Data submission and evidence generation in Europe – an EMA update

CDISC EU Interchange 2023

Presented by Eftychia Eirini Psarelli on 26 April 2023
Methodology Workstream, Data Analytics and Methods Task Force, EMA

An agency of the European Union

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.

Meet the Speaker

Eftychia Eirini Psarelli

Title: Seconded National Expert, Methodology, Data Analytics and Methods Task Force

Organisation: European Medicines Agency

Eftychia is statistician on secondment at EMA in the Methodology Workstream of the Data Analytics and Methods Task Force, where she has been managing EMA's Raw Data project, focusing on utilising raw data to generate evidence for better and more efficient regulatory decision making. Prior to joining the EMA in July 2020, she spent 8 years as a Senior Statistician at the Liverpool Clinical Trials Centre within the University of Liverpool, UK, where she has gained strong analytical skills in the area of statistical programming and data curation.

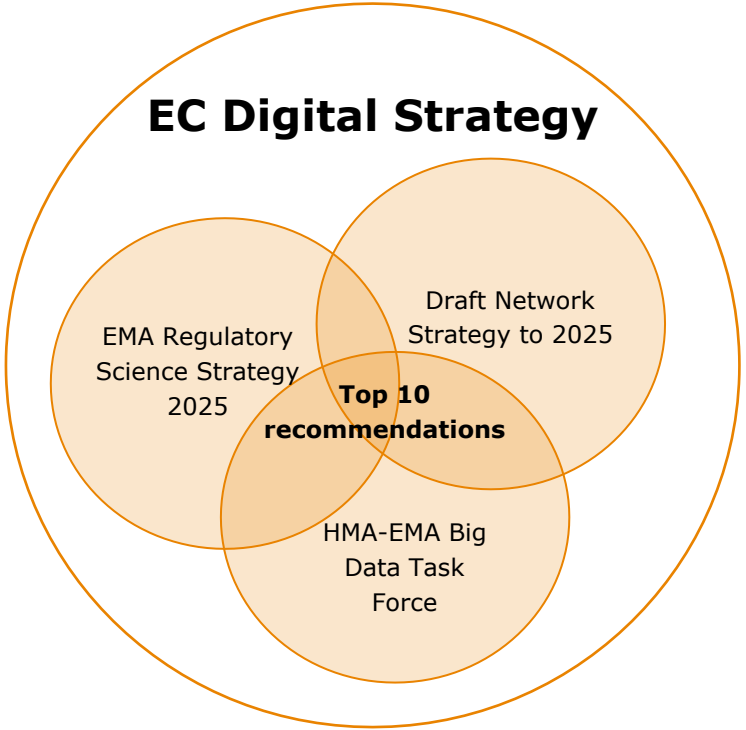
Eftychia fosters EMA activities where data standards can have an added value, particularly for clinical trial data. She is also an observer in Europe's CDISC Coordinating Committee (E3C).

Outline

- Introduction to selected EMA's activities
  - DARWIN EU ®
  - Submission of individual patient data from clinical trials
  - EMRN's Data Standardisation Strategy
- The way ahead…

The timing is now…

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

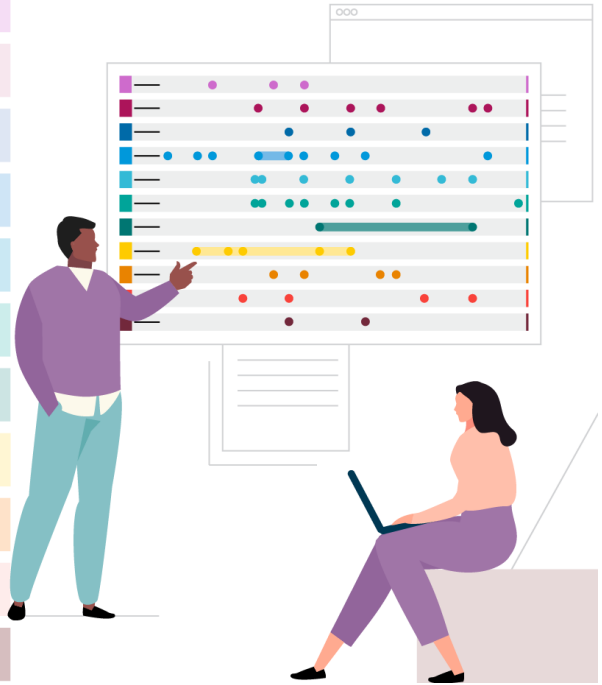


Vision: innovate to turn data into decisions on medicines that create a healthier world

Big Data Steering Group workplan 2022-2025

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



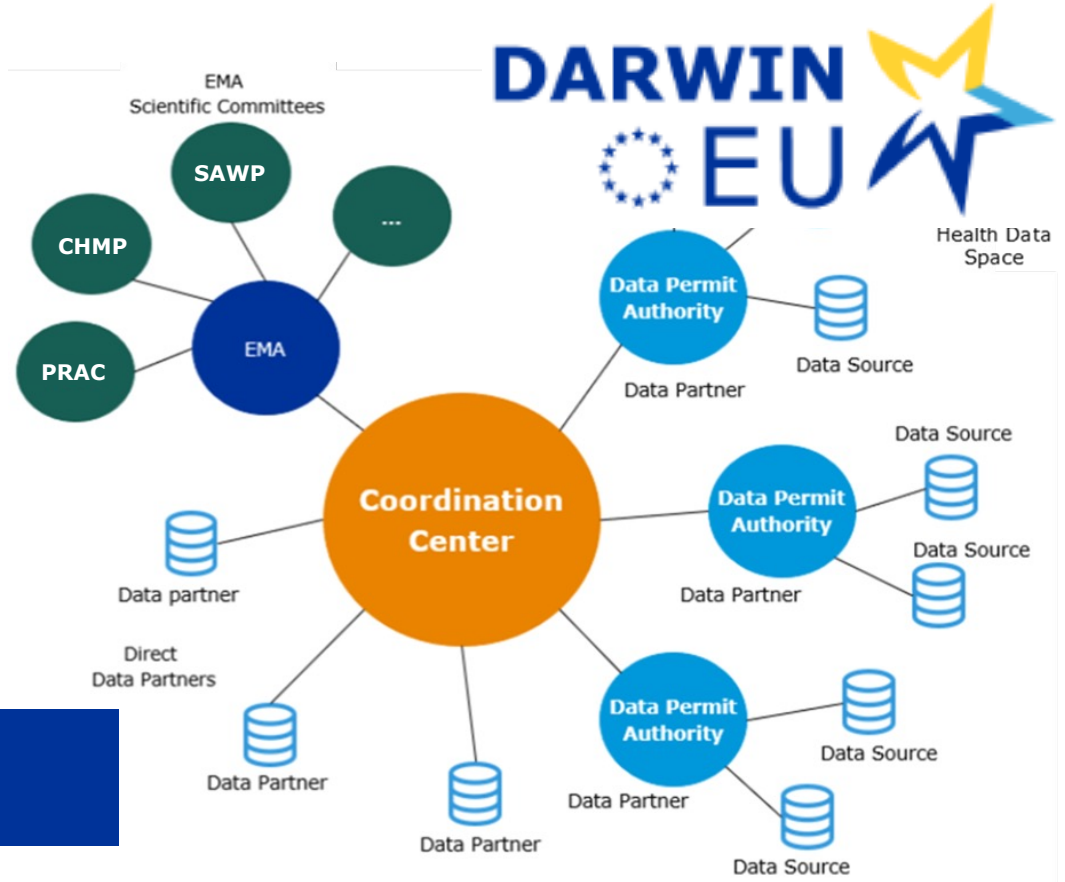
Data Analysis and Real-World Interrogation Network - DARWIN EU ®

Data Analysis and Real-World Interrogation Network

DARWIN EU® is a federated **network** of **data**, **expertise** and **services** that generates **evidence from real world healthcare data**

NETWORK PRINCIPLES

- Data stays **local**
- **Use of Common Data Model** (where applicable) to perform studies in a timely manner and increase consistency of results



By 2025 DARWIN EU will deliver 150 RWE studies annually

DARWIN EU Data partners – Year 1

10 data partners in year one: additional 10 in year 2

UK

1. Clinical Practice Research Datalink (CPRD GOLD)

Belgium

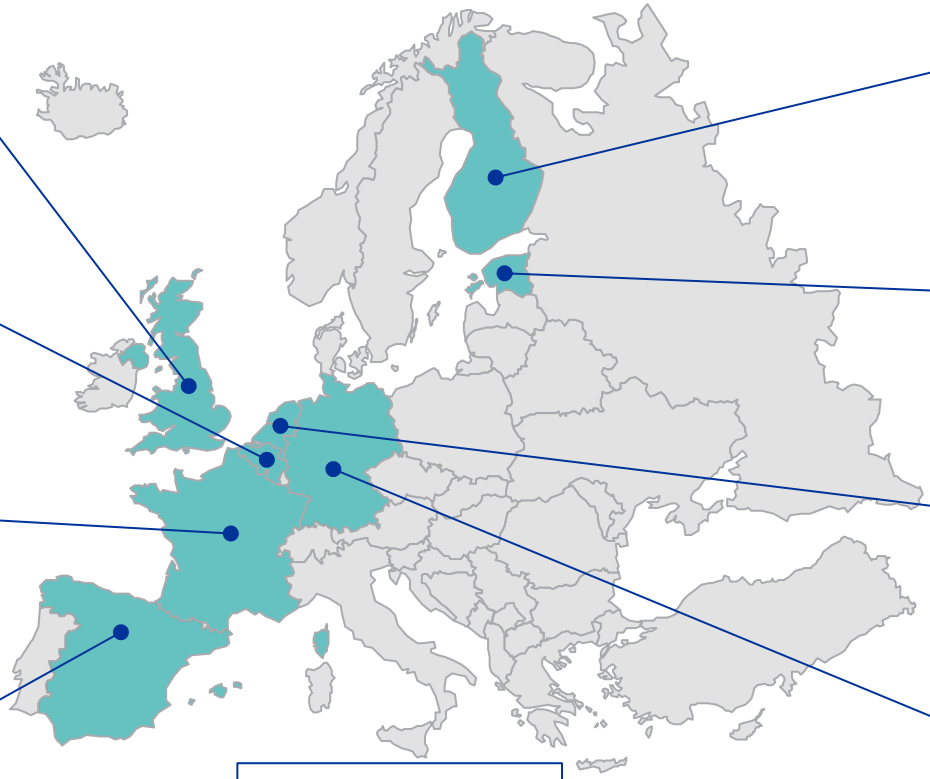
2. IQVIA Belgium Longitudinal Patient Data

France

3. Bordeaux University Hospital

Spain

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



~26 million active patients

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

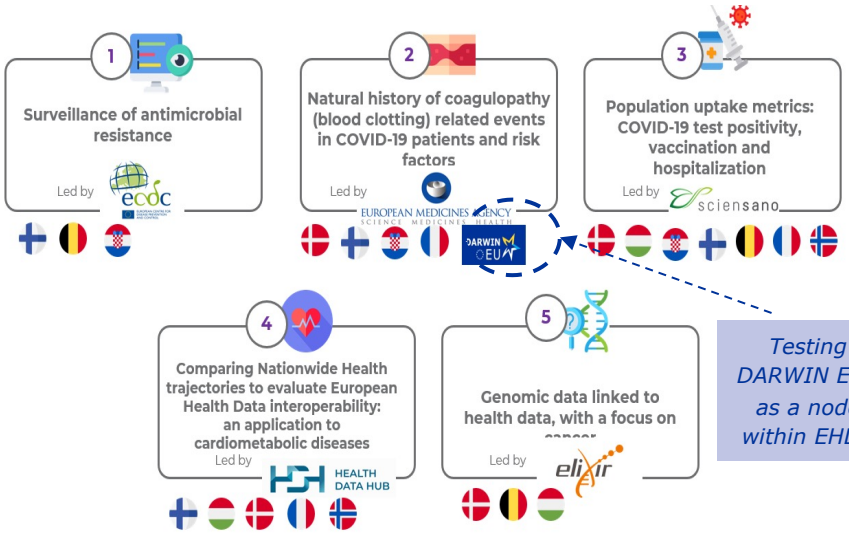
DARWIN EU Completed or Ongoing studies (year 1)

Studies	Data Partners	Planned RWE use
Population level epidemiology study on prevalence of **rare blood cancers** from 2010.	NL, ES, UK, BE, DE	Support EMA's Committee for Orphan Medicinal Products (COMP) in orphan designation decision making & useful as background rates for other committees
Patient level **drug utilization** study of **valproate-containing medicinal products** in women of childbearing potential from 2010	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	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** old	NL, ES x2, UK, EE	Support CHMP post-authorisation inform future decision making

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

European Health Data Space (EHDS) pilot

- EC proposed legislation to establish a European Health Data Space: aims to enable the effective use of health data in the EU
- Covers two aspects: the primary use of health data for care (MyHealth@EU) and the re-use or secondary use of health data (HealthData@EU)
- Secondary use of data: a 2-year pilot phase (HealthData@EU pilot) kicked off in Oct 22
- Five use cases selected to inform the design, development, and deployment of HealthData@EU frameworks*, including a DARWIN EU® - use case on blood clots in Covid-19 patients
  - Integration of DARWIN EU® will be tested
  - *Learnings on governance, IT infrastructure, data quality, data availability and data standardisation approaches

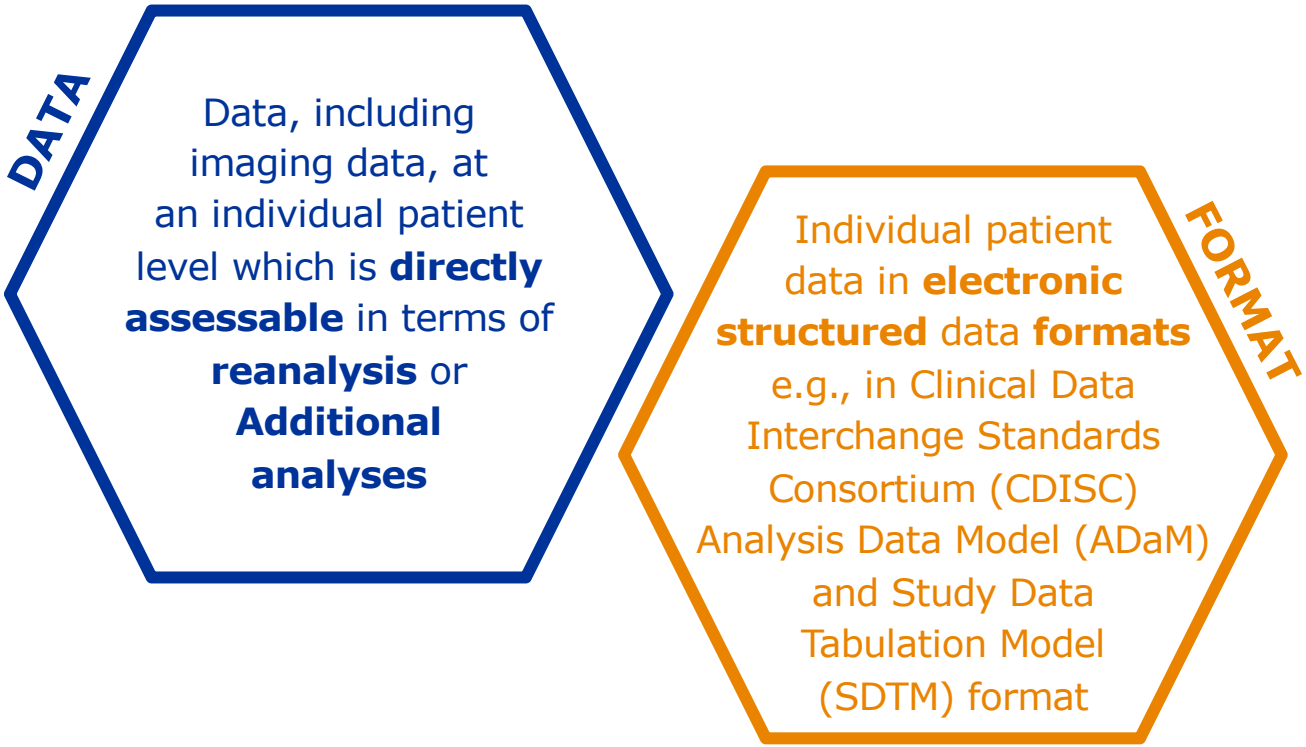


EHDS: we need **R**apid, **W**ide and **D**eep access to healthcare data

Submission of individual patient data from clinical trials

Definitions

Raw data / Individual Patient Data (IPD) / Patient Level Data (PLD) / is **defined** as:



EMA's Raw Data project

- **Determine the regulatory benefit of access to raw data** via **pilots of analysis of raw data** from clinical trials, before coming back with **recommendations to the Committee for Medicinal Products for Human Use** (CHMP)**.**
- Ultimate aim is for **Network to understand and take informed decisions** 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** in order establish the value of IPD and to build, step by step, capacity to analyse raw data.

Raw data pilot – summary

- **Timeline:** Approx. **10 regulatory procedures over two years** from September 2022 (interim report after 12 months).
- **Scope: Initial Marketing Authorisation Applications (iMAAs)** and **post-authorisation applications** (e.g., variations or extensions). No restrictions for clinical characteristics of dossier.
- **Participation:** Procedures will be selected based on **voluntary participation of CHMP Rapporteurs** and **assessment teams** as also **applicants/marketing authorisation holders (MAHs).**
- **Usage:** Analyses that are considered relevant to the assessment will be **shared with the applicant or MAH via the assessment report (AR)** and be used for decision-making by the CHMP. Analyses will be conducted on clinical data (considering modelling & simulation, Good Clinical Practice data).
- **Resources:** Three **resourcing scenarios for who is doing the analysis** are going to be explored: (1) the Rapporteurs' assessment team, (2) EMA or (3) EMA contractor (Danish Medicines Agency - DKMA).

Data access and analysis – learnings so far

- **Submission of data** to EMA via Gateway (eCTD); **no change**
  - Data submission meeting taking place
- Raw data received **complies with CDISC standards** (SDTM, ADaM)
  - Pinnacle 21 was used by EMA's contractor (DKMA) for validation
  - XPORT transport file formats accepted as per FDA and PMDA (other file transport files accepted upon mutual agreement, e.g. JSON and XML)
  - Data definition files in CDISC XML format required
- **Software** being 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

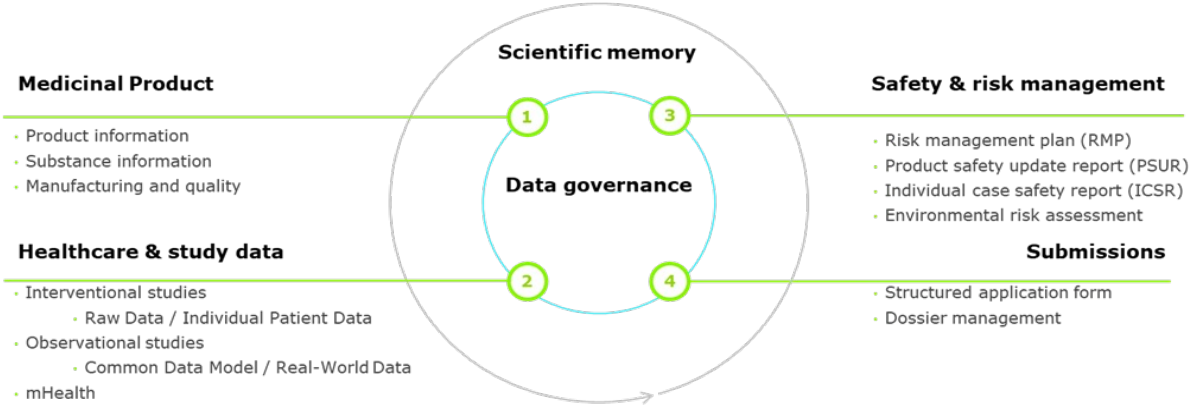
European Medicines Regulatory Network – Data Standardisation Strategy

Data Standardisation Strategy - Recommendations

Published on the EMA Big data webpage:

Direct link

Recommendations:



Data Standardisation Strategy - Aim

- This data standardisation strategy document is an important deliverable of the Big Data Steering Group (BDSG) and will be **maintained overtime** to reflect changes in priorities and additions of new requirements. The strategy has been adopted by both the BDSG and the EU Network Data Board (EUNDB).
- Until now the approach taken to develop and implement data standards has been ad hoc and slow. The creation of a strategy should enable the **reduction of effort and a quicker approach to adopting and implementing data standards**.
- The document will **support the work to create and implement internationally applicable data standards** and to support delivering the Network strategy to 2025

Active recommendations and related activities

Product information

Ongoing activity to develop **an implementation of the current electronic product information (ePI) standard** that has been developed with FHIR resources. Further integration with IDMP and SPOR systems will be undertaken following completion of the pilot.

Interventional studies

The development of the **ICH M11 structured protocol** is being actively supported and a proof of concept implementing FHIR resources is planned. Learnings from the raw data pilot will be assessed by documenting practical learnings, including **feedback on adoption of relevant CDISC standards for the submission of raw data**.

Observational studies

The standard being developed for clinical trial protocols and study design are being reviewed to see if can be extended to included observational studies. Following the **DARWIN EU assessment of Common Data Models** the decision to use **OMOP** was announced in DARWIN EU multi-stakeholder information webinar held in February 2022.

Structured application form

The electronic application form FHIR messages currently being developed is being reviewed to see if they can be extended to support pre-application phase activities and include metadata to run regulatory processes. The **DADI project** is implementing FHIR messaging and will be adding additional forms for different procedures over time.

Dossier management

The use of FHIR messaging for regulatory data and document exchange is being reviewed to see if it is the best option for the future. The **current eCTD 3.2 system** used for regulatory data exchange is being **planed to be replaced with a new system that will use eCTD 4.0** (HL7 V3 messaging).

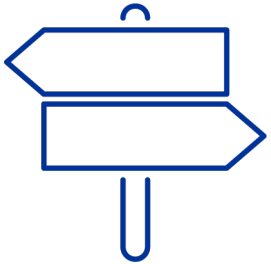
What’s next?

The way ahead…

- **DARWIN EU ® - Additional data partners**
  - Ten additional data partners will be onboarded this year (open call for expression of interest: www.darwin-eu.org)
  - Increasing the capacity of studies and piloting use cases with stakeholders

- **Submission of IPD - Data landscape & data standards**
  - Quality and manufacturing structured data
  - Non-clinical data (SEND standard)
  - Beyond CDISC data format (e.g. CDASH, HL7 FHIR)

- **Data Standardisation Strategy - Implementation**
  - Implementation of standards will follow a stepwise approach in order to support NCAs, network systems and effective change management
  - Will support collaboration and coordination within the EU regulatory Network
  - Will support international regulatory parties on common requirements by clearly setting out EU needs and direction



Any questions?

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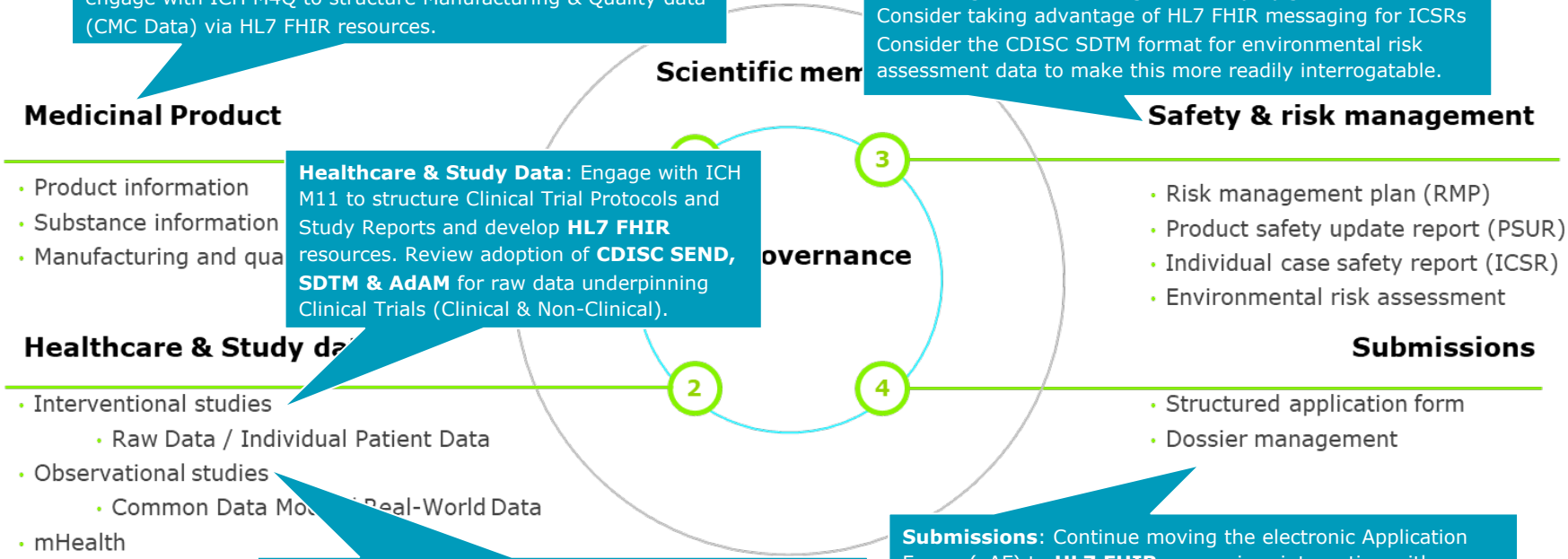
Back-up slides

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