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SCIENCE MEDICINES HEALTH

Enhancing Evidence Generation Across the Product Life Cycle

Learnings from a series of workshops

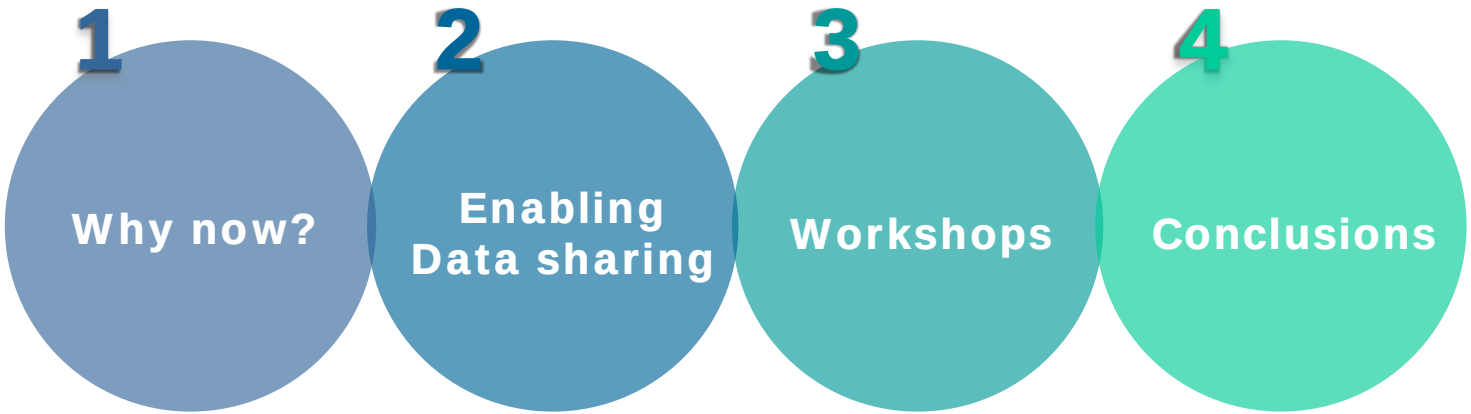
Patients' and Consumers' Organisations (PCWP) and Healthcare Professionals' Organisations (HCPWP) joint meeting

April 17th 2018

Presented by Alison Cave on 17 April 2018
Principal Scientific Administrator
Pharmacovigilance and Epidemiology Department - Presentation revised for publication

Disclaimer

Structure



What is the need? Why now?

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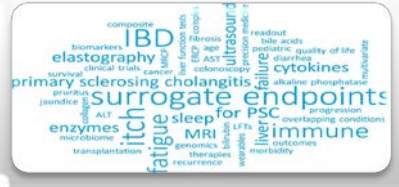
Lack of information on **generalisability** of clinical trial results to normal clinical practice and in **high risk** groups requires new approaches to gather complementary evidence

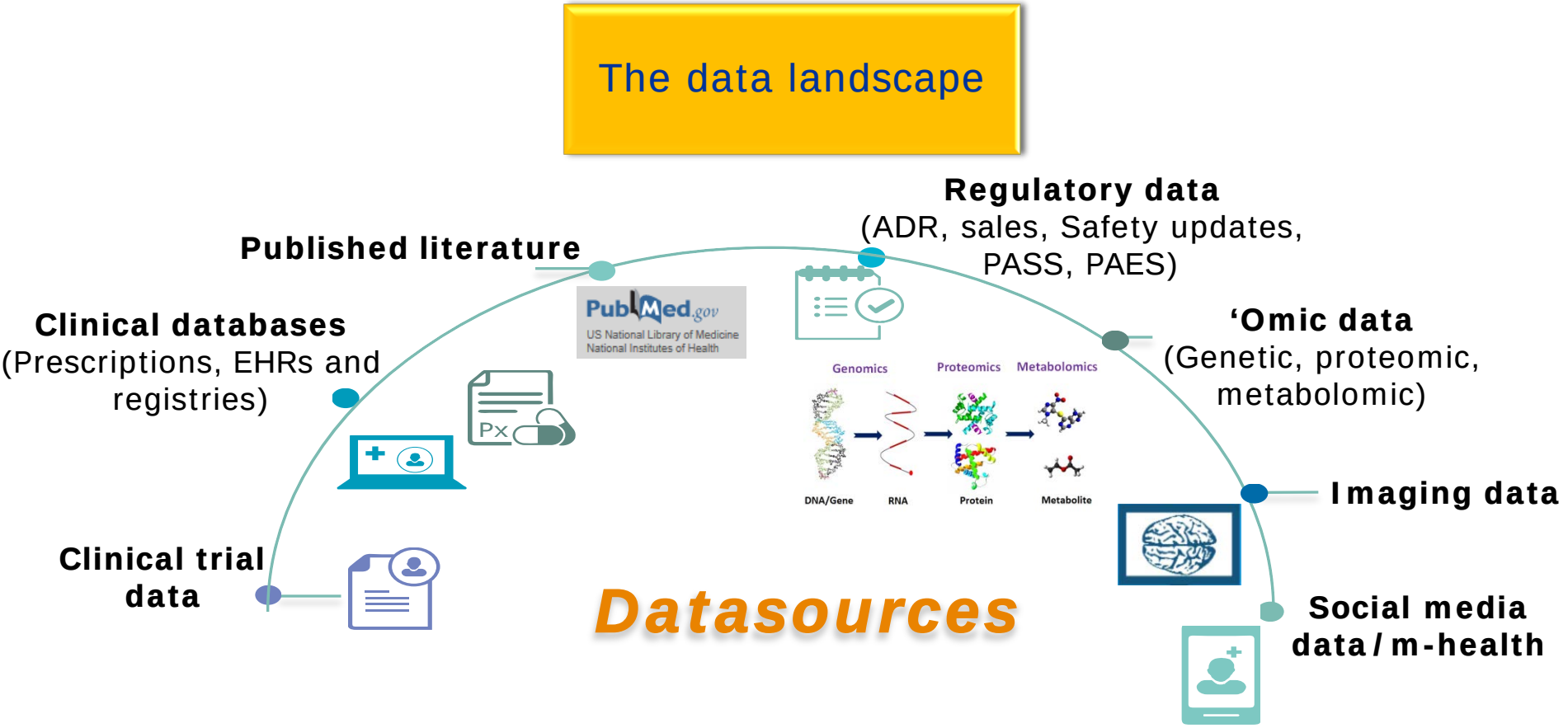
A changing scientific landscape driving increasing patient stratification is leading to smaller, focused RCTs or creating situations where a RCT is not possible or feasible



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?



Moving towards Integrated Personalised Omics Profiling

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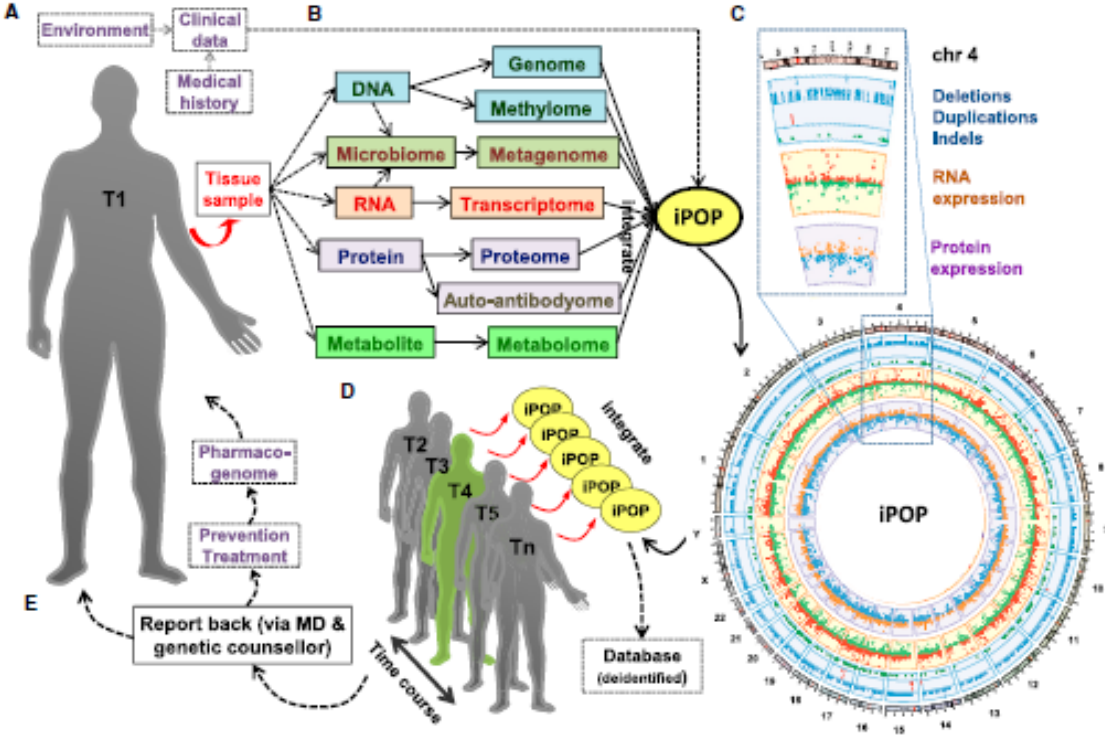
Resource

Cell

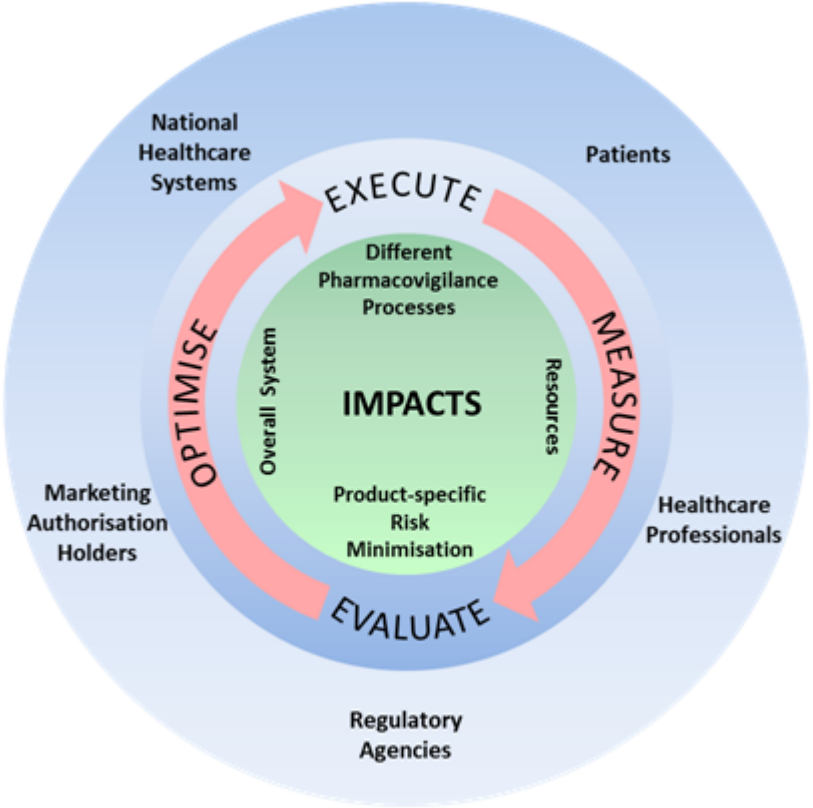
Personal Omics Profiling Reveals Dynamic Molecular and Medical Phenotypes

Rui Chen,[1,11] George I. Mias,[1,11] Jennifer Li-Pook-Than,[1,11] Lihua Jiang,[1,11] Hugo Y.K. Lam,[1,
Elana Miriami,[1] Konrad J. Karczewski,[1] Manoj Hariharan,[1] Frederick E. Dewey,[3] Yong Cheng
Hogune Im,[1] Lukas Habegger,[6,7] Suganthi Balasubramanian,[6,7] Maeve O'Huallachain,[1] Joel
Sara Hillenmeyer,[1] Rajini Haraksingh,[1] Donald Sharon,[1] Ghia Euskirchen,[1] Phil Lacroute,[1] Keith
Maya Kasowski,[1] Fabian Grubert,[1] Scott Seki,[2] Marco Garcia,[2] Michelle Whirl-Carrillo,[1] Merc
Maria A. Blasco,[9] Peter L. Greenberg,[4] Phyllis Snyder,[1] Teri E. Klein,[1] Russ B. Altman,[1,5] Atul
Mark Gerstein,[6,7,8] Kari C. Nadeau,[2] Hua Tang,[1] and Michael Snyder[1,*]



"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
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/01/WC500199756.pdf

RWD forms part of the pharmacovigilance data landscape

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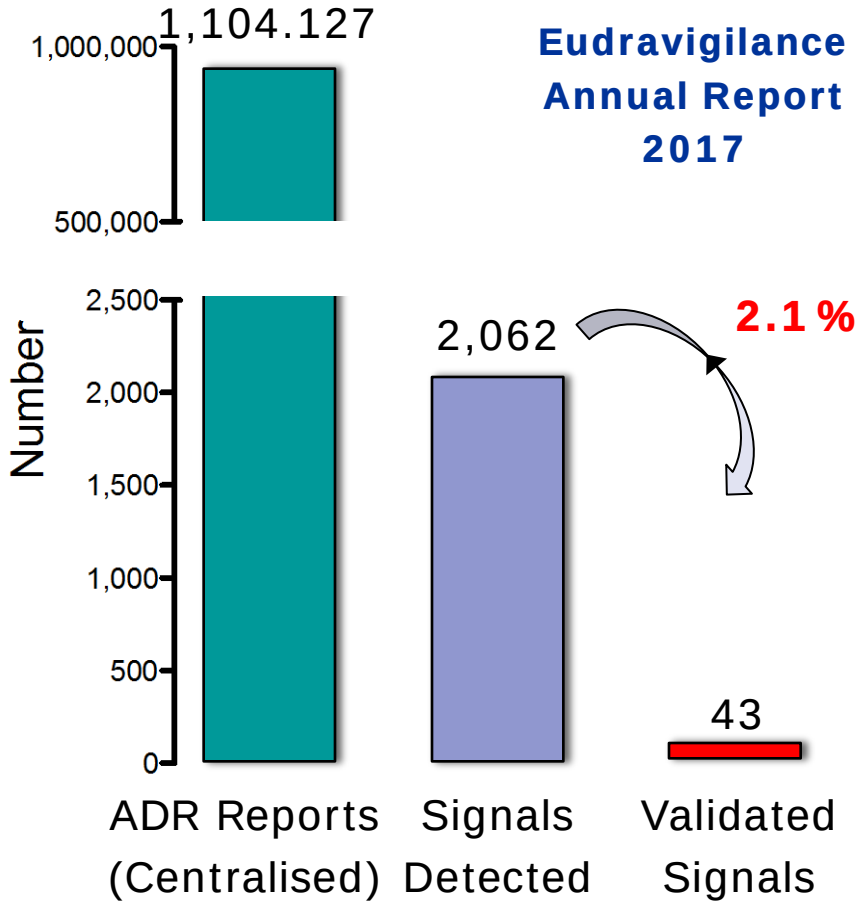
Multiple sources of evidence of **varying quality** from **multiple stakeholders** are balanced to inform decision making.

Many validated signals required further evidence to define and understand.

RWD forms part of this jigsaw.



What is needed to realise this vision?

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Enabling Data Sharing

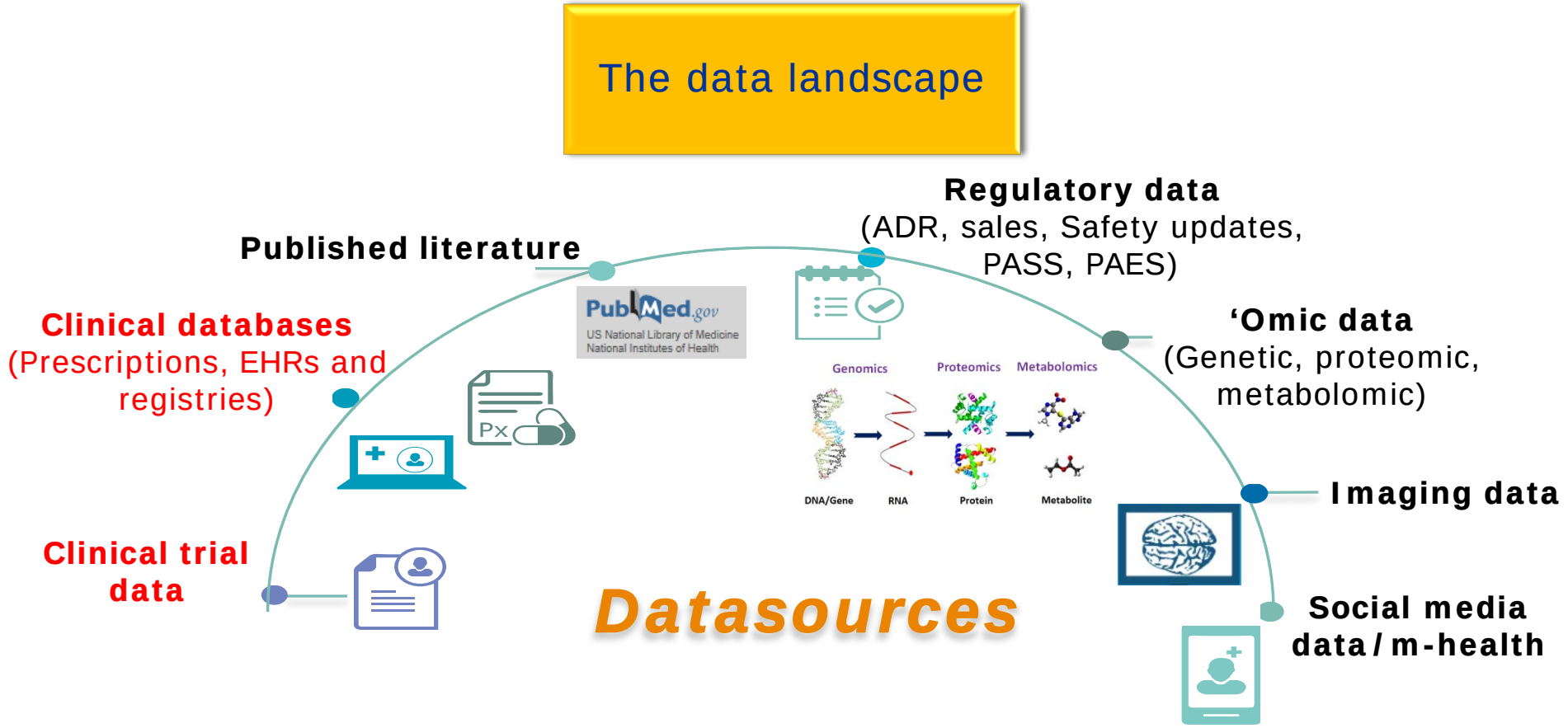
Heterogenous data from multiple sources

Ensuring Data Privacy across borders

Need to build systems which enable fast reliable access

Timeliness is key especially for safety issues

The data landscape: which data?



Policy 0070 / Clinical Data Publication (CDP)

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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 & amen
statistical metho
- **Implementatio**

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

Phase II

- 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**

Enabling Sharing Clinical Trial Data

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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)

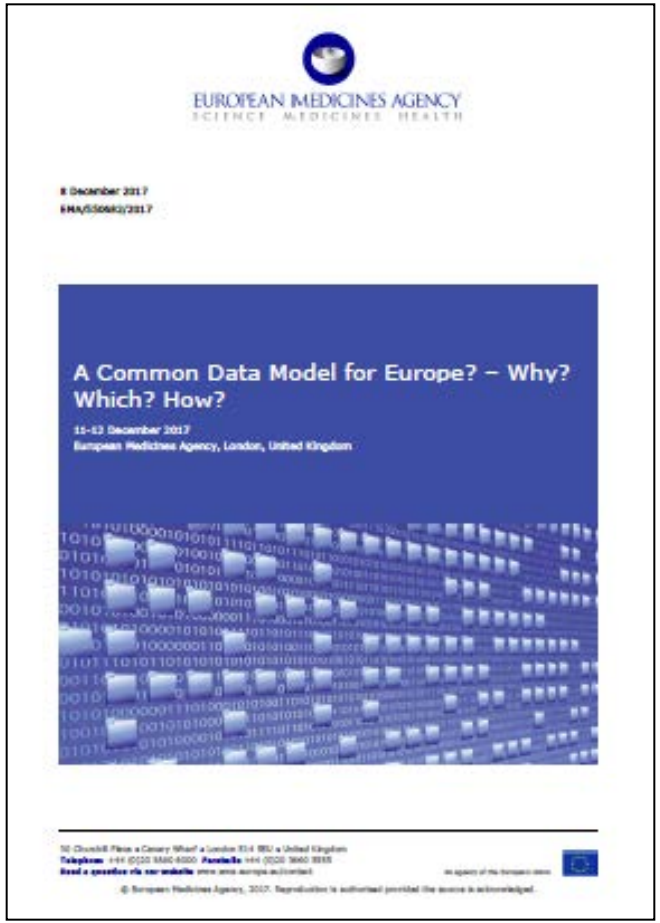
Outputs:

- 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**

Enabling Sharing of Real World Data



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

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Cystic Fibrosis Registries Workshop: 14th June 2017

Multiple-Sclerosis Registries Workshop: 7th July 2017

CAR T Cell therapies Registries Workshop: 9th February 2018

Participants: regulators, companies, registry holders, HTA bodies, patients' and HCPs' representatives

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

Lessons learned from the EMA registries workshops

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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

Need to build systems which enable fast reliable access

Timeliness is key especially for safety issues

Delivering access to RWD - Distributed Data Networks

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Sentinel Initiative

Sentinel is a network of distributed data approach which allows the FDA to rapidly and securely access information via a CDM [illegible] m large amounts of electronic healthcare data, such as EHR[illegible] claims data and registries. Pilot project delivers ac[illegible] patient lives, 2,9 billion drug prescriptions and [illegible]spital stays

CNODES
CANADIAN NETWORK FOR OBSERVATIONAL [illegible]

The [illegible] delivers access to the health and [illegible]s of over 40 million people and a widely [illegible]network of academic and data analytics experts [illegible]pidly evaluate the risk:benefit profiles of medicines

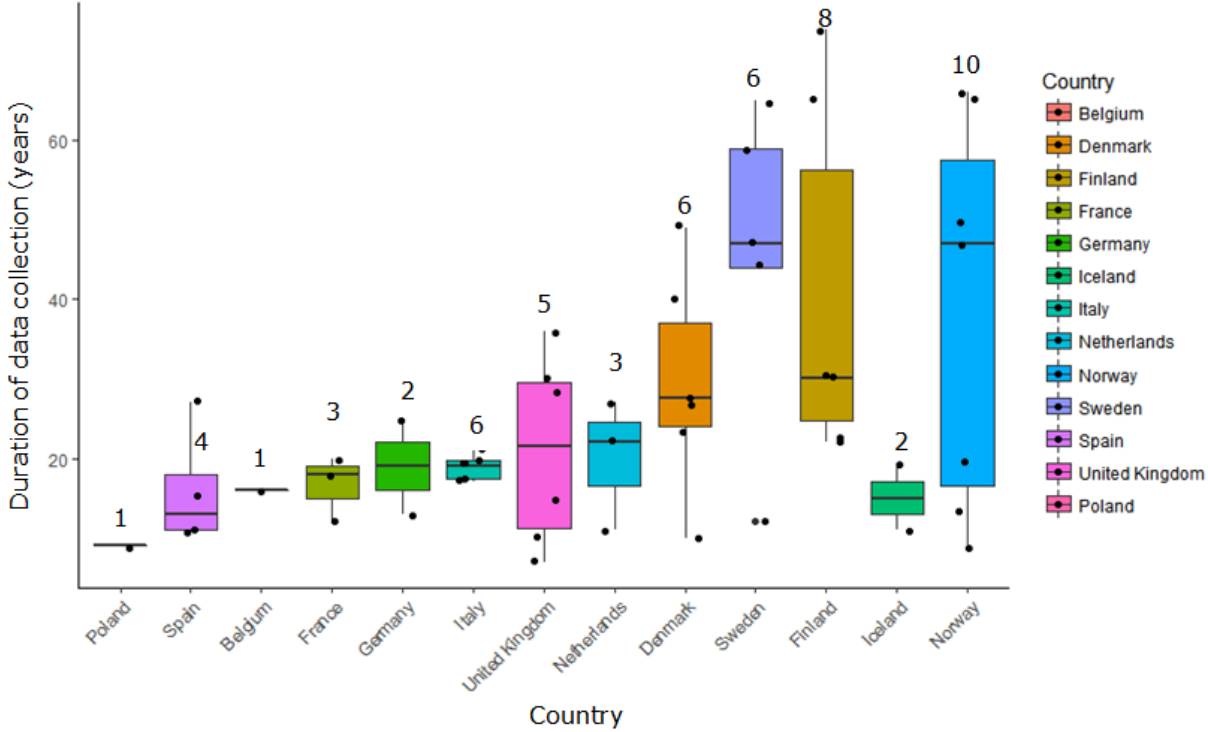
No equivalent pan European Framework

OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

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 milliion patients

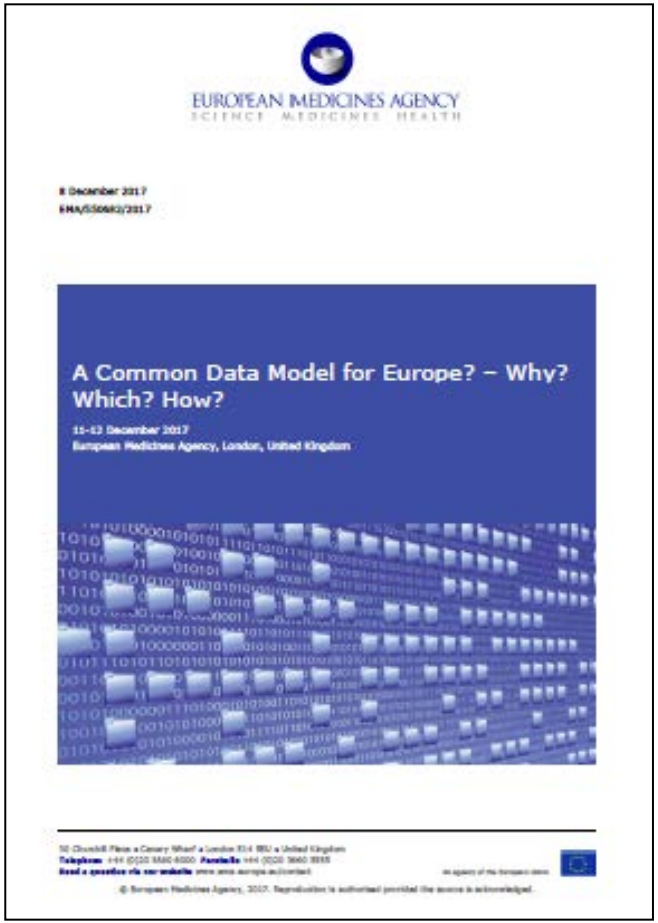
Multiple Approaches

Vaccine Safety Datalink (VSD)



Following an analysis of electronic healthcare databases across Europe, only 34 databases across 13 member states relevant for regulatory decision making

A Common Data Model for 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.

Draft Key Messages

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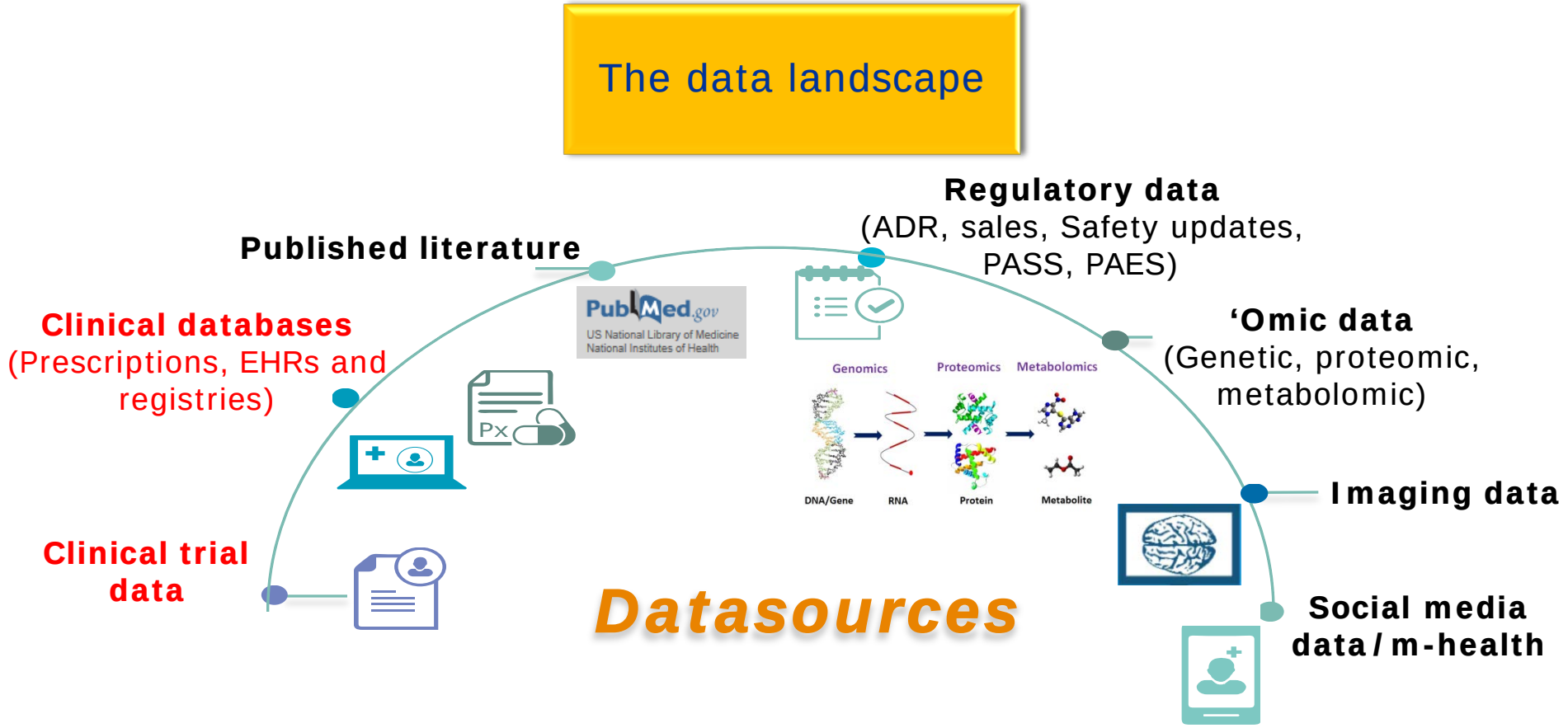
- Enhancing evidence generation requires **timely access** to RWD from as **broad a geographic region as possible.**
- **Different methods** will apply for **different questions** across **different stakeholders.** A CDM forms **part of the solution** but **multiple approaches** will be required.
- Data 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?



Data Available per individual is Changing

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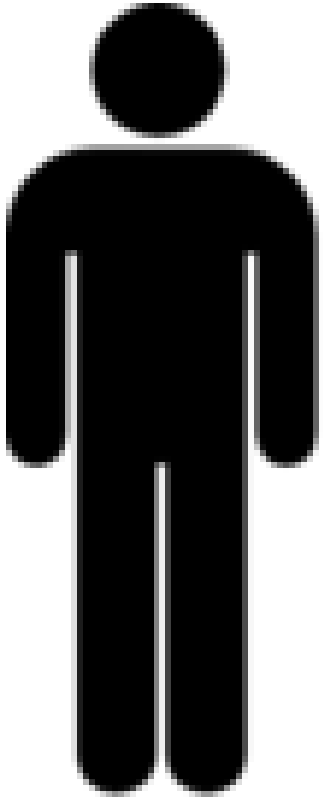
By 2020 40 Zettabytes = 40,000 Terabytes

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**

What are the key challenges in realising this vision?

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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

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

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

Regulatory science initiatives - planned activities and projects

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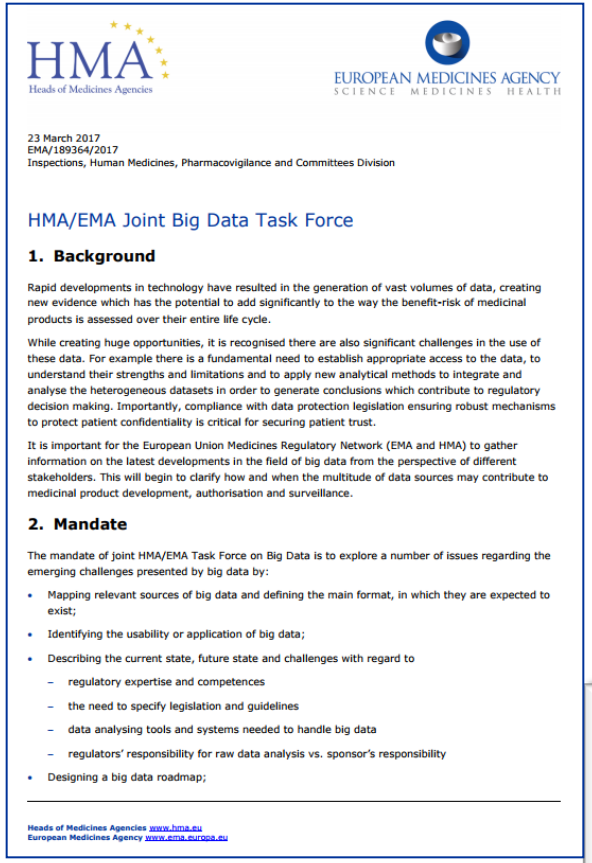

HMA
Heads of Medicines Agencies

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SCIENCE MEDICINES HEALTH

23 March 2017
EMA/189364/2017
Inspections, Human Medicines, Pharmacovigilance and Committees Division

HMA/EMA Joint Big Data Task Force

1. Background

Rapid developments in technology have resulted in the generation of vast volumes of data, creating new evidence which has the potential to add significantly to the way the benefit-risk of medicinal products is assessed over their entire life cycle.

While creating huge opportunities, it is recognised there are also significant challenges in the use of these data. For example there is a fundamental need to establish appropriate access to the data, to understand their strengths and limitations and to apply new analytical methods to integrate and analyse the heterogeneous datasets in order to generate conclusions which contribute to regulatory decision making. Importantly, compliance with data protection legislation ensuring robust mechanisms to protect patient confidentiality is critical for securing patient trust.

It is important for the European Union Medicines Regulatory Network (EMA and HMA) to gather information on the latest developments in the field of big data from the perspective of different stakeholders. This will begin to clarify how and when the multitude of data sources may contribute to medicinal product development, authorisation and surveillance.

2. Mandate

The mandate of joint HMA/EMA Task Force on Big Data is to explore a number of issues regarding the emerging challenges presented by big data by:

- Mapping relevant sources of big data and defining the main format, in which they are expected to exist;
- Identifying the usability or application of big data;
- Describing the current state, future state and challenges with regard to
  - regulatory expertise and competences
  - the need to specify legislation and guidelines
  - data analysing tools and systems needed to handle big data
  - regulators' responsibility for raw data analysis vs. sponsor's responsibility
- Designing a big data roadmap;

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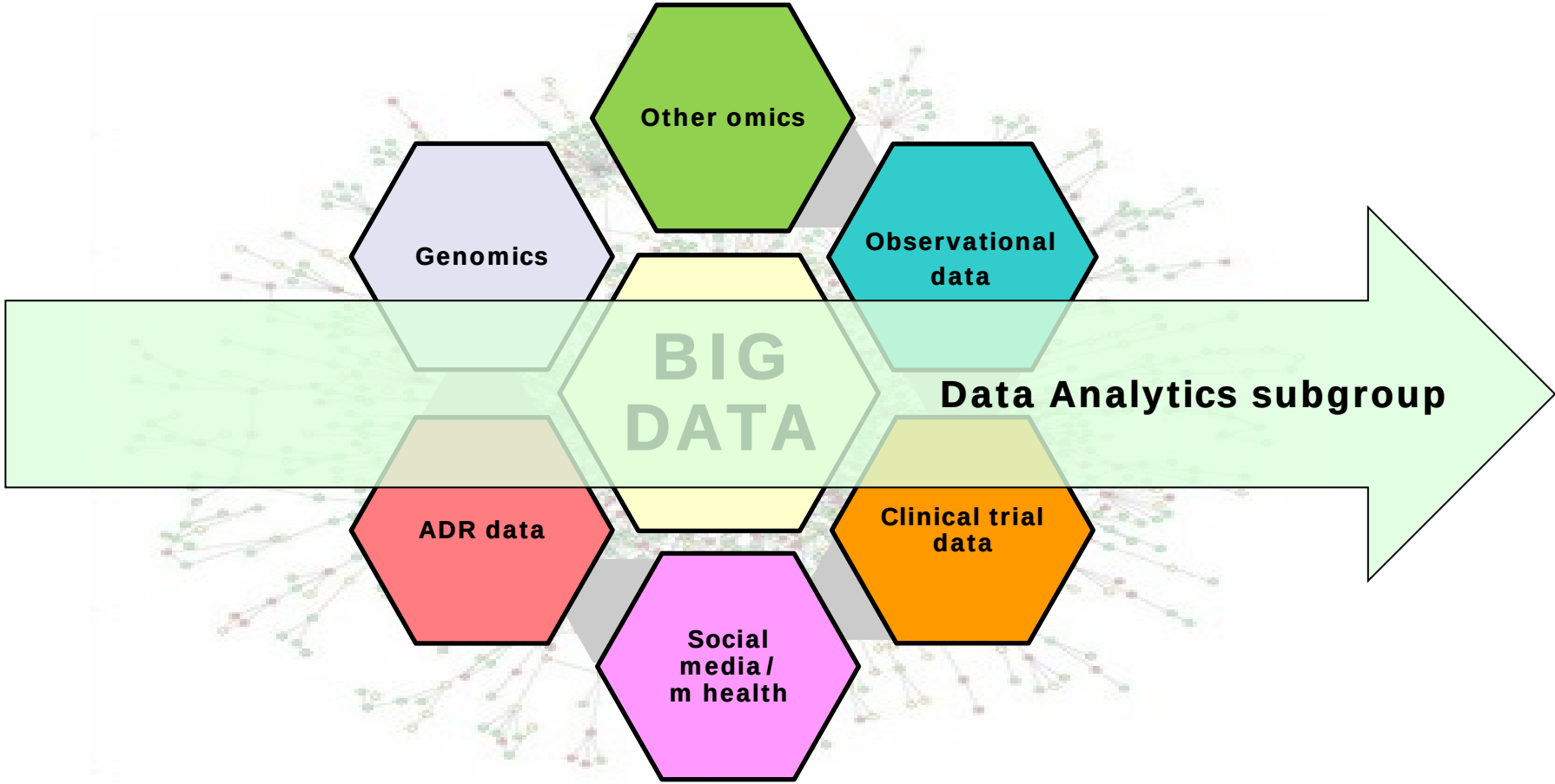
European Medicines Agency www.ema.europa.eu

1 The Task Force should ***characterise*** relevant sources of big data and define the main format, in which they can be expected to exist in

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

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

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


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

CHALLENGES

Workshop -27th June 2017

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

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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

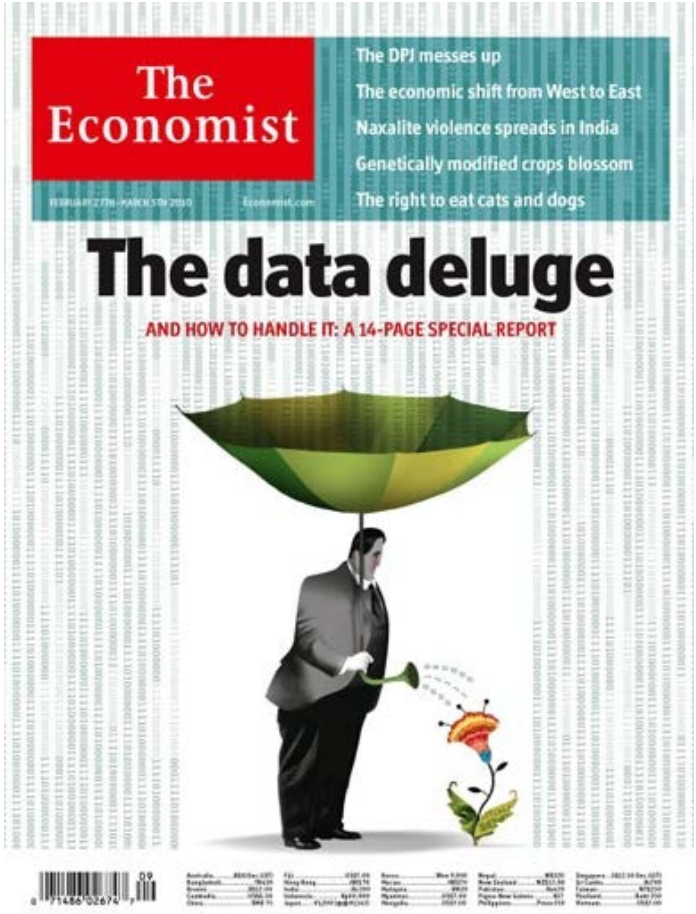
Data ownership and **access – creating a data sharing culture**

Concerns around **data commercialisation**

Workshop – May 4th 2018

Moving the conversation on to identify **solutions** to the challenges posed by Big Data from perspective of **regulators, academia and industry**


The Economist
Theresa May v Brussels
Ten years on: banking after the crisis
South Korea's unfinished revolution
Biology, but without the cells
The world's most valuable resource
Google
Data and the new rules of competition


The Economist
The DPJ messes up
The economic shift from West to East
Naxalite violence spreads in India
Genetically modified crops blossom
The right to eat cats and dogs
The data deluge
AND HOW TO HANDLE IT: A 14-PAGE SPECIAL REPORT

Take home messages

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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

Contact me at alison.cave@ema.europa.eu

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