GENERALIZING FROM RCTS TO REAL WORLD POPULATIONS

APBG WEBINAR

25TH JULY 2019

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Content

- Introduction to the decision problem
- IMI GetReal
- Reweighting of RCT results
- Modelling approach
- Real world control arms
- Pragmatic studies
- Augmentation of trail population

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 trail 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 .

The IMI project also has looked at ways in which RWE can be used in designing your RCT (Pragmatic designs and Augmentation of an RCT)

IMI GetReal

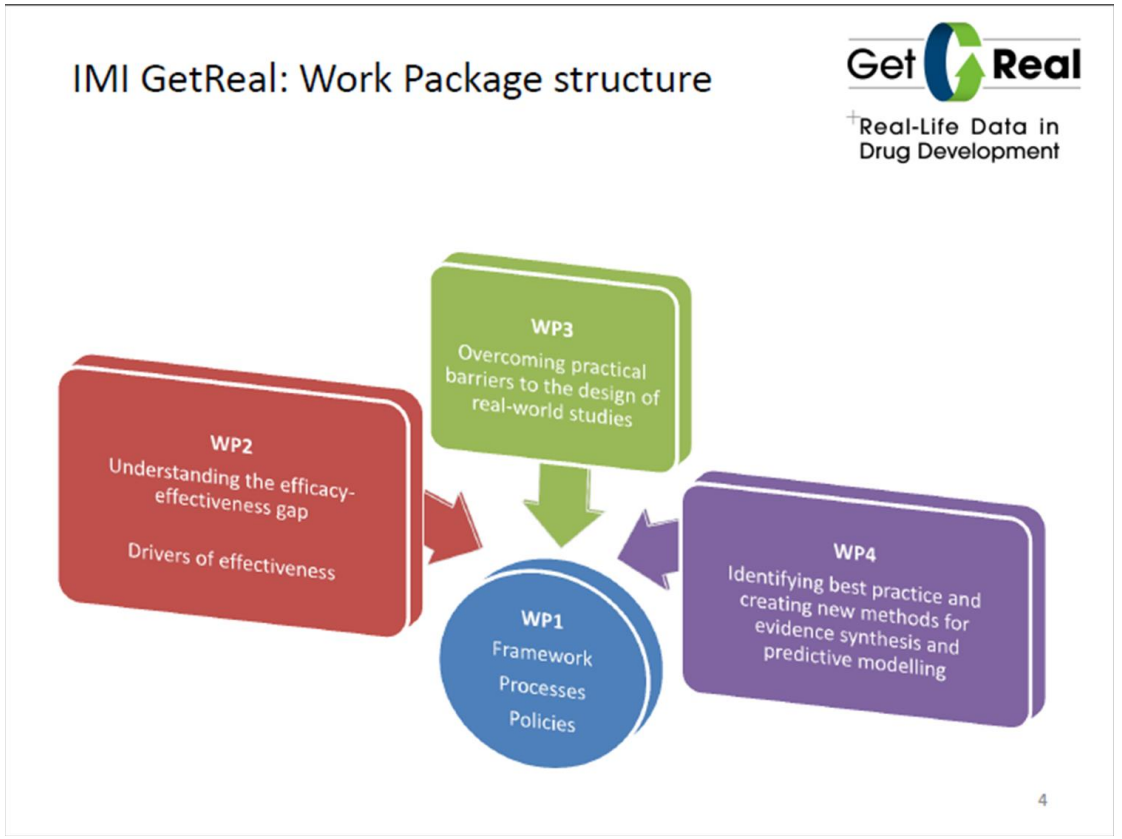
Get Real

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” Approach

RCT

Observational

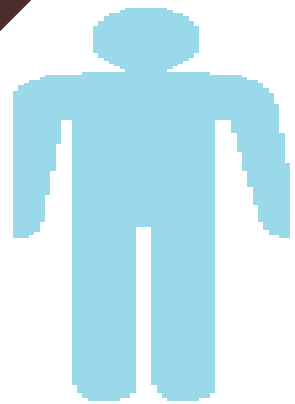
Female
Never smoked
Cardio medical History
66 years old

…

Male
Smoker
Prior Radiotherapy
74 years old

…

Weight RCT using an *algorithm*
(Inverse propensity score method or Entropy Balancing)
to *match* with Observational on
selected baseline characteristics



Weighting Approaches

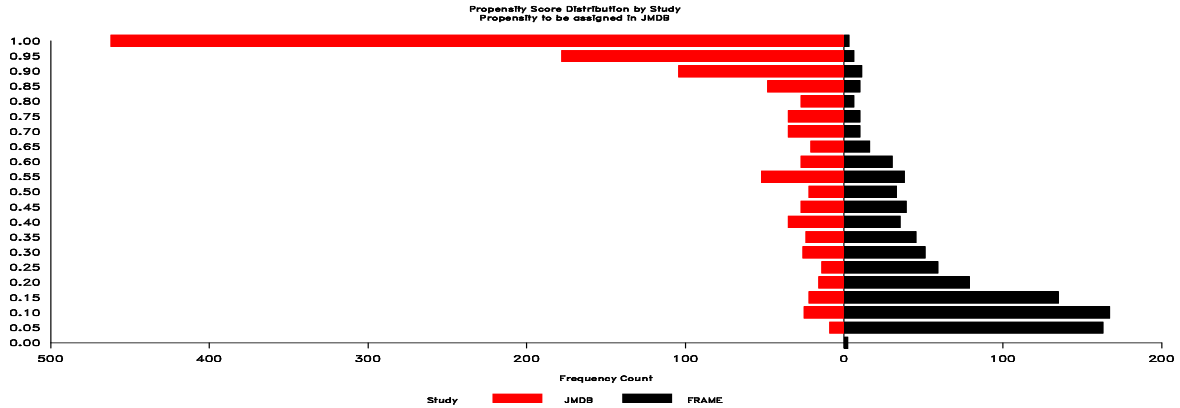
- Two key approaches employed
  1. Inverse propensity score method (IPS)[1.]
  2. Entropy balancing method[2.]
- Both approaches calculate weights for the RCT population subject to matching selected baseline characteristics to the general population of interest (Observational study)
- Weights are assessed for outliers and are applied to the RCT outcome of interest to estimate the weighted treatment effect
- Error of weighted treatment effect comes from the Bootstrap sampling distribution of weighted treatment effect

[1.] Faries, Douglas, Andrew C. Leon, Josep Maria Haro, and Robert L. Obenchain. 2010. Analysis of Observational Health Care Data Using SAS®. Cary, NC: SAS Institute Inc. Analysis of Observational Health Care Data Using SAS® Copyright © 2010, SAS Institute Inc., Cary, NC, USA

[2] Hainmueller *Political Analysis* 2012 20(1);25-46

Weighting Approaches: IPS

- A propensity score model is fitted that **predicts participation** in either RWE or RCT, given a set of *common total* baseline characteristics (RWE and RCT data are pooled for that purpose)
- Resulting propensity scores are used to
  - **assess** the **difference/overlap** between the two cohorts, and



  - Calculate **weights to apply to RCT outcomes**
- 'Classic' propensity scoring methods are typically used to mimmick RCTs in RWE setting. 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

Predicting RWE outcomes

- Work was led by Eva-Maria Didden and colleagues from the University of Bern, Switzerland.
- With the objective to predict the drug effectiveness pre-launch in a real world setting, using RCT data and real world evidence. The methodology was illustrated through a case study on Rheumatoid Arthritis.
- Method requires longtitudinal patient level from the RCT, and patient level data from a Real world data source, where the RWD source includes an intervention similar to the new intervention being studied in the RCT.
- Two predictive models are developed
    - Factors associated with treatment outcome
    - Factors associated with treatment allocation

- Using baseline patient data from RWD source (registry, claims) sample patients to run through both predictive models to estimate the treatment outcomes that would be observed.

Suggested Framework

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

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Limitations

- Both methods have their limitations, and answer very different questions. Although if treatment allocation is randomised in the predictive modelling approach, then similar results could be expected from both methods.

Limitations to the reweighting approach

- 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

Limitations to the Predictive modelling approach

- Databases provide evidence on all relevant effect modifiers.
- Unmeasured or undetected confounder may lead to biased predictions.
- Quality, and representative of the RW registry
- Consistency of definitions across data sources.
- The proposed prediction framework should not be applied if the overlap between the RCT and the target real-world population is small.
- Reliability of the predictive models (Model validation)

OTHER APPROACHES USING RWD

Use of RWE controls (extrapolation of treatment effect)

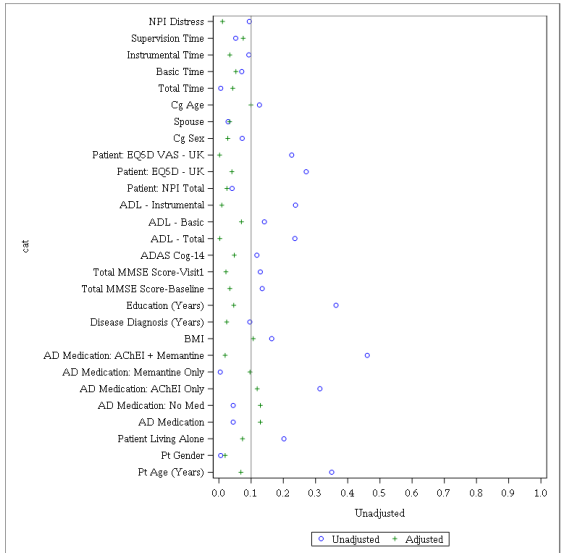
Original Research

The Journal of Prevention of Alzheimer's Disease - JPAD
Volume 6, Number 2, 2019

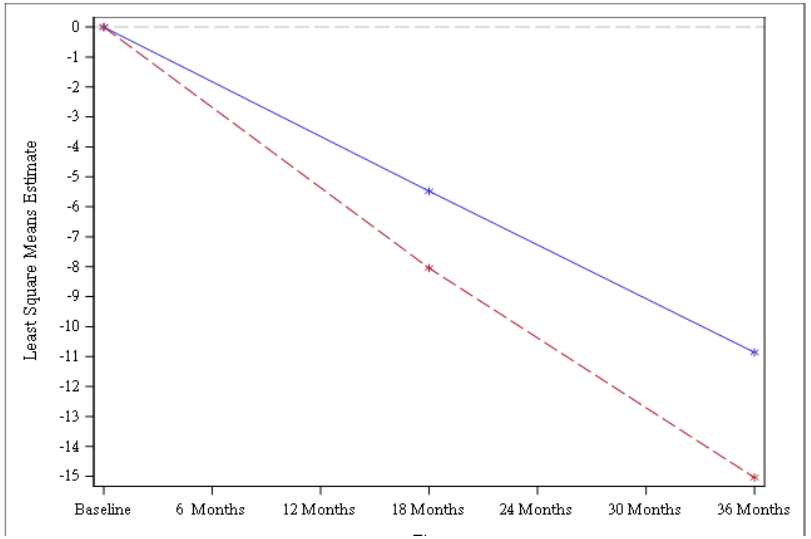
Utilization of Observational Data as a Proxy Cohort for Comparison Purposes with Open-Label Study Results: An Example from Alzheimer's Disease

C. Reed[1], M. Happich[1], J. Raskin[2], A. Tockhorn-Heidenreich[1], M. Belger[1]

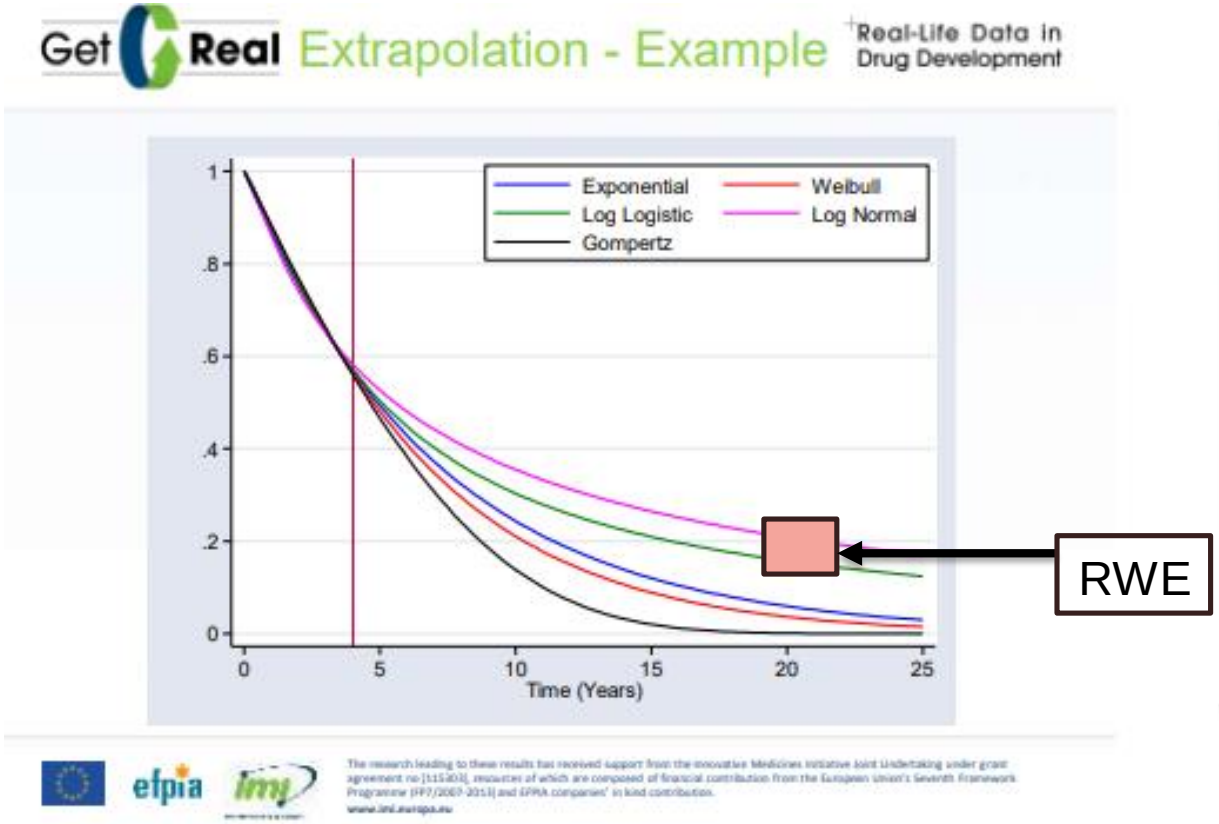
1. Eli Lilly and Company Limited, Windlesham, UK; 2. Eli Lilly and Company, Indianapolis, IN, USA



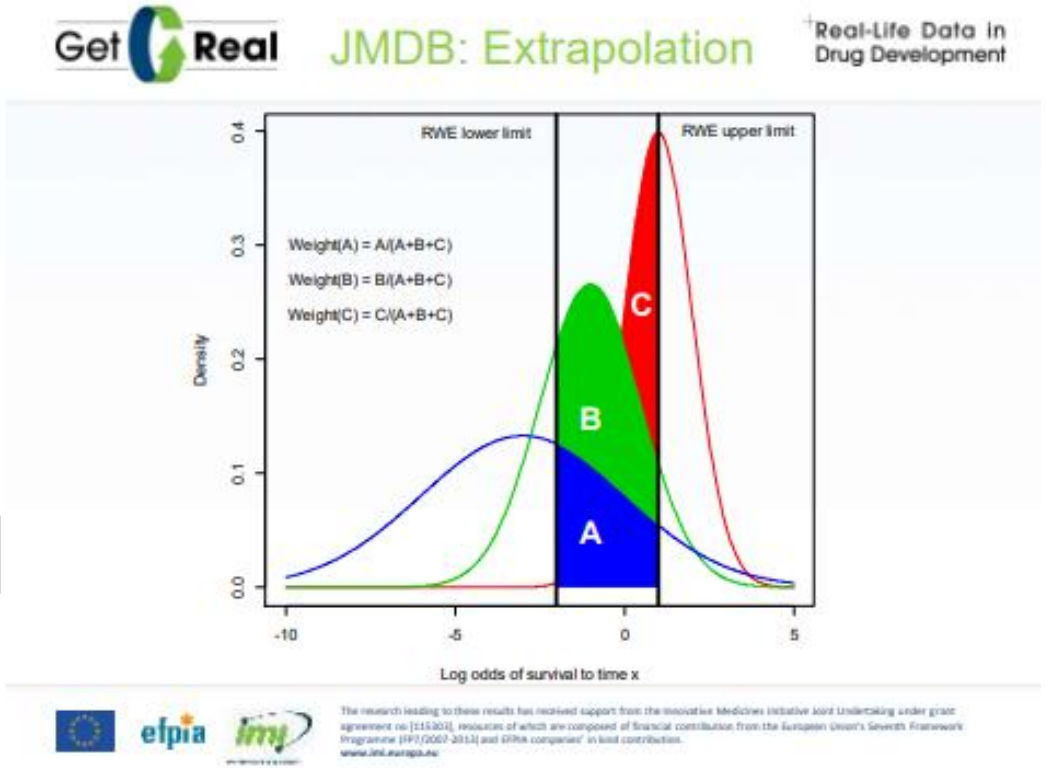
- Adjust for baseline differences between RCT and Observational study
- Test for no differences between Placebo arm and observational study at end of randomised stage of the RCT
- Extrapolate treatment effect by comparing open extension phase of the RCT with the longer term outcomes from the observational study acting as placebo.



Extrapolation & Generalizability of treatment effects over time



Use RWE data source to anchor the extrapolation



Alternatively take a Bayesian model average approach

Keith R Abrams PhD
Department of Health Sciences, University of Leicester, UK

Pragmatic Trials (PT)

Schwartz and Lellouch (1967): 'explanatory' vs 'pragmatic'

Explanatory Trial:

Can *intervention work under optimal circumstances*

- High validity
- Controlled environment
- Homogenous setting/patient
- Mostly Phase II-III
- Focus on treatment per se

Pragmatic Trial:

Does intervention work in usual care

- **High generalisability**
- **Usual Care**
- **Diverse settings/patient**
- **Mostly PhIV (can be PhIII)**
- **Focus on tx strategy**

Getting heterogeneity into RCTs, Karcher H., Laser Analytica

Real-world study to test eligibility criteria in schizophrenia

- Method*: use real-world data to optimize clinical trials
  1. Study patient characteristics and interplay between factors and outcome in a real-life schizophrenia population (SOHO cohort)
  2. Identify the subpopulation eligible for a typical pre-authorization trial : "RCT population"
  3. Re-include in this "RCT population" a minimal subset of patients who would usually be excluded (=broaden the eligibility criteria)
     - Method of quotas (stratification) for patient inclusion in trials
     - Combined with predictive modeling to evaluate the outcome in the RW population
  4. Measure how "efficient" each re-inclusion is

* "Reverse" of the method used in *Schneeweiss et al. Increasing Levels of Restriction in Pharmacoepidemiologic Database Studies of Elderly and Comparison With Randomized Trial Results. Med Care. 2007*

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Figure 1: Real-world patients typically excluded from Phase III by type of exclusion criterion

Exclusion (enrichment) criterion:

age > 65 years, duration of illness < 3 years, patients with few previous suicide attempts, patients with history of alcohol or substance abuse, and patients treated at private practices

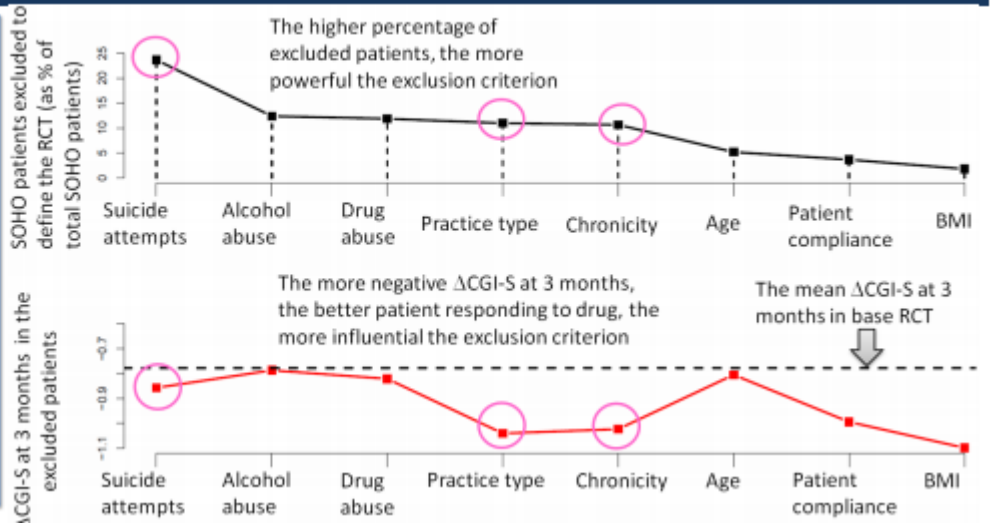
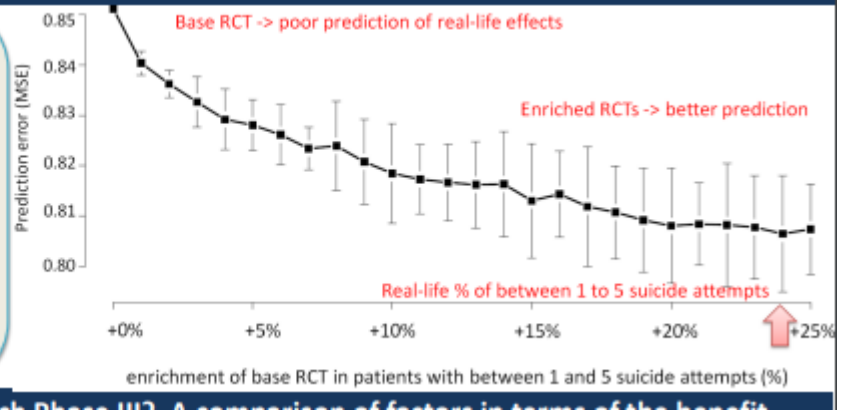


Figure 3: Predicted error and CI using different RCTs enriched with few "suicide attempts"

- Error on the prediction of real-life effects (y-axis) decreased with increasingly re-introducing a small proportion of the patients (eg, with few suicide attempts) typically excluded from RCTs by replacement
- In practice, this trial enrichment is implemented through stratification.



QUESTIONS