Real World Evidence

RWD focussed Activities – Electronic Health Records
HMA-EMA Joint Big Data Taskforce

STAMP Commission Expert Group
8 June 2018
EMA Relocation: Business Continuity

Due to uncertainties on staff loss and other relocation implications, all activities on real world data, big data and registries between September 2018 and June 2020, will need to be prioritised in the context of business continuity planning.
Two workstreams relevant to real world data

- **RWD Focussed work**
  - Regulatory access
  - Common data models

- **HMA-EMA Joint Big data taskforce**
Real world data across the product life cycle

Evidence Generation by Design

- Identify missing data/gaps
- PROs
- Budget impact
- Unmet need/disease burden
- Patient recruitment
- Understand standard of care and NHD
- Trial design

Support targeted and planned data collection

Support the development/amendment of a registry

Planning of post authorisation studies

- Post marketing commitments (safety etc.)
- Utilization/prescribing patterns
- Adherence
- Effectiveness
- Head to head comparative effectiveness
- Differentiation in sub-populations
- Target populations
- Usage Difference
- Effects of switching on outcomes
- Differentiate with or vs. protected galenics

IMPACT studies

Now

Past

Source: IMI GetReal

Launch
Conditional pricing review
New competition
New formulation/indication
Competitor goes generic

Real world data across the product life cycle

Evidence Generation by Design

- Identify missing data/gaps
- PROs
- Budget impact
- Unmet need/disease burden
- Patient recruitment
- Understand standard of care and NHD
- Trial design

Support targeted and planned data collection

Support the development/amendment of a registry

Planning of post authorisation studies

- Post marketing commitments (safety etc.)
- Utilization/prescribing patterns
- Adherence
- Effectiveness
- Head to head comparative effectiveness
- Differentiation in sub-populations
- Target populations
- Usage Difference
- Effects of switching on outcomes
- Differentiate with or vs. protected galenics

IMPACT studies

Now

Past

Source: IMI GetReal
Current Mechanisms of Access to RWE

**Direct Access**
- **Advantages:**
  - EMA has direct access to 3 datasources which enables quick queries and in house studies to be run
  - Enables collaborative studies to be performed with the EU network

- **Limitations:**
  - Need for internal resources
  - Limited geographical coverage
  - Collaborative studies can be slow

**Indirect Access**
- **Common Protocol**
  - Multiple RWE Data Sources
  - Integration and analysis

- **Advantages:**
  - More willingness to participate because there is no transfer of data
  - Access to expertise
  - Staged implementation
<table>
<thead>
<tr>
<th>EMA-funded studies</th>
<th>N databases</th>
<th>N countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/H1N1 pandemic vaccines and pregnancy outcomes</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Impact of risk minimisation in patients treated with rosiglitazone-containing products</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Isotretinoin and the effectiveness of the Pregnancy Prevention Programme in Europe</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Patterns and determinants of use of oral contraceptives in the EU</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Monitoring the effectiveness of risk minimisation in patients treated with pioglitazone-containing products</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Risk of cardiac valve disorders associated with the use of biphosphonates</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Association between anxiolytic or hypnotic drugs and total mortality</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Metformin use in renal impairment</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Study of regulatory communication and risk awareness following the Article 31 referral of Combined Hormonal Contraceptives in relation to thromboembolism</td>
<td>n/a</td>
<td>6</td>
</tr>
<tr>
<td>Characterising the risk of major bleeding in patients with Non-Valvular Atrial Fibrillation: non-interventional study of patients taking Direct Oral Anticoagulants in the EU</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Study of utilisation of Combined Hormonal Contraceptives in Europe</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Anti-microbial resistance: choice of therapeutic interventions and outcomes for the treatment of infections caused by MDR Gram negative pathogens</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Methods and data sources for determining long-term effects of drug exposure during pregnancy, with application to antiepileptic medicines</td>
<td>n/a</td>
<td>28</td>
</tr>
<tr>
<td>Impact of EU label changes for systemic diclofenac products: post-referral prescribing trends</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Impact of EU label changes for hydroxyzine products: post-referral prescribing trends</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>
Current Mechanisms of Access to RWE

**Direct Access**

- **Advantages:**
  - EMA has direct access to 3 data sources which enables quick queries and in-house studies to be run.
  - Enables collaborative studies to be performed with the EU network.

- **Limitations:**
  - Need for internal resources.
  - Limited geographical coverage.
  - Collaborative studies can be slow.

**Indirect Access**

- **Advantages:**
  - More willingness to participate because there is no transfer of data.
  - Access to expertise.
  - Staged implementation.

- **Limitations:**
  - Slower process for studies to be run.
  - Potential lack of interest from partners to participate in regulatory questions.
How can we Achieve Timely Access to RWE?

Direct Access

Advantages:
- EMA has direct access to 3 datasources which enables quick queries and in house studies to be run
- Enables collaborative studies to be performed with the EU network

Limitations:
- Need for internal resources
- Limited geographical coverage
- Collaborative studies can be slow

Indirect Access

Common Protocol

Advantages:
- More willingness to participate because there is no transfer of data
- Access to expertise
- Staged implementation

Limitations:
- Slower process for studies to be run
- Potential lack of interest from partners to participate in regulatory questions

Integration and analysis

Multiple RWE Data Sources

Direct interrogation

Results

No one solution – a hybrid approach will be required

Indirect Access

Common Data

Advantages:
- More willingness to participate because there is no transfer of data
- Access to expertise
- Staged implementation
- Fast

Limitations:
- Upfront resource investment
- Potential loss of information in transfer to CDM
- Need for validation of model

Integration and analysis

Three RWE Data Sources

Direct interrogation

Results

No one solution – a hybrid approach will be required
OHDSI is a multi-stakeholder, interdisciplinary collaborative to bring out the value of health data through large-scale analytics. All the solutions are open-source. Currently the community has converted >50 databases covering >660 million patients.

Sentinel is a network of distributed data approach which allows the FDA to rapidly and securely access information via a CDM from large amounts of electronic healthcare data, such as EHRs, insurance claims data and registries. The project delivers access to 99 million patient lives, 2.9 billion drug prescriptions, and 38 million acute hospital stays.

Sentinel Initiative

OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

Delivering access to RWD - Distributed Data Networks

Sentinel Initiative

Sentinel

European network

All using or testing a Common Data model. Currently no equivalent pan-European network delivers access to the health and prescription records of over 40 million people and a widely distributed network of academic and data analytics experts to rapidly evaluate the risk/benefit profiles of medicines.

CNODES

Canadian Network of Observational DrugEffect Studies

Sentinel Initiative

CNODES

Canadian Network of Observational DrugEffect Studies

MID-NET (Medical Information Database Network)

MID-NET
Multiple Disparate Initiatives Across Europe
Objectives:
To define the **opportunities and challenges** around implementation of a common data model in Europe to support regulatory decision making.

Output:
To **propose guiding principles** for the development of Common Data model in Europe including **key criteria for validation** in the context of regulatory decision making.
Interim Key Messages

- Key regulatory need for **timely access to decision relevant data**. The challenge is how to **balance flexibility with timeliness**.

- Regulatory decisions are binary with immediate public health impact. Hence **validation of any model cannot be left to chance**.

- The Sentinel system provides the FDA with the **ultimate level of control** but this requires significant financial resources. The challenge for Europe is how to **achieve this level of re-assurance** when the European regulatory system **cannot exert the same level of control**.

- Any system should be the **simplest** that **achieves validity and data sufficiency** but equally should ensure **transparency and reproducibility of data, tools, study design**.

- To meet regulatory needs, any future European framework must be **sustainable with a governance structure** which **respects data privacy obligations** and involves **appropriately all stakeholders**.
Two workstreams relevant to real world data

- RWD Focussed work
  - Regulatory access
  - Common data models

- HMA-EMA Joint Big data taskforce
90%
Of the world’s data has been created in the past 2 years.

24 months
Frequency at which electronic healthcare data doubles

75%+
Percentage of patients expected to use digital health services in the future

Variability
Complexity/heterogeneity/quality/provenance
Define the Big Data landscape from a regulatory perspective

Clarify the opportunities and the challenges

Identify what is needed for Big Data to be exploited to support medicines development and regulatory decision making
### Clinical Utility
- Deciding which data to collect starts by asking the right questions about the benefits sought and problems faced.
- The opportunities and the questions are different depending of the stage during the product lifecycle and the context of the disease.

### Accessibility
- Access to data is a significant hurdle especially for observational data.
- Data governance and privacy protection are key to allow data sharing.

### Validation
- Mechanisms to integrate the data to generate meaningful knowledge are needed.
- Validation that associations are causal is key in generating evidence to support regulatory decision making.

**Need to develop a deep understanding of the data, to define the strengths and limitations so that the evidence arising from its analysis can be appropriately challenged**
Mandate HMA / EMA Joint Task Force Big Data

Priority: Reinforce the scientific and regulatory capacity and capability of the network, Innovation and access to new medicines, Optimisation of the regulatory operations

Chair: Thomas Senderovitz, DK
Co-chair: Alison Cave, EMA
Acting co-chair: Nikolai Brun, DK

Members: DE, DK, ES, FI, HU, IE, NL, NO, RO, UK, MT, EMA
The Task Force should **characterise** relevant sources of big data and define the main format, in which they can be expected to exist in.

Identify areas of **usability and applicability** of data

**Gap analysis** – describe the current status of expertise, future needs and challenges

The Task Force will generate a **list of recommendations** and **Big Data Roadmap**
The Task Force should **characterise** relevant sources of big data and define the main format, in which they can be expected to exist in
Big Data

Genomics

Other omics

Observational data

Clinical trial data

ADR data

Social media/ m health

Data Analytics subgroup
**Key messages – Data Sharing**

**Challenges**
- Heterogeneity of structure and terminology
- Different healthcare systems - different content
- Sharing of personal health information
- Governance to ensure privacy across borders
- Reluctance to share data
- Need for global harmonisation/implementation

**Enablers**
- Global common standards - data format/terminologies/dictionaries/data elements and/or data models
- Robust data protection – distributed data platforms
- Political support/rewards – data sharing culture
- Patient/HCP engagement and communications

**Risks**
- Funding
- Lack of sustainability
- Overly onerous access
- Limited access
- Duplication
- Future proofing
Data Linkage

**Challenges**
Dynamic, complex and evolving data  
Spatial, cell type and organelle dependent  
Data dependent on sample choice and storage conditions  
Variable quality  
Commercial interests

**Enablers**
Sharing raw and processed data and meta data  
Standardisation of data collection: instrumentation, assays, devices  
Reproducible sample collection and storage  
Characterisation of data content  
IT solutions – new ways of presenting and analysing increasing complex data

**Risks**
Funding  
Lack of sustainability  
Spurious conclusions  
Pace of change
Acceptability

Challenges
Validation - Differentiating causal from co-incidental
Reproducibility – consideration of sample choice, storage conditions and temporal factors
Large data volumes may increase the precision of measurements – but not necessarily the accuracy
Understanding and quantifying the uncertainty
“Black box” and potentially biased algorithms

Risks
Maintaining expertise
Developing regulatory guidelines which keep pace with the changing landscape

Enablers
Transparency
Justification for database choice
Novel methodological approaches
Framework to address bias
Reproducibility of associations
Methodology and analytics
The Task Force should characterise relevant sources of big data and define the main format, in which they can be expected to exist in

Identify areas of usability and applicability of data

Gap analysis – describe the current status of expertise, future needs and challenges

The Task Force will generate a list of recommendations and Big Data Roadmap

End of 2018
Take Home Messages

- HMA-EMA Joint Big data task force will report by end of year. Recommendations which will highlight **opportunities, challenges and risks**.
- RWD already contributes to regulatory decision-making, mainly in safety.
- To meet regulatory needs, any future European framework will need to provide **sustainable** and **timely** access to **decision-relevant data** with a governance framework which **respects data privacy obligations**.
- Uncertainties with regard to relocation, mean any EMA activities on big data/real world data will need to prioritised in the context of **business continuity planning**.
Any questions?

Further information

Alison.Cave@ema.europa.eu
European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 Facsimile +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Follow us on @EMA_News