Is the goal of universal comparative effectiveness evidence across jurisdictions achievable?

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Issue Panel: Is the goal of universal comparative effectiveness evidence across jurisdictions achievable?

Panelists:

Hans-Georg Eichler, European Medicines Agency
Sarah Garner, UK National Institute for Health and Care Excellence
Rob Thwaites, Takeda Development Centre Europe
Pall Jonsson, UK National Institute for Health and Care Excellence
A recent example....

‘The rate of moderate or severe exacerbations was significantly lower, by 8.4% (95% confidence interval, 1.1 to 15.2)’

Efficacy vs effectiveness

• Patient benefit and harm when the technology is actually applied in everyday practice.
  - Pragmatic clinical trials
  - Observational studies
  - Synthesis

• ‘Dirty’ - a lot of variability and biases

• Patient benefit and harm in experimental and closely monitored research studies, normally RCTs.
• Design minimises bias - high internal validity
• Generalisability questionable
  – restricted entry criteria
  – unrepresentative settings

"Evidence used for decision-making that is not collected in conventional randomized controlled trials (RCTs)" ISPOR
Why the need for change?

**Environment**
- Increasing strength and demands of HTA/payers
- Pressures for earlier access to new medicines of value
- Possibility of more flexible reimbursement and access arrangements
- Rare disease populations more prominent, hard to fit into trial paradigm
- Willingness of regulators to engage

**Data and methods**
- Recognition that data arriving at HTA are sub-optimal, especially the key data on relative effectiveness
- Growing availability (at least in principle) of RWD
- New methods to synthesize data and adjust for bias
- IT infrastructure: new possibilities for data collection and integration

Integrating the requirements of regulators and payers/HTA

<table>
<thead>
<tr>
<th>Current paradigm</th>
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MA = Marketing Authorisation; RCT = randomised controlled trial
Integrating the requirements of regulators and payers/HTA

Current paradigm

Future paradigm?

Assessors
Regulators | Payers
---|---
Assessment Focus
Quality, Safety, Efficacy, Benefit-Risk Profile | Relative Efficacy / Effectiveness, Cost vs Health Benefit, Budget Impact (4th hurdle)
Studies / Data
Emphasis on: RCT, most often placebo-controlled | Active-controlled RCT; Observational studies, Cost-effectiveness/utility analyses, Budget impact analysis

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Towards a new model of evidence generation?

a. Conventional
Prior to licensing all patients in trials
Rapid growth after licensing: most patients not in studies
Some further trials: new indications, risk management

b. Adaptive
Earlier ‘initial’ licence, based on less trial data
Slower growth, but all patients in trials or obs. Studies
Pre-arranged second review, for full licence
Continued surveillance, evidence generation
Possible further cycles of evaluation and label change

IMI GetReal is one project moving the RE debate

Aim
To develop a common understanding of the acceptability and usefulness of innovative development programmes which use real-world evidence (RWE) to estimate the effectiveness of new medicines.

Focus
Use of RWE in an early setting, prior to marketing authorisation or reimbursement.

Overall vision
To provide pharma R&D with guidance on the most appropriate ways for developing evidence of relative effectiveness.

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

Growing list of outputs from GetReal
Demonstrating effectiveness is already part of evidence planning within pharma

*Examples*

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<th>Post-marketing</th>
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<td>• Analyse RWD to assess effectiveness of existing medicines</td>
<td>• Include evidence on use and effectiveness of existing medicines in submissions</td>
<td>• Assess relative effectiveness of our new medicine in claims and EMR database analyses</td>
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<td>• Highlight shortcomings in existing treatments using RWE</td>
<td>• Conduct network meta-analysis to estimate relative efficacy (or effectiveness) of new medicine</td>
<td>• Synthesise studies on relative effectiveness vs competitor medicines</td>
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<td>• Incorporate RWD to estimate cost-effectiveness using economic models</td>
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We can – and may need to – bring new methods of demonstrating effectiveness earlier into development

*Examples*

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<td>• Conduct early epi- and economic modelling</td>
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<tr>
<td>• Use historical cohorts to provide context for single arm clinical studies</td>
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<td>• Greater use of analytics to help design clinical trials</td>
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<td>• Include trial designs that are more “pragmatic”</td>
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<td>• Consider novel techniques to simulate relative effectiveness</td>
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<td>• Seek greater dialogue with regulators and HTA agencies</td>
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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.

www.imi.europa.eu
Convergence of RWD methods and approaches across jurisdictions will impact pharma

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<td>• Encourage dialogue earlier to understand extent of (expected) convergence</td>
<td>• May modify pharma’s pathway for evidence generation</td>
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<td>• Reduce uncertainty in global evidence planning</td>
<td>• scope for introducing some (more) pragmatic elements into Phase 3(a) and 3(b) trials</td>
<td>• May create earlier competitive pressure based on others’ RWE</td>
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To what extent should we push towards convergence of real world methods and policies across jurisdictions?