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

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WP4

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Agenda

• Key questions we’re addressing
• Tackling the problem: methods reviews, case studies, ADDIS software
• Guidance and best practice recommendations
Key questions we’re addressing
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<td>2) How efficacious and safe is this drug compared to alternative therapies?</td>
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Tackling the problem: methods reviews, case studies and software tool
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.*
Case studies

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

• Case study:抑郁症(Utrecht), to explore methods for the network meta-analysis of individual patient-level data.

• Case study:精神分裂症(Ioannina) to extend methods for a joint network meta-analysis of RCTs and observational data.

• Case study:类风湿关节炎(Bern), to explore methods on modelling to predict real-world effectiveness using RCT and observational data.
ADDIS software platform

ADDIS
Aggregate Data Drug Information System

State-of-the-art evidence synthesis (NMA, NMR) → State-of-the-art decision analysis (MCDA)

Study-oriented repository of (summary level) trial data

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ADDIS software platform

• 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
Guidance and best practice recommendations
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

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

• 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.

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

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?

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?

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