Scaling-up Real-World Evidence generation in Europe – DARWIN EU

International Congress on Rare Diseases and Orphan Drugs – Virtual

Presented by Patrice Verpillat on 01 March 2024
Data Analytics and Methods Taskforce, Real World Evidence Workstream

An agency of the European Union

Disclaimer

These slides are copyright of the European Medicines Agency
Reproduction is permitted provided the source is acknowledged

The presenter does not have any conflict of interest

The views expressed in this presentation are 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

Classified as confidential by the European Medicines Agency

Clinical evidence 2025: Real world evidence

Enable the Use & Establish the Value of RWE

- Enable data access (including via EHDS)
- Build processes
- Set standards
- Validate methods
- Train/share knowledge & Manage change
- Establish value across various use cases
- Internationalise (build on ISPE-ISPOR, ICMRA, ICH)

PERSPECTIVES

PERSPECTIVE

Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value

Peter Arlett[1]*, Jesper Kjær[2], Karl Broich[3] and Emer Cooke[1]

We outline our vision that by 2025 the use of real-world evidence will have been enabled and the value will have been established across the spectrum of regulatory use cases. We are working to deliver this vision through collaboration where we leverage the best that different stakeholders can bring. This vision will support the development and use of better medicines for patients.

Real-world data (RWD) and real-world evidence (RWE) are already used in the regulation of the development, authorisation, and supervision of medicines in the European Union. Their place in safety monitoring and distant epidemiology are well-established while their evidentiary value for additional use cases, notably for demonstrating efficacy, requires further evaluation.[1] During the coronavirus disease 2019 (COVID-19) pandemic, RWE rapidly provided impactful evidence on drug safety, vaccine safety, and effectiveness and we were reminded of the importance of robust study methods and transparency.[2] Our vision, anchored in the European Medicines Regulatory Network (EMRN) strategy to 2025, is that by 2025 the use of RWE will have been enabled and the value will have been established across the spectrum of regulatory use cases.[3] Delivering this vision will support the development and use of better medicines for patients.

In December 2018, the US Food and Drug Administration (FDA) published its framework for RWE underpinned by three pillars: whether RWD are fit for use, whether the study design can provide adequate evidence, and whether the study conduct meets regulatory requirements.[4] In 2019 in the European Union, we published the OPTIMAL framework for RWE also consisting of three pillars: operational, technical, and methodological.[5] More recently, the EU approach places RWE in the wider context of big data and is guided by the priority recommendations of the Big Data Task Force. These recommendations are being implemented through the Big Data Steering Group and the second multi-annual work plan was published in August 2021.[6] Figure 1 represents the workplan with its 11 workstreams which will deliver our vision for RWE by 2025. The workplan places emphasis on collaboration across stakeholders and with international regulatory partners. This work also needs to be seen in the wider EU policy context, most notably the European Commission's plans for a European Health Data Space.[7]

Acknowledging different frameworks to conceptualise the challenges and opportunities of RWE, we believe the two main priorities for the European Union are to enable its use and establish its value for regulatory decision making. The EMRN is working to deliver on both priorities through a collaborative approach where we leverage the best that different stakeholders can bring, and where those stakeholders can complement the central role of industry in generating evidence.

ENABLING USE

To enable use, we are working on multiple fronts with our stakeholders, including patients, healthcare professionals, industry, regulatory and public health agencies, health technology assessment bodies, payers, and academia. We are initiating work to establish a data quality framework, not just for RWD but for all data used in regulatory decision making. We are striving to improve the discoverability (findability) of RWD through agreement of metadata for RWD and through a public catalogue of RWD sources[8] that builds on the early work of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). The ENCePP Guide on Methodological Standards in Pharmacoepidemiology,[9] extensively updated in 2021, is the core of our efforts to drive up the standards of study methods for RWE, and this is complemented by recently published guidance on conducting studies based on patient registries.[10]

The European Medicines Agency (EMA) and some national medicines agencies

[1]European Medicines Agency, Amsterdam, Netherlands; [2]Danish Medicines Agency, Copenhagen, Denmark; [3]BfArM, Bonn, Germany. *Correspondence: Peter Arlett (Peter.Arlett@ema.europa.eu)

Received March 1, 2021; accepted November 1, 2021. doi:10.1002/cpt.2479

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 0 NUMBER 0 | March 2021

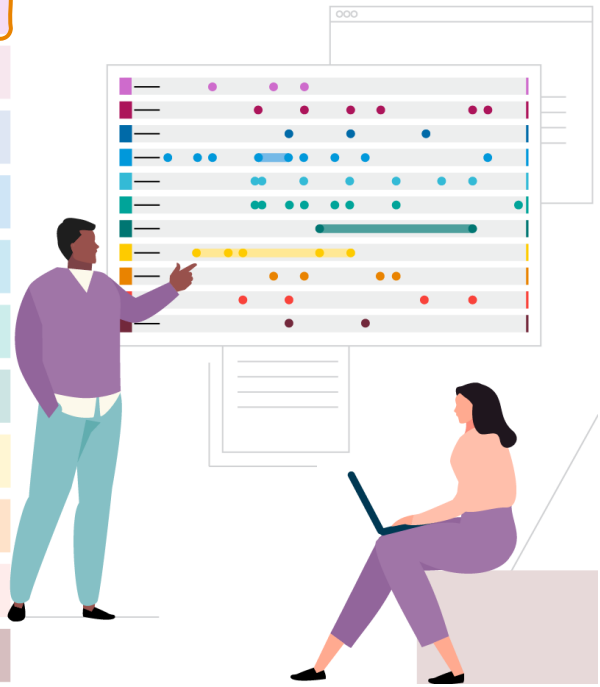
1

Classified as confidential by the European Medicines Agency

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



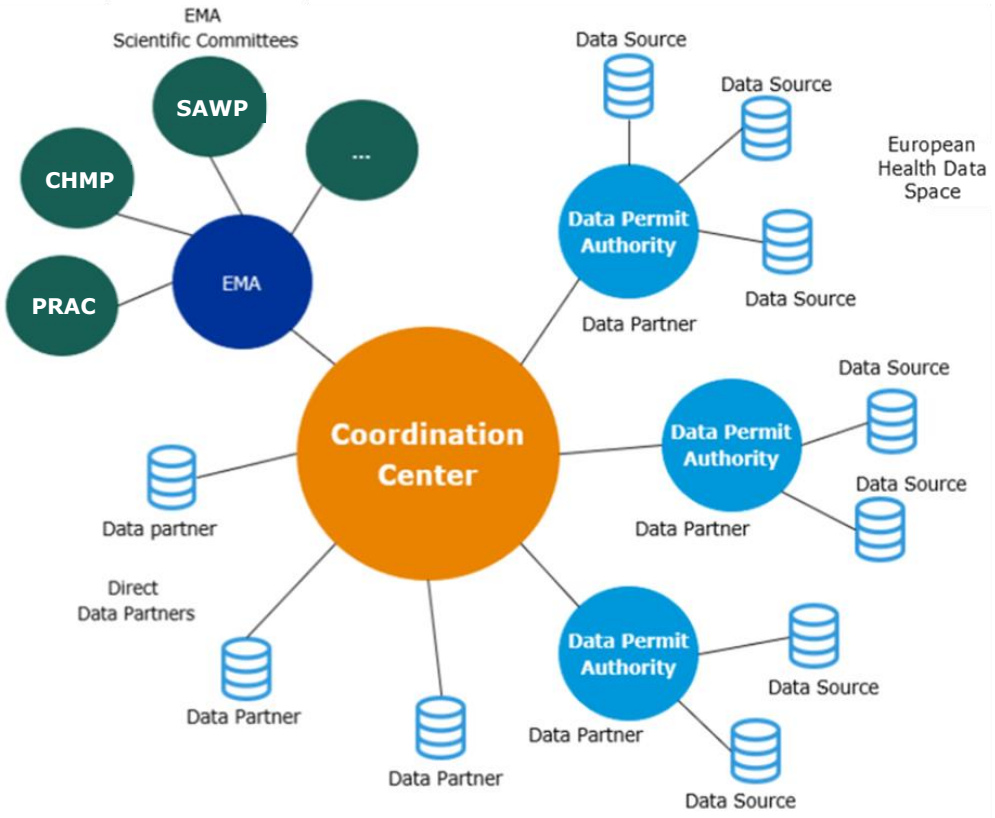
Classified as confidential by the European Medicines Agency

DARWIN EU® Data Analysis and Real-World Interrogation Network

Federated **network** of **data**, **expertise** and **services** that supports better decision-making throughout the product lifecycle by generating valid and reliable **evidence from real world healthcare data**

FEDERATED NETWORK PRINCIPLES

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



Classified as confidential by the European Medicines Agency

UK

1. Clinical Practice Research Datalink (CPRD GOLD)

10. UK Biobank

Netherlands

2. Integrated Primary Care Information

3. Netherlands Comprehensive Cancer Organisation

Belgium

4. IQVIA Belgium Longitudinal Patient Data

France

5. Bordeaux University Hospital

11. Système National des Données de Santé

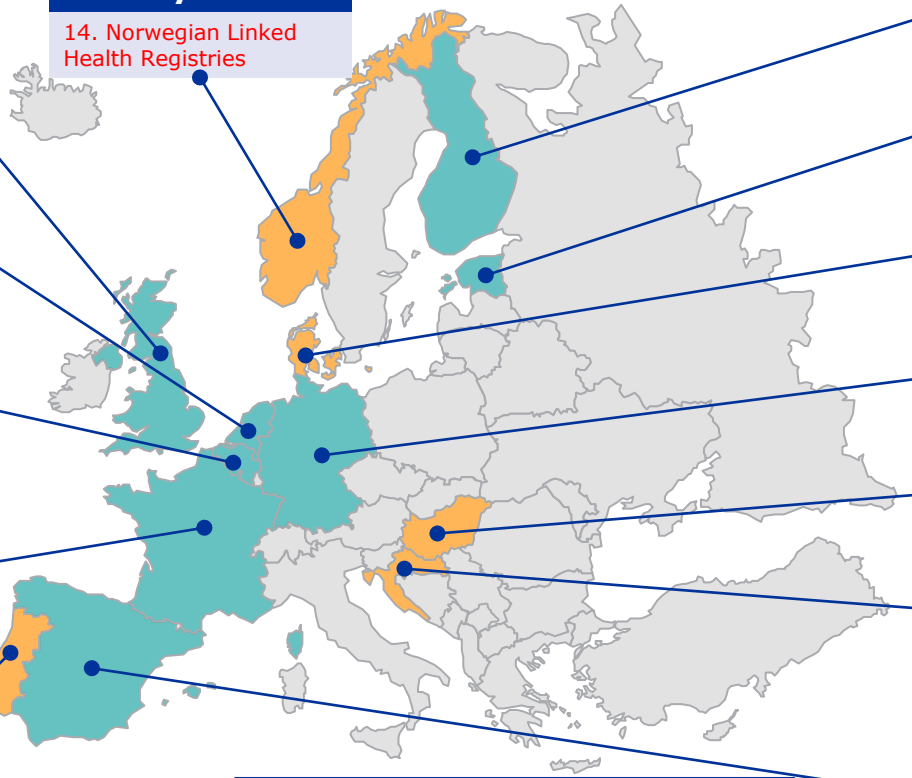
Portugal

19. Unidade Local de Saúde de Matosinhos

20. Egas Moniz Database

Norway

14. Norwegian Linked Health Registries



Finland

15. FinOMOP

Estonia

8. University of Tartu (Biobank)

Denmark

16. Danish Health Data Registries

Germany

9. IQVIA Germany Disease Analyser

Hungary

17. Semmelweis University

Croatia

18. Croatian National public health information system

Spain

6. IDIAPJGol

7. Parc Salut Mar Barcelona, Hospital del Mar (IMIM)

12. BiFAP

13. Valencia Health System Integrated Database

Red font – Phase II data partners

additional geographical coverage

~26 million active patients from Phase I

Adding >100 million active patients from Phase II

Classified as confidential by the European Medicines Agency

Use cases: How RWE can support decision-making?

1 Understand the clinical context

- Disease epidemiology
- Clinical management
- Drug utilisation

2 Support the planning and validity

- Design and feasibility of studies
- Representativeness and validity of completed studies

3 Investigate associations and impact

- Effectiveness and safety studies
- Impact of regulatory actions

Classified as confidential by the European Medicines Agency

What studies DARWIN EU® delivers?

Category of observational analyses and studies	Description
Off-the-shelf studies	Studies for which a generic protocol is adapted to a research question • Estimate the prevalence, incidence or characteristics of exposures • Health outcomes • Describe population characteristics
Routine repeated analyses	Routine analyses based on a generic study protocol • Periodical estimation of drug utilisation • Safety monitoring of a medicinal product • Estimation of the incidence of a series of adverse events
Complex Studies	Studies requiring development or customisation of specific study designs, protocols and Statistical Analysis Plans (SAPs), with extensive collection or extraction of data • Etiological study measuring the strength and determinants of an association between an exposure and the occurrence of a health outcome considering sources of bias, potential confounding factors and effect modifiers
Very Complex Studies	Studies which cannot rely only on electronic health care databases, or which would require complex methodological work • Studies where it may be necessary to combine a diagnosis code with other data such as results of laboratory investigations, or studies requiring additional data collection

Classified as confidential by the European Medicines Agency

DARWIN EU® timelines

Phase I – February 2022

- Start running pilot studies to support EMA committees – **First benefits delivered**
- Consultation of stakeholders

Phase II - 2023

- Support the majority of Committees in their decision-making with reliable RWE
- Expand to other stakeholders

Phase III - 2024

Up-scale delivery and **capacity to routinely support scientific evaluations** of EMA's committees by delivering studies and maintaining data sources

Operation - 2025/2026

- DARWIN EU fully operational and evolves to meet the needs of the EU Regulatory Network
- **Integration with the EHDS**

	Phase I	Phase II	Phase III	Operation 2	Operation 3
Total number of studies	4	16	72	145	145

Classified as confidential by the European Medicines Agency

Examples of ongoing/recently completed DARWIN EU studies

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

CHMP
Complex

EHDS natural history & risk factors for coagulopathy and COVID-19

EC / EHDS
Complex

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

ECDC - VMP
Complex

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

CHMP
OTS

Multiple myeloma: patient characterisation, treatments and survival [EUPAS105033]

HTA / Payers
OTS

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

NCA
OTS

Naloxone use in treatment of opioid overdose [EUPAS105644]

CHMP
OTS

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

PRAC
OTS

OTS = off-the-shelf study

Classified as confidential by the European Medicines Agency

Where do we want to be?

Past *2018-2022* | **Future** *2024-2025* *~2025*

EMA Today

2023

Past model → **As-is state, ongoing pilots** → **Scale-up** → **Optimised usage of RWE**

RWE maturity across the Agency	*Low/ medium*	*Low/ Medium*	*Medium*	*High*
Number of RWE studies per year	*~20-30*	*~40-50*	*~80-100*	*~160*

Increase capacity (access to data sources, breadths of studies/analytical pipelines), shorter timelines, etc

Our vision:
By 2025 enable use & establish value of RWE


PERSPECTIVE

Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value

Classified as confidential by the European Medicines Agency

Any questions?

Further information

Contact me at patrice.verpillat@ema.europa.eu

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

Follow us on **@EMA_News**

Classified as confidential by the European Medicines Agency