How are RWE transforming the EU regulatory network

Big Data Forum December 2023

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EUROPEAN MEDICINES AGENCY

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

- European Medicines Regulatory Network (EMRN) strategy to 2025 -

Transformation

- **Enabling use**
  - Access, business processes, validate and set standards

DARWIN EU

- **Establishing value**
  - Use cases
  - *Guideline development*
  - *Regulatory Science through collaborative Horizon Europe projects*

PERSPECTIVES

PERSPECTIVE

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

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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, authorization, and supervision of medicines in the European Union. Their place in safety monitoring and disease 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.[1] 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 conceptualize 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

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RWD analyses support regulatory decision-making

1 Support the planning and validity of applicant studies

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

2 Understand the clinical context

- Disease epidemiology
- Clinical management
- Drug utilisation

3 Investigate associations and impact

- Effectiveness and safety studies
- Impact of regulatory actions

Real-world evidence report to support EU regulatory decision making published, with infosheet
(from September 2021 to February 2023)

61
research topics

49	8	4
In-house	DARWIN EU	FWC

RWE needs

- **Needs** for RWE of CxMP and SAWP;
- **Ability** and **capacity** of the current RWE framework;
- **Usefulness** of the RWE provided.

Suitability of data sources

- **Suitability** of available **RWD sources** and **pathways**;
- **Methodological challenges.**

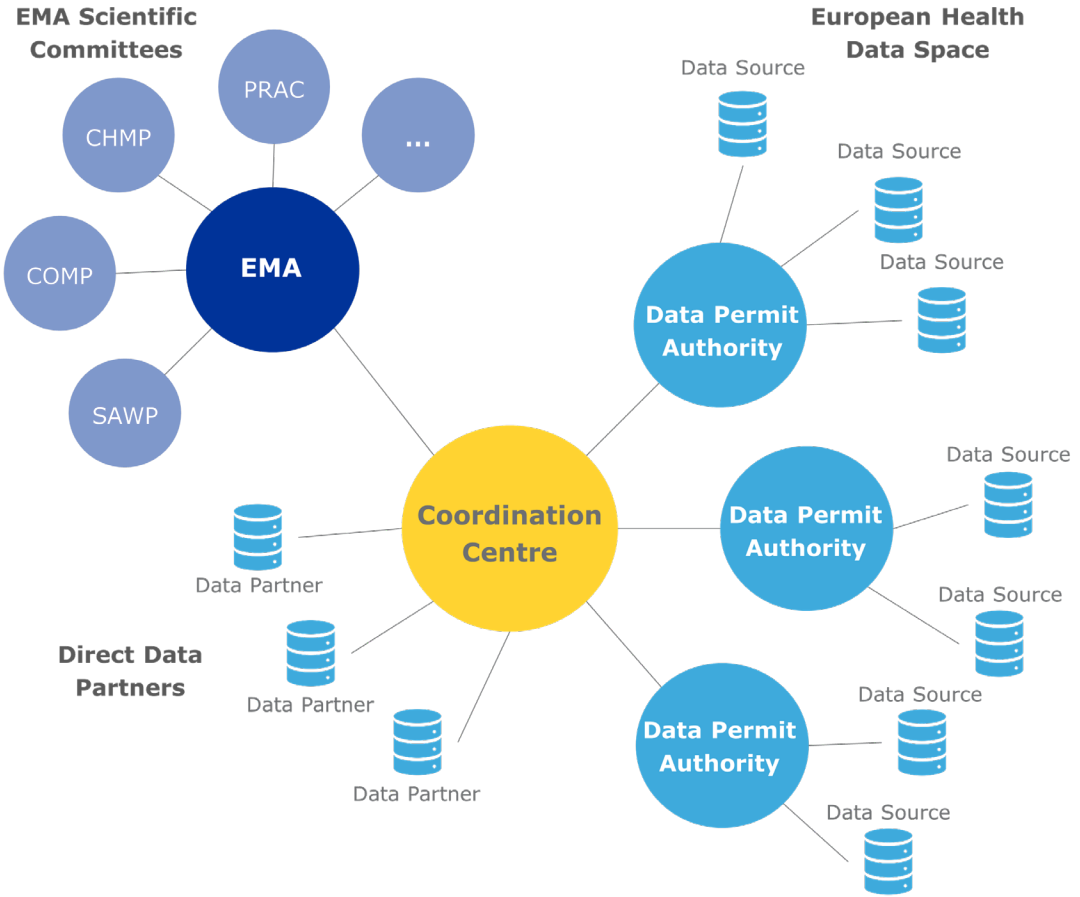
Process for RWE studies

- **Study requests**;
- **Proactively offering** and **conducting** RWE studies;
- Identify **opportunities for improvements.**

DARWIN EU

Federated **network** of **data**, **expertise** and **services**

Generating reliable **evidence from real world healthcare data**



Onboarding work in progress

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

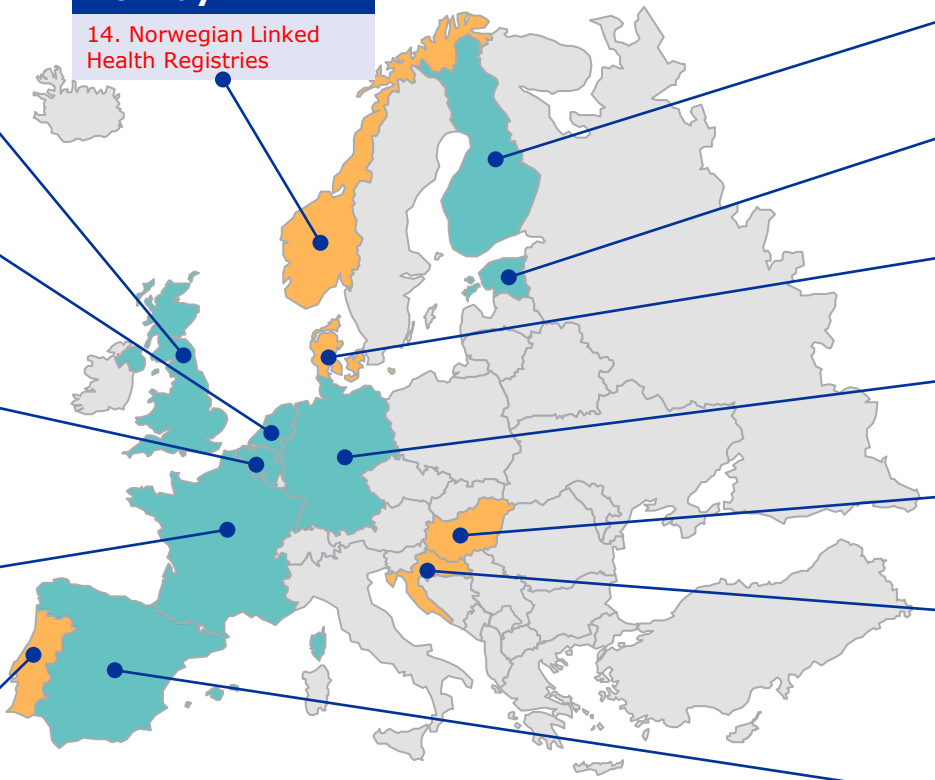
Portugal

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

~26 million active patients from Phase I

Adding >100 million active patients from Phase II

Red font - New data partners

additional geographical coverage

DARWIN EU® establishment in 2022 and 2023

- ✓ 2nd year of establishment in progress, delivery on target and according to plan
- ✓ Focus on selection of further Data Partners and study conduct (various use cases)
- ✓ Establishment of standard analytical pipelines and codes

		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

Examples of ongoing/recently completed studies

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

CHMP
Complex

Naloxone use in treatment of opioid overdose. [EUPAS105644]

CHMP
OTS

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

PRAC
OTS

Effectiveness of HPV vaccines against cervical cancer

ECDC - VMP
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

DUS of medicines at risk of **shortages**

EMA TRS
OTS

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

NCA
OTS

EHDS coagulopathy of COVID-19

EC / EHDS
Complex

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

HTA / Payers
OTS

OTS = off-the-shelf study

completed

Examples of ongoing/recently completed studies

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

PDCO
OTS

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

PDCO
OTS

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

ECDC
OTS

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

ECDC
OTS

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

HTA Payer
Complex

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

EMA
OTS

Rates of occurrence of treatment-related intercurrent events in patients with **major depressive disorder** [EUPAS106685]

EMA TA
OTS

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

EMA
OTS

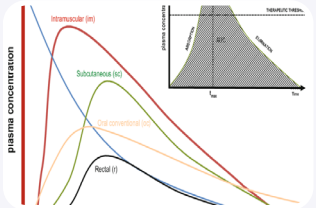
Monitoring prescription of essential **medicines administered in ICU**

EMA TRS
OTS

OTS = off-the-shelf study

completed

Methodology Working Party key areas for guidance



Clinical Pharmacology

Real World Evidence

Clinical Trial Modernisation

Pharmaco - genomics

Data Science & AI

Ensuring high quality decision making in rapidly developing environment

Real World Evidence

Real World Evidence

- Increased use of RWD to generate RWE for non-interventional studies in MAAs
- Roadmap to identify and prioritise future guidance development, taking into account existing (international) guidance

<u>High priority/short-term:</u>

- Reflection Paper on use of RWD to generate RWE in *non-interventional studies*
- *Roadmap for the development of RWE guidance* (e.g., reflection on trial designs with external control data).

Regulatory science & multi-stakeholder collaboration

Horizon Europe

MetReal Cluster of 5 projects

New methods for the effective use of real-world data and/or synthetic data in regulatory decision-making and/or in health technology assessment

ERAMET & INVENTS projects

Modelling and simulation to address regulatory needs in the development of orphan and paediatric medicines.

Regulatory science & multistakeholder collaboration

MetReal cluster

Real4Reg

More-EUROPA

ONCOVALUE

REALM

REDDIE

Very strong involvement & leadership of regulatory & HTA network.

(BDSG members, National Agencies, CHMP members, MWP members, HTA)

ERAMET & INVENTS

Includes using RWD to support modelling & simulation and improved clinical trial design.

Accelerate

- Methodology, validation & standards
- Use cases & data sources
- Development of framework(s) to assess credibility of novel approaches.

Closing remarks: Transformation

- DARWIN EU® scale-up direct and increasing impact (enabling use).
- Guideline development attuned to the rapidly developing environment.
- New large collaborative projects developing the regulatory science and and use case base.

Thank you for listening

Further information

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