Bridging efficacy to effectiveness: The IMI GetReal project

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Co-leads WP4 (Evidence synthesis and predicting effectiveness)
Disclaimer (Chrissie Fletcher)

- The views expressed herein represent those of the presenter and do not necessarily represent the views or practices of Amgen or the views of the general Pharmaceutical Industry.
Innovative Medicines Initiative: Joining Forces in the Healthcare Sector
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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Nat Med 2014;20:5.
Background: GetReal

CRITICAL QUESTIONS REQUIRING JOINT APPROACH

- What combination of possible studies will provide the most valuable information to customers controlling access - in order to maximise the probability of positive access outcomes?
- What is the cost and feasibility of the study options pre-launch and what would be required as commitments post launch?
- How do options reconcile with the regulatory process?

- With all the available data, would we predict an improvement in patient outcome or care pathway efficiency over and above current practice in my healthcare system - with a reasonable level of certainty?
- Would we accept the uncertainty for a period of time while waiting for studies to complete or for new studies to be run?
Background: GetReal

CRITICAL QUESTIONS REQUIRING JOINT APPROACH

<table>
<thead>
<tr>
<th>Phase 3a</th>
<th>Phase 3b</th>
<th>Conditional Licensing</th>
<th>Conditional Access</th>
<th>Phase IV</th>
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<tbody>
<tr>
<td>“optimise”</td>
<td>“supplement”</td>
<td>?</td>
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<td>“commit”</td>
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In recent years there has been considerable attention paid to the post-authorisation evaluation of treatments in real world clinical practice in areas such as study design and data-analytical methodology for assessing relative effectiveness and use of registries and electronic healthcare records data.

It may be possible to improve the relevance and value (in terms of predicting effectiveness) of evidence available at initial market authorisation by incorporating these techniques into pre-authorisation drug development.
GetReal: Project Vision

For pharmaceutical R&D and healthcare decision makers to better understand how real-world data and analytical techniques can be used to improve the relevance of knowledge generated during development, e.g., through innovation in clinical trial design. This can contribute to the knowledge base, particularly to inform clinical decision making and improve the efficiency of the R&D process.

Lasting impact of the project

To provide a methodological and analytical framework that informs policy and process evolution beyond the life of the project and at an international level; and to provide tools, techniques and training that ensure that the potential of real world data can be exploited in drug development.
Architecture of GetReal

Developing a framework for the assessment of development strategies addressing relative effectiveness objectives

Value of Registration RCTs & IIIb study designs informing RE at launch

Operational aspects of conducting RE research pre-launch

Evidence synthesis and modelling

Project management, Governance, Dissemination

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WP1: Case study approach
Development strategy redesign workshops

**Information Sources**
- Publicly available documents (reg, HTA)
- Stakeholder interviews
- Company commentaries & presentations
- Original company source documents

**Workshop 1 Outputs**
- Discussion summary / minutes
- Key scientific questions (sources of bias and uncertainty in REff)
- Alternative development design options

**Workshop 2 Outputs**
- Discussion summary / minutes
- Stakeholder insight & reactions to potential options
- Scenario Summary
- Contribute to decision framework
- Publications

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WP 2: better understand the gap (drivers) between efficacy & effectiveness

Clinical trials (efficacy)

Real world (effectiveness)
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## Examples of WP2 activities

<table>
<thead>
<tr>
<th>Identification of Drivers of Effectiveness</th>
<th>Assessment of design parameters and analytical tools to better anticipate effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy to Effectiveness gaps (Literature review → Publication)</td>
<td>Phase 2/3 trials that tried to address effectiveness (Literature review)</td>
</tr>
<tr>
<td>Exploring case studies in Schizophrenia, Anti-hypertensives, Hogkins Lymphoma,</td>
<td>Use of simulation studies to assess analytical tools used in different types of trials (e.g. pre and post launch clinical trials, observational studies, pragmatics trials)</td>
</tr>
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</table>
WP3: overcoming practical barriers in undertaking pre-launch RE research.

“In an increasingly complex world, sometimes old questions require new answers.”

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WP3 focus on peri-launch relative effectiveness studies and pragmatic trial designs

**Aim:**
- Identify operational challenges (per design feature)
- Analyse impact on practical feasibility of PT, acceptability, generalizability and bias
- Offer solutions for operational challenges (where possible)

**Help PT designers to be aware of consequences of their choices & maximize the pragmatic nature of the study design while ensuring operational feasibility**

**Key activities:**
- Literature reviews & stakeholder interviews to identify operational challenges
- Create a structure which describes & links design features – operational challenges – implications & interrelationships in a usable way
- Develop practical solutions to specific operational challenges
- Create a toolbox which brings all knowledge together

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WP4: Promote best practice in evidence synthesis and predictive modelling
WP4 Developing a predictive model for relative effectiveness

Flow of work

Internal validity

- RCTs (phase II)
- RCTs (phase III)
- Pragmatic RCTs
- Cohort studies

External validity

- Clinical databases

Assessment of studies and re-analysis where applicable

Network meta-analysis and meta-regression analysis

Statistical package

Mathematical simulation model

Incidence and prevalence data

Guidance and recommendations

Activities

1) Identify suitable case-studies

2) Assess patient characteristics and risk of bias

3) Re-analyze individual patient data if available

4) Obtain best estimates of RE for different patient groups

5) Predict RE and absolute benefits and harms in different patient groups

6) Develop user-friendly software

7) Develop guidance and recommendations

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WP4 Best practices in evidence synthesis and predictive modelling

Evidence synthesis and mathematical modelling for assessing treatment effects across populations: current practice and recommendations

GetReal methods review group

Mark Belger¹, Silvie Bozzi², Maximo Carreras³, Thomas Debray⁴, Orestis Efthimiou⁵, Matthias Egger⁵⁺, Christine Fletcher⁷, Roif H. H. Groenwold⁸, Sandro Gsteiger⁹, Noemi Hummel⁹, Gablu Kilcher⁹, Brice Kitio-Dschassi², Amr Makady⁹, Brigitta Monz⁹, Karel G.M. Moons⁴, Klea Panayidou⁶, Johannes B. Reitsma⁴, Georgia Salanti⁵, Aijing Shang³, Sven Trelle⁶, Gert van Valkenhoef¹⁰

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WP4 have generated 3 publications of best practices in evidence synthesis and predictive modelling.

Methods for network meta-analysis: a systematic review

Orestis Eftimiou¹, Thomas P. A. Debray², Gert van Valkenhoef³, Sven Trelle⁴, Klea Panayidou⁵, Karel G. M. Moons², Johannes B. Reitsma¹, Aijing Shang⁶, and Georgia Salanti¹ on behalf of GetReal methods review group

Methods for Individual Participant Data meta-analysis of relative treatment effects: a systematic review

Thomas P. A. Debray¹, Rolf H. H. Groenwold¹, Gert van Valkenhoef³, Orestis Eftimiou³, Noemi Hummel¹, Karel G. M. Moons¹, Johannes B. Reitsma¹ on behalf of GetReal methods review group

1 accepted and 2 under review with Research Synthesis Methods

Mathematical modelling for predicting real world effectiveness from RCT efficacy data: a systematic review

Klea Panayidou¹, Sandro Gsteiger¹, Gablu Kilcher¹, Matthias Egger¹, Maximo Carreras², Orestis Eftimiou³, Thomas Debray⁴, Sven Trelle⁵, Noemi Hummel¹ on behalf of the GetReal methods review group
Examples of methodology being explored in WP4 case studies – evidence synthesis

**IPD network meta-analysis: one-stage or two-stage?**

Thomas Debray, Ewoud Schuit, Orestis Efthimiou, Jeroen Jansen, John Ioannidis, Karel Moons on behalf of the IMI Getreal Consortium

**Background:** Individual participant data meta-analysis (IPD-MA) can be conducted to compare the relative efficacy of multiple treatments. It is currently unclear whether a so-called one-stage or two-stage approach is preferred, and which type of model should be implemented.

**Methods:** We describe and compare 3 approaches for IPD-MA of multiple treatments: a one-stage network meta-analysis (NMA) approach, a two-stage NMA approach using arm-level evidence and a two-stage NMA approach using trial-level evidence.
Examples of methodology being explored in WP4 case studies – evidence synthesis (cont.)

• To **jointly synthesize** evidence on **relative treatment effects** coming from RCTs as well as observational studies.

• For this we will **assess existing methodology and develop new methods** for combining IPD and AD from randomized trials as well as IPD from observational studies in a network meta-analysis (NMA).
Examples of methodology being explored in WP4 case studies – predictive modelling

- Assessment and description of possible efficacy-effectiveness gaps, i.e. differences in the outcomes observed in clinical practice as compared to randomized controlled trials (RCTs)
- Combination of results from different study and data types, and use of mathematical modelling to predict real-world effectiveness
  - generalization of results from RCTs
  - description and prediction of treatment effects in particular subgroups of patients that may be non- or under-represented in RCTs

Real world RA population

Real world timeframe

RCT RA population

RCT timeframe

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Examples of methodology being explored in WP4 case studies – predictive modelling (cont.)

• Approaches identified in systematic review
  – Micro-simulation model
  – Discrete event simulation model

• «Simple» prediction models, using
  – covariate-by-treatment interactions from RCTs, and
  – differences in covariate distributions in RCTs vs. observational studies, to derive treatment effect estimates in real-world population

• Bayesian hierarchical meta-regression model
  – Combine all available evidence in one model: observational and RCT, AD and IPD
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WP4 review of evidence synthesis and predictive modelling software

Meta-analysis statistical packages:
1. GeMTC R package http://cran.r-project.org/web/packages/gemtc/index.html
2. pcnetmeta R package http://cran.r-project.org/web/packages/pcnetmeta/index.html
3. netmeta R package http://cran.r-project.org/web/packages/netmeta/index.html
4. copas R package http://cran.r-project.org/web/packages/copas/index.html
5. meta R package http://cran.r-project.org/web/packages/meta/index.html
6. metafor R package http://cran.r-project.org/web/packages/metafor/index.html
7. metaLik R package http://cran.r-project.org/web/packages/metaLik/index.html
8. rmeta R package http://cran.r-project.org/web/packages/rmeta/index.html
9. bspmma R package http://cran.r-project.org/web/packages/bspmma/index.html
10. metamisc R package http://cran.r-project.org/web/packages/metamisc/index.html
11. mmeta R package http://cran.r-project.org/web/packages/mmeta/index.html
12. metaest R package http://cran.r-project.org/web/packages/metaest/index.html
13. metagen R package http://cran.r-project.org/web/packages/metagen/index.html
14. PubBias R package http://cran.r-project.org/web/packages/PubBias/index.html
15. selectMeta R package http://cran.r-project.org/web/packages/selectMeta/index.html
16. SAMURAI R package http://cran.r-project.org/web/packages/SAMURAI/index.html
17. extfunnel R package http://cran.r-project.org/web/packages/extfunnel/index.html
18. mvmeta R package http://cran.r-project.org/web/packages/mvmeta/index.html
19. mvmeta R package http://cran.r-project.org/web/packages/mvmeta/index.html
20. metaSEM R package http://r-forge.r-project.org/projects/metasem/
21. dosresmeta R package http://cran.r-project.org/web/packages/dosresmeta/index.html
22. robustmeta R package http://cran.r-project.org/web/packages/robustmeta/index.html
23. Gmisc R package http://cran.r-project.org/web/packages/Gmisc/index.html
24. ipdmeta R package http://cran.r-project.org/web/packages/ipdmeta/index.html

Meta-analysis user interfaces:
1. ADDIS 1.x http://drugis.org/software/addis1/
2. RevMan http://tech.cochrane.org/Revman
4. OpenMetaAnalyst http://www.cebm.brown.edu/open_meta
6. MIX http://www.meta-analysis-made-easy.com/
7. MetaEasy http://www.jstatsoft.org/v30/i07
WP4 review of evidence synthesis and predictive modelling software

Predictive modeling user interfaces:
1. SIMUL8 http://www.simul8.com/
2. EMMA https://simtk.org/home/emma
3. TreeAge https://www.treeage.com/
6. Microsoft Excel

Predictive modeling statistical packages:
1. genSurv R package http://cran.r-project.org/web/packages/genSurv/index.html
2. PermAlgo R package http://cran.r-project.org/web/packages/PermAlgo/index.html
4. prodlim R package http://cran.r-project.org/web/packages/prodlim/index.html
5. gems R package http://cran.r-project.org/web/packages/gems/index.html
6. simMSM R package http://cran.r-project.org/web/packages/simMSM/index.html
7. simPH R package http://cran.r-project.org/web/packages/simPH/index.html
8. survsim R package http://cran.r-project.org/web/packages/survsim/index.html
9. msm R package http://cran.r-project.org/web/packages/msm/index.html
10. etm R package http://www.jstatsoft.org/v38/i04
11. Epi R package http://www.jstatsoft.org/v38/i06
12. mstate R package http://www.jstatsoft.org/v38/i07
13. timereg R package http://www.jstatsoft.org/v38/i02
14. mhsmm R package http://www.jstatsoft.org/v39/i04
15. ggm R package http://www.jstatsoft.org/v15/i06

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### Key deliverables for GetReal

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<th>Deliverable</th>
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<tr>
<td>A decision-making framework to aid the design of drug development strategies. This will lay out the different study design options and associated pros and cons from key stakeholder perspectives including acceptability in evidence review processes.</td>
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<tr>
<td>Recommendations will be made for regulatory and HTA policy development.</td>
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<tr>
<td>Guidance and publications on methodologies for conducting and analysing relative effectiveness research pre-authorisation</td>
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<tr>
<td>Guidance and publications on methodologies for using EHR in conducting studies pre-authorisation</td>
</tr>
<tr>
<td>Guidance, publications and practical tools and templates to address operational, statistical and ethical issues in conducting pragmatic/adaptive designs pre-authorisation</td>
</tr>
<tr>
<td>Guidance and publications on methodologies for conducting data synthesis integrating a wide range of source studies of different types</td>
</tr>
<tr>
<td>Software for conducting data synthesis integrating a wide range of source studies of different types</td>
</tr>
<tr>
<td>Training and education resources</td>
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Lessons Learned

• It takes time to build relationships and select appropriate case studies
• Case study selection: be specific on diseases or drug class before consortium starts
• Be clear on roles and responsibilities
• Start External Communications at very start of project
• Make better use of governance structure
Conclusions

• GetReal aims to deliver a framework for decision making developed jointly by Regulatory, HTA and Industry experts

• GetReal aims to provide practical solutions to enable implementation of studies with greater value of information for relative effectiveness assessment

• GetReal will utilise recent advances in methodology to reliably predict effectiveness from available data sources

• GetReal aims to align innovation in evidence generation with evolution of regulatory and HTA processes
For more information:

• Visit the GetReal website:
  imi-getreal.eu

Welcome to the GetReal Website!

Launched in October 2013, GetReal is a three-year project of the Innovative Medicines Initiative (IMI), a EU public-private consortium consisting of pharmaceutical companies, academia, HTA agencies and regulators (e.g., NICE, HAS, EMA and ZIN), patient organisations and SMEs.

GetReal aims to show how robust new methods of RWE collection and synthesis could be adopted earlier in pharmaceutical R&D and the healthcare decision making process. The consortium is doing this by:

- Bringing together healthcare decision makers, academics, pharmaceutical companies, clinicians, and other societal stakeholders;
- Assessing existing processes, methodologies, and key research issues;
- Proposing innovative trial designs and assessing the value of information;
- Proposing and testing innovative analytical and predictive modelling approaches;
- Assessing operational challenges and proposing and testing the impact of solutions;
- Creating new decision making support, and building tools to allow for the evaluation of development programmes and use in the assessment of the value of introducing new treatments;
- Sharing and discussing deliverables with healthcare decision makers, academics, pharmaceutical companies, clinicians, and other societal stakeholders;