Get Real

Real-Life Data in Drug Development

Evidence Synthesis and Predictive Modelling of Relative Effectiveness – Paving the Way to Best Practice

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WP4

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.
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Agenda

- Key questions we're addressing
- Tackling the problem: methods reviews, case studies, ADDIS software
- Guidance and best practice recommendations

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Key questions we're addressing

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Questions	Outcomes	Applicability	Data sources	Evidence synthesis	Conditions
1) How efficacious and safe is this drug?	Efficacy, safety	Typical patients included in clinical trials	Phase II/III randomised clinical trials	Clinical trials, standard meta-analysis	Study conditions
2) How efficacious and safe is this drug compared to alternative therapies?	Relative efficacy, relative safety	Typical patients included in clinical trials	Phase II/III randomised clinical trials	Network meta-analysis	Study conditions
3) How effective and safe is this drug compared to alternative therapies, in the patients who will likely receive it post-launch?	Relative effectiveness, relative safety in predicted study populations	Patients predicted to receive the drug post-launch	Phase II/III randomised clinical trials, clinical databases and registries	Individual patient data (IPD) network meta-analysis and meta-regression	Study conditions
4) How effective and safe is this drug compared to alternative therapies, in the patients who will likely receive it in the real world of a health care system?	Relative effectiveness, relative safety in predicted real world populations	Patients predicted to receive the drug post-launch in a given health care system	Phase II/III randomised clinical trials, clinical databases and registries, expert opinion, patient preferences	Mathematical modelling	Real world conditions

Egger, Fletcher, Moons. JRSM 2016

Tackling the problem: methods reviews, case studies and software tool

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Methods reviews

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

- ✓ network meta-analysis (NMA)
- ✓ individual participant data (IPD) meta-analysis
- ✓ 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 are published in Research Synthesis Methods.

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Case studies

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 network 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 modelling to predict real-world effectiveness using RCT and observational data.

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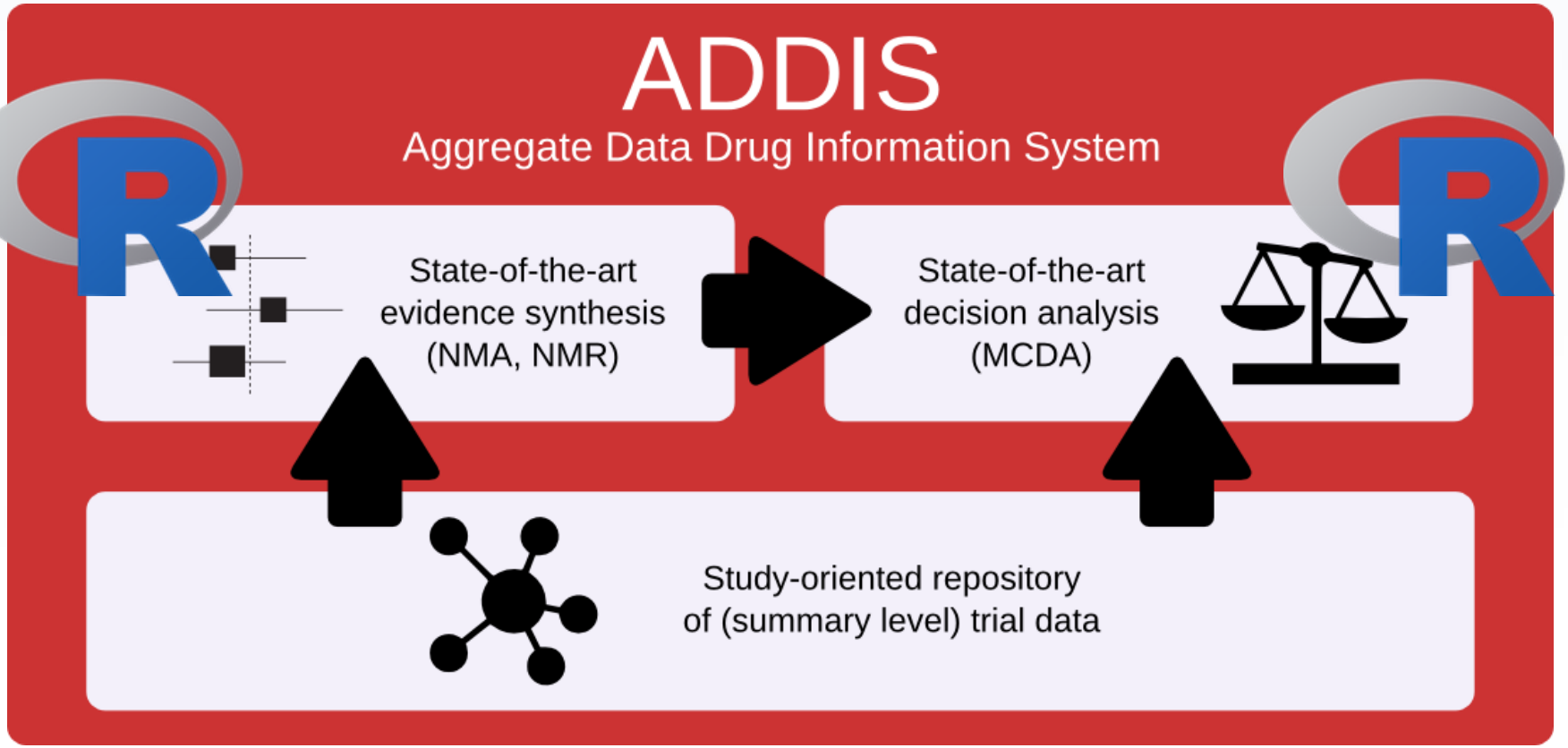
ADDIS software platform



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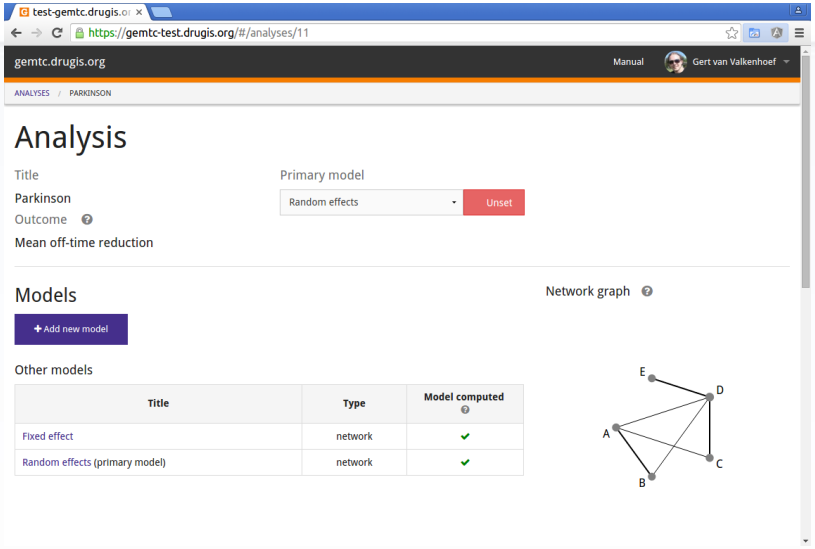

- Evidence synthesis:
  - Network meta-analysis
  - Network meta-regression
  - Down-weighting observational data
- Web-based user interface
- Analysis code:
  - All analyses built as R packages
  - Models based on established best practice (NICE DSU, MDM guidance)
  - Additional code provided in WP4 publications

Make your own experience with ADDIS:
12:30-14:00 at the WP4 stand

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Guidance and best practice recommendations

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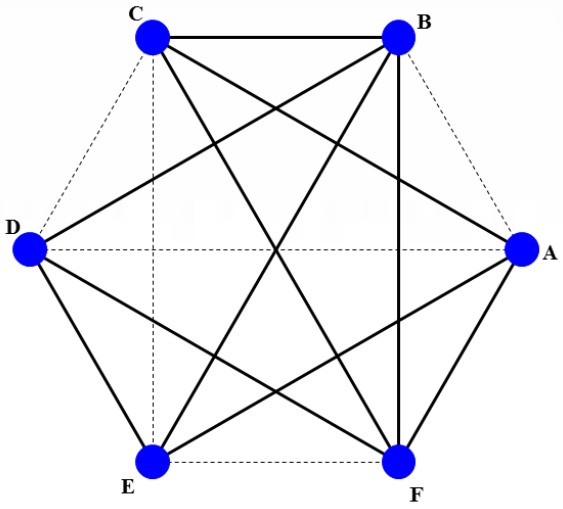
Guidance from methods reviews

- Get Real in NMA: A review of the methodology
  - Presentation of the advantages and limitations of alternative approaches
  - Discussion of methods to assess the validity of the underlying assumptions
  - Summary of technical details on NMA, accounting for the risk of bias, multiple outcomes and repeated measures, defining the number of nodes, etc.
  - Collection of software tools for fitting an NMA



Efthimiou et al. *GetReal in network meta-analysis: a review of the methodology*. Res Synth Methods. 2016

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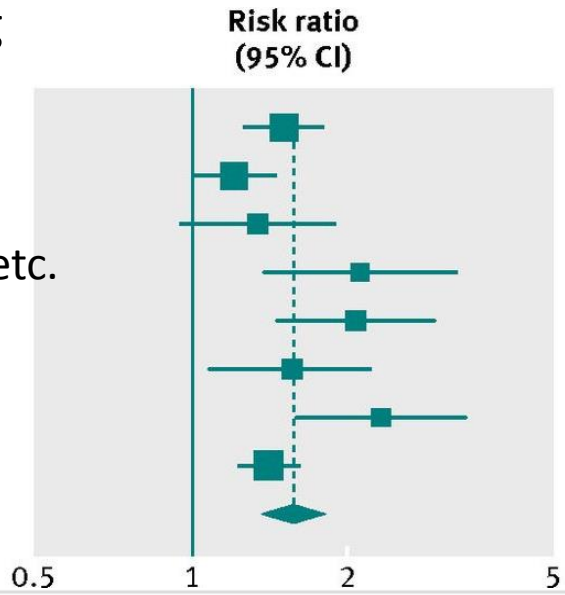
Guidance from methods reviews

- GetReal in meta-analysis of IPD: A review of the methodology
  - Outline of the advantages and limitations of existing approaches for IPD-MA
  - Description of statistical methods and underlying assumptions
    - investigating heterogeneity of treatment effect,
    - combining IPD and published aggregate data,
    - including evidence from non-randomized studies etc.
  - Overview of existing software, including example code in R



Debray et al. *Get real in individual participant data (IPD) meta-analysis: a review of the methodology*. Res Synth Methods. 2015

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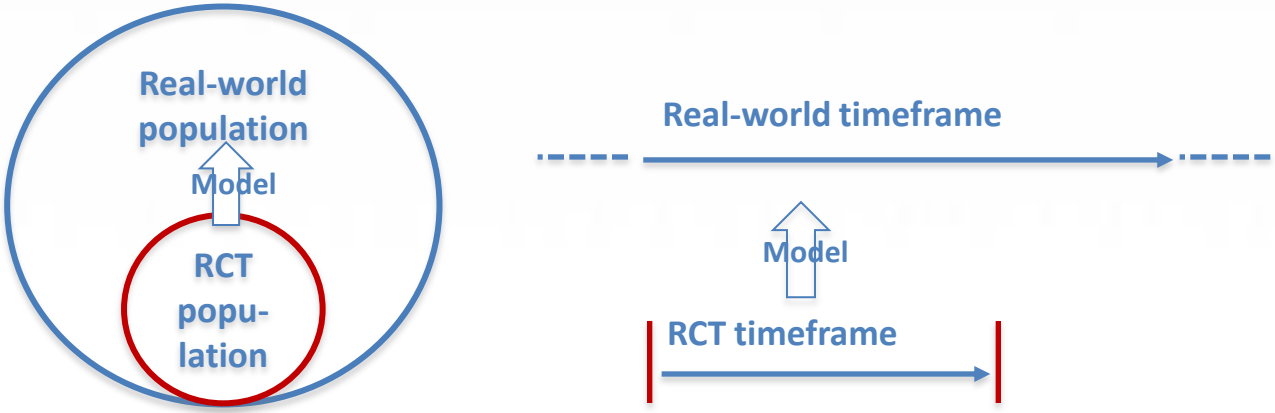
Guidance from methods reviews

- GetReal in mathematical modelling: A review of studies predicting drug effectiveness in the real world
  - 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 (only 12 articles identified), and are not well validated.



Panayidou et al. *GetReal in mathematical modelling: a review of studies predicting drug effectiveness in the real world*. Res Synth Methods. 2016

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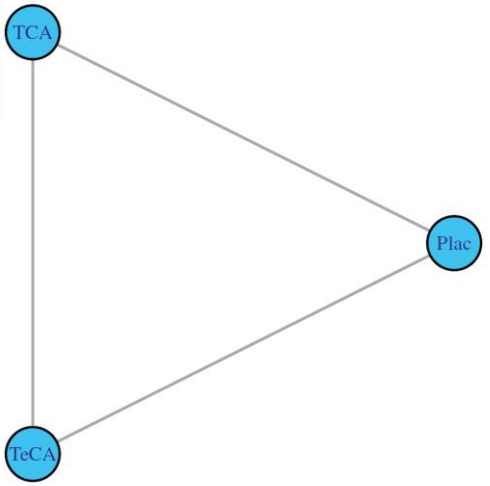
Recommendations for NMA

- NMA including IPD from RCT
  - Start with 2-stage NMA
  - Tailoring of NMA model to avoid heterogeneity and network inconsistency, pre-specify design choices in protocol
  - Sensitivity analyses to understand impact of modelling assumptions
  - When to include IPD?
  - Prioritization of IPD retrieval



Debray et al. *An overview of methods for network meta-analysis using individual participant data: when do benefits arise?* Stat Methods Med Res 2016

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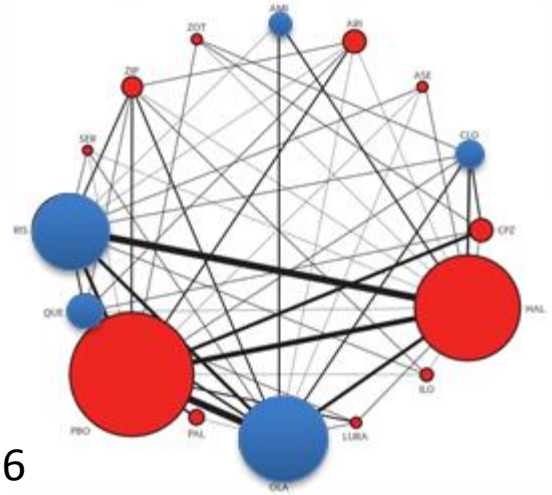
Recommendations for NMA

- NMA including RWE
  - Adjusting estimates from NRS to minimize risk of bias
  - Comparing evidence from RCT and NRS: analyze RCT and RWE separately
  - Choice of appropriate method, describe method choice in the protocol
  - Sensitivity analyses to assess impact of possible biases in NRS
  - When to include RWE?



Efthimiou et al. *Combining randomized and non-randomized evidence in network meta-analysis.* submitted in Stat Med 2016

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Recommendations for predictive modelling

- Incorporate **expert opinion**
  - when selecting prognostic factors, effect modifiers and treatment predictors
  - when choosing appropriate outcome measures
  - when defining “drug similarity” and identifying an appropriate “similar” treatment
- Perform **internal validation** and **sensitivity analyses** to check robustness of modelling choices and to fully appraise their potential usefulness
- Modelling to predict effectiveness **most suitable** for:
  - exploratory analyses, e.g. to decide whether to conduct Ph III/IV trials
  - early HTA: What effect do we need to find to support the development of a new drug?

Didden et al. *Prediction of Real-World Treatment Effectiveness based on Randomized and Observational Evidence*. In preparation 2016

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THANK YOU

to all the WP4 members who made the project a huge success!!

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