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SCIENCE MEDICINES HEALTH

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

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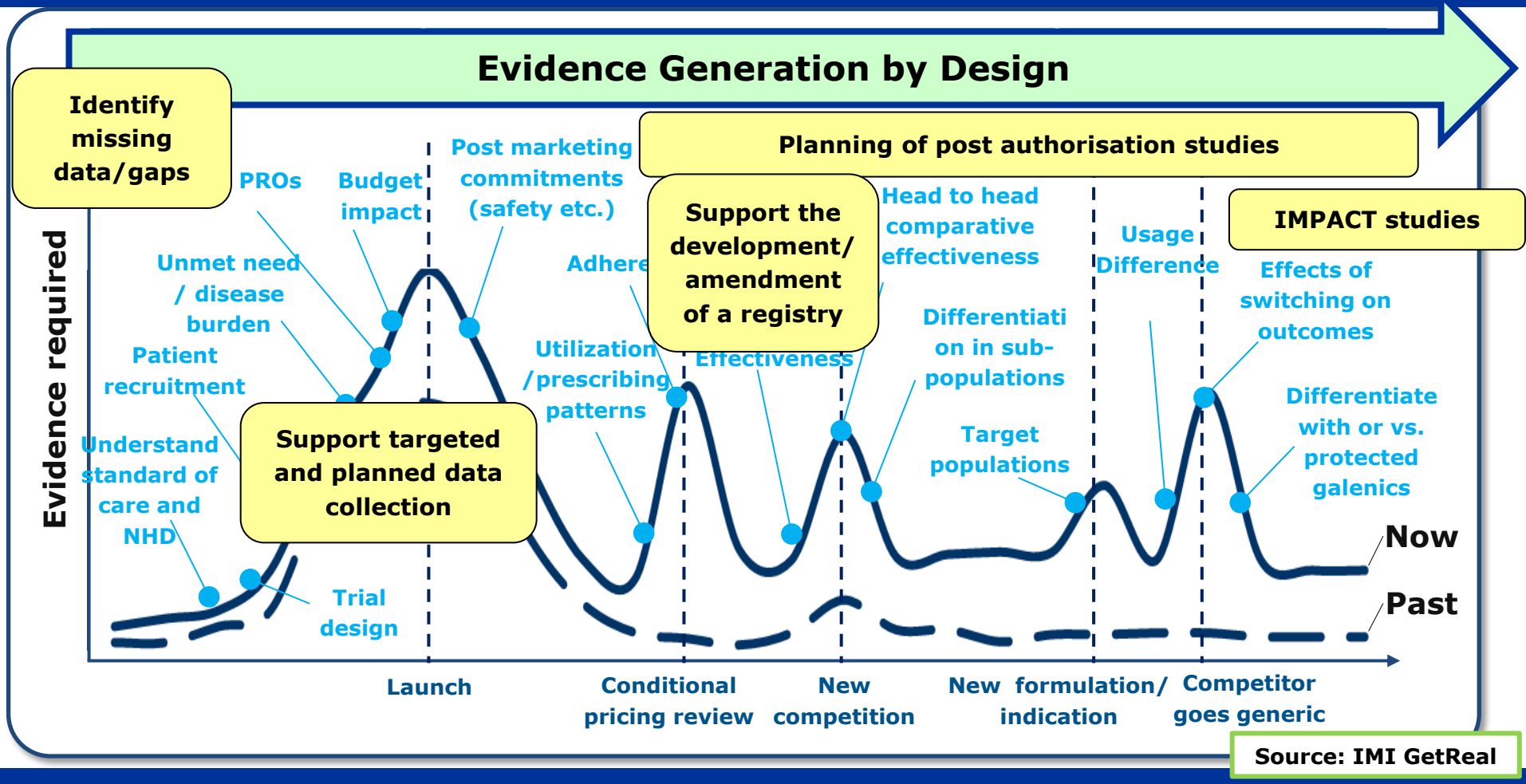

Source: IMI GetReal

Current Mechanisms of Access to RWE

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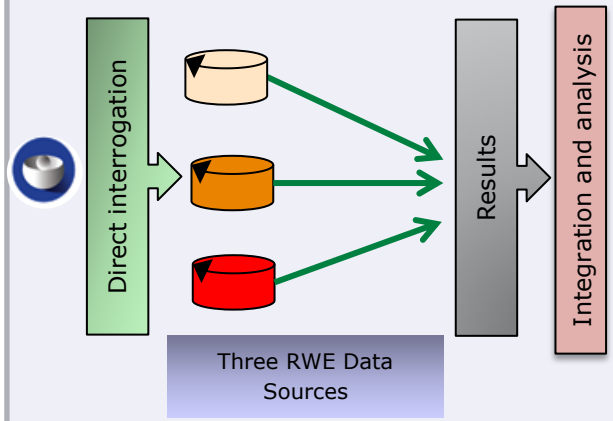
Direct Access



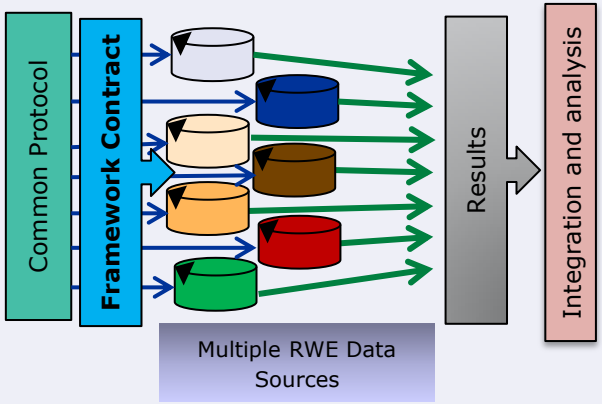
Advantages:

- 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

EMA-funded studies	N databases	N countries
A/H1N1 pandemic vaccines and pregnancy outcomes	1	1
Impact of risk minimisation in patients treated with rosiglitazone-containing products	2	2
Isotretinoin and the effectiveness of the Pregnancy Prevention Programme in Europe	5	3
Patterns and determinants of use of oral contraceptives in the EU	5	3
Monitoring the effectiveness of risk minimisation in patients treated with pioglitazone-containing products	3	3
Risk of cardiac valve disorders associated with the use of biphosphonates	6	3
Association between anxiolytic or hypnotic drugs and total mortality	2	2
Metformin use in renal impairment	2	2
Study of regulatory communication and risk awareness following the Article 31 referral of Combined Hormonal Contraceptives in relation to thromboembolism	n/a	6
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	9	6
Study of utilisation of Combined Hormonal Contraceptives in Europe	3	3
Anti-microbial resistance: choice of therapeutic interventions and outcomes for the treatment of infections caused by MDR Gram negative pathogens	4	1
Methods and data sources for determining long-term effects of drug exposure during pregnancy, with application to antiepileptic medicines	n/a	28
Impact of EU label changes for systemic diclofenac products: post-referral prescribing trends	4	3
Impact of EU label changes for hydroxyzine products: post-referral prescribing trends	4	3

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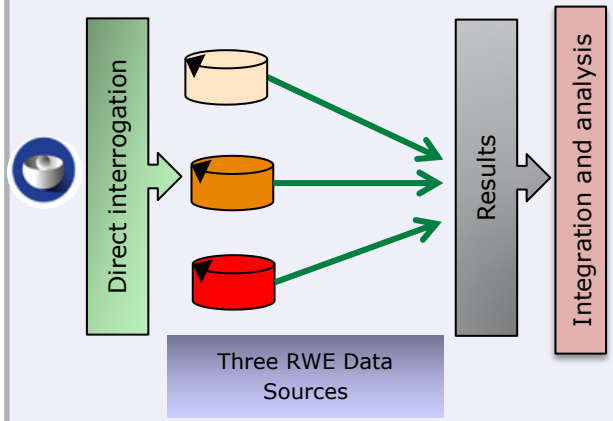

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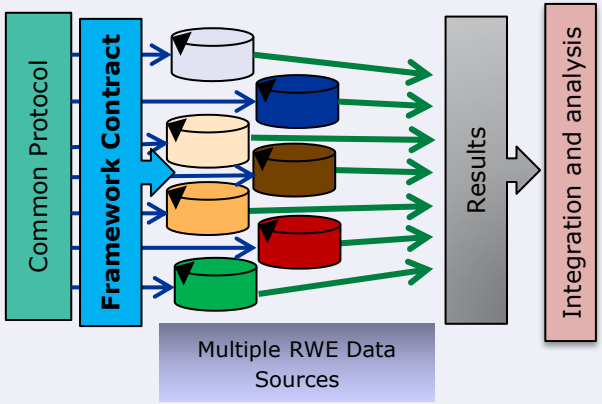

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Limitations:

- 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?

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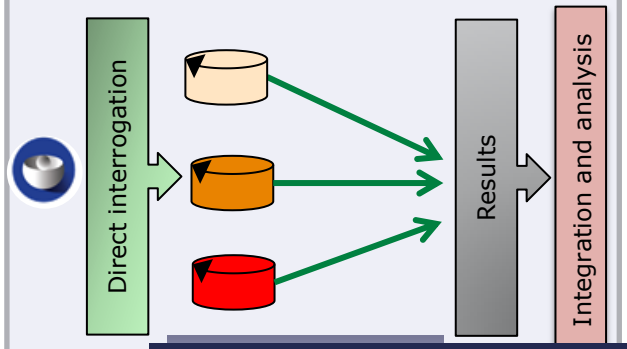

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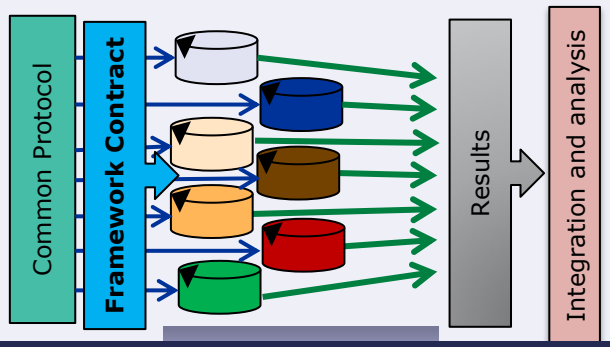

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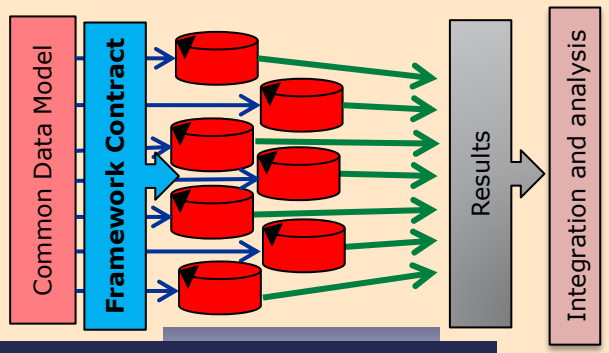
Indirect Access Common Data



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

No one solution – a hybrid approach will be required

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 from large amounts of electronic healthcare data, such as EHRs, insurance claims data and registri… t project delivers access to 99 million patient lives, 2,9 billion dru… and 38 million acute hospital stays

OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

OHDSI is a multi-stakeholder, interdisciplina… t the value of health data through large-scale analytics. All the so… currently the community has converted >50 databases covering …

CNOD…
CANADIAN NETWORK FO…

…work delivers access to the health and prescription … over 40 million people and a widely distributed network of …demic and data analytics experts to rapidly evaluate the … risk/benefit profiles of medicines

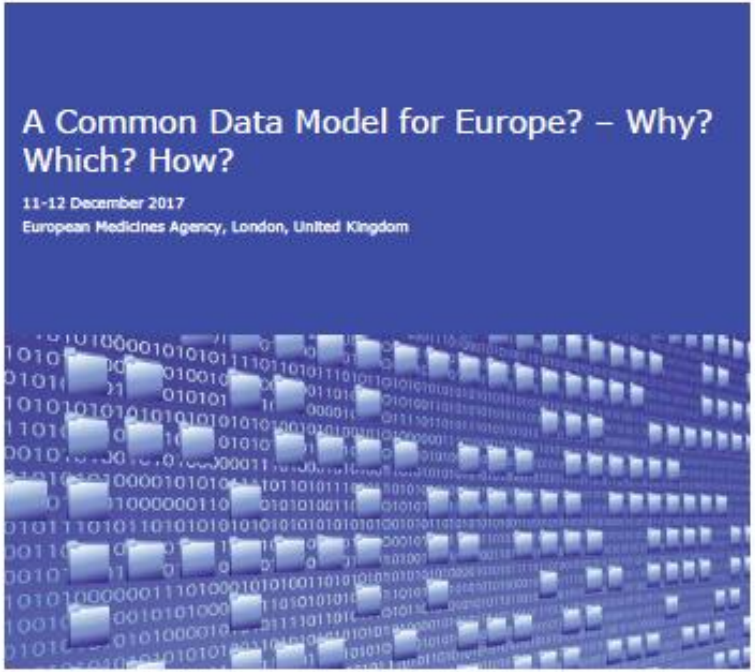
All using or testing a Common Data model. Currently no equivalent pan European network

MID-NET
Medical Information Database Network

MID-NET（Medical Information Database Network）

Multiple Disparate Initiatives Across Europe

Vaccine Safety Datalink (VSD)



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

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- 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**

Big Data Challenges

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

EMA Big Data Workshop – November 2016

- **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**

Key emerging trends and issues identified

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

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.

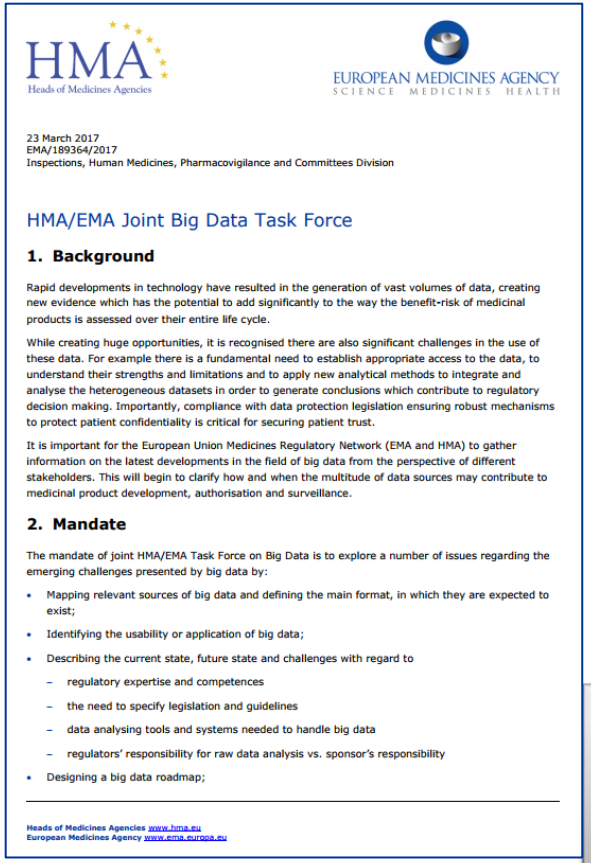
HMA Heads of Medicines Agencies
EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

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



HMA Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
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

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

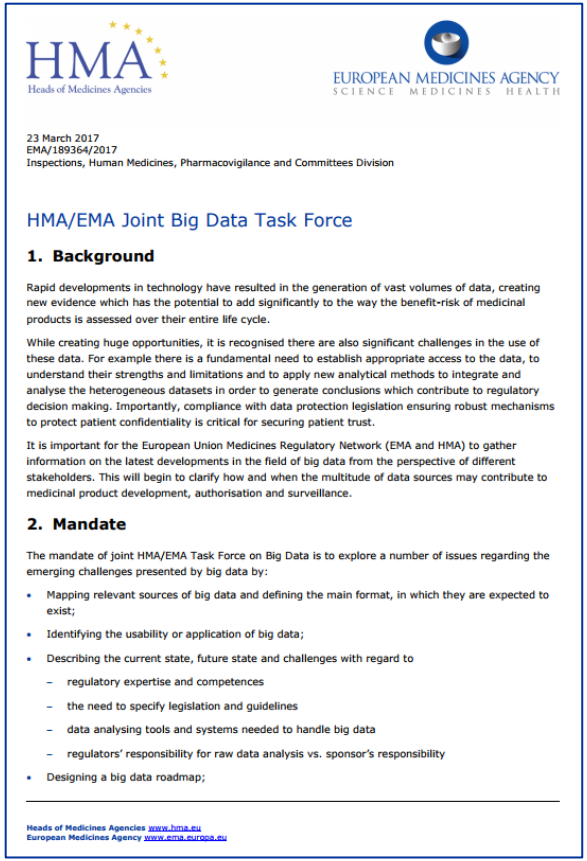
2

3

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**

4



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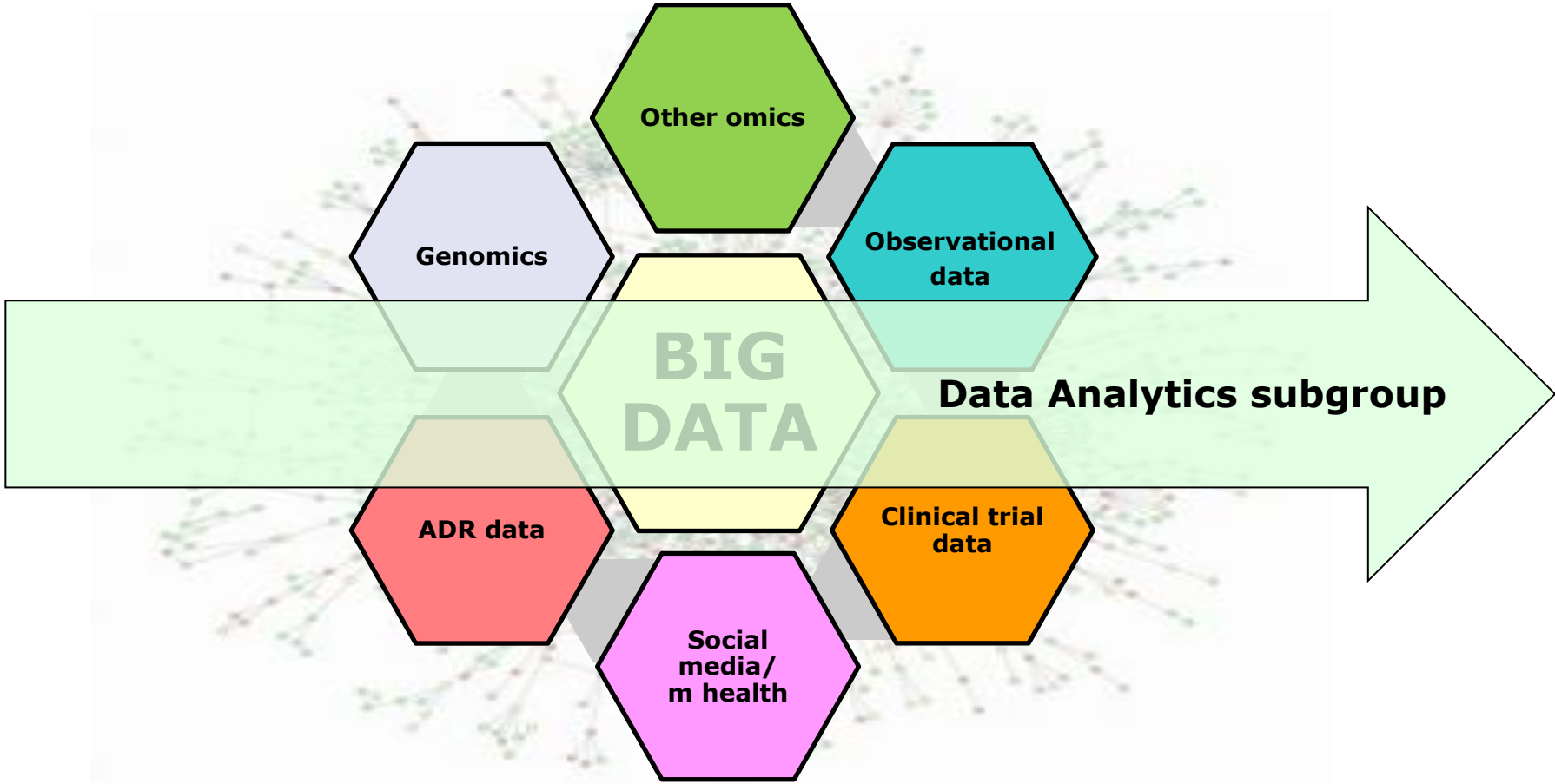
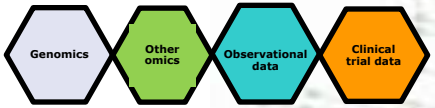

Other omics
Genomics
Observational data
BIG DATA
Data Analytics subgroup
ADR data
Clinical trial data
Social media/ m health

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

Risks

- Funding
- Lack of sustainability
- Overly onerous access
- Limited access
- Duplication
- Future proofing

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

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

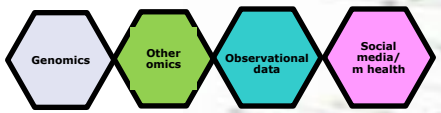
Risks

Funding
Lack of sustainability
Spurious conclusions
Pace of change

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

Acceptability



Challenges

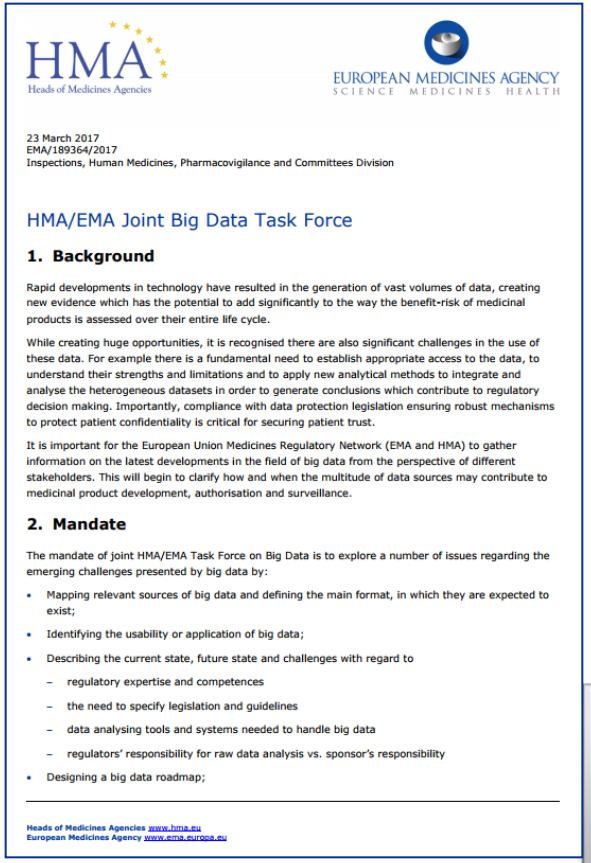
Validation -Differentiating causal from co-incidental
Reproducibility – consideration of sample choice, storage conditions and temporal factors
Large data volumes may increase the precision of measurements –but not necessarily the accuracy
Understanding and quantifying the uncertainty
"Black box" and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



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4 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
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