Data submission and evidence generation in Europe – an EMA update

CDISC Japan Interchange 2023

Presented by Marcia Rueckbeil on 10 July 2023
Methodology Workstream, Data Analytics and Methods Task Force, EMA

Meet the speaker

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Biostatistician (Seconded National Expert)

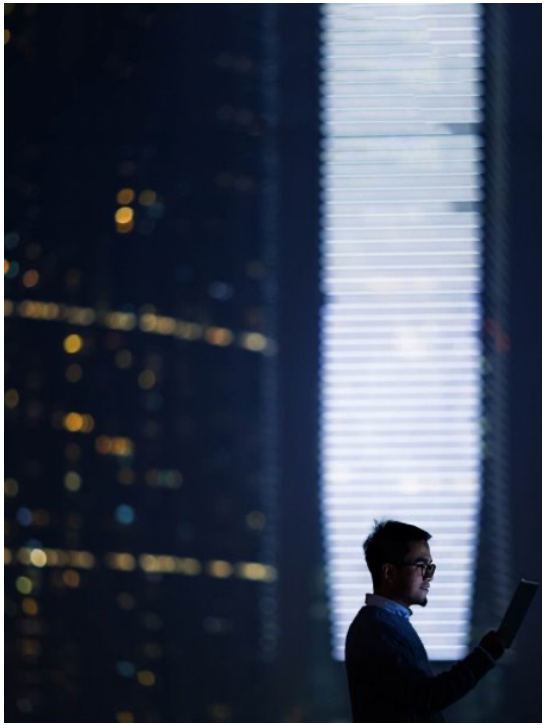
European Medicines Agency - Data Analytics and Methods Task Force

Disclaimer

The views expressed in this presentation are my personal views and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

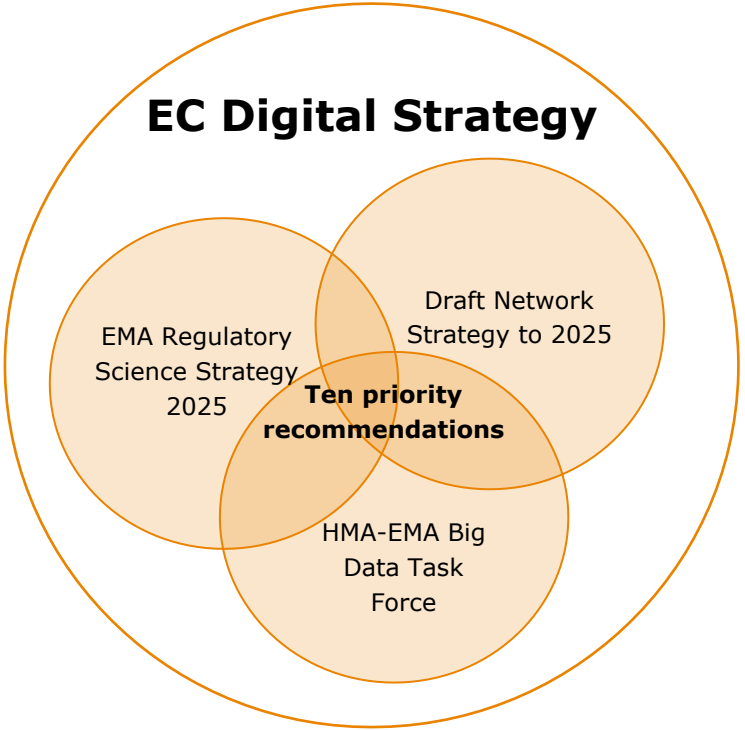
Outline

- Update on selected European activities linked to data standards
  - DARWIN EU ®
  - Submission of individual patient data from clinical trials
  - EU Regulatory Network Data Standardisation Strategy
- The way ahead…



The timing is now…

- Key initiatives referred to the Commission digital strategy **"EU health data space"** (EHDS):
  - **European Medicines Regulatory Network (EMRN) Strategy to 2025** (data & digital pillar)
  - **EMA Regulatory Science Strategy to 2025**
  - **Joint HMA-EMA Big Data Task Force**; and resulting **priority recommendations**
- Synergistic initiatives:
  - **Pharmaceutical strategy for Europe**
  - **European Health Union**



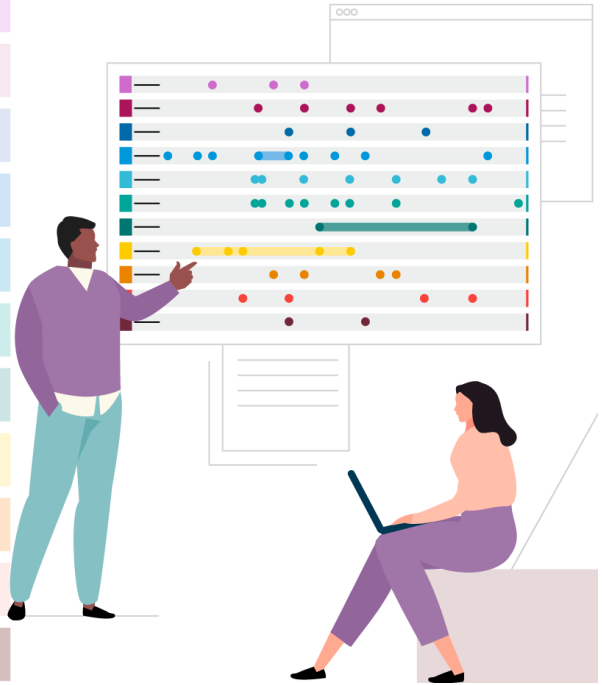
Vision: innovate to turn data into decisions on medicines that create a healthier world

Big Data Steering Group workplan 2022-2025

[HMA/EMA joint Big Data Steering Group (BDSG) workplan 2022-2025]

Framework - to enable use of data and facilitate its integration into regulatory decision making

- DARWIN EU
- Data quality & representativeness
- Data discoverability
- EU Network skills
- EU Network processes
- Network capability to analyse
- Delivery of expert advice
- Governance framework
- International initiatives
- Stakeholder engagement
- Veterinary recommendations



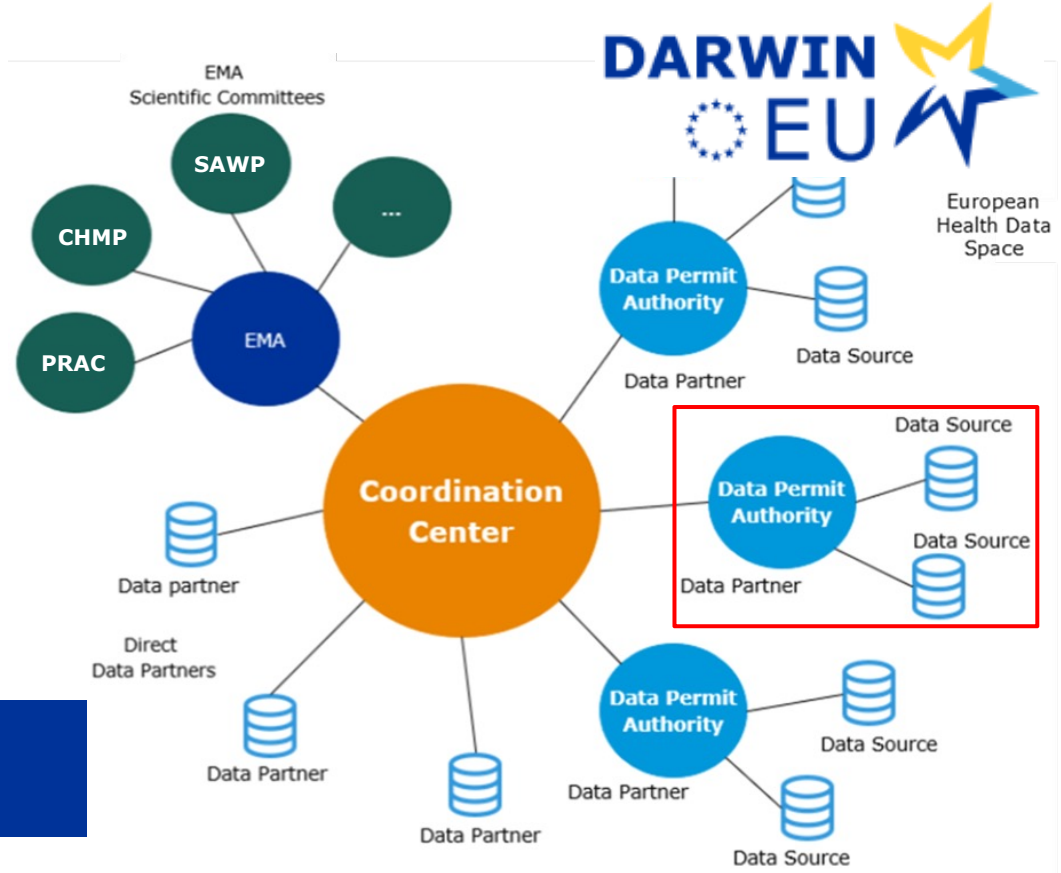
Data Analysis and Real-World Interrogation Network - DARWIN EU ®

Data Analysis and Real-World Interrogation Network

A **federated network** of **data**, **expertise** and **services** that generates **evidence from real world healthcare data**

NETWORK PRINCIPLES

- Data stays **local**
- Use **Common Data Model** (where applicable)



By 2025 DARWIN EU® will deliver 150 RWE studies annually

DARWIN EU ® data partners – year 1 (2022)

10 data partners in 2022 (year 1), additional 10 data partners in 2023 (year 2)

UK

1. Clinical Practice Research Datalink (CPRD GOLD)

Belgium

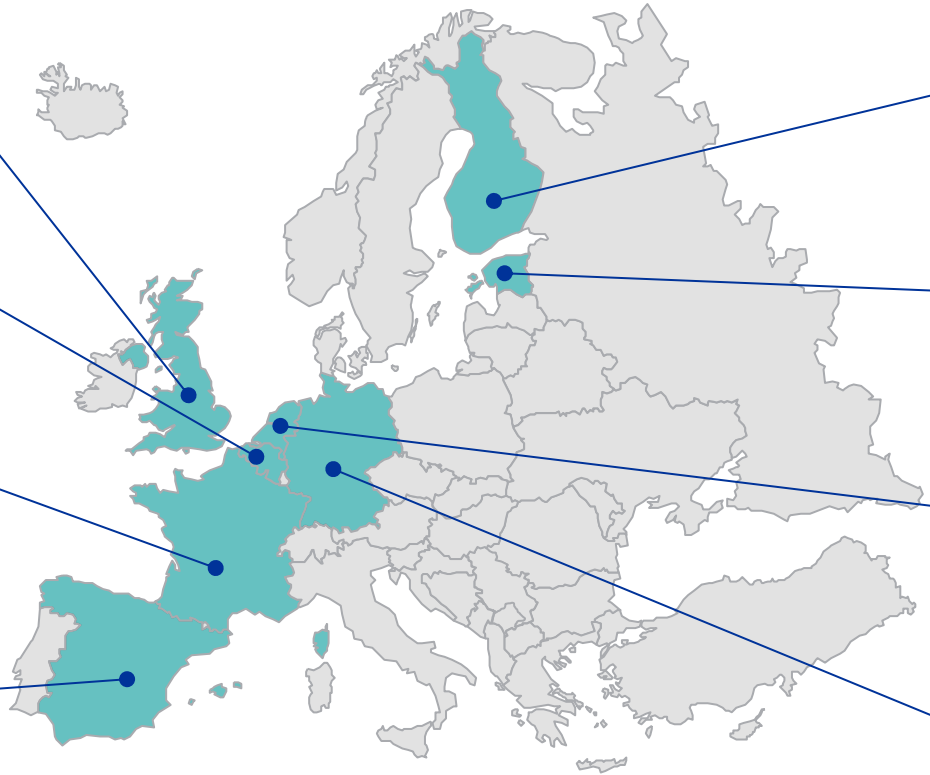
2. IQVIA Belgium Longitudinal Patient Data

France

3. Bordeaux University Hospital

Spain

4. IDIAPJGol
5. Parc Salut Mar Barcelona, Hospital del Mar (IMIM)



Finland

6. Auria Clinical Informatics at Hospital District of Southwest Finland (HDSF)

Estonia

7. University of Tartu (Biobank)

Netherlands

8. Integrated Primary Care Information
9. Netherlands Comprehensive Cancer Organisation

Germany

10. IQVIA Germany Disease Analyser

~26 million active patients

DARWIN EU ® completed or ongoing studies - year 1

Studies	Data Partners	Planned RWE use
Population level **epidemiology** study on **prevalence** of **rare blood cancers** from 2010 (link)	NL, ES, UK, BE, DE	Support EMA's Committee for Orphan Medicinal Products (COMP) on decision about orphan designation; potential background rate for other committees
Patient level **drug utilisation** study of **valproate-containing medicinal products** in women of childbearing potential from 2010 (link)	NL, ES, UK, BE, DE, FI	Assess the use of valproate after safety referral
Patient level **drug utilisation** study of **antibiotics** on the Watch list of the WHO AWaRe classification, 2010-2021 (link)	NL, FR, ES, DE, UK	Inform EMA's Pharmacovigilance Risk Assessment Committee (PRAC)/Committee for Medicinal Products for Human Use (CHMP) decision making, antimicrobial resistance strategy
Background all-cause **mortality rates** in patients with **severe asthma aged ≥12** years (link)	NL, ES x2, UK, EE	Support CHMP post-authorisation, inform future decision making

... Additional **16 studies** to follow this year (2023), addressing needs from different committees, European Centre for Disease Prevention and Control (ECDC)/Vaccine Monitoring Platform, Health Technology Assessments/payers, European Health Data Space (EHDS)……..

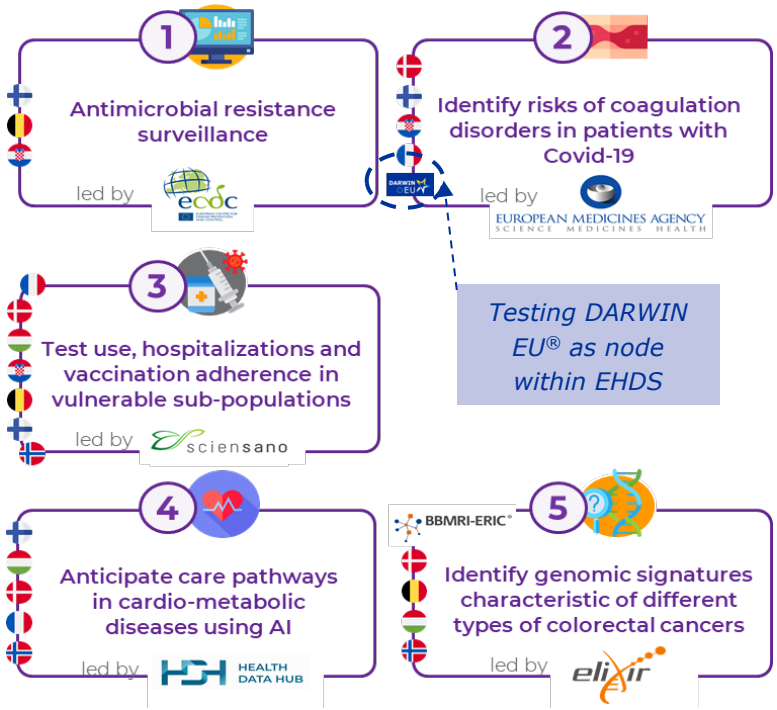
European Health Data Space (EHDS) - pilot

European Health Data Space proposed in EC legislation to enable **effective use of health data**

- Primary use of health data for care (MyHealth@EU)
- Re-use or secondary use of health data (HealthData@EU)

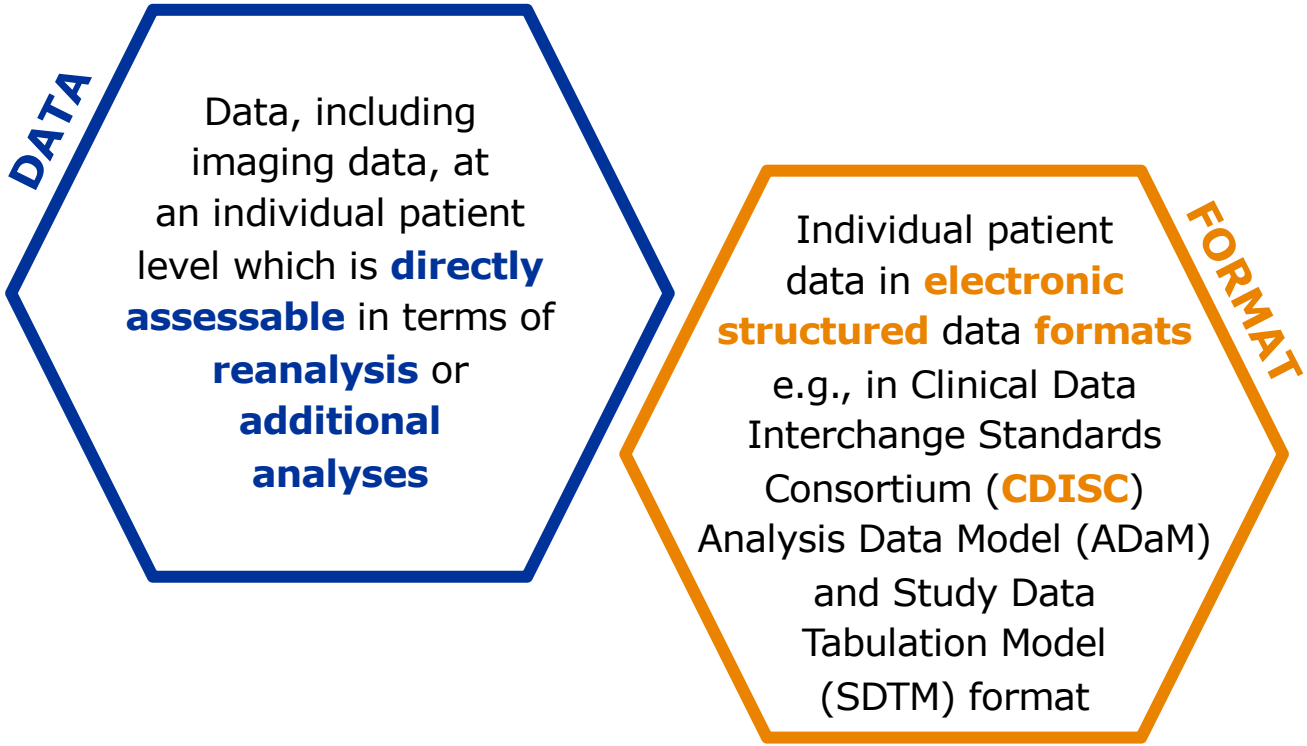
Secondary use of data: 2-year pilot kicked off in Oct 22 (HealthData@EU pilot)

- **Five use cases** to inform design, development, and deployment of HealthData@EU frameworks
- EMA-led use case on blood clots in Covid-19 patients, testing **integration of DARWIN EU®**
- **Learnings** on governance, IT infrastructure, data quality, data availability and **data standardisation approaches**



Submission of individual patient data from clinical trials

Definition of ‘raw data’ / individual patient data



EMA's Raw Data project

- Determine **regulatory benefit of access to raw data**, resulting in recommendations to EMA's **Committee for Medicinal Products for Human Use** (CHMP)
- Support **EU Regulatory Network** to understand and **take informed decision** on the place of analysis of **raw data for future regulatory submissions**

- Put in place **procedures and safeguards to process clinical trial raw data,** in accordance with data protection legislation
- Perform a **proof-of-concept pilot** to establish the value of individual patient data and to build, step by step, capacity to analyse raw data

Raw Data Pilot - overview

- **Timeline:** Approx. **10 regulatory procedures over 2 years** from September 2022 (interim report after 12 months)
- **Scope: Initial marketing authorisation applications** and **post-authorisation applications**. Focus on data from **clinical trials**
- **Participation:** Procedures will be selected based on **voluntary participation of CHMP Rapporteur teams** and **companies**
- **Usage:** Analysis of clinical data to inform assessment of underlying dossier. Information on analysis methods and results will be **shared with company**, asking them to **replicate the analyses**
- **Resources:** Three **resourcing scenarios for data analysis** will be explored: the CHMP Rapporteur team, EMA staff or EMA contractors

Data access and analysis – learnings so far

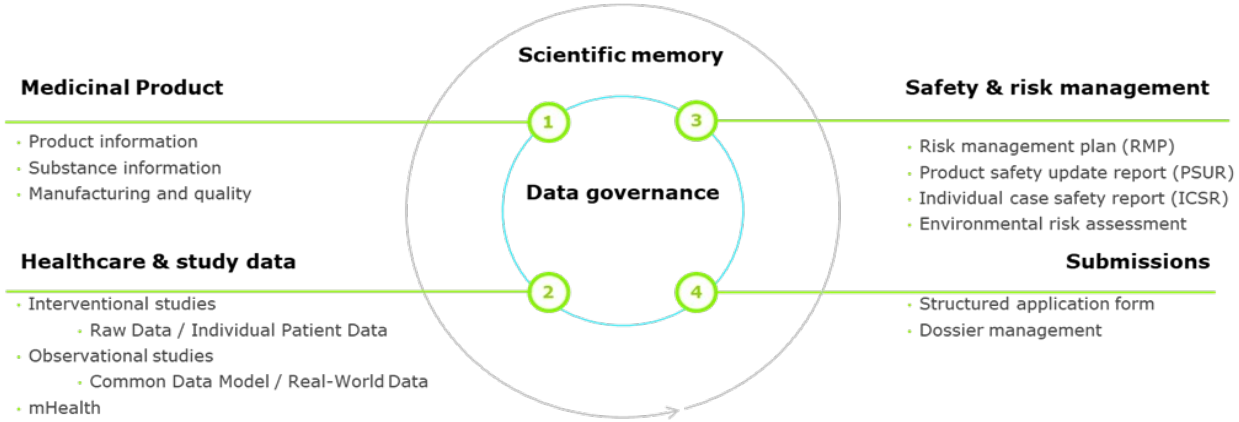
- **Submission of raw data packages** to EMA
  - Stand-alone submission via Gateway (in addition to main dossier); not subject to eCTD validation
  - Data submission meeting
- Raw data received **compliant with CDISC standards** (SDTM, ADaM)
  - Pinnacle 21 used by EMA's contractor (DKMA) for validation
  - XPORT transport format as requested by FDA and PMDA; other formats, e.g. JSON and XML, can be agreed
  - Data definition files in CDISC Define-XML format
- **Statistical software** explored
  - SAS and R for statistical analysis
  - SAS JMP clinical for visualisation

Register your interest to participate in the pilot with a specific procedure: rawdatapilot@europa.eu

European Medicines Regulatory Network – Data Standardisation Strategy

Data standardisation strategy - recommendations

European Medicines Regulatory Network **Data Standardisation Strategy** (link) **recommendations**



Published in Dec 2021

Data standardisation strategy - scope & aim

- Adopted by **BDSG** and **European Network Data Board**; aligned with **EMRN Strategy to 2025**
- **Maintain over time** to reflect changes in priorities and new requirements
- Objectives:
  - enable **quicker adoption of international data standards**
  - support **adaptation of existing** and **development of new data standards**
  - **improve data quality**
  - enable **data linkage and data analysis** to support medicine regulation

HMA
Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE · MEDICINES · HEALTH

16 December 2021
EMA/447502/2021

European Medicines Regulatory Network Data Standardisation Strategy

Adoption by Big Data Steering Committee	16 September 2021
Adoption by European Network Data Board	8 October 2021
Endorsed by Heads of Medicines Agencies	24 November 2021
Endorsed by EMA Management Board	15-16 December 2021

See websites for contact details

Heads of Medicines Agencies www.hma.eu
European Medicines Agency www.ema.europa.eu

The European Medicines Agency is an agency of the European Union

Active recommendations and related activities

Product information

Pilot implementation of **electronic product information standard,** based on FHIR (link).

Further integration with **IDMP and SPOR** systems following completion of the pilot.

Interventional studies

Support development of **ICH M11 structured clinical trial protocol,** plan proof of concept implementing FHIR resources (link).

Raw data pilot includes feedback on **CDISC standards for clinical trial data**.

Observational studies

Consider **extension of clinical trial protocol standards** to observational studies.

For **DARWIN EU**, decision to use **OMOP Common Data Model** (link).

Structured application form

Consider extension of electronic application form FHIR messages to support **pre-application phase** activities.

DADI project implements FHIR messaging; add forms for different procedures over time.

Dossier management

Review use of **FHIR messaging** for regulatory data and document exchange.

Replace current eCTD 3.2 system for regulatory data exchange with new **eCTD 4.0 system** (HL7 V3 messaging).

What’s next?

The way ahead…

DARWIN EU ® - Upscaling

- Ten additional data partners will be onboarded in 2023 (open call for expression of interest: www.darwin-eu.org)
- Increase capacity of studies and pilot use cases with stakeholders

Submission of individual patient data - Data landscape & data standards

- Pilot interim report in Q4 2023
- Quality and manufacturing structured data
- Non-clinical data (CDISC SEND standard)

Data Standardisation Strategy - Implementation

- Stepwise approach to support NCAs, Network systems and effective change management
- Support collaboration & coordination within EU Regulatory Network
- Support work with international regulators on common requirements by setting out EU needs and direction

Any questions?

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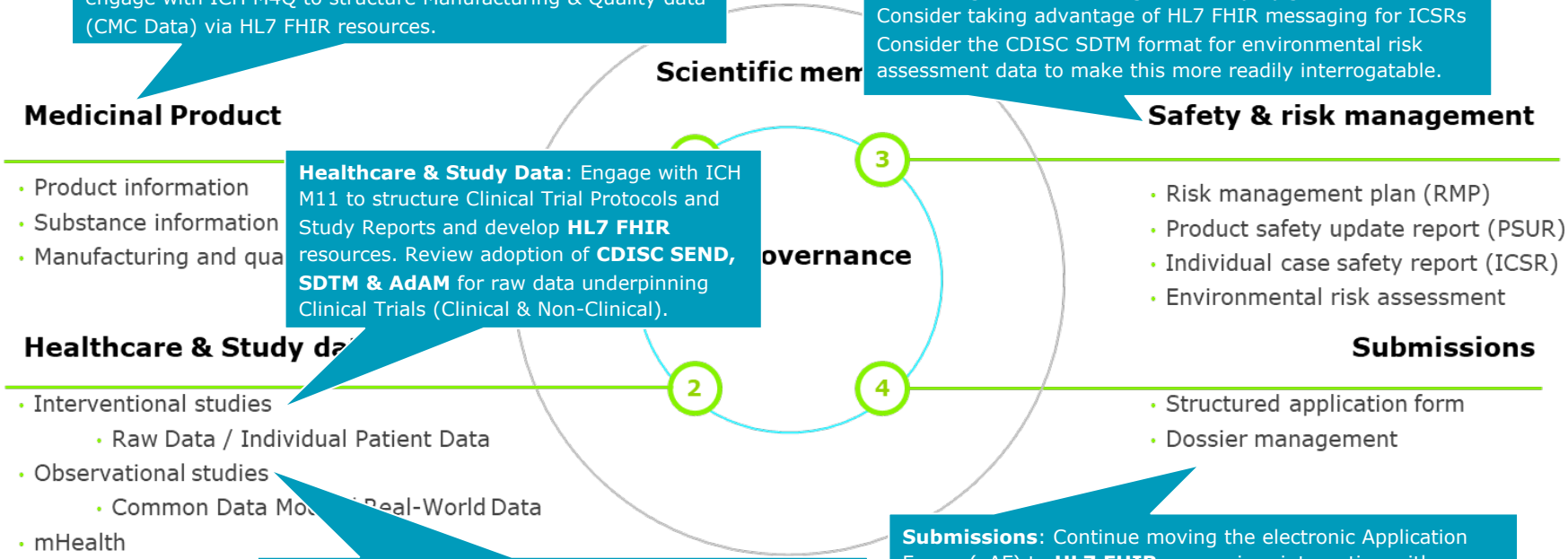
Back-up slides

Data Standardisation Strategy Recommendations

Medicinal Product: Continually expand and improve the **HL7 FHIR** standard in terms of product and substance information. Build on **ISO IDMP**, extensions introduced as part of **ePI** and engage with ICH M4Q to structure Manufacturing & Quality data (CMC Data) via HL7 FHIR resources.

Safety & Risk Management: Consider developing a new standard for eRMPs following ICH E2E guidelines. Consider structuring PSURs following ICH E2C (R2) guidelines. Consider taking advantage of HL7 FHIR messaging for ICSRs Consider the CDISC SDTM format for environmental risk assessment data to make this more readily interrogatable.



Healthcare & Study Data: Engage with ICH M11 to structure Clinical Trial Protocols and Study Reports and develop **HL7 FHIR** resources. Review adoption of **CDISC SEND, SDTM & AdAM** for raw data underpinning Clinical Trials (Clinical & Non-Clinical).

Healthcare & Study Data: Consider the possibility of expanding the work on Clinical Trial Protocols and Study Reports to observational studies. Engage in setting the direction for a Common Data Model for Real-World Data via the European Health Data Space and DARWIN EU.

Submissions: Continue moving the electronic Application Forms (eAF) to **HL7 FHIR** messaging, integrating with resources developed for medicinal products. Assess the benefits of **eCTD4** in light of submissions increasingly moving to structured messages.

Quality and discoverability of RWE

HMA/EMA Big Data priorities

- DARWIN EU
- Data quality & representativeness
- Data discoverability
- EU Network skills
- EU Network processes
- Network capability to analyse
- Delivery of expert advice
- Governance framework
- International initiatives
- Stakeholder engagement
- Veterinary recommendations

*DQF & metadata catalogues will **feed** into future EU catalogues*

Collaborative process between
EMA/HMA & TEHDAS

Metadata list for real-world data sources and studies

+

EU's current framework for RWD/RWE

2021

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 October 2021
EMA/426390/2021
Committee for Human Medicinal Products (CHMP)

Guideline on registry-based studies

Oct 2021: Link to document

HMA Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 December 2021
EMA/447502/2021

European Medicines Regulatory Network Data Standardisation Strategy

Dec 2021: Link to document

2022 - 2025

DARWIN EU

2022 – 2025: Data Analysis and Real-World Interrogation Network

2022

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EMA EUROPEAN MEDICINES AGENCY

31 May 2022
EMA/563896/2022

List of metadata for Real World Data catalogues

May 2022: Link to list of metadata

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

enepp European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

EMA/95098/2010 Rev.10

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
(Revision 10)

June 2022: Link to ENCePP guide

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 September 2022
Data Analytics and Methods Task Force
European Medicines Agency

Data Quality Framework for EU medicines regulation

Start of public consultation	10 October 2022
End of consultation	18 November 2022

Comments should be provided using this template. The completed comments form should be sent to dataqualityframework@ema.europa.eu

1 September 2022
EMA/787647/2022
European Medicines Agency

Good Practice Guide for the use of the Metadata Catalogue of Real-World Data Sources
V 1.0

Start of public consultation	27 September 2022
End of consultation	16 November 2022

Comments should be provided using this template. The completed comments form should be sent to metadata@ema.europa.eu

Sept 2022: Link

2023

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 October 2017
EMA/813938/2011 Rev 3*

Guideline on good pharmacovigilance practices (GVP)
Module VIII – Post-authorisation safety studies (Rev 3)

For revision in 2023: Guideline on GVP