Get Real

Real-Life Data in Drug Development

Evidence Synthesis and Predictive Modelling:

Literature Reviews and Follow-Up Research

- Pre-reading material for WP4's webinar, 10th May 2016 -

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- on behalf of GetReal -

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Topics Covered

- **Literature reviews**
  - GetReal in **N**etwork **M**eta-**A**nalysis (NMA)
  - GetReal in meta-analysis of **I**ndividual **P**articipant **D**ata (IPD)
  - GetReal in mathematical modelling
- **Methods**
  - NMA based on **R**eal-**W**orld **E**vidence (RWE)
  - IPD-NMA
  - Mathematical modelling framework to predict effectiveness from efficacy data and RWE

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Introduction:

Integration of real-world evidence in network meta-analyses and outcome prediction

Key questions:

- How well can relative effectiveness be estimated from phase II and III RCT efficacy studies alone?
- How should RCTs, additional relative effectiveness studies and observational data, best be integrated to address specific decision making needs of regulatory and HTA bodies at launch?
- How can effectiveness be predicted from available efficacy and observational data?

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Literature Reviews:

Best practices in evidence synthesis and predictive modelling of relative effectiveness

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We performed three **systematic reviews** on methods for:

1. Network meta-analysis (NMA)
2. Individual participant data (IPD) meta-analysis
3. Mathematical modelling to predict real-world effectiveness based on evidence from randomized controlled trials (RCTs)

Our **aim** was to identify and describe state-of-the-art methods in these three research areas, to summarize methodological challenges and limitations and to give recommendations on the use of the discussed methods.

All three reviews were accepted for publication in the Research Synthesis Methods journal

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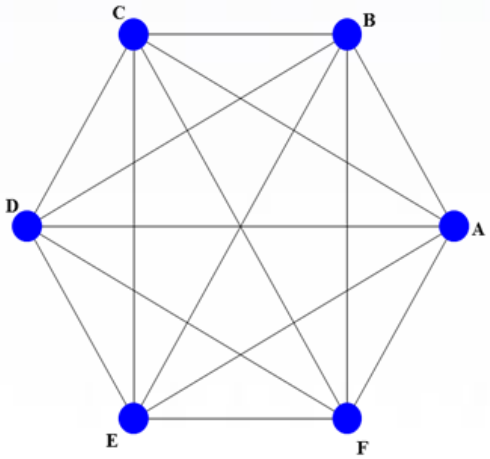
1. Get Real in network meta-analysis: a review of the methodology



Orestis Efthimiou , Thomas P. A. Debray, Gert van Valkenhoef, Sven Trelle, Klea Panayidou, Karel G. M. Moons, Johannes B. Reitsma, Aijing Shang and Georgia Salanti

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Introduction

- Standard meta-analytical methods are limited to the case of **two** competing treatments. Often, though, studies compare different sets of treatment choices.
- In such cases, pairwise meta-analyses **cannot give a definitive answer** regarding which treatment works best for a target condition.
- NMA can be used for meta-analyzing evidence from studies that compare **multiple competing interventions.**
- The methodology of NMA rests on assumptions that are sometimes poorly understood and inadequately assessed. Moreover, recent articles have presented new, alternative approaches to issues related to NMA, rendering past reviews obsolete.
- An **updated review of the methodology of NMA** was thus deemed necessary.

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Methods

- We conducted a systematic search of the literature on **methods for NMA**. We searched for articles that contribute to the methodology of NMA by introducing new methods and models, articles that provide recommendations or offer guidance on how to perform NMA, as well as articles that review the existing methodology

- We organized the articles we identified according to their context and included them in a **publicly available**, online database. https://www.zotero.org/groups/wp4_-_network_meta-analysis/items.

- A total of 186 papers included in our database were categorized using **tags** assigned according to type of research, methodological topics, and software used to implement the methods

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- **Guidance:**
  - ✓ Presented the advantages and limitations of alternative approaches.
  - ✓ Discussed in depth methods to assess the validity of the underlying assumptions
  - ✓ Provided technical details regarding a series of special issues: network meta-regression, accounting for the risk of bias, multiple outcomes and repeated measures, defining the number of nodes, planning future studies, etc.
  - ✓ Listed software tools for fitting NMA and for assessing its assumptions.

- Our review constitutes the **most comprehensive collection** of methods for NMA to date and can be a **valuable tool** for both experienced researchers as well as researchers taking their first steps in NMA

Efthimiou, O., Debray, T. P. A., van Valkenhoef, G., Trelle, S., Panayidou, K., Moons, K. G. M.,Reitsma, J. B., Shang, A., Salanti, G., GetReal in network meta-analysis: a review of the methodology. Res. Syn. Meth.

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2. GetReal in meta-analysis of individual participant data: a review of the methodology

Thomas P. A. Debray, Karel G. M. Moons, Gert van Valkenhoef, Orestis Efthimiou, Noemi Hummel, Rolf H. H. Groenwold, Johannes B. Reitsma

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Background

- Meta-analysis is often based on published aggregate data (AD), but can be of limited value
  - when AD poorly reported, derived and presented differently across studies
  - when AD are more likely to be reported when statistically or clinically significant
  - when there is substantial heterogeneity in estimates of relative treatment effect
- Need for IPD
  - to increase statistical power & reduce bias
  - to increase flexibility of statistical analyses
  - to identify whether treatment effects vary across clinical subgroups or because of effect modification
- IPD-MA is considered as the gold standard approach for investigating treatment efficacy

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Methods

- We conducted a systematic search of the literature on **methods for IPD-MA**. We searched for articles that contribute to the methodology of IPD-MA by introducing new methods and models, articles that provide recommendations or offer guidance on how to perform IPD-MA, as well as articles that review the existing methodology

- We organized the articles we identified according to their context and included them in a **publicly available**, online database. https://www.zotero.org/groups/wp4_-_ipd_meta-analysis.

- A total of 153 papers included in our database were categorized using **tags** assigned according to type of research, methodological topics, and software used to implement the methods

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Guidance

- Advantages and limitation of existing approaches for IPD-MA
- Description of statistical methods and underlying assumptions
  - Investigating heterogeneity of treatment effect
  - Combining IPD and published AD
  - Dealing with missing participant data
  - Modelling different types of outcomes
  - Including evidence from non-randomized studies
- Overview of existing software tools
- Example code in the R software package

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Considerations

- Implementation of IPD-MA requires additional effort and statistical expertise
- IPD-MA should not be conducted without a systematic review
- IPD-MA is no panacea against poorly designed and conducted primary research

Recommendations

- Before undertaking an IPD-MA, it may be helpful to perform a meta-analysis of aggregate data (AD)
- Researchers should carefully assess whether the potential advantages of IPD outweigh the extra effort involved

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Guidance

Research Synthesis Methods

Tutorial

Get real in individual participant data (IPD) meta-analysis: a review of the methodology

OPEN

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3. GetReal in mathematical modelling: a review of studies predicting drug effectiveness in the real world

Klea Panayidou, Sandro Gsteiger, Matthias Egger, Gablu Kilcher, Maximo Carreras, Orestis Efthimiou, Thomas P. A. Debray, Sven Trelle, Noemi Hummel

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Introduction

- Mathematical models are widely used to support decision-making at all stages of drug development.
- The generalizability of results observed in an RCT into a **real-world settings** is a fundamental issue for drug development, regulators, and HTA
- The potential difference between RCT outcomes and effects in everyday clinical practice has been called the "**efficacy-effectiveness gap**"
- Approaches to bridge this gap and predict real-world effectiveness from RCT efficacy data include **evidence synthesis models**, which in turn can be used to make predictions or to inform dedicated **prediction models**
- Mathematical models can emulate the course of disease for an individual or a group of patients under various interventions and conditions

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Methodology and findings

- We searched the literature for methods used to predict real-world effectiveness of drugs from randomized controlled trial (RCT) efficacy data
- We identified four approaches used in only 12 articles: multi-state models, discrete event simulation models, physiology-based models, and survival and generalized linear models.
- Outcomes were predicted over time, for new patient populations and drug doses.
- Most studies included sensitivity analyses, but external validation was done in only three studies.
- Methods predicting real-world effectiveness are not widely used at present, and are not well validated.
- The articles are included in a publicly available, online database

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Importance of the review

- We identified only 12 articles and therefore conclude that mathematical modelling is not yet widely used for this purpose.
- Our review of relevant models and applications is nevertheless useful to readers wishing a broader understanding and awareness of the current use of mathematical modelling to predict the relative effectiveness of drug interventions in comparative effectiveness research.
- We expect that both the methodological development and application of mathematical modelling in comparative effectiveness research will grow substantially in the near future.

Panayidou. K., Gsteiger, S., Egger, M., Kilcher, G., Carreras, M., Efthimiou, O., Debray, T.P.A., Trelle, S., Hummel, N., and GetReal Methods Review Group (2016) GetReal in mathematical modelling: A review of studies predicting drug effectiveness in the real world. Accepted in Res. Syn. Meth.

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Case Study Applications

Based on the findings from our three systematic reviews, we have employed the following case studies:

- Case study: ***depression*** *(Utrecht),* to explore methods for the meta-analysis of individual patient-level data.
- Case study: ***schizophrenia*** *(Ioannina)* to extend methods for a joint network meta-analysis of RCTs and observational data.
- Case study: ***rheumatoid arthritis*** *(Bern),* to explore methods on predictive modelling using RCT and observational data.

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Methods:

Integration of real-world evidence in network meta-analyses and outcome prediction

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IPD-NMA (1/2)

Background

- Network meta-analysis (NMA) often based on AD
- Previous reviews have demonstrated that about 1/8th of AD-NMA suffer from network inconsistency
- In the presence of heterogeneity, the usefulness of NMA may also be limited

What are the potential benefits of IPD-NMA?

- Case study in 18 depression trials comparing placebo with 3 and 4-cyclic antidepressants.
- 2-6 week follow-up on Hamilton Depression scores
- Substantial drop-out of participants (up to 40% after 6 weeks), mostly in trials involving a placebo arm.

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IPD-NMA (2/2)

Findings

- AD-NMA leads to excessive network inconsistency and/or heterogeneity
- IPD-NMA models achieved improved consistency and less heterogeneity
  - By modelling longitudinal outcomes with informative drop-out
  - By allowing for participant-level treatment-covariate interaction
- IPD-NMA models achieved higher precision
- Our findings confirm the recommendations from the literature, and indicate that access to IPD may be helpful to improve the validity and usefulness of summary estimates of relative treatment effect.

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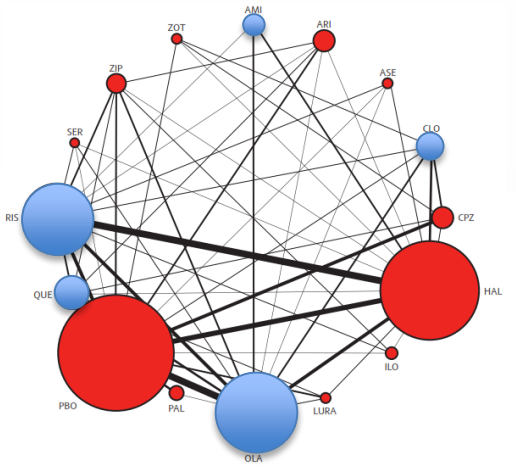
NMA based on RWE (1/4)

Background

- NMA is usually **limited** to the synthesis of evidence from RCTs, while observational evidence is often disregarded
- In recent years there is a growing interest for including **non-randomized studies** (NRSs) in the decision-making process.
- The aim of this project was to present and evaluate **statistical methods** for combining RCTs and NRSs in an NMA setting and to **make recommendations** about their use.
- We applied our methods to a published network of 167 RCTs which compare 15 antipsychotics and placebo for **schizophrenia**, augmented by observational data on 5 interventions coming from a large cohort study.



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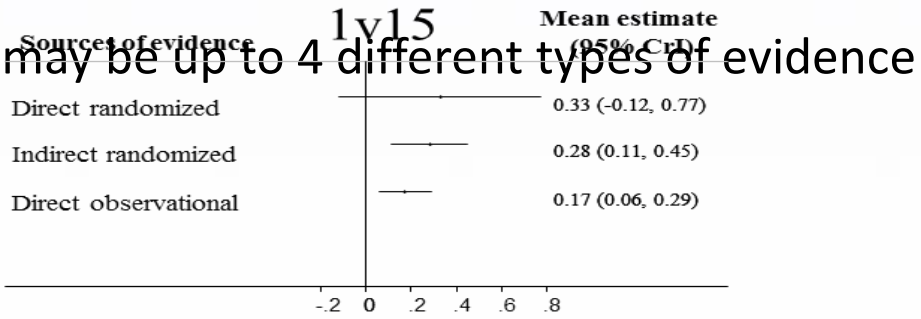
NMA based on RWE (2/4)
Methods

- We first described graphical and statistical methods for assessing the **compatibility** between the various sources of evidence
- For each treatment comparison there may be up to 4 different types of evidence
  - ✓ Direct randomized
  - ✓ Indirect randomized
  - ✓ Direct observational
  - ✓ Indirect observational



- Important differences between the various sources might be indicators of biases and need to be explored

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NMA based on RWE (3/4)

Methods

- We then presented and compared an **array of alternative methods** that allow the inclusion of observational studies in an NMA of RCTs:
  - ✓ the naïve data synthesis
  - ✓ the design-adjusted synthesis
  - ✓ the use of observational evidence as prior information
  - ✓ 3 alternative three-level hierarchical models.

- We discussed in depth:
  - ✓ The **assumptions** underlying each approach
  - ✓ The **challenges** associated to each approach and how to overcome them
  - ✓ Which method is **preferable** to use under different scenarios of data availability

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NMA based on RWE (4/4)

Findings

- Findings from the case study suggest that the inclusion of RW evidence from NRSs can **corroborate findings** of an NMA based on RCTs alone, **increase precision** and **enhance the decision-making process.**
- The choice between the various approaches can be driven by considerations related to data availability and also the resources and the technical expertise available in the research team
- Whatever method researchers choose to use in a future NMA they should bear in mind that possible biases introduced by including observational studies in an NMA are difficult to predict, both in magnitude and direction
- Thus, a **sensitivity analysis** is an indispensable part of any endeavor to jointly synthesize randomized and non-randomized evidence

Combining randomized and non-randomized evidence in a network meta-analysis, Efthimiou O., Debray T.P.A., Samara M, Leucht S.,Belger M., Mavridis D. and Salanti G.

Predictive Modelling (1/5)

Research task

Set up a mathematical model that allows to predict the real-world effect of a new biologic treatment in patients with *Rheumatoid Arthritis* (RA) if…

- **only RCT data on the new treatment and …**
- **no observational data on the new treatment, but …**
- **observational data on an existing similar treatment …**

are available?

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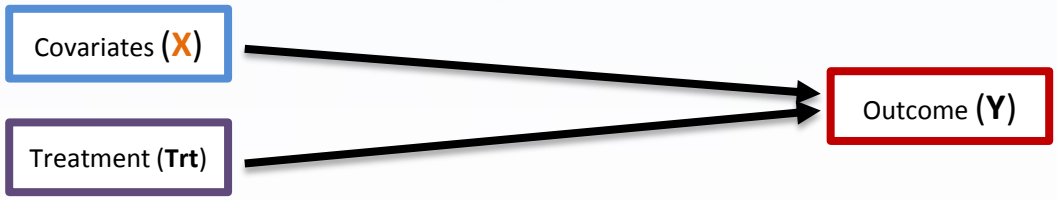
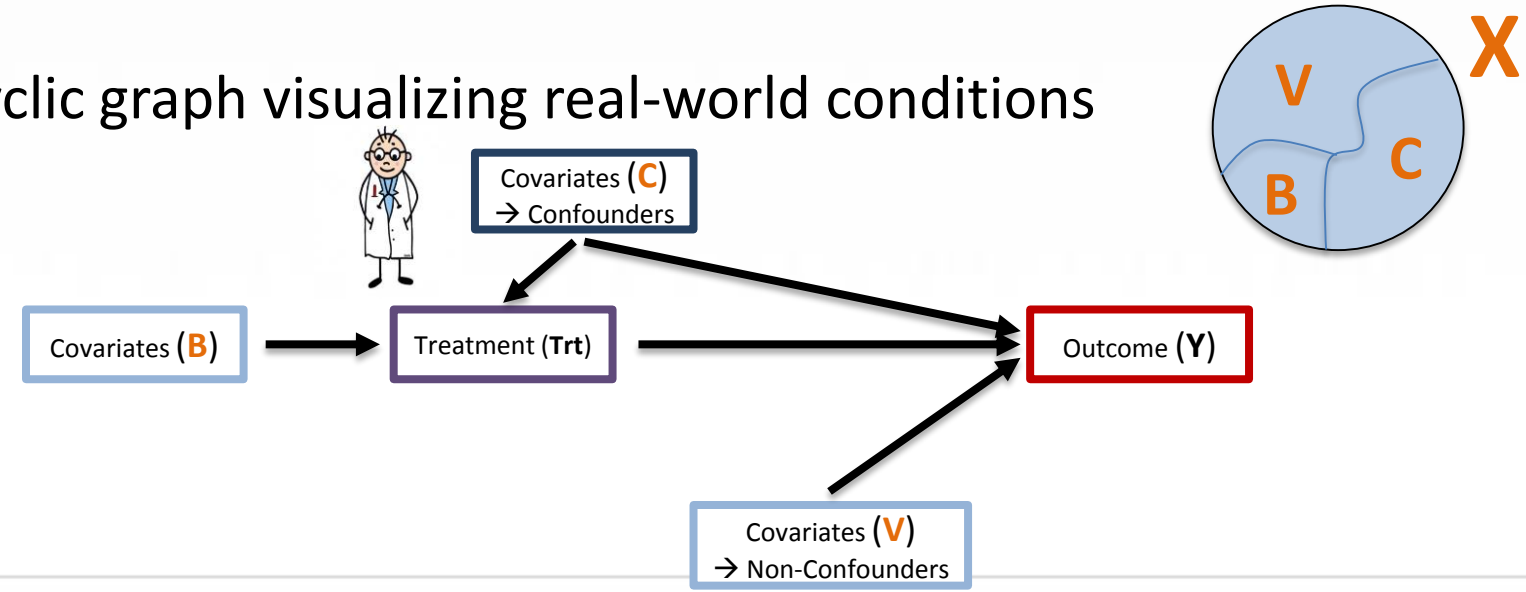
Predictive Modelling (2/5)

RCT vs. real-world conditions: graphical overview

- Acyclic graph visualizing RCT conditions



- Acyclic graph visualizing real-world conditions



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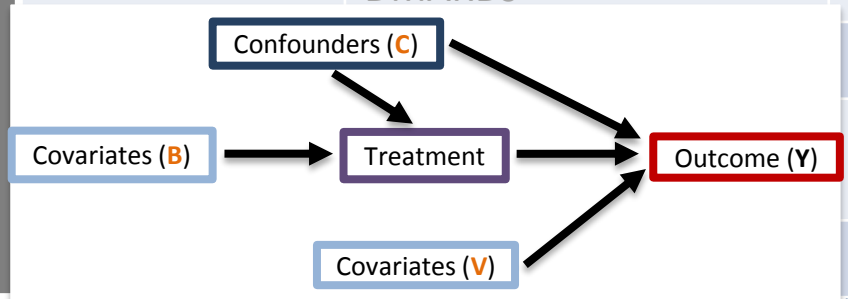
Predictive Modelling (3/5)

Case study on Rheumatoid Arthritis (RA): Variable selection

Outcome: Change in	RCT DATA Covariates X	OBSERVATIONAL/REGISTRY DATA Covariates B	Covariates V	Confounders C	Expert (RA)
DAS28	gender	calendar year	**BMI/obesity**	**age**	
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 selec-ted
				…..	



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Predictive Modelling (4/5)

Modelling concept

1. Use a model that allows to adjust for confounders, and …
   - include RCT-based prior knowledge on the effect of the new treatment
   - adopt an appropriate variable classification & selection scheme from previous observational studies to predict treatment decision

Data availability:

- **RCT data on the new treatment**
- **no observational data on the new treatment**
- **observational data on an existing similar treatment**

2. Predict the effect of the new treatment for a new real-world population

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Predictive Modelling (5/5)
Discussion

- Pro's of the proposed predictive modelling approach
  - Outperformance of comparable approaches that do not consider confounders
  - Inclusion of prior knowledge, possibly gained from multiple data sources
  - Logical soundness, clear structure and technical validity
  - Flexibility and extendability

- Work in progress
  - Inclusion of results from our network meta-analyses on IPD and AD
  - Inclusion of insights from a wider range of RCTs and observational studies (IPD and/or AD)
  - Consideration of dynamic treatment regimes with time-varying confounders and censoring information

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