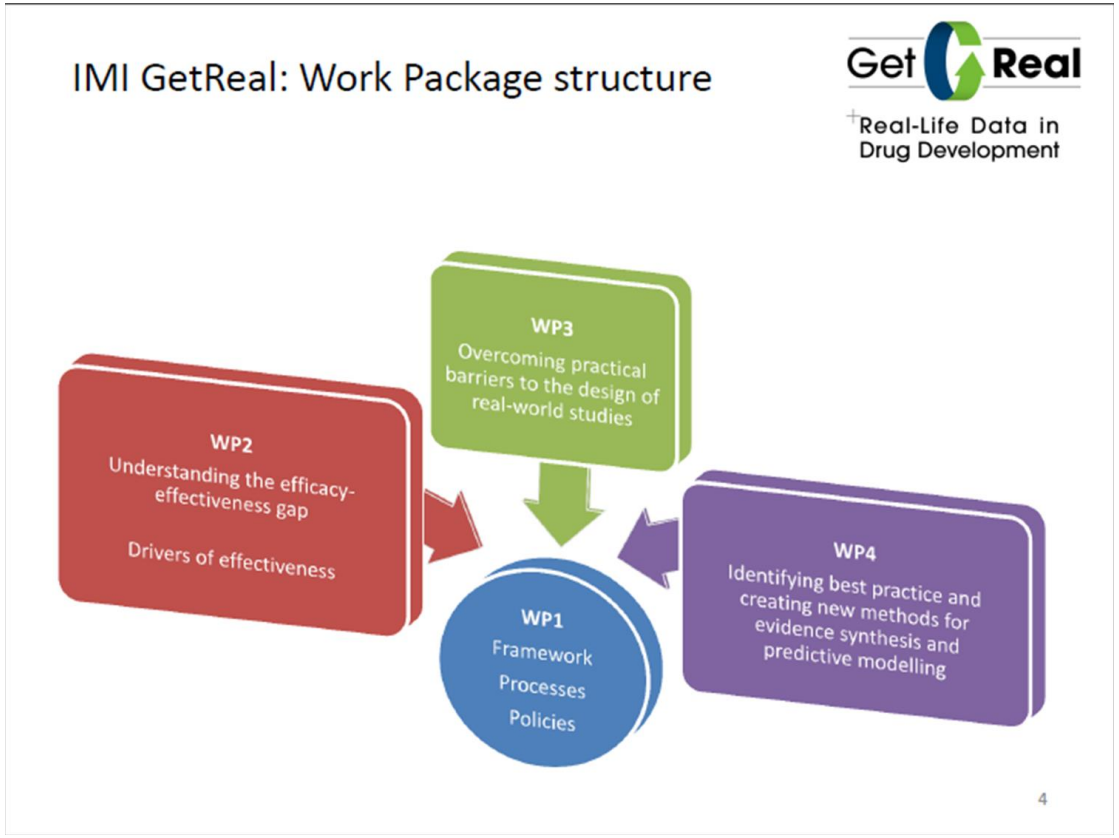
Get Real

Real-Life Data in Drug Development

About IMI

- The **Innovative Medicines Initiative** (IMI) is Europe's largest public-private partnership aiming to improve the drug development process by supporting a more efficient discovery and development of better and safer medicines for patients.
- With a €2 billion euro budget, IMI supports collaborative research projects and builds networks of industrial leader, academic experts & health care decision maker in Europe that will boost innovation in healthcare.
- IMI supports a number of projects, among them GetReal about „Incorporating real-life clinical data into drug development"

https://www.imi-getreal.eu/



Reweighting of RCT's to better reflect real Life

- Method reweights the RCT results based on propensity score or entropy balancing to the patient characteristics from a real world data source to reflect the population of interest


Reweighting Randomized Controlled Trial Evidence to Better Reflect Real Life – A Case Study of the Innovative Medicines Initiative

Michael Happich[1,*], Alan Brnabic[2], Douglas Faries[3], Keith Abrams[4], Katherine B. Winfree[3], Allicia Girvan[3], Pall Jonsson[5], Joseph Johnston[3], Mark Belger[1] and IMI GetReal Work Package 1

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Reweighting Approach: Weight RCT's to better reflect real Life

Method reweights the RCT results based on propensity score or entropy balancing to the patient characteristics from a real world data source to reflect the population of interest. Some important considerations before applying this method.

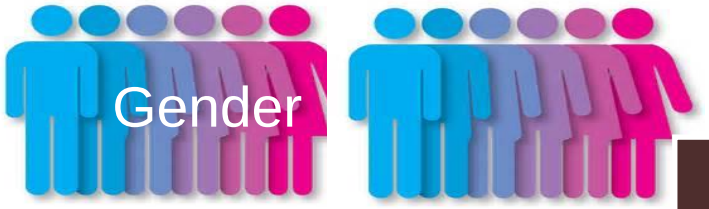
- Identification of Treatment effect modifiers
- Is the RWD representative of the population of interest?
- Is the RWD available at summary level or at IPD?
- Variables used in the re-weighting are defined in the same way for the RCT and RWD
- Outcomes are defined the same in both data sources
- The RCT includes patients within the range of the target population
  - RCT in moderate, RWD in moderate and severe severity (where severity is a known treatment effect modifier)

Weighting Methods

RCT

Observational

Gender



Weight RCT using an algorithm

(Inverse propensity score method, Generalised method of moments or Entropy Balancing)

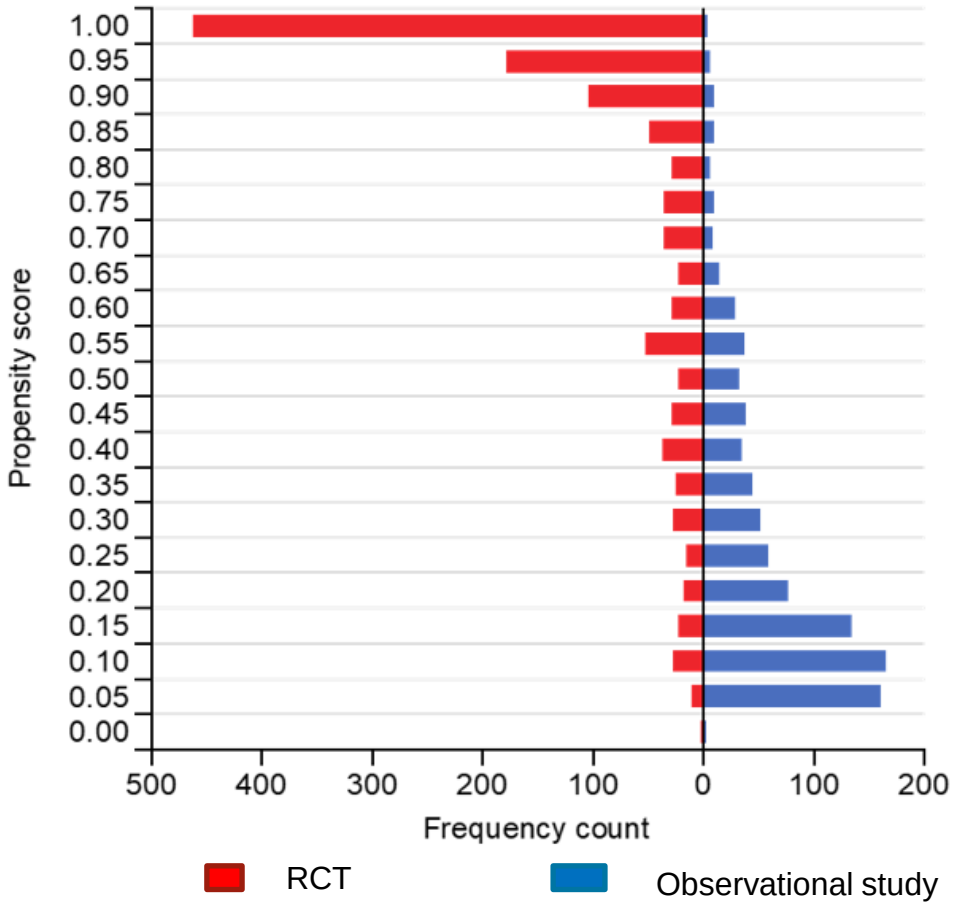
to *match* with Observational data on selected baseline characteristics/effect modifiers

Age

Clinical Characteristics

Weighting Methods: Individual Patient Data

- A propensity score model is fitted that **predicts participation** in either RWE or RCT (given a set of *common total* baseline characteristics)
- Resulting propensity scores are used to
  - **Assess** the **difference/overlap** between the two cohorts, and
  - Calculate **weights to apply to RCT outcomes**
- Here, propensity scoring is used to mimmick RWE in RCT setting.
- Prior to launch, **only baseline RWE information needed** to assess RCT outcomes under RWE conditions



Methods to match RWE aggregated data: Signorovitch's method

The weights were estimated with the methods described in Signorovitch 2010.

- Signorovitch used the methods of moments to estimates weights of individual patient level data to match aggregated results of a set of variables to then conduct matched indirect comparisons.
  - Note that this method is referenced in the NICE TSD 18 (Phillippo 2016) for a similar statistical topic, the matched-adjusted indirect comparison (Phillippo 2016)
- In this current work, only the first part is used i.e. the weighting estimation
- This methods used the method of moments at the first level (i.e. only the means)
  - Equations are set up to estimate the weights of each patient so that, the mean of each covariate to match corresponds to the mean of each covariate of the weighted patients individual patients.
  - These equations (as many covariates to match and number of patients in our IPD set are available (in our case 6+462=468 equations)) are solved with the methods from Newton-Raphson method (also known as Newton's method)
  - Signorovitch highlights that adding the second level (i.e. the SD) into the equation doesn't improve much the estimate and needs extensive computations.
- This method weights the individual level data to match the combined treatment groups to the aggregated covariates

Limitations

- Definitions of variables can be different between RCT and RWE studies
  - Baseline characteristics
  - Outcome measures
- Unmeasured confounders
- Non-overlapping propensity scores
- Specific categories of a variable are not available in RCT
- Effective sample size

Summary

- To answer questions on the relevance of a clinical trial to a specific population the Generalisability method can be used to reweight the Trial outcomes to reflect the population of interest.
- If Individual patient level data is not available for the Target population the methodology can be adapted to use just the aggregated data
- These methods are beginning to be used as part of the evidence submitted to HTA's

REFERENCES

1. Happich, M., Brnabic, A., Faries, D., Abrams, K., Winfree, K. B., Girvan, A., Jonsson, P., Johnston, J., Belger, M., & IMI GetReal Work Package 1 (2020). Reweighting Randomized Controlled Trial Evidence to Better Reflect Real Life - A Case Study of the Innovative Medicines Initiative. *Clinical pharmacology and therapeutics*, *108*(4), 817–825. https://doi.org/10.1002/cpt.1854
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QUESTIONS