WP1: Towards a framework for guiding evidence generation strategies to support evaluation of relative effectiveness of new drugs

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on behalf of Work Package 1 of GetReal
RELEVANCE OF RELATIVE EFFECTIVENESS FOR DECISION MAKERS

Sarah Garner
Effectiveness: The ‘Fourth Hurdle’
Data Paradigms: The Big Picture

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no 115546, 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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3.3 Types of evidence

Non-randomised and non-controlled evidence

3.3.4 The problems of confounding, lack of blinding, incomplete follow-up and lack of a clear denominator and end point occur more commonly in non-randomised studies and non-controlled trials than in RCTs.

3.3.5 Observational (or epidemiological) studies do not apply an intervention, but instead compare outcomes for people who use the technology under appraisal with outcomes for people who do not use the technology. These studies may be biased in that the people who use the technology may fundamentally differ in their risk of the outcome than the people who do not use the technology. Some observational studies lack a control group, and include only people who receive the technology.

3.3.6 Inferences will necessarily be more circumspect about relative treatment effects drawn from studies without randomisation or control than those from RCTs. The potential biases of observational studies should be identified, and ideally quantified and adjusted for. When possible, more than 1 independent source of such evidence should be examined to gain some insight into the validity of any conclusions.

3.3.7 Evidence from sources other than RCTs is also often used for parameters such as the valuation of health effects over time into QALYs, and for costs. Study quality can vary, and so systematic review methods, critical appraisal and sensitivity analyses are as important for review of these data as they are for reviews of data on relative treatment effects from RCTs.
Potential uses of RWE at NICE

- **Research the effectiveness of interventions or practice** in real-world (UK) settings (e.g. through monitoring outcomes or proxy outcomes).
  - Inform the modelling of clinical and/or cost effectiveness as part of guidance production.
  - Resolve uncertainties that have been identified in existing NICE guidance.

- **Provide epidemiologic information.**
  - For example prevalence/incidence of diseases, natural history, co-morbidities.

- **Provide information on current practice and resource use**

- **Audit the implementation of guidance.**
  - For example, to assess the equity of implementation across different groups (including socioeconomic, geographic, demographic and groups differentiated by different diseases/health conditions); this may also form part of performance monitoring systems.

- **Evaluate the potential impact of guidance**
## Recent NICE appraisals

<table>
<thead>
<tr>
<th>TA</th>
<th>Description</th>
<th>Observational data used</th>
</tr>
</thead>
<tbody>
<tr>
<td>TA 232</td>
<td>Retigabine for the adjunctive treatment of partial onset seizures in epilepsy.</td>
<td>Clinical trials mandated forced (protocol-driven) titration rather than titration tailored to individual patient as is seen in practice.</td>
</tr>
<tr>
<td>TA278</td>
<td>Omalizumab for treating severe persistent allergic asthma (review of TA 133 and 201).</td>
<td>Observational data used for extrapolation of treatment effect and for HRQoL in children amongst other things.</td>
</tr>
<tr>
<td>TA279</td>
<td>Vertebral fractures – Vertebroplasty and kyphoplasty</td>
<td>Observational data used by committee to accept mortality benefit (however committee could not use the data to quantify it).</td>
</tr>
<tr>
<td>TA283</td>
<td>Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion</td>
<td>Observational data used by committee to assess safety compared with unlicensed bevacizumab, however committee stopped short of using it for cost-effectiveness analysis.</td>
</tr>
</tbody>
</table>
Use of non-RCT data for estimating clinical efficacy in modelling

<table>
<thead>
<tr>
<th>TA</th>
<th>Disease/Condition</th>
<th>Data Source Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TA151</td>
<td>Diabetes – Insulin pumps</td>
<td>Clinical efficacy from a registry – Insulin Pumps Clinical database - much larger, of longer duration and more representative of people likely to be considered for CSII therapy in routine clinical practice than the populations in the RCTs available</td>
</tr>
<tr>
<td>TA165</td>
<td>Organ preservation (renal) - machine perfusion and static storage</td>
<td>Prospective cohort study and multi-national registry study used for efficacy in model</td>
</tr>
<tr>
<td>TA166</td>
<td>Hearing impairment - cochlear implants</td>
<td>Baseline risk of operative mortality in model, other parameters in modelling as judged most appropriate source</td>
</tr>
<tr>
<td>TA185</td>
<td>Soft tissue sarcoma – trabectedin</td>
<td>Three uncontrolled phase II trials of trabectedin</td>
</tr>
<tr>
<td>TA188</td>
<td>Human growth hormone (somatropin) for the treatment of growth failure in children (review)</td>
<td>Kabi International Growth (KIGS) observational database</td>
</tr>
<tr>
<td>TA202</td>
<td>Chronic lymphocytic leukaemia – ofatumumab</td>
<td>NO RCT- conditional license</td>
</tr>
<tr>
<td>TA209</td>
<td>Gastrointestinal stromal tumours (unresectable/metastatic) – imatinib</td>
<td>One non-randomised retrospective cohort study</td>
</tr>
<tr>
<td>TA241</td>
<td>Leukaemia (chronic myeloid) - dasatinib, nilotinib, imatinib (intolerant, resistant)</td>
<td>Twelve studies were observational (seven of dasatinib, four of nilotinib and one retrospective study of both) three single-arm studies of high-dose imatinib – available RCTs were of poor quality</td>
</tr>
</tbody>
</table>
Appraisals using non-RCT data for some parameters in model

<table>
<thead>
<tr>
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<th>Description</th>
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</tr>
</thead>
<tbody>
<tr>
<td>TA167</td>
<td>Abdominal aortic aneurysm - endovascular stent-grafts</td>
<td>Large registries of relevance to UK practice - baseline risk of operative mortality in model, other parameters in modelling as judged most appropriate source</td>
</tr>
</tbody>
</table>

Appraisals using non-RCT data for longer term effectiveness

<table>
<thead>
<tr>
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<th>Description</th>
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</tr>
</thead>
<tbody>
<tr>
<td>TA177</td>
<td>Eczema (chronic) – alitretinoin</td>
<td></td>
</tr>
<tr>
<td>TA211</td>
<td>Constipation (women) – prucalopride</td>
<td></td>
</tr>
<tr>
<td>TA221</td>
<td>Thrombocytopenic purpura – romiplostim</td>
<td></td>
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<tr>
<td>TA247</td>
<td>Rheumatoid arthritis - tocilizumab (rapid review TA198)</td>
<td></td>
</tr>
<tr>
<td>TA293</td>
<td>Thrombocytopenic purpura – eltrombopag (review)</td>
<td></td>
</tr>
</tbody>
</table>

Other uses of non-RCT data in appraisal

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>TA238</td>
<td>Arthritis (juvenile idiopathic, systemic) – tocilizumab</td>
<td>observational study of 146 patients - adjustment factor - difference in the proportion of responders between the total population with JIA and the subpopulation with systemic JIA. Used to correct for ACR response rates in the indirect comparison</td>
</tr>
</tbody>
</table>
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WP1 Frameworks
Processes
Policies

WP2 Understanding the efficacy-effectiveness gap
- Simulation of trials to improve design

WP3 Overcoming practical barriers to the design of real-world studies

WP4 Identifying best practice and creating new methods for evidence synthesis and predictive modelling

- Standardising terminology
- Interviews to understand and the perspectives and policies of different stakeholders
- Designing a framework for decision-making during development

5 Case studies using drugs that had difficulty at regulation and HTA
- 360 degree reviews
- Re-designing development pathways to include real-world data
- Simulation
- Ascertaining impact on decision makers
Developing a framework for the assessment of development strategies that provide evidence of relative effectiveness

- Develop an agreed glossary of different types of study designs that considers study attributes and suitability for different applications.
- Identify stakeholder policy and perspectives with respect to alternative study designs.
- Identify and engage with other related initiatives, either EU-wide or in individual member states or internationally.
- Predict the impact of the inclusion of alternative study decisions on the decision-making processes of industry, regulators and HTA agencies (case study simulations)
- Support subsequent policy development: develop and pilot a framework for assessing options for the inclusion of non-standard study designs in development strategies
GetReal: Delivering Efficient Fourth Hurdle Solutions

- Shared understanding of the technical and process issues from each perspective
- In-depth exploration of 5 challenging disease areas to highlight the issues
- Exploration of novel methodological solutions
- Compilation of best-practice recommendations
- Future research agenda
- Collaboration and trust
WP1: BRINGING TOGETHER STAKEHOLDER COMMUNITIES TO DISCUSS ACCEPTABILITY OF RWD/RWE
IMI GetReal WP1

Aim
To develop a common understanding amongst healthcare decision makers and pharmaceutical R&D of the acceptability and usefulness of innovative development programmes which use RWE to estimate the effectiveness of new medicines.

Focus
Use of real-world evidence (RWE) in an early setting (before marketing authorisation).

Overall vision
For healthcare decision makers to have relevant evidence to assess effectiveness of new drugs when used in standard practice.

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WP1 case studies: highlighting approaches with real-world data in pharma R&D and evidence synthesis
Case Study Example 1: Stakeholder views on the role and acceptability of **pragmatic trials**

When should early pragmatic clinical trials be considered?

**OBJECTIVE:** Can we identify which effectiveness questions would be regarded by stakeholders as particularly suited to be addressed by early PCTs?

How strongly would results from pragmatic designs be accepted as evidence?

**OBJECTIVE:** Can we identify the factors that influence whether pragmatic trial data would be considered as “strong” or “weak” evidence by decision maker?

How can we maximise the value and acceptability of PCTs?

**OBJECTIVE:** How do we build on positive opportunities to utilise PCTs and address any barriers to acceptability?
Case Study Example 2: RWE combined with RCT data to generate relative effectiveness estimates in NMAs

“Useful as long as the addition of RWE into the NMA does not increase decision uncertainty (HTA)

“Limitations when endpoints change over time (Pharma)

“Need to improve transparency of methodology and ‘user-friendliness’; develop pan-European guidelines (HTA)

“Reservations about how useful this approach would be in a regulatory setting (Reg)

“Has a role in providing confirmatory evidence (Reg)
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Example GetReal Outputs

Original research
- Drivers of effectiveness
- Analytical methods
- Prediction models
- Methodological guidance

Methods
- Detection of bias
- Adjustment of bias
- Aggregate RWD in NMAs
- Individual patient RWD in NMAs

Tools
- Software
- Checklists & templates
- Design options for pragmatic clinical trials

Summaries
- Study types
- Sources of data
- Methods
- Literature reviews

Case studies
- Retrospective analyses of relative effectiveness issues
- Disease area specific issues
- Stakeholder views

*Illustrative examples – not a complete list of GetReal outputs

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Framework Content: Progress

Status:
Ready for format/layout: 36%
The Real-World Evidence Framework

Two main functions:

An educational resource to help find out more in general about the potential use of RWD to support the development of new medicines.

An expert resource to guide users to specific types of analyses or study designs relevant to RWE, many of which have been tested by the GetReal project.
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The GetReal Real-World Evidence Framework: A Resource for Everyone!

- A shared platform addressing the inclusion of alternative study designs in medicine development strategies.

- Reflects stakeholder perspectives as far as possible.

- A comprehensive resource regarding alternative evidence development pathways.

- An index of study designs, data sources and policies relating to real-world evidence.

- Educational resource, clarifying potential effectiveness challenges and identifying potential RWE options.

- Signposts to authoritative resources, tools and policies relevant to real-world evidence.

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For Discussion

• Likely acceptability of RWE – your views?
• Priority areas of methods or policy development?

RWE Framework:
• What is the value of a RE E framework?
• What would you like to see in the framework?
• How might you incorporate the framework into your planning activity within your organisation?
• How can extend this framework to include the patient voice?