Co-Creating Real-World Evidence Excellence for Decision-Making:

Meeting Regulatory and HTA/Payer Needs

Moderator: Dr Karen Facey, Evidence Based Health Policy Consultant

22 April 2021

RWE4Decisions REAL WORLD EVIDENCE

Agenda

16h30	Welcoming remarks & Opening Statement
	Jo De Cock, CEO of RIZIV/INAMI
16h40	Introduction to EMA's Guideline on registry-based studies, DARWIN and Big Data Stakeholder Implementation Forum
	Dr Xavier Kurz, Senior pharmacoepidemiologist and head of data analytics, European Medicines Agency
17h00	Panel interventions from HTA/Payer community
	Moderated by **Dr Karen Facey,** Evidence Based Health Policy Consultant • **Dr Roisin Adams**, Head of HTA Strategy and External Engagement, National Centre for Pharmacoeconomics (NCPE) - Ireland • **Dr Antje Behring**, Acting Head of Drug Department, Federal Joint Committee (G-BA) - Germany • **Dr Pier Paolo Olimpieri,** Data Analyst Coordinator, Monitoring Registries Office, Italian Medicines Agency (AIFA) - Italy • **Piia Rannanheimo**, Pharmacoeconomist, Finnish Medicines Agency (FIMEA) – Finland • **Prof Cláudia Furtado**, Head of Health Technology Assessment, Pricing and Reimbursement Division (DATS) and the Information and Strategic Planning Division (INFARMED) – Portugal
17h30	Panel discussion and Q&A with the audience
17h55	Closing Remarks
	Jo De Cock, CEO of RIZIV/INAMI
18h00	Meeting Close

Our speakers today

Welcoming remarks

Jo De Cock
CEO, **INAMI-RIZIV**

Keynote introduction

Dr. Xavier Kurz
Head of Data Analytics,
European Medicines Agency (EMA)

HTA/Payers panel:

Dr Roisin Adams
Head of HTA Strategy and External Engagement, **National Centre for Pharmacoeconomics (NCPE)**

Dr Antje Behring
Acting Head of Drug Department, **Federal Joint Committee (G-BA)**

Prof Cláudia Furtado
Head of HTA, Pricing and Reimbursement Division, **National Authority of Medicines and Health Products (INFARMED)**

Dr Pier Paolo Olimpieri
Data Analyst Coordinator, Monitoring Registries Office, **Italian Medicines Agency (AIFA)**

Piia Rannanheimo
Pharmacoeconomist, **Finnish Medicines Agency (FIMEA)**

Welcoming remarks

Jo De Cock, CEO INAMI-RIZIV

INAMI-RIZIV

RWE4Decisions REAL WORLD EVIDENCE

What is RWE4Decisions?

WHAT?

Pragmatic and agile **Learning Network on RWE focused on HTA/Payer needs**

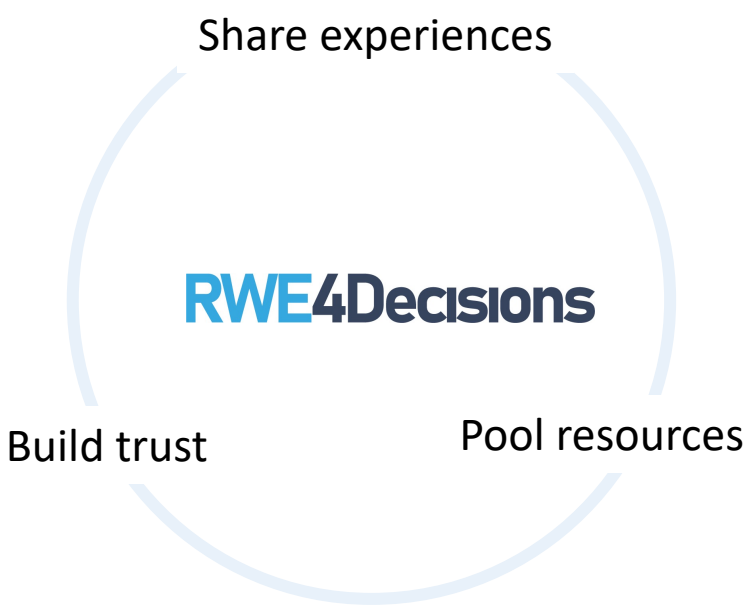
To improve evidence-informed decision-making on highly innovative technologies

WHO?

Involves HTA bodies/Payers, regulators (EMA), patient representatives, researchers, clinicians/ERNs, data analyst, industry, academics...

WHY?

Encourage development of robust RWE to address the operational, technical and methodological gaps



WHY DISTINCTIVE?

Payer led (INAMI-RIZIV)

Multi-stakeholder in approach

- Identified actions for each stakeholder group
- Collaborative approach
- Calling for transparent RWD collection and RWE generation

A **'Learning by doing' approach**

RWE4Decisions

Call to Action

RWE4Decisions calls for a Multi-Stakeholder EU Learning Network on Real-World Evidence within the European Health Data Space

RWE4Decisions calls for the creation of a **multi-stakeholder EU Learning Network on Real-World Evidence**, which is based on a transparent governance mechanism. This Learning Network is designed for Member States to implement evidence-based decision-making and:

1. clarify **when, by whom and how** real-world data should be collected in order to generate real-world evidence that **meets the needs of patients and healthcare systems;**
2. be based on a **voluntary mechanism**;
3. be underpinned by **robust methodologies** in alignment with other initiatives.

INAMI-RIZIV

Case study workshops
9 June & 16 June 2021

- **Evidence generation framework**
- **Checklist of needs for reimbursement**
- **When to do an outcomes based MEA**

Webinar series

- **Webinar 1: 22 April**
- **Webinar 2: Sept**
- **Webinar 3: Oct**

RWE4Decisions

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Introduction to the HMA/EMA Big Data Taskforce, DARWIN EU and the Guideline on registry-based studies

Webinar **Co-Creating Real-World Evidence Excellence for Decision-Making: Meeting Regulatory and HTA/Payer Needs**
22 April 2021

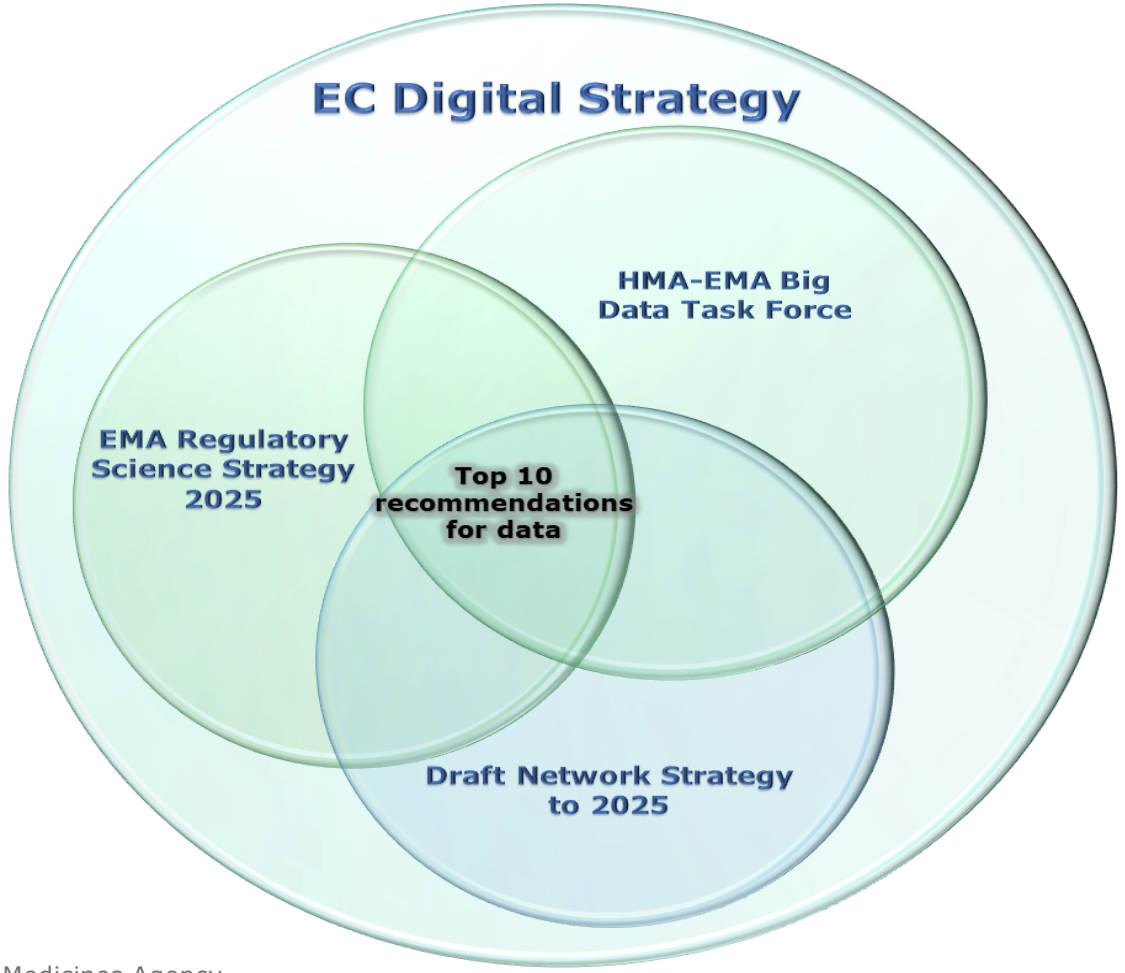
Xavier Kurz,
Head of Data Analytics (EMA),
Data Analytics ad Methods Task Force

HMA-EMA Big Data Task Force

Vision: innovate to turn data into decisions on medicines that create a healthier world

The timing is now!

- Commission digital strategy: **"EU health data space"**
- Joint HMA EMA Big Data Task Force **Top-ten data recommendations**
- **EMA Regulatory Science Strategy to 2025**
- **EU Network Strategy to 2025** includes data and digital pillar
- EC **Pharma Strategy** and **Health Union**



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Big Data Task Force Priority recommendations

1	Deliver a sustainable platform to access and analyse healthcare data from across the EU (Data Analysis and Real World Interrogation Network: DARWIN EU)
2	Establish an EU framework for data quality and representativeness
3	Enable data discoverability
4	Develop EU Network skills in Big Data
5	Strengthen EU Network processes for Big Data submissions
6	Build EU Network capability to analyse Big Data (technology / analytics)
7	Modernise the delivery of expert advice
8	Ensure data are managed and analysed within a secure and ethical governance framework
9	Engage with international initiatives on Big Data
10	Establish an EU Big Data 'stakeholder implementation forum'
11	Veterinary recommendations

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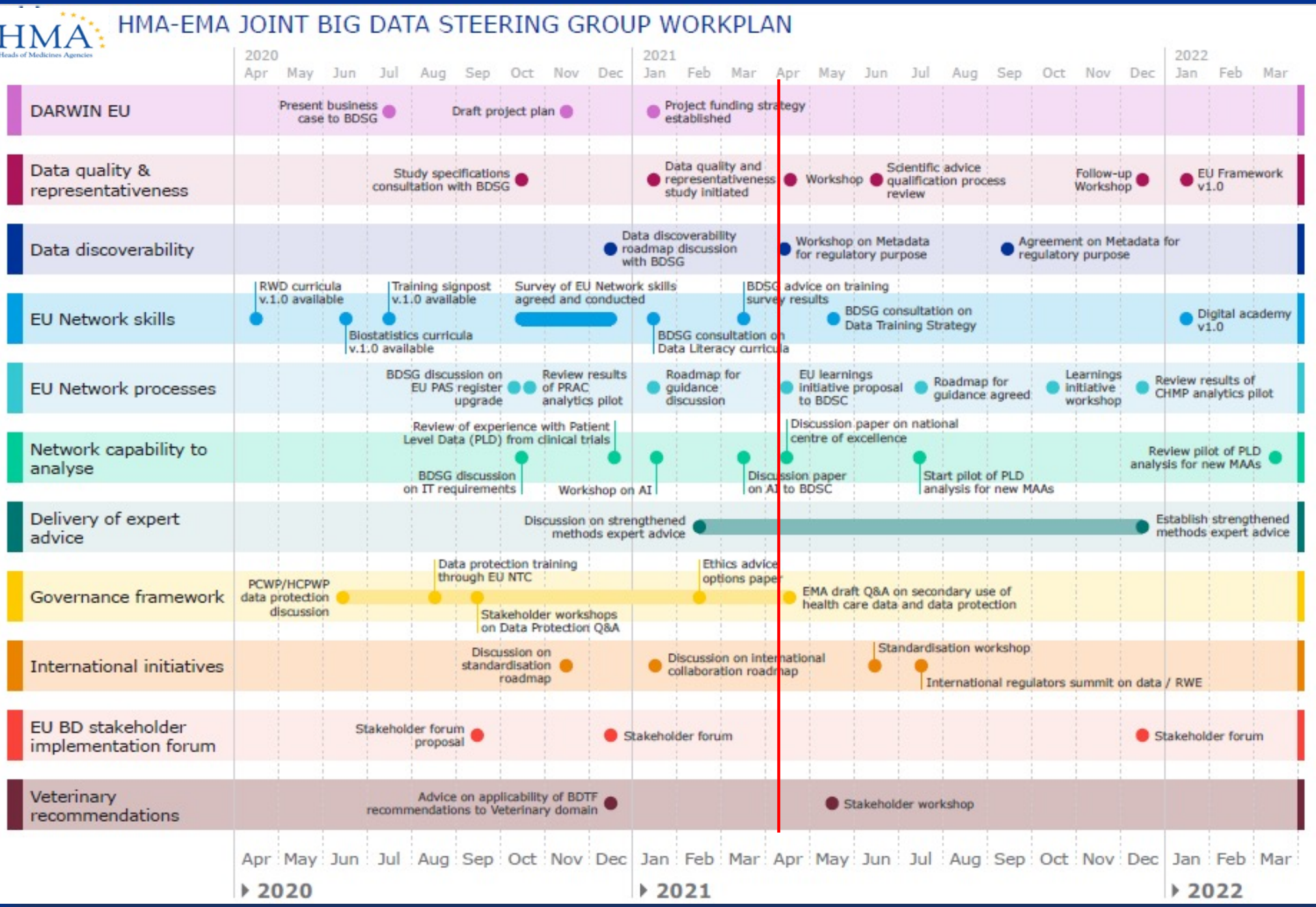
HMA-EMA JOINT BIG DATA STEERING GROUP WORKPLAN



On track with milestones and deliverables

[Making best use of big data for public health: publication of the Big Data Steering Group workplan for 2020-21]

How will the future look …

- **DARWIN EU network as part of the EU Health data space** will support better decision-making throughout the product lifecycle via its network of expertise/partnerships and databases.
- **RWE will be an established source of evidence** as a complement to clinical trials
- **Data will be discoverable and of known quality and representativeness** allowing choice of optimal data source, enabling regulators to expertly assess study results
- **EMA and EU Network will have knowledge and experience** in data science, methods and analytics to advise companies developing products and to expertly assess application dossiers.
- **Learning initiative will allow to continue to** learn and evolve to rapidly be able to answer new regulatory needs, including response to future health crisis.
- **Suite of EU and international guidelines and standards available** to help industry and regulators develop and supervise medicines (built on learnings from submissions of Big Data and enhanced study transparency (EU PAS Register)
- **Full compliance with data protection and ethics** of data sharing
- **Collaboration** with all stakeholders, will be key

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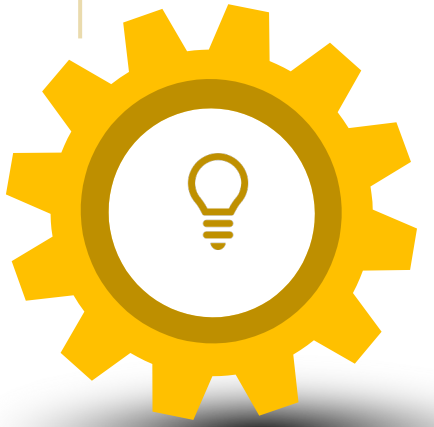
Priority Recommendation – 1 – DARWIN EU

Why

- Current EU access to healthcare data limited
- Complex and slow analysis

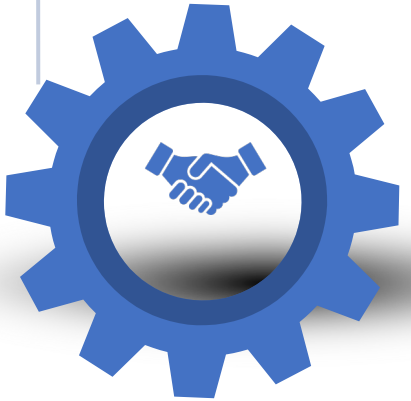


How

- **Establish a network of data, expertise, and services to support better decision-making by EMA and NCA scientific committees (D**ata **A**nalysis **and R**eal **W**orld **I**nterrogation **N**etwork **(DARWIN EU))**

Benefits

- Supports the development, authorisation and supervision of medicines



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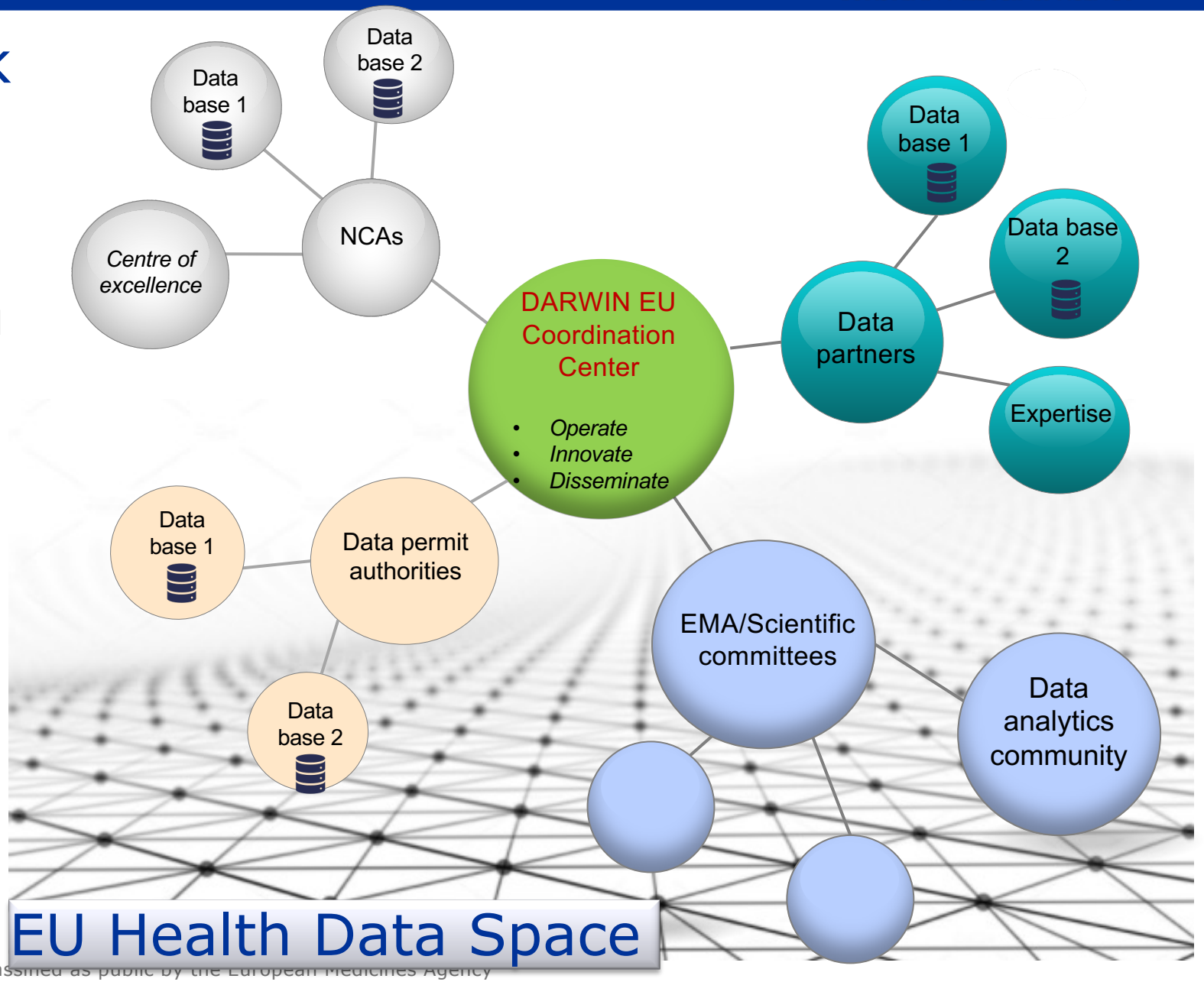
The DARWIN EU network

- Distributed data access for fast analysis
- Federated network - Data stays local, exchange anonymous data and queried remotely
- Hybrid approach:
  - Use of a common data model for fast analysis
  - Use a common protocol
  - Use of rapid analytics software
- Third-party Coordination centre
  - data management / quality activities,
  - study analyses
- Will leverage the EU Health data Space initiative and fully integrated into EC Digital strategy.



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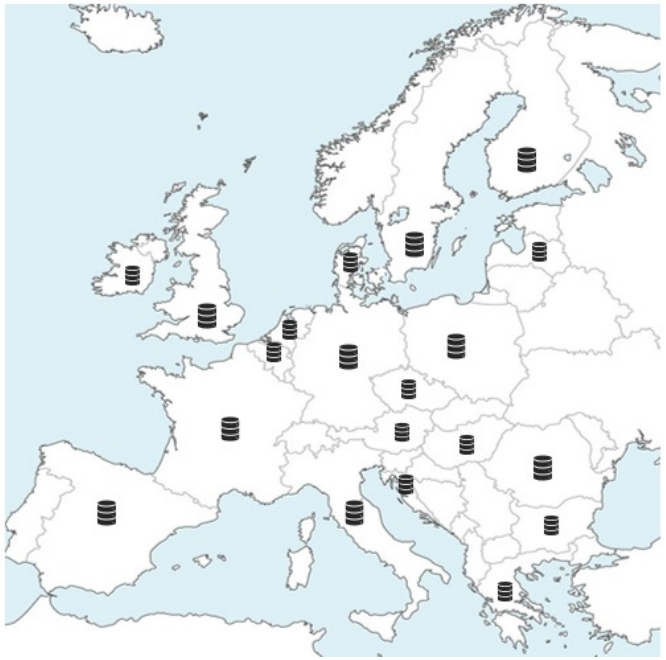
DARWIN EU as pathfinder initiative in EU Health Data Space: evolution

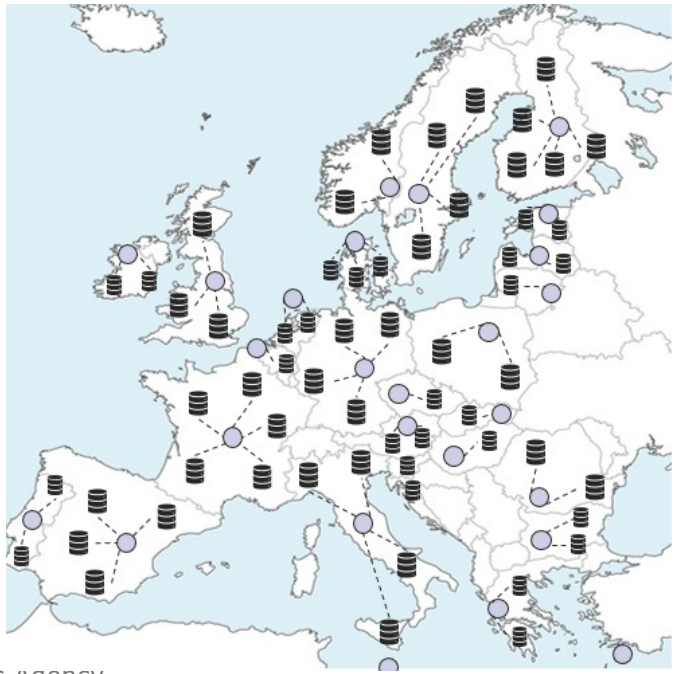
DARWIN EU **2023**

- Coalition of existing datasets
- Federated access data analysis



DARWIN EU **evolution**

- Node in the EHDS
- Includes Data Permit Authorities ( )



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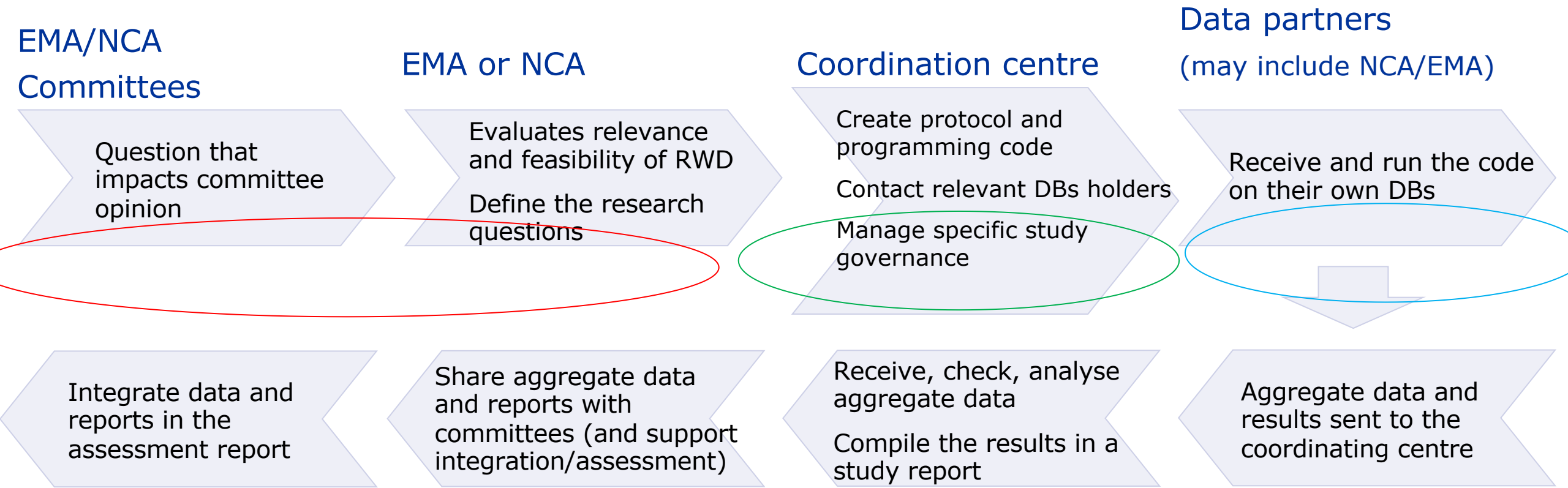
DARWIN EU network operation: EMA/National Agency initiates an analysis



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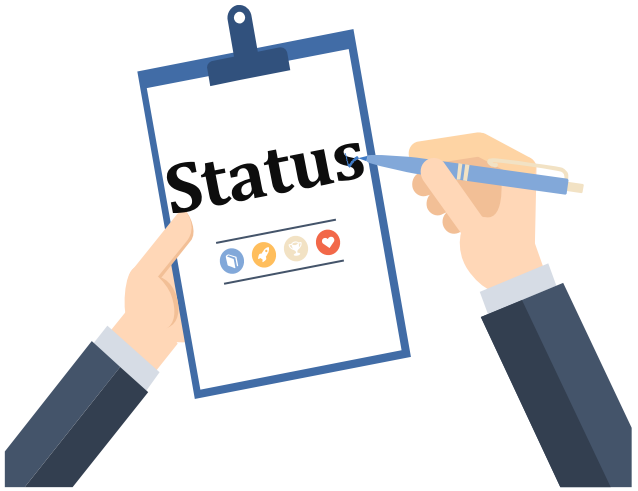
DARWIN EU: Status

Achievements 2020

- Project initiated
- Funding identified including revised EMA fees regulation
- Preliminary delivery model established
- Support Commission to plan pilot with EU Health Data space



Looking forward to 2021

- Develop network skills and processes
- Initiate coordinating centre service establishment
- Governance: DARWIN Network Coordination Group established
- Pilot with EU Health Data space initiated

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Priority Recommendation – 2 – Data quality

Why

- Limited information on quality of data sources and their representativeness
- Need to identify appropriate real-world data sources

How

- **Establish an EU framework for data quality and representativeness**
- Develop guidelines and **a strengthened process for data qualification through scientific advice**
- Promote across Member States the uptake of electronic health records, registries, genomics data, and secure data availability

Benefits

- Recommend best data source to generate evidence for marketing authorisation through scientific advice
- Judge evidentiary value of the results when assessing marketing authorisation applications
- Help NCAs to know their national data including its quality and relevance to regulation by strengthening links to national healthcare data sets

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Priority Recommendation – 3 – Data discoverability

Why

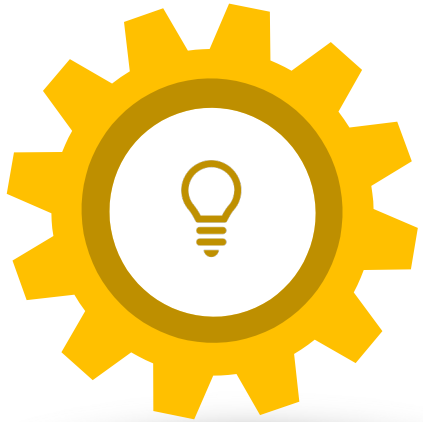
- Lack of knowledge of data in the MSs
- Lack of knowledge on characteristics of such data

How

- **Enable data discoverability** via an external study to **agree key (meta) data that describe a data source**;
- Include key (meta) data in an **enhanced EU resources database** as a sign-posting tool for the most appropriate data,
- Promote the **use of the FAIR principles** (Findable, Accessible, Interoperable and Reusable)

Benefits

- MSs, industry, and academia will have a more comprehensive knowledge of data sources available.
- Supports better drug development and choice of data source for post-authorisation studies.



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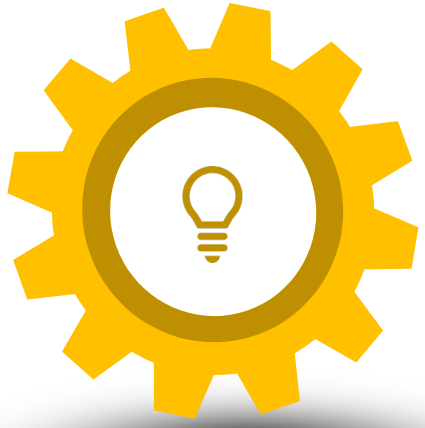
Priority Recommendation – 4 – EU Network skills

Why

- Currently limited skills and knowledge in the EU Network in key Big Data areas, including: statistics, epidemiology, data science, 'omics, advanced analytics / AI / ML.



How

- **Develop big data training curriculum and strategy** based on a skill analysis across the Network, roll-out training, targeted recruitment, collaboration with academia.

Benefits

- EU Network assessors have the knowledge and experience to advise on Big Data sources, to conduct analyses in house, to support assessment of MA applications,
- Enable the EU Network as a reference for data-driven regulation.

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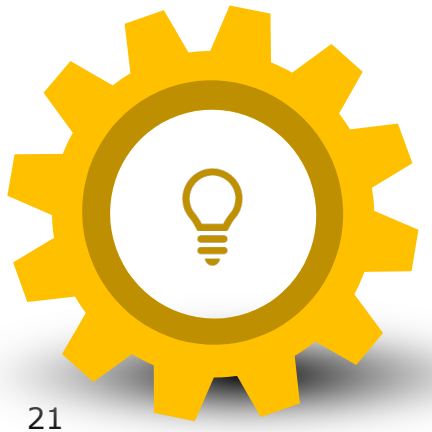
Priority Recommendation – 5 – Regulatory processes

Why

- Currently we have limited experience of scientific advice and of MA application assessments that include Big Data.
- We do not systematically track and learn from the applications we do have.



How

- **Strengthen EU Network processes for Big Data submissions**
- Launch Network "**Big Data Learnings Initiative**" - track and learn from relevant Big Data applications through the product life-cycle and feed learnings to reflection papers and guidance.
- Enhance transparency of Big Data study methods through the **EU Post-Authorisation Studies Register**.

Benefits

- Forms the foundation of guidance for the industry.
- Each submission received and study posted in the register feeds the knowledge of the EU Network and its assessors.

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EMA Study on use of RWD/RE in marketing authorisation applications (MAA) and Extensions of Indication (EoI)

Objective

To characterise RWD/RWE submitted in marketing authorisation applications and line extensions for new indications in 2018-2019 and its contribution to benefit-risk decision-making.

Methods

- Identification of all CAPs with submission for MAA and Type II variations for line extension between January 2018 and December 2019
- Exclusion of MAAs for generics, informed consent, well established use & duplicate applications
- Manual review of Final CHMP Report and Rik Management Plan (data lock: 31 August 2020)
- Other reports and documents consulted for additional information if applicable (e.g. D180 CHMP Rapp/co-Rapp report for withdrawn products, PASS protocol, …)
- Extraction of data using standard form by 6 investigators from DAT (Sep-Dec 2020)
- Verification by two independent reviewers of sample of MAAs reviewed by each investigator

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Working definition of RWE

INCLUDED AS RWD/RWE

- Non-interventional pre- or post-authorisation studies with primary or secondary data collection
- Use of real-world data source (e.g. registry, electronic health care records, medical charts, etc.) with observational design in the context of clinical trials (e.g. representativeness of control groups, comparator groups)
- Analyses of patient-based observational data in the context of the MAA (e.g. natural history of disease, drug utilisation of reference Rx)
- Published articles of product-related non-interventional studies (e.g. on safety or effectiveness of the product in other indications)
- Product related literature review

NOT INCLUDED AS RWD/RWE

- Non-product related literature review (e.g. on epidemiology of the disease)
- Use of aggregated epidemiological data
- Interventional studies (Phase I, II), including pre-clinical studies, toxicological studies, dose-response studies, drug-drug interaction studies
- CT without RWD/RWE use (e.g. single-arm study without comparator group from RWD)
- Open-label follow-up studies of clinical trial patients
- Routine pharmacovigilance activities in RMP
- Active surveillance based on spontaneous reporting
- Surveys not based on individual patients (e.g. surveys of physicians to assess awareness of risk minimisation measures)

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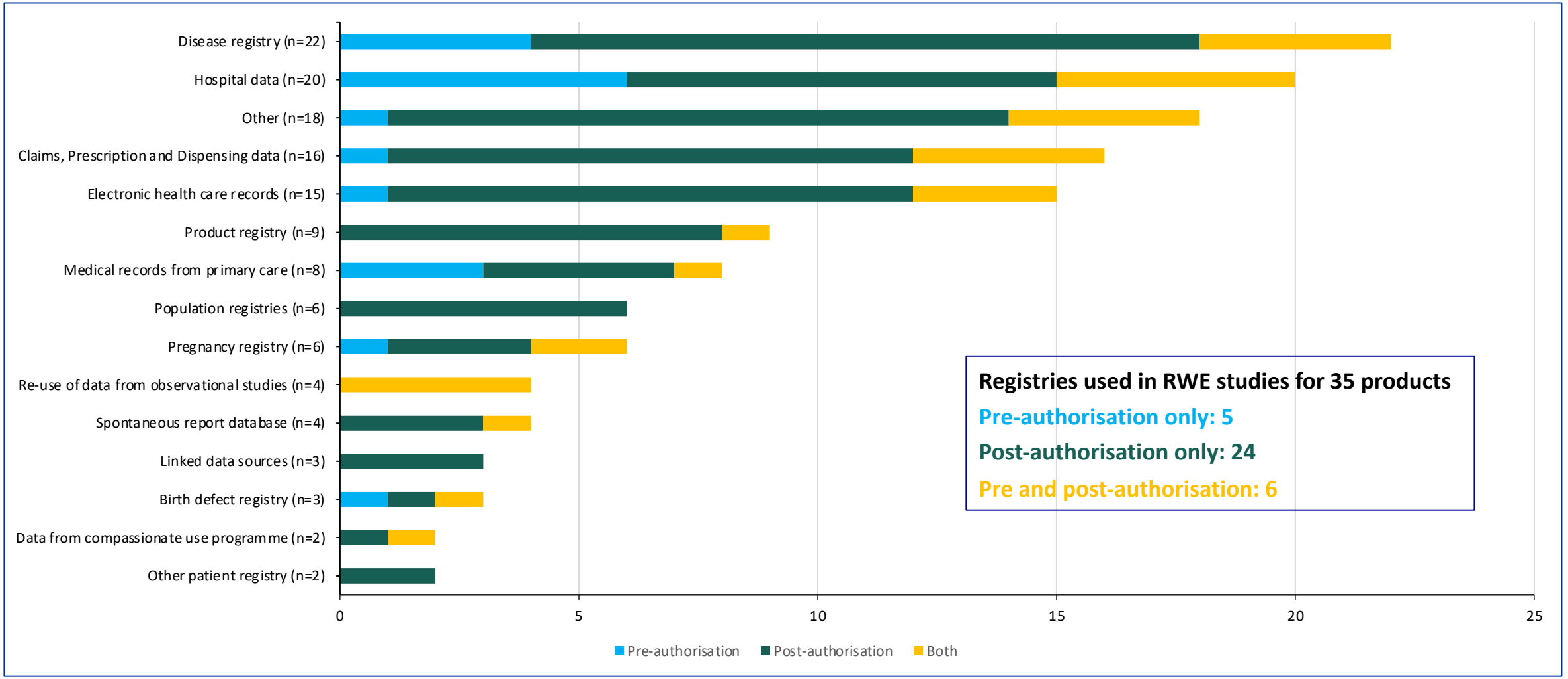
Preliminary results: MAAs

RWE studies (n=138), products submitted (n=63)

Type of data sources used



** Example of "Other": follow-up questionnaires of cases of medication errors, medical charts, data sources not specified. "Other" is mainly selected in combination with other specified data sources*

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Guideline on registry-based studies - background

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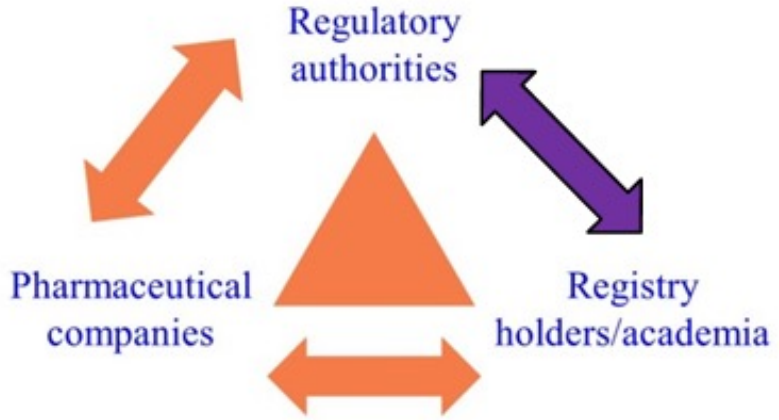
- EMA Patient registry Initiative launched, September 2015

- Aims to facilitate use of disease registries by introducing and supporting a systematic approach to their contribution to the benefit-risk evaluation of medicines

Key components of the initiative

- To promote dialogue between regulators, companies and registry holders to understand barriers and opportunities of using disease registries.

- To provide guidance to clarify methodological concepts and requirements for use of registries for regulatory purpose



Source: Nicola Ruperto, PRINTO

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The Guideline on registry-based studies

Objective:

To provide recommendations on key methodological aspects of registry-based studies and the relevant legal basis and regulatory requirements for MAAs/MAHs

Also relevant to patients and to persons involved in the funding, creation and management of registries, those participating in the collection and analysis of registry data, and those planning to use the registry to perform registry-based studies with a possible regulatory purpose.

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Table of content (1)

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en.pdf

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Table of content (2)

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***Patient registry**: (draft revised definition based on consultation)*

A patient registry is defined as an organised system that collects data and information on a group of patients defined by a particular disease, condition or exposure, and that serves a pre-determined scientific, clinical and/or public health (policy) purpose

***Registry-based study**: (draft revised definition based on consultation)*

Investigation of a research question using the data collection infrastructure or patient population of one or more existing or new patient registries.

Differences between a patient registry and a registry-based study highlighted in terms of: Definition, Duration of follow-up, Patient enrolment, Data collection, Data quality control

No recommendation on when a registry-based study is considerable acceptable for a specific regulatory purpose (case by case basis)

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Feasibility analysis:

To be performed by the MAA/MAH or research organisation initiating the registry-based study in collaboration with registry holders to facilitate the discussion with regulators, HTAs, payers and other parties

- Description of the registry(-ies) (check list derived from ReQuesT tool)
- Availability of the data elements needed for the study and of the capacity to collect any additional ones or introduce additional data collection
- Processes in place for AEs/ADRs and capacity to introduce additional data collection if needed.
- Data on the numbers of registered patients, active patients and patient flows
- Potential selection bias due to inclusion/exclusion criteria
- Potential confounding if some data elements are not available
- Analytical issues that may arise
- Any data privacy issues and governance-related issues
- Overall evaluation of the suitability of the registry for the specific study.

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Questions

EUROPEAN MEDICINES AGENCY

- How could interactions between HTAs/payers and the Big Data Steering Group be strengthened to promote collaborations on the implementation of the ten BDTF recommendations?
- Where do you see the role of HTAs and payers in the DARWIN EU network? Do you envision they could provide research questions directly to the Coordination Centre?
- In such case, where could the research questions be integrated and where could a feasibility analysis be performed (role of EMA for regulatory questions)?
- Do you see a role of pharmaceutical companies in DARWIN EU?
- The Guideline on registry-based studies has been primarily developed to promote better use of disease registries for regulatory purposes. How applicable it is to the needs of HTAs and payers?
- Any major comments on the draft Guideline on registry-based studies published for consultation?

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Thank you for your attention

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Send it to: secretariat@rwe4decisions.com

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