Supporting submission and standardisation of data – an EMA update

CDISC EU Interchange 2024

Presented by Eftychia Eirini Psarelli on 24 April 2024
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

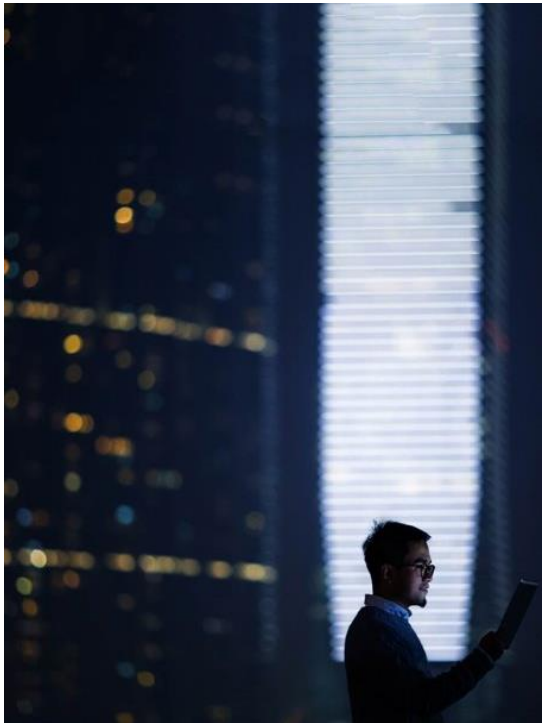
Organisation: European Medicines Agency

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).

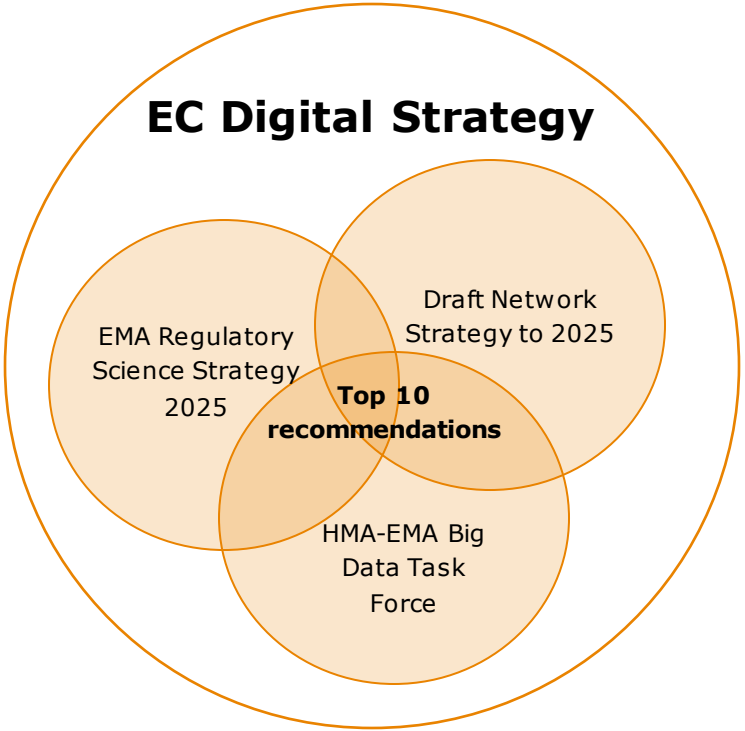
Outline

- Spotlight on selected EMA's activities
  - DARWIN EU ®
  - Catalogues of real-world data sources and studies
  - Submission of individual patient data from clinical trials
  - Submission of non-clinical data in SEND format
- Next steps and synergies with data governance & quality framework



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**

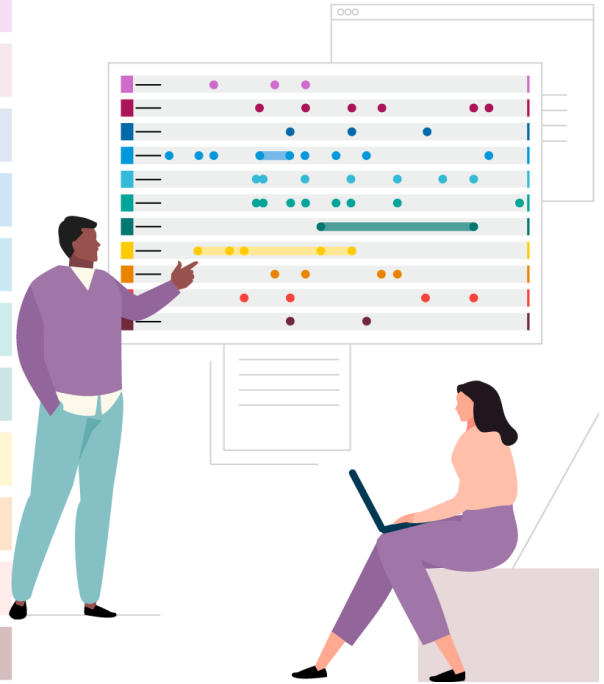


Vision: innovate to turn data into decisions on medicines that create a healthier world

Big Data Steering Group workplan 2023-2025

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

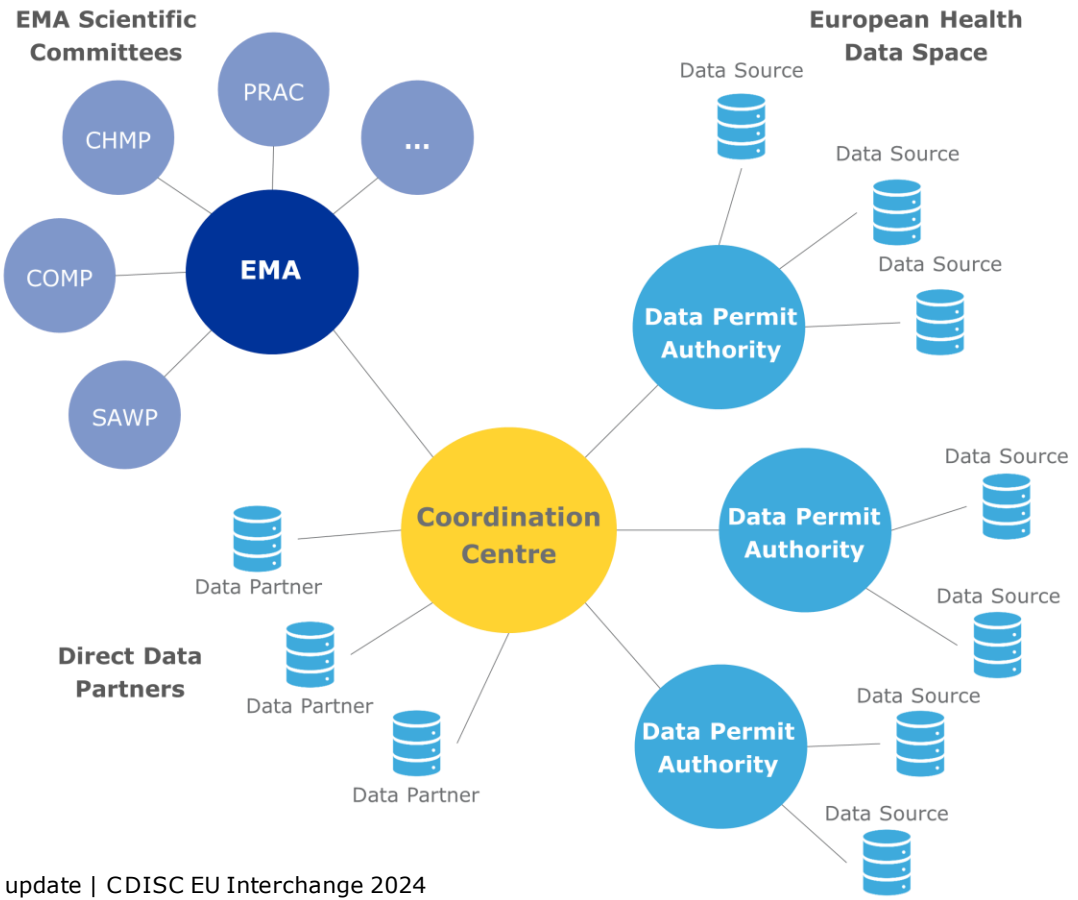
- DARWIN EU
- Data quality & representativeness
- Data discoverability
- EU Network skills
- EU Network processes
- Network capability to analyse
- Delivery of expert advice
- Governance framework
- International initiatives
- Stakeholder engagement
- Veterinary recommendations



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 supports better decision-making throughout the product lifecycle by generating reliable **evidence from real world healthcare data**



FEDERATED NETWORK PRINCIPLES

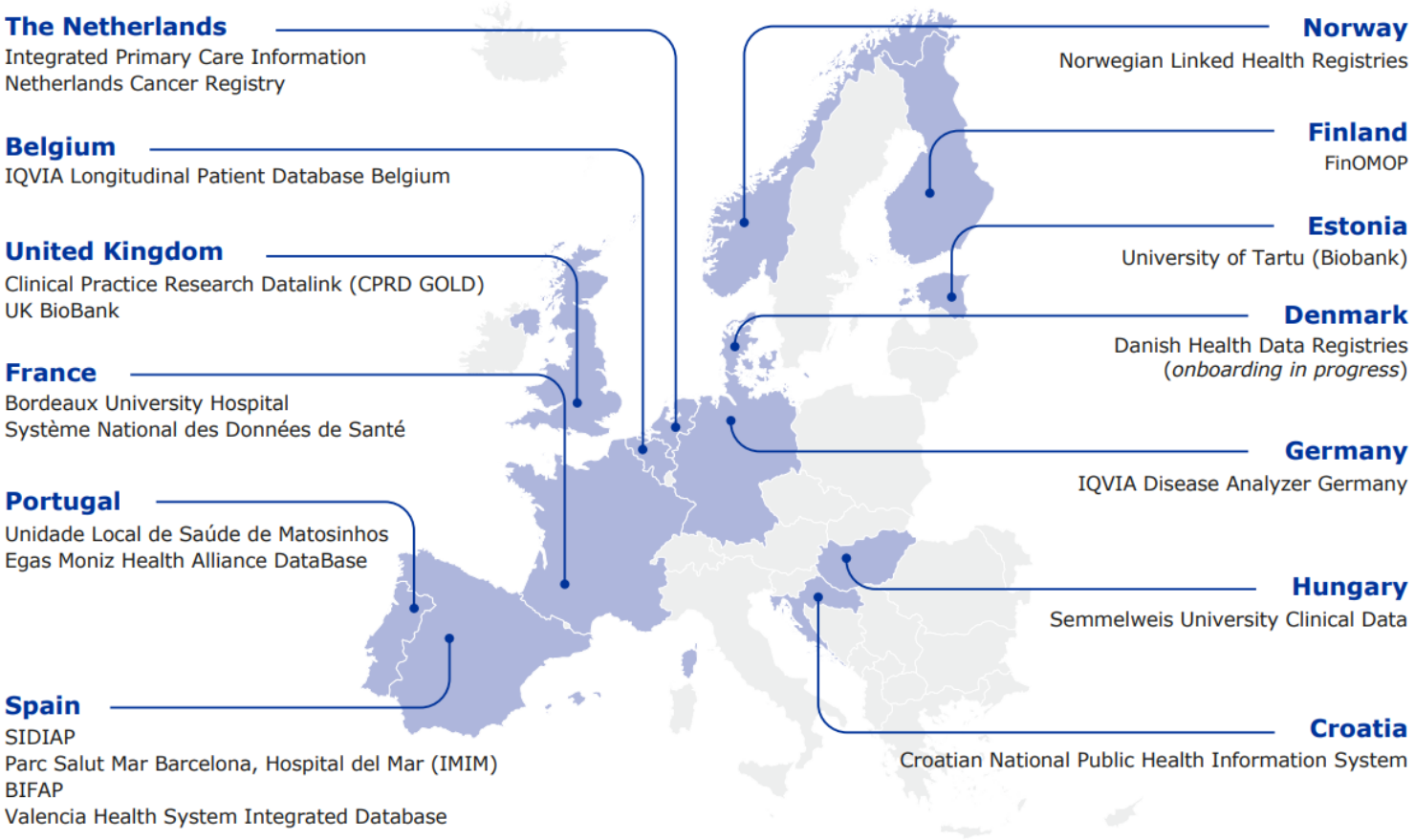
- Data stays **local**
- **Use of OMOP Common Data Model** (where applicable) to perform studies in a timely manner and increase consistency of results

DARWIN EU® establishment in 2022 and 2023

- ✓ 2nd year of establishment completed in Feb 2024
- ✓ Establishment of standard analytical pipelines and codes allows their reuse with a time saving
- ✓ Focus on selection of further Data Partners and study conduct (various use cases) and scale up to ~70 studies in 2024 (yellow highlight)

		Year 1	Year 2	Year 3	Year 4	Year 5
Studies	Off the shelf	2	6	30	60	60
	Routine repeated	1	6	30	60	60
	Complex study	1	4	12	24	24
	Very complex	0	0	0	1	1
Data Partners (total)		10	20	30	40	40

Data Partners – Phase I and II



Examples of recently DARWIN EU® completed studies

a. Background all-cause **mortality rates in patients with severe asthma aged ≥12 years** old [EUPAS103936]

Committee for Medicinal Products for Human Use **(CHMP)**

Complex

b. Drug utilisation study on co-prescribing of **endothelin receptor antagonists** (ERAs) and **phosphodiesterate-5 inhibitors** (PDE-5is) in pulmonary arterial hypertension. [EUPAS106052]

CHMP

OTS

c. Naloxone use in treatment of opioid overdose. [EUPAS105644]

CHMP

OTS

d. Drug utilisation study of prescription **opioids**. [EUPAS105641]

Pharmacovigilance Risk Assessment Committee **(PRAC)**

OTS

e. Drug utilisation study of **medicines with prokinetic properties** in children and adults diagnosed with gastroparesis

National Competent Authority (NCA)

OTS

f. EHDS coagulopathy of COVID-19

European Commission / European Health Data Space

Complex

g. Multiple myeloma: patient characterisation, treatments and survival in the period 2012-2022 [EUPAS105033]

Health Technology Assessment / Payers

OTS

h. Age-specific incidence rates of **RSV-related disease** in Europe [EUPAS107708]

ECDC

OTS

i. Use of antivirals for the treatment of chronic **hepatitis B and C.** [EUPAS107650]

ECDC

OTS

j. Natural history of **dermatomyositis** (DM) and **polymyositis** (PM) in adults and paediatric populations [EUPAS107454]

Paediatric Committee **(PDCO)**

OTS

k. Treatment patterns of drugs used in adult and paediatric population with **lupus** [EUPAS106436]

PDCO

OTS

OTS = off-the-shelf study

completed

DARWIN EU® study reports due in Q1-Q2 2024

m. Effectiveness of **COVID-19** vaccines against severe COVID-19 and post-acute outcomes of SARS-CoV-2 infection.

ECDC - Vaccine Monitoring Platform
Complex

n. Effectiveness of HPV vaccines against cervical cancer

ECDC – Vaccine Monitoring Platform
Complex

o. Overall survival in patients with advanced or metastatic non-small cell lung (**NSCLC**) cancer treated with selected **immunotherapies as first line** of treatment.

Health Technology Assessment / Payers
Complex

p. Drug utilisation study of medicines at risk of **shortages**

EMA Regulatory Science and Innovation Task force
OTS

q. Monitoring prescription of essential **medicines administered in ICU**

EMA Regulatory Science and Innovation Task force
OTS

r. Comparing **direct and indirect** methods to **estimate prevalence** of chronic diseases using real-world data

EMA
OTS

s. Polypharmacy among adults aged 65 and above with cancer at the time of diagnosis

EMA/CHMP workplan (geriatrics)
OTS

OTS = off-the-shelf study

More detail in protocols + study reports in EU PAS Register

+shiny apps

Table of contents

1. DESCRIPTION OF STUDY TEAM 7
2. DATA SOURCES 8
3. ABSTRACT 10
4. LIST OF ABBREVIATIONS 13
5. AMENDMENTS AND UPDATES 13
6. MILESTONES 13
7. RATIONALE AND BACKGROUND 13
8. RESEARCH QUESTION AND OBJECTIVES 14
9. RESEARCH METHODS 16
9.1 Study Type and Study Design 16
9.2 Study Setting and Data Sources 16
9.3 Study Period 19
9.4 Follow-up 19
9.4.1 Population-level Utilization of antibiotics from the WHO Watch list 19
9.5 Study Population with inclusion and exclusion criteria 20
9.5.1 Population-level Utilisation of the antibiotics of interest 20
9.5.2 Patient-level Utilisation of antibiotics 20
9.6 Variables 22
9.6.1. Exposure/s 22
9.6.2. Outcome/s 22
9.6.3. Other covariates, including confounders, effect modifiers and other variables 22
9.7 Study size 26
9.8 Data transformation 26
9.9 Statistical Methods 26
9.9.1 Patient privacy protection 26
9.9.2 Statistical model specification and assumptions of the analytical approach considered 26
9.9.3 Methods to derive parameters of interest 27
9.9.4 Methods planned to obtain point estimates with confidence intervals of measures of occurrence 28
9.9.5 Methods to control for potential sources of bias 30
9.9.6 Methods to deal with missing data 30
9.9.7 Description of sensitivity analyses 30
9.9.8 Evidence synthesis 31
9.10 Deviations from the protocol 31
10. DATA MANAGEMENT 31
10.1. Data management 31
10.2. Data storage and protection 31
11. QUALITY CONTROL 32
12. RESULTS 32
12.1. Population-level DUS 32
12.1.1. Participants 32
Table 12.1.1: Number of participants in each source population during the study period overall 34

DARWIN EU

Study Report for C1-003

Author(s): Katia Verhamme, Maria de Ridder, Talita Duarte Salles, Dani Prieto Alhambra, Miguel-Angel Mayer, Romain Griffier

Version: v3.1

Dissemination level: Public

12.1.2. Descriptive Data 35
12.1.3. Outcome Data 35
12.1.4. Main Results 35
Incidence rates of the antibiotics of the WHO Watch list 35
Incidence rates of the antibiotics of the WHO Watch list by sex and age groups 52
Incidence rates of the antibiotics of the WHO Watch list by route of administration 68
Prevalence of the antibiotics of the WHO Watch list 68
12.2. Patient-level DUS 83
12.2.1. Duration of use 83
12.2.2. Indication of use 85
12.2.5 Other Analysis 86
13 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS 86
14 DISCUSSION 86
14.1 Key Results 86
14.2 Limitations of the research methods 87
14.3 Results in context 87
14.4 Generalisability 88
14.5 Other information 88
15 CONCLUSION 88
16 REFERENCES 89
17 ANNEXES 90
Table 1: List with Concept Definitions for indication of use 90
Table 2: Lists with concept definitions for exposure 92

Document History

Version	Date	Description
V1.0	23/01/2023	First Version for EMA review
V2.0	06/02/2023	Second Version for EMA review
V3.0	15/02/2023	Final version incorporating EMA comments
V3.1	27/03/2023	Link to Shiny App added

Catalogues of real-world data sources and studies

Launched in 2024

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

*Data Quality Framework & metadata catalogues will **feed** into future EU catalogues*

*Collaborative process between **EMA/Heads of Medicines Agencies & TEHDAS***

Metadata list for real-world data sources and studies

+

Catalogues of RWD sources & studies – scope overview

Launched 15 February 2024

Catalogue of RWD sources

replaces the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Resources Database

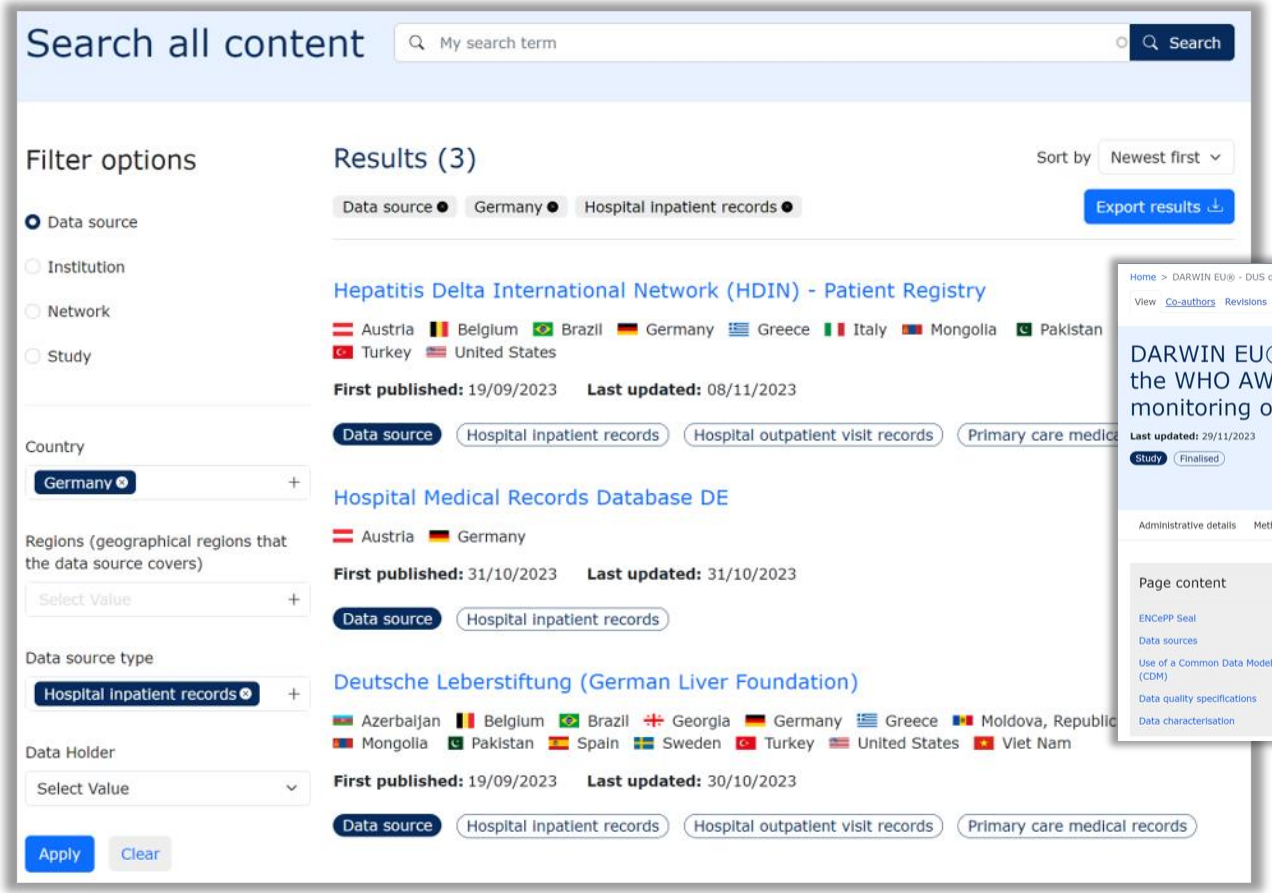
Catalogue of RWD studies

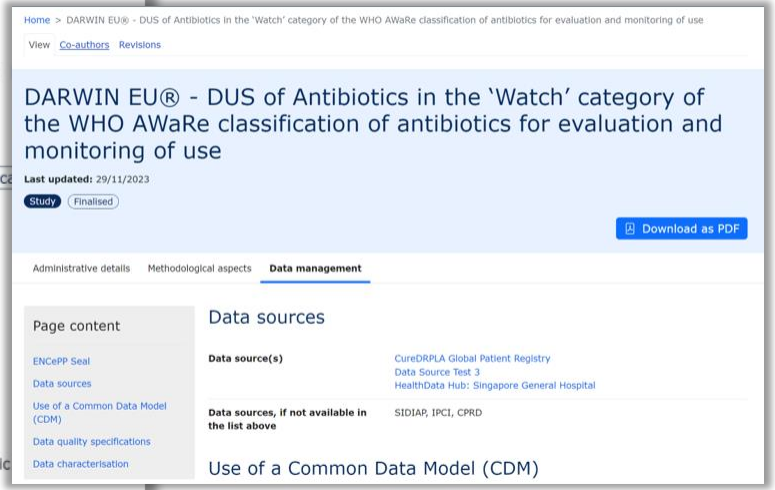
enhances the European Union electronic register of post-authorisation studies (EU PAS Register®)

- The catalogues are primarily aimed at data sources useful in the context of **medicine regulation** and promoting the use of real-world data sources and observational studies in the regulatory process.
- **Freely available access** via the catalogues webpage**,** hosted on EMA public website
- **User-friendly platform** for researchers, regulators, pharmaceutical companies, data source holders and general public
- Enhancing **discoverability of data sources and studies,** facilitating the use of RWD sources and studies related to medicines, ultimately supporting evidence-based decision-making
- Promotion of good practices aligning with **'FAIR' data principles** for **F**indable, **A**ccessible, **I**nteroperable, and **R**eusable data

https://catalogues.ema.europa.eu/

Catalogues of RWD sources & studies

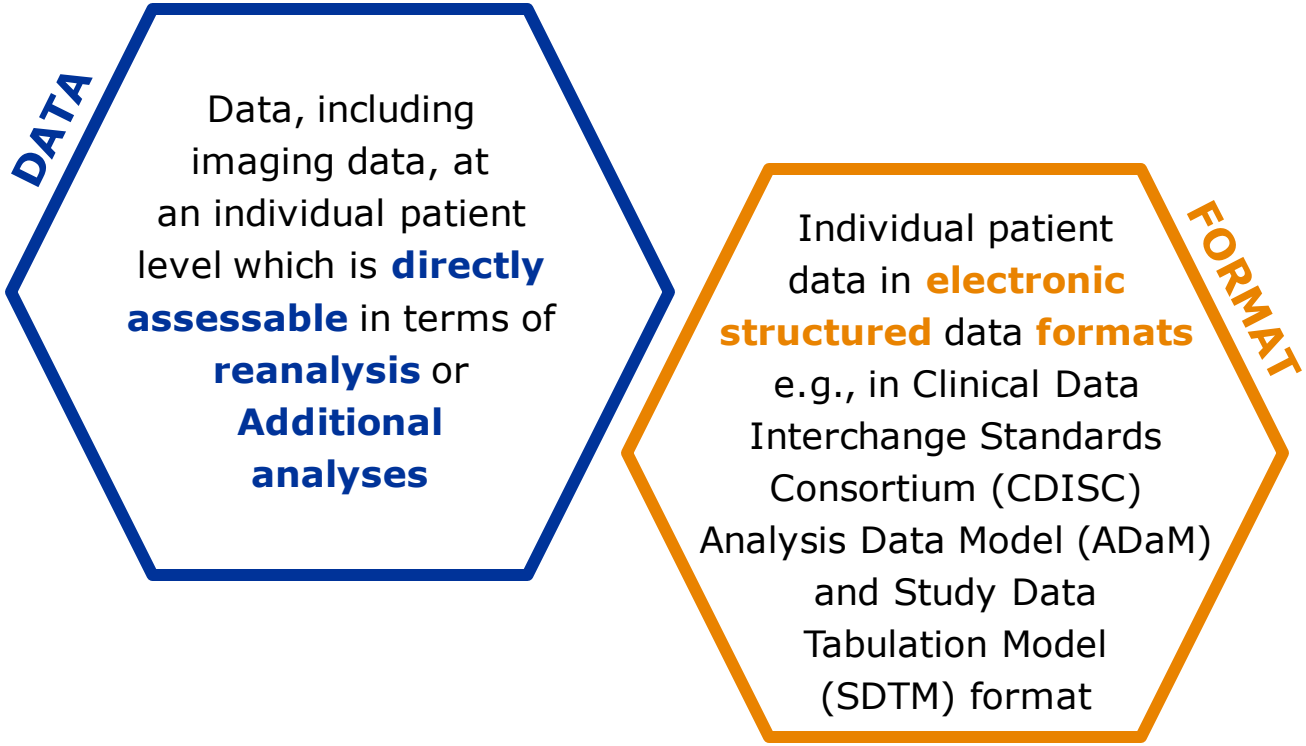




Link between **data sources and associated studies**

Submission of individual patient data from clinical trials

Definitions



EMA's Raw Data project

Aim

- 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**

How

- 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 – summary

- **Timeline:** Approx. **10 regulatory procedures over two years** from September 2022; **8 procedures included** so far
- **Scope: Initial Marketing Authorisation Applications (iMAAs)** 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.** Companies may be asked to ***replicate* 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

- Raw data received continues to **comply 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 – only **2 spaces** left: rawdatapilot@europa.eu

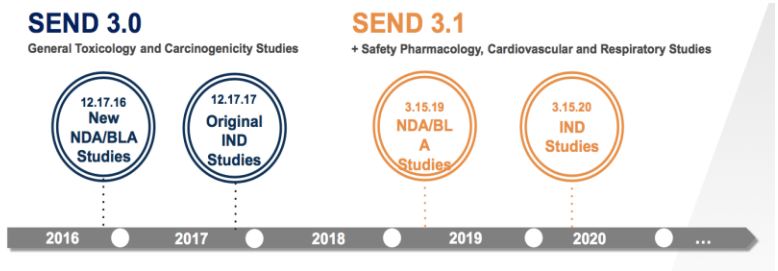
Interim pilot report to be publicly available in Q2 2024

Submission of non-clinical data in SEND format

A proof-of-concept study, initiated in 2024

What is SEND

- **S**tandards for **E**xchange of **N**on-clinical **D**ata
- Initiated by FDA to improve **predictability, consistency** & **efficiency** of review process
- **Required** by FDA since December 2016

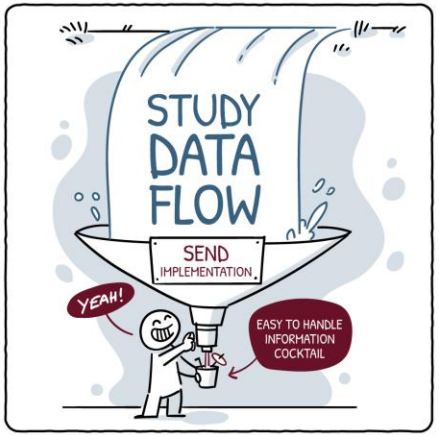


  - All general toxicology and carcinogenicity studies started on or after December 17, 2016 are required to be submitted using SEND 3.0
  - Non-clinical studies for New drug Application/Abbreviated New Drug Application and certain Biologics License Applications/Investigational New Drug Application submissions, that were initiated on or after March 15 2020, must comply with SEND 3.1

- **Until 2023, processes and tools at EMA were not facilitating submission**
  - SEND has been highlighted as an important tool in EMA's regulatory science strategy 2020-2025
  - In 2020 a working group consisting of non-clinical assessors from several National Competent Authorities was formed with the goal of evaluating the potential benefits and limitations of implementing SEND visualisation in the regulatory review process resulting into recommendations

What is happening in 2024

- Proof-of-concept study to evaluate if availability of non-clinical information in SEND format will improve **quality, consistency** and **efficiency** of assessments
- Expected benefits
  - Improved and more consistent assessment **quality**
  - More **science driven** & less **data driven** questions to Applicant
  - **Fewer non-clinical rounds** and/or **faster completion** of the review of the non-clinical dossier
- Applicants are encouraged to submit their (already available) non-clinical SEND data packages, in addition to the electronic common technical document format, as part of their eCTD MAA submission



For additional information you can reach out to: SEND@europa.eu

What’s next?

Next steps and synergies

- **DARWIN EU ®**
  - DARWIN EU completed establishment and scale-up enable this: focus on Data Partners, studies, pilot use cases and developing standard analytical pipelines
  - As of 2024: bigger network and higher study volume (30 off-the-shelf, 30 routine repeated studies, 12 complex studies) and shorter timelines for studies
  - Another 10 data partners to be onboarded in 2024

- **Submission of 'raw data'**
  - Decision on IPD submission requirements expected in late 2024/early 2025
  - No experience yet in receipt of non-interventional studies and applicable data standards
  - Quality and manufacturing structured data

- **Data Quality framework**
  - Work in progress for delivering a Real-World Data specific chapter of the published Data Quality Framework for medicines regulation (estimated to conclude towards the end of 2024)
  - Further prioritisation for other use cases to be carried out in Q2 2024

- **Governance framework**
  - European Medicines Regulatory Network Data strategy will be published end of 2024; focus on data management and data governance
  - Continue supporting European Health Data Space (EHDS) in establishing the value of an infrastructure and data ecosystem for the reuse of health data

More information

Big Data

Subscribe here to receive future issues of the Big Data Highlights

Any questions?

eftychiaeirini.psarelli@ema.europa.eu

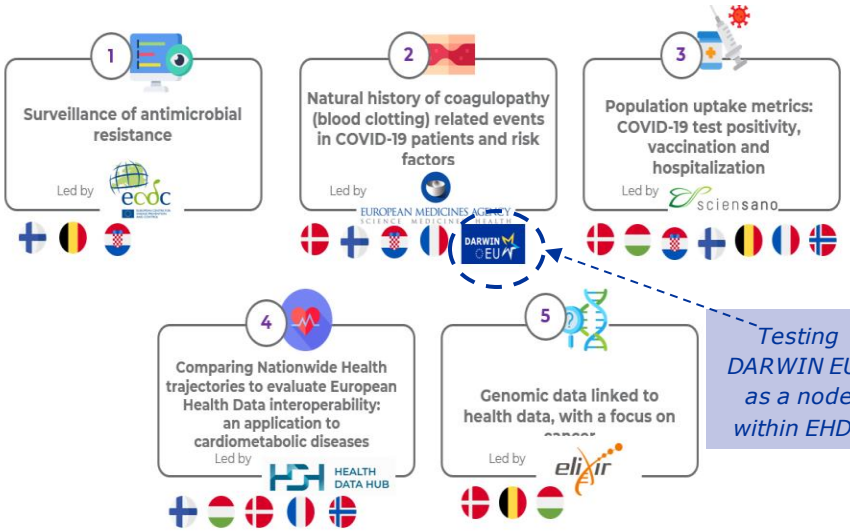
Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Telephone +31 (0)88 781 6000
Send us a question Go to www.ema.europa.eu/contact

Follow us on **@EMA_News**

Back-up slides

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

Changes & Improvements

Main highlights

The replacement of the current ENCePP Resource database and EU PAS Register with a **new platform** with a **revised list of data elements** captured. It will require users to have an **EU Login account** to submit and manage their content.

Download of data will be possible, along with the possibility to **link such data to other EMA regulatory documents** (future release). Information on data sources and studies are **publicly available.**

Summary of changes and improvements:

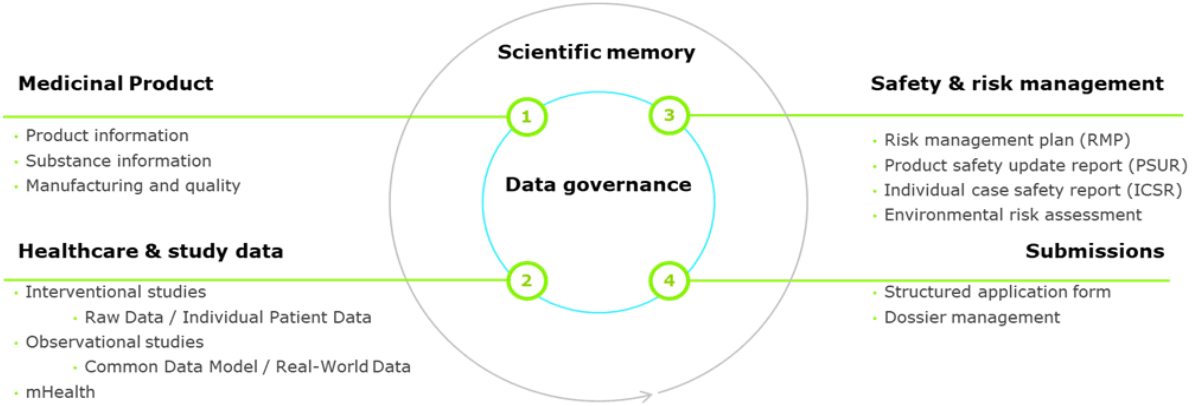
- The RWD Catalogues have moved away from the ENCePP website to https://catalogues.ema.europa.eu/
- **Revised data elements** collected for both data sources and studies (metadata list).
- **Access to records / login** processes and procedures → EU Login account and multi-factor authenticaton. step.
- New platform that enables users to **easily access and manage content** as well as **collaborate on editing** content.
- A data management system built in ensuring ease of **maintenance** and a **data validation** module ensuring reliable data is published.
- **Enhanced search & export functionalities** possibility to filter, sort and export search results and records.

Data Standardisation Strategy - Recommendations

Published on the [EMA Big data]webpage:

[Direct link]

Recommendations:



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