GetReal: 3 Years on!

BBS Spring Seminar
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Eva-Maria Didden, on behalf of GetReal

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www.imi.europa.eu
GetReal Project – Part of the Innovative Medicines Initiative (IMI)

€711,963,033
Infectious diseases

€214,136,227
Drug discovery

€182,980,698
Brain disorders

€116,880,300
Metabolic disorders

€116,287,312
Drug safety

€78,225,417
Stem cells

€72,710,786
Cancer

€70,310,746
Data management

€37,966,496
Lung diseases

€47,222,763
Vaccines

€49,310,000
Geriatrics

€55,930,958
Biologics

€69,739,527
Inflammatory disorders

€30,601,855
Sustainable chemistry

€37,378,289
Education and training

€14,910,397
Relative effectiveness

€8,118,249
Drug kinetics

€20,482,255
Drug delivery

Source: Innovative Medicines Initiative
To show how/which new methods of real-world evidence (RWE) collection and synthesis could be developed and considered for adoption earlier in

- pharmaceutical R&D
- the healthcare decision making process

- Requires companies, healthcare decision-makers and other stakeholders to work together

- Requires the generation of a consensus on best practice in the use of RWE in regulatory and reimbursement decision-making

- Requires alternative evidence generating strategies
### 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 real-world data (RWD)
- **New methods** to synthesize data and adjust for bias
- **IT infrastructure**: new possibilities for data collection and integration
3 Years of a *Real* Public Private Partnership

**11 Public partners:**
- University Medical Center Utrecht, the Netherlands
- University Medical Center Groningen, the Netherlands
- University of Ioannina, Greece
- University of Bern, Switzerland
- University of Leicester, UK
- University of Manchester, UK
- European Organisation for Research and Treatment of Cancer, Belgium
- Zorginstituut Nederland, the Netherlands
- Haute Autorité de Santé, France
- National Institute for Health and Care Excellence, UK
- European Medicines Agency, UK

**15 EFPIA companies:**
- GlaxoSmithKline
- Amgen
- AstraZeneca
- Bayer
- Boehringer Ingelheim
- Bristol Myers Squibb
- Eli Lilly
- Janssen
- LASER
- Merck Serono
- MSD
- Novartis
- Novo Nordisk
- Roche
- Sanofi
- Takeda

**Patients’ organizations:**
International Alliance of Patients’ Organizations
Through this partnership, GetReal could address a range of RWE issues

- Shared understanding of the technical and process issues from each perspective
- In-depth exploration of different challenging disease areas to highlight the issues
- Exploration of novel methodological solutions
- Compilation of best-practice recommendations
- Future research agenda
- Collaboration and trust
Using RWD is already part of evidence planning within pharma...

**Examples**

**Development**
- Analyse RWD to assess effectiveness of existing medicines
- Highlight shortcomings in existing treatments using RWE
- Incorporate RWD to estimate cost-effectiveness using economic models

**File and launch**
- Include evidence on use and effectiveness of existing medicines in registration package
- Conduct network meta-analysis to estimate relative efficacy (or effectiveness) of new medicine

**Post-marketing**
- Assess relative effectiveness of a new medicine in claims and electronic medical records (EMR) database analyses
- Synthesize studies on relative effectiveness vs competitor medicines
...but evidence generation is evolving and GetReal is a key contributor – and resource

**Examples**

- Plan early – consider adaptive pathways
- Use historical cohorts to provide context for single arm clinical studies
- Greater use of analytics to help design clinical trials
- Include trial designs that are more “pragmatic”
- Consider novel techniques to simulate relative effectiveness
- Seek greater dialogue with regulators and HTA agencies
GetReal Consortium & Work Packages (WPs)

WP1: Assessment of...
- the acceptability and usefulness of real-world evidence (RWE)
- approaches to the analyses of RWE
  ...in collaboration with key stakeholders

WP2: Test the scientific validity of RWE study designs
- Explore analytical approaches
  ...to better inform pharmaceutical researchers and healthcare decision makers

WP3: Identify the operational challenges and develop practical solutions
  ...to better inform the planning and delivery of RWE studies early in the medicine development process

WP4: Develop best practices for evidence synthesis and prediction modelling
- Provide user-friendly guidelines and an evidence synthesis software platform

WP5: Consortium Project Management
## Example: Questions Tackled by WP4

<table>
<thead>
<tr>
<th>Questions</th>
<th>Outcomes</th>
<th>Applicability</th>
<th>Data sources</th>
<th>Evidence synthesis</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) How efficacious and safe is this drug?</td>
<td>Efficacy, safety</td>
<td>Typical patients included in clinical trials</td>
<td>Phase II/III randomised clinical trials</td>
<td>Clinical trials, standard meta-analysis</td>
<td>Study conditions</td>
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<tr>
<td>2) How efficacious and safe is this drug compared to alternative therapies?</td>
<td>Relative efficacy, relative safety</td>
<td>Typical patients included in clinical trials</td>
<td>Phase II/III randomised clinical trials</td>
<td>Network meta-Analysis (NMA)</td>
<td>Study conditions</td>
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<tr>
<td>3) How effective and safe is this drug compared to alternative therapies, in the patients who will likely receive it post-launch?</td>
<td>Relative effectiveness, relative safety in predicted study populations</td>
<td>Patients predicted to receive the drug post-launch</td>
<td>Phase II/III randomised clinical trials, clinical databases and registries</td>
<td>Individual patient data (IPD) network meta-analysis and meta-regression (NMR)</td>
<td>Study conditions</td>
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<tr>
<td>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?</td>
<td>Relative effectiveness, relative safety in predicted real world populations</td>
<td>Patients predicted to receive the drug post-launch in a given health care system</td>
<td>Phase II/III randomised clinical trials, clinical databases and registries, expert opinion, patient preferences</td>
<td>Mathematical modelling</td>
<td>Real world conditions</td>
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>> Egger, Fletcher, Moons. JRSM 2016 <<
GetReal Outputs (not complete)

**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
<table>
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<tr>
<th>Examples</th>
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<tbody>
<tr>
<td>Modelling effectiveness in the real-world (with case studies)</td>
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<td>Incorporating RWE in NMA (with case studies)</td>
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<td>Software for evidence synthesis (ADDIS)</td>
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<td>Patient powered research networks</td>
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<td>Social media</td>
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<td>Drivers of effectiveness (with case studies)</td>
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<td>Real-world evidence (RWE) to inform RCT design</td>
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<td>Adjusting for confounding in early post launch settings (with case study)</td>
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GetReal Tools

– PRAGMAGIC –

a decision support tool for pragmatic trial design

>> www.pragmagic.eu <<
GetReal Tools (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

>> https://drugis.org/index <<
Summary of Outputs, Guidelines and Recommendations

Real-world evidence (RWE) Navigator

The Real-world evidence (RWE) Navigator:

- **Is an educational resource** helping users to find out more about the potential issues in demonstrating relative effectiveness of new medicines (referred to as ‘effectiveness issues’).
- **Provides guidance** guiding users to specific types of analyses or study designs using RWE to support the development of medicines.
- **Is a directory of resources** a comprehensive resource on the use of RWE in medicines, signposting to outputs from the GetReal projects and other authoritative sources of information on RWE.

The RWE Navigator has been designed for a wide variety of users. For example, pharmaceutical companies may find it useful to increase awareness about the use of RWE among their staff members, or patients may use it to understand concepts related to RWE and better understand challenges of using or generating RWE.

>> [https://rwe.navigator.eu](https://rwe.navigator.eu) <<
Some (practical) lessons learned...

- External stakeholder engagement is important, but takes time
- It takes time to build up trust and establish ways of working together
- Case studies with actual examples are helpful to gather views on usefulness, acceptability and impact of solutions...
  ...but data request, transfer and pre-processing are time-consuming
- Staff turnover can be an issue (esp. private sector)
- Good communication of issues and solutions is required
- Sustainability and implementation plans beyond the projects are needed
..., but GetReal was worth all these efforts

Thank you to all GetReal collaborators who made this project a great success!!!

>> Thank you to WP1 for the slides (esp. to Sarah Garner)! <<
>> Thank you to WP4 and the Bern group for the inspiring team work! <<
>> Thanks to all external stakeholders who provided their feedback and attended our workshops <<
>> ... <<