Enhancing Evidence Generation Across the Product Life Cycle

Learnings from a series of workshops

Patients’ and Consumers’ Organisations (PCWP) and Healthcare Professionals’ Organisations (HCPWP) joint meeting

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Structure

1. Why now?
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4. Conclusions
What is the need? Why now?

Lack of information on **generalisability** of clinical trial results to normal clinical practice and in **high risk** groups requires new approaches to gather complementary evidence.

A **changing scientific landscape** driving increasing patient stratification is leading to smaller, focused RCTs or creating situations where a RCT is not possible or feasible.

To understand **current treatment and outcome patterns** as well as understanding the relevance of **short term surrogate endpoints** to long term beneficial clinical outcomes.

An **increasing data availability** coupled with **technological advances** is offering new possibilities to store, mine and analyse data across multiple datasources.
The data landscape: which data?

Datasources

- Clinical trial data
- Clinical databases (Prescriptions, EHRs and registries)
- Published literature
- Regulatory data (ADR, sales, Safety updates, PASS, PAES)
- Imaging data
- Social media data/m-health
- "Omic data (Genetic, proteomic, metabolomic)"

Datasets

- Genomics
- Proteomics
- Metabolomics

Published literature

Clinical databases (Prescriptions, EHRs and registries)

Social media data/m-health
Moving towards Integrated Personalised Omics Profiling

Personal Omics Profiling Reveals Dynamic Molecular and Medical Phenotypes

“An integrated personal omics profile (iPOP), an analysis that combines genomic, transcriptomic, proteomic, metabolomic and autoantibody profiles from a single individual over a 14 month period. Our iPOP analysis revealed various medical risks, including type 2 diabetes.”
Development of a Learning Healthcare System

PRAC Impact Strategy

Seeks to assess the public health impact (outcome) of the risk minimisation measure, not simply that the change has occurred.

Pharmacovigilance Risk Assessment Impact Strategy
RWD forms part of the pharmacovigilance data landscape

Multiple sources of evidence of varying quality from multiple stakeholders are balanced to inform decision making.

Many validated signals required further evidence to define and understand.

RWD forms part of this jigsaw.

Eudravigilance Annual Report 2017

- ADR Reports (Centralised): 1,104,127
- Signals Detected: 2,062
- Validated Signals: 43

2.1%
What is needed to realise this vision?

Enabling Data Sharing

Heterogenous data from multiple sources

Ensuring Data Privacy across borders
Timeliness is key especially for safety issues

Need to build systems which enable fast reliable access
The data landscape: which data?

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Policy 0070 / Clinical Data Publication (CDP)

June 2013: draft Policy 0070 for consultation
October 2014: Policy 0070 adoption
January 2015: Policy 0070 effective
October 2016: 1st publication

- Enables public scrutiny of not only the company’s data but also the regulatory decision
- Inform future research reducing duplication of effort
Policy implementation

Phase I
- Clinical reports = clinical overview, clinical summary, clinical study reports, protocol & amendments, documentation of statistical methods
- Implementation of Phase I started in October 2016
- Individual patient data (IPD) = individual data separately recorded for each participant in a clinical study
- Later stage: EMA will review various aspects in relation to IPD

Phase II
- Total number of CSRs: 4,173
- Number of views: (36,877) (1,134 in 2018)
- Number of downloads: 121,463

Policy implementation
Enabling Sharing Clinical Trial Data

Objectives of workshop:
- To propose **guiding principles** to enable international data sharing in the public interest
- Building on the platform of work by EMA, to **review anonymisation approaches** applicable to a broader set of data which ensure privacy protection and meet the standards required to maintain **accessibility and the scientific utility** of the data
- To examine **opportunities for harmonisation** of international clinical data sharing, taking into consideration data protection in the different jurisdictions.

Scope:
- **Clinical trial data** and **real world data** (in the context of patient registries and individual cohort studies)

Outputs:
- A report describing a **clear set of recommendations**
Draft Key Messages

• **International definitions** for common terms across regions are required to enable anonymisation approaches to be applied **globally**
• Anonymisation techniques should **protect patient privacy** but must preserve the **scientific utility** of the data
• Anonymisation must be **re-assessed periodically** in the light of future scientific and technological advances, legislative or data environment changes
• **No data** should be **exempt** a priori from data sharing.
• A risk base approach should be followed: a **zero risk is not achievable**
• There should be **transparency** in the informed consent that the data will be shared in an anonymous form and the risks of re-identification must be explained
• **Engagement with all stakeholders** is necessary to communicate the benefits of data sharing
• **Globally recognised metrics** should be developed to **reward data sharing**
Three workshops on:

- **Cystic Fibrosis**: 14th June 2017
- **Multiple-Sclerosis**: 7th July 2017
- **Car-T cells**: 9th February 2018
- **Haemophilia (FVIII)**: 8th June 2018
Exploring Challenges of Data Harmonisation

Cystic Fibrosis Registries
Workshop: 14th June 2017

Multiple-Sclerosis Registries
Workshop: 7th July 2017

CAR T Cell therapies Registries
Workshop: 9th February 2018

Why were these diseases chosen?

- Number of products have been authorised or are in the authorisation process
- New products in the business pipeline
- EU disease registries have requested support for harmonisation
- On-going qualification procedure for two EU-wide registry platforms

Participants: regulators, companies, registry holders, HTA bodies, patients’ and HCPs’ representatives
Lessons learned from the EMA registries workshops

### Common core data elements
- All participants could agree on **core data elements to be collected** in disease-specific registries as a basis for regulatory evaluations.
- Difference made between “must have” and “nice to have”
- Additional data can be collected if needed to support a study – needs early discussions

### Data quality
- **Key components**: uniformity, representativeness, consistency, completeness, accuracy, timeliness - source data verification procedure
- **Data quality control system** to be established internally, external audit to be considered
- **Data quality indicators and metrics** to be defined
- Data quality to be similar in routine and in registry-based studies

### Governance
- Regulators and MAHs to be aware of data that can be feasibly be collected by registries and inform registries on their data needs - needs early discussions
- Registry holders to establish system for centralised data application requests
- Registry holders to develop policy for data sharing based on data protection and informed consent
- Process for **collection and reporting of AEs** to be defined and described in study protocol - process to be in place in the registry to ensure physicians report AEs to national PhV system
Timeliness is key especially for safety issues.

Need to build systems which enable fast reliable access.
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. Pilot project delivers access to 99 million patient lives, 2.9 billion drug prescriptions and 38 million hospital stays.

The CNODES 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.
Multiple Approaches
Following an analysis of electronic healthcare databases across Europe, only 34 databases across 13 member states relevant for regulatory decision making.
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.
Draft Key Messages

• Enhancing evidence generation requires **timely access** to RWD from as **broad** a geographic region as possible.
• **Different methods** will apply for **different questions** across **different stakeholders**. A CDM forms **part of the solution** but **multiple approaches** will be required.
• Data must be “**fit for purpose**”, generated by appropriate methods with a satisfactory level of precision.
• **Robustness** and **replicability** are key attributes with results remaining valid across different study designs and datasets.
• **Unique challenges** exist for European data. However the **centralised** healthcare and **cradle to grave** culture deliver a richness of data which offers huge opportunities.
• A **carefully designed CDM** may provide a **transparent** data environment that not only limits some of the potential sources of bias associated with observational studies but also facilitates **rapid replication**.
The data landscape: which data?

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Data Available per individual is Changing

By 2020 40 Zettabytes = 40,000 Terabytes

- 70% Social and Environment And Behavioral
- 20% Genomics Factors
- 10% Clinical Factors

1100 Terabytes Generated Per lifetime
6 Terabytes Per lifetime
0.4 Terabytes Per lifetime
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
Data is siloed at individual centres, hard to access, analyse and use.

Productivity tools (especially IT) built for individual local usage focusing on local data analytics solutions.

Bringing the data together is very hard. It needs to be “standardised”, structured and stored together to deliver insight.

Data needs to be **FAIR**: Findable, Accessible, Interoperable and Reusable.

We need centralised IT solutions to store data safely and securely and enable machine learning solutions.

What are the key challenges in realising this vision?
The Task Force should **characterise** relevant sources of big data and define the main format, in which they can be expected to exist.

**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**
Other omics
Genomics
Observational data
ADR data
Clinical trial data
Social media/m health
BIG DATA
Data Analytics subgroup
Objective

To gather information on the latest developments in the field of big data from the perspective of different stakeholders.

To clarify how and when the multitude of data sources may contribute to medicinal product development, authorisation and surveillance.
Key Messages

**Quality** – needs to be *sufficient* but may not be able to be pre-defined. It will always be dependent on the *question and datasource*.

**Data Analytics** - Challenge is to keep *pace* with the changing landscape e.g. understanding underlying *algorithms*.

**Applicability** - Not universally useful – need to understand the added value – *effort vs benefit*.

**Validation** - *Balance* needs to be found between using the data messy and data curation

**Data ownership** and **access** – creating a data sharing culture

Concerns around *data commercialisation*
Moving the conversation on to identify solutions to the challenges posed by Big Data from perspective of regulators, academia and industry.
The world’s most valuable resource
Data and the new rules of competition

The data deluge
AND HOW TO HANDLE IT: A 14-PAGE SPECIAL REPORT
**Take home messages**

**Data sharing and linkage** are key needs across the data landscape. However, mechanisms are needed to **standardise the collection, recording and storage of data**.

**Proactive sharing** of all forms of clinical data demands mechanisms to **ensure privacy is protected but** data anonymisation approaches must also preserve the **scientific utility** of the data.

Transformation of RWD into a **common data model** enables harmonisation of datasources and could deliver **timely access** to pan European RWD. **Validation of the methodology** is required to understand the potential information loss in European datasets.

**Policy initiatives** across all stakeholders are needed to motivate and drive a **data sharing culture**

Together these actions will deliver the ability to **proactively and prospectively** drive data generation appropriate for decision making.
Thank you for your attention

Further information

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