What are the real-world evidence tools and how can they support decision making?

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Disclaimer

The views expressed in this presentation are my personal views and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.
Objectives

• Which data and When?
• Opportunities for real world data
• Patient Registries Initiative
• Conclusions
Real world evidence is defined as data that are collected outside the constraints of conventional randomised clinical trials.
RWE - What are the Opportunities across the product life cycle?

**Development**
- Understand standard of care and NHD
- Patient recruitment
- Trial design
- Unmet need / disease burden
- PROs

**Growth phase**
- Post marketing commitments (safety etc.)
- Budget impact
- Adherence
- Utilization / prescribing patterns
- Effectiveness

**Mature phase**
- Head to head comparative effectiveness
- Differentiation in sub-populations
- Target populations
- Usage Differ-ence
- Effects of switching on outcomes
- Differentiate with or vs. protected galenics
- New competition
- New formulation/ indication
- Competitor goes generic

- Conditional pricing review
- New competition
- Usage Differences
- Effects of switching on outcomes

**Evidence required**
- Past
- Now

Source: IMI GetReal
Medicines Development

- Population-based databases to characterize frequency and distribution of disease
- Identify the population to be treated
- Identify whether the disease affects high risk populations e.g. paediatrics
- Identify unmet medical need
- Identifying prevalence of disease (orphan medicines)
- Current standard of care
- Clinical trial recruitment
- Real World clinical trials
At and Following Authorisation

- The EU Risk Management Plan is key to driving proactivity and promoting better targeted studies
  - Safety Specification – important known and potential risks + missing information
  - Pharmacovigilance Plan – routine PhV + additional studies
  - +/- Risk Minimisation Plan – including effectiveness measures
- Future – Benefit risk management plans
Post-authorisation safety

- The entire evidence hierarchy
- Detecting signals (new or changing safety issues)
- Confirming signals e.g.: observed vs. expected; impact / burden
- Continuous safety monitoring in real world
- Formal association studies in case control, cohort, etc
- Assessing rare, delayed or chronic exposure adverse reactions
- Effectiveness studies
- Health outcome and HTA studies
Data – Which data and when?

- Environmental data
- Electronics health records
- M-Health
- Epigenetics
- Structural biology
- Pharmaco genomics
- Registries
- Genomics
- Social Media
- In silico modelling
- Transciatomics
- Proteomics
- Functional Phenotypes
- RCTs
- Metabolomics
- Lipodomics
- RWE
- Environmental data
Registry roles

Multiple:

• Describe natural history of a disease
• Determine clinical effectiveness of healthcare products / services
• Measure / monitor safety / harm
• Measure quality of care

All may inform research and medicines approval & monitoring
### Registry Analysis 2005-2013:

Determined number of registries imposed as an obligation at the time of authorisation from 2005-2013

<table>
<thead>
<tr>
<th>Category</th>
<th>No Registry</th>
<th>Registries</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n=335)</td>
<td>304</td>
<td>31</td>
</tr>
<tr>
<td>Orphan (n=70)</td>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>Non-orphan (n=265)</td>
<td>254</td>
<td>11</td>
</tr>
<tr>
<td>Conditional (n=17)</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Exceptional circumstances (n=21)</td>
<td>7</td>
<td>14</td>
</tr>
</tbody>
</table>

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EMA Activities: Registry analysis 2005-2013

![Bar chart showing registry analysis](chart.png)
## Registry analysis 2005-2013

### Results

**Registries characteristics**

<table>
<thead>
<tr>
<th>Registries characteristics</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease registry</td>
<td>11</td>
<td>35%</td>
</tr>
<tr>
<td>Product registry</td>
<td>20</td>
<td>65%</td>
</tr>
<tr>
<td>New registry</td>
<td>24</td>
<td>77%</td>
</tr>
<tr>
<td>Existing registry</td>
<td>6</td>
<td>19%</td>
</tr>
<tr>
<td>Both (combination of new and existing)</td>
<td>1</td>
<td>3%</td>
</tr>
</tbody>
</table>
## Registry objectives

### Results

<table>
<thead>
<tr>
<th>Primary objectives</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>22</td>
<td>71%</td>
</tr>
<tr>
<td>Effectiveness/efficacy</td>
<td>3</td>
<td>10%</td>
</tr>
<tr>
<td>Safety in pregnancy</td>
<td>3</td>
<td>10%</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>10%</td>
</tr>
<tr>
<td>Secondary objective effectiveness/efficacy</td>
<td>12</td>
<td>39%</td>
</tr>
</tbody>
</table>
Registry analysis 2005-2013

Results

Collection of HTA-related variables in registry

- No HTA-related variables: 64%
- Measurement of resource use: 10%
- Quality of life questionnaire: 26%
Registry analysis 2005-2013

Results

Problems reported with registries

- Enrolment reduced due to other issues
- Low use of product
- Low data quality or missing data
- Protocol amendment required
- Low accrual rate
- Delayed start
- No problems reported

➢ Percentages are based on a total of 24 registries that initiated patient inclusion.
Registry analysis 2005-2013

Difference between planned numbers of patients and actual numbers of patients included

Accrual of patients to registries

(Only 14 of 31 registries give data)
Current Challenges with Registries

• Majority of imposed registries are for orphan products and/or products approved under exceptional circumstances and imposed for safety reasons.

• Registries face challenges around:
  
  ➢ Recruitment: lack of physician engagement due to administrative burdens, patient consent, low product usage and competing registries
  
  ➢ Data Quality: compliance, study design, representativeness of registry population
  
  ➢ Companies predominantly choose to establish individual product registries rather than utilise existing disease registries.

• This often results in duplication of effort, a likely slower resolution of the initial concern and multiple, relatively inflexible registries with limited application in the future

• Lack of sustainability of current disease registries
EMA Strategy on Registries

MAA = Marketing Authorisation Applicant
MAH = Marketing Authorisation Holder
NCA = National Competent Authority
Status of Pilot Phase

- Creation of a taskforce composed of representatives of EMA Scientific committees and working parties, the European Commission, experts from national competent authorities and EMA staff
- Currently >12 expressions of interest received (pharmaceutical companies and registry managers)
- Suitability of candidates discussed within the Cross-Committee Task Force
- Four case studies have been identified which together represent the need to
  - Establish a new registry
  - Use of an existing disease registry
  - Switching from product registry to disease registry
Learnings to date

Collaborations would be facilitated by:

• Early dialogue between the MAHs and registry owners
• Clear lines of communication between the stakeholders
• Definition of a clear protocol at an early stage in order that the registry can establish the feasibility of any collaboration
• Clear governance models to address issues such as consent and data ownership
• Clear information from the registry on the model of collaboration, structure, governance, data collection mechanisms and points of contact.
Patient Registries Workshop

Brought together registry owners, industry, HTA representatives, regulators to discuss solutions to better use existing patient registries that collect high-quality data from the use of medicines in clinical practice

**Aims**
- Identify the challenges faced by registries and industry when collaborating;
- Understand the technical challenges presented by disparate datasets;
- Identify solutions to best facilitate collaborations & avoid duplication.

**Output**
Recommendations for tools and standards to support a systematic and standardised approach to best use of registries, especially for post-marketing evaluation of safety & effectiveness - 2017
Session 1: Setting the scene
Challenges and Opportunities for Collaboration

Session Chair: Peter Arlett, EMA

09.10-09.30  Challenges and Opportunities for Collaboration
European Society for Blood and Marrow Transplantation (EBMT)
Jürgen Kuball, Head of Department, Hematology, University Medical Centre, Utrecht, The Netherlands

09.30-09.50  Ensuring sustainability
Jim Green, President of the International Niemann-Pick Disease Registry, UK

09.50-10.05  Product versus disease registry – what drives the choice?
Jonathan Appleby, Chief Scientific Officer, Rare Diseases Gene Therapy, GlaxoSmithKline, UK

10.05-10.20  The Health Technology Assessment perspective
François Meyer, Director, International Affairs, Haute Autorité de la Santé, France and EUnetHTA

10.20-10.30  A Regulator’s perspective
Nils Feltelius, Member of the Rheumatology-Immunology Working Party (RIWP), Senior Expert and Clinical Assessor, Medical Products Agency, Sweden

10.30-11.00  Questions and panel discussion

Panel Moderators:
Sabine Straus, Pharmacovigilance and Risk Management Committee (PRAC) member, staff member at the Medicines Evaluation Board, The Netherlands and Associate Professor at the Erasmus Medical Centre, Department of Medical Informatics, Rotterdam
Peter Mol, Vice-Chair, Scientific Advice Working Party (SAWP), Principal Clinical Assessor, Medicines Evaluation Board, The Netherlands
Summary of the challenges

- Financial stability and sustainability of the registry
- Clarity of data ownership including linked data
- Data access
- Mismatch between the required standards for industry and registry
- Regulatory guidance to increase understanding among registries around MAH obligations and required data standards
Session 2: Success factors for international collaborations

Session Chair: Alison Cave, EMA

11.20-11.40  Standardisation of cancer registries data collection and validation at European level
Carmen Martos – Joint Research Centre (JRC), ISPRA, Italy

11.40-12.00  The Pharmachild project: the PRINTO pharmacovigilance registry
Nicola Ruperto, Pharmachild project, Genoa, Italy

12.00-12.30  Case Study:
Challenges of comparator groups and the role of disease registries in medicines development

12.00-12.15  Jamie Geier, Senior Director of Epidemiology, Pfizer Inc., USA
12.15-12.30  Kimme Hyrich, Principal Investigator of BSRBR-RA registry, Professor of Epidemiology, University of Manchester, UK

12.30-13.00  Questions and panel discussion
Panel Moderators:
Tomas Salmonson, Chair, Committee for Medicinal Products for Human Use (CHMP), Senior Scientific Advisor, Medical Products Agency, Sweden
Jan Span, Member of the Cross-Committee Task Force on Registries and Senior Clinical Assessor, Medicines Evaluation Board, The Netherlands
Summary of the key success factors

- Need for guidance on standardised data collection and coding
- Recoding of medicines information, response to treatment, changes in disease state etc
- Flexibility and capacity to accommodate methodological differences across multiple studies
- Defined contact points to facilitate communication
- Appropriate approvals/established governance to allow data access and sharing
- Feedback to healthcare professionals and participating families
Session 3: Possible solutions

Session Chair: Xavier Kurz, EMA

14.00-14.20  Is the answer active data extraction from hospital records?
Fergus Caskey – Medical Director, UK Renal Registry

14.20-15.05  Integration of data across multiple data sources
14.20-14.35  Jan Hillert, Group Leader, Neurogenetics, Multiple Sclerosis, Karolinska Institute, Sweden
14.35-14.50  Metka Zaletel, PARENT Joint Action, Head of Health Data Centre, National Institute of Public Health, Slovenia
14.50-15.05  Johan van Bussel, Head of healthdata.be, Scientific Institute of Public Health, Brussels, Belgium

15.05-15.25  Designing integrated platforms for rare diseases research
Emma Heslop, Project Manager, RD CONNECT, UK
Possible solutions

.......to facilitate the consistent use of registry data for post-marketing evaluation of medicines.

• Sustainable funding
• Need to establish common infrastructure/platform, consistent ontologies and common data elements
• European inter-operability framework principles
• Need for good governance and data management
• Need for bioinformatics and statistical skills
• Sharing of collaborative experiences
Deliverables from the Workshop and the Initiative

• An understanding of the challenges faced by registries and industry alike when collaborating
• An understanding of how regulators can better facilitate relations to avoid duplication of effort
• The identification and evaluation of existing data tools
• A toolkit of methodological guidelines building on those created by PARENT JA
• A review and evaluation of privacy and governance models
• Planning the collection of data and information is a critical success factor for product development throughout the lifecycle.

• Planning for the post-authorisation phase and for real-world evidence collection is as important as pre-authorisation and clinical trials.

• Scientific Advice provides a vehicle to bring stakeholders together and ensure expert input on planning data collection.

• The EMA initiative on patient registries was initiated based on the observation that 75% of all registries requested by regulators to industry were product registries. While we see increased interest from companies to collaborate with patient registries, registries coordinators will also need to raise to the challenge to establish mechanisms to facilitate such collaborations.

• Together with the EU regulatory network, the EMA is committed to play a role in this critical development. The workshop demonstrated that this involvement will include supporting initiatives to deliver maximum utility of registries for the benefit of all patients through better governance principles, better access to high quality data, facilitation of collaborations and mechanisms for sustainable funding.

• This will require a concerted effort from all stakeholders

Conclusions
Thank you for your attention
Back up slides
Effectiveness of Fluticasone Furoate–Vilanterol for COPD in Clinical Practice


Published in final edited form as:

Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines

Steven Black, Juhani Eskola, Claire-Anne Siegrist, Neal Halsey, Noni MacDonald, Barbara Law, Elizabeth Miller, Nick Andrews, Julia Stowe, Daniel Salmon, Kirsten Vannice, Hector S Izurieta, Aysha Akhtar, Mike Gold, Gabriel Oselka, Patrick Zuber, Dina Pfeffer, and Claudia Vellozzi
Research Article

Usage, Risk, and Benefit of Weight-Loss Drug

Tomas Forslund,1 Pauline Raaschou,2 Paul Hjemdahl,1 Ingvar Krakau,3 and Björn Wettermark4

Clinical and epidemiological research

EXTENDED REPORT

Drug survival on TNF inhibitors in patients with rheumatoid arthritis comparison of adalimumab, etanercept and infliximab

M Neovius,1 E V Arkema,1 H Olsson,1 J K Eriksson,1 L E Kristensen,2 J F Simard,1 J Asking,1,3 for the ARTIS Study Group
**RALES:** RCT 25mg spironolactone + usual treatment v placebo + usual treatment

**THE EFFECT OF SPIRONOLACTONE ON MORBIDITY AND MORTALITY IN PATIENTS WITH SEVERE HEART FAILURE**

Bertram Pitt, M.D., Faiez Zannad, M.D., Willems J. Remme, M.D., Robert Cody, M.D., Alain Castaingne, M.D., Alfonso Perez, M.D., Jolie Palensky, M.S., and Janet Wittes, Ph.D.

For the Randomized Aldactone Evaluation Study Investigators*
Rates of Hyperkalemia after Publication of the Randomized Aldactone Evaluation Study

David N. Juurlink, M.D., Ph.D., Muhammad M. Mamdani, Pharm.D., M.P.H., Douglas S. Lee, M.D., Alexander Kopp, B.A., Peter C. Austin, Ph.D., Andreas Laupacis, M.D., and Donald A. Redelmeier, M.D.

**Figure 1.** Rate of Prescriptions for Spironolactone among Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors.

Each bar shows the observed spironolactone prescription rate per 1000 patients during one four-month interval. The line beginning in the second interval of 1999 shows projected prescription rates derived from interventional autoregressive integrated moving-average (ARIMA) models, with 1 bars representing the 95 percent confidence intervals.

**Figure 2.** Rate of Hospital Admission for Hyperkalemia among Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors.

Each bar shows the rate of hospital admission for hyperkalemia per 1000 patients during one four-month interval. The line beginning in the second interval of 1999 shows projected admission rates for hyperkalemia derived from interventional ARIMA models, with 1 bars representing the 95 percent confidence intervals.

**Figure 3.** Rate of In-Hospital Death Associated with Hyperkalemia among Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors.

Each bar shows the rate of in-hospital death associated with hyperkalemia per 1000 patients during one four-month interval. The line beginning in the second interval of 1999 shows projected death rates derived from interventional ARIMA models, with 1 bars representing the 95 percent confidence intervals.

Post-RALES: Spironolactone use & outcomes in community practice, Ontario, Canada