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SCIENCE MEDICINES HEALTH

Real-world evidence & training needs: a regulatory perspective

Real4Reg: Insights into Stakeholder Needs

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European Medicines Agency

An agency of the European Union





Disclaimer

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



Outline

1. EMA vision and activities on RWE
2. Main issues regulators face with RWE
3. Big Data Training Curriculum for regulators



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Clinical evidence: regulatory vision

- More evidence-based decision making throughout the lifecycle of medicines
- Knowledge gap -> research question -> scientific study
 - Clinical trials remain core
 - Non-interventional studies (NIS) can complement evidence from CTs



Real-World Data



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Data that describe patient characteristics (including treatment utilisation and outcomes) in routine clinical practice

Reflection Paper on use of real-world data to generate real-world evidence in non-interventional studies

Real-World Evidence



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Evidence derived from the analysis of RWD

Reflection Paper on use of real-world data to generate real-world evidence in non-interventional studies



European Medicines Regulatory Network (EMRN) Strategy 2025

“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”

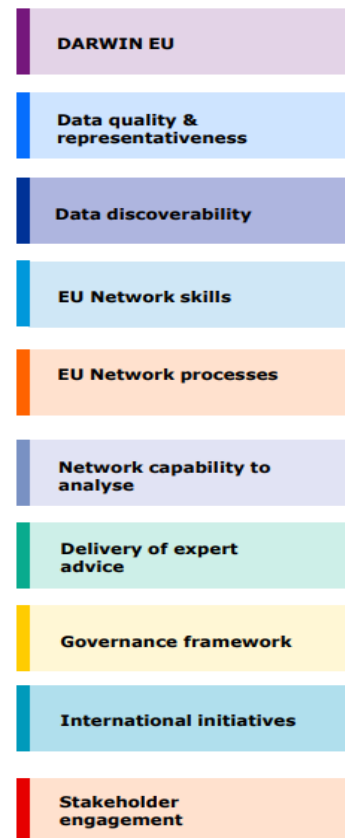


Arlett P. et al. Clin Pharmacol Ther. 2022 Jan;111(1):21-23. doi: 10.1002/cpt.2479.

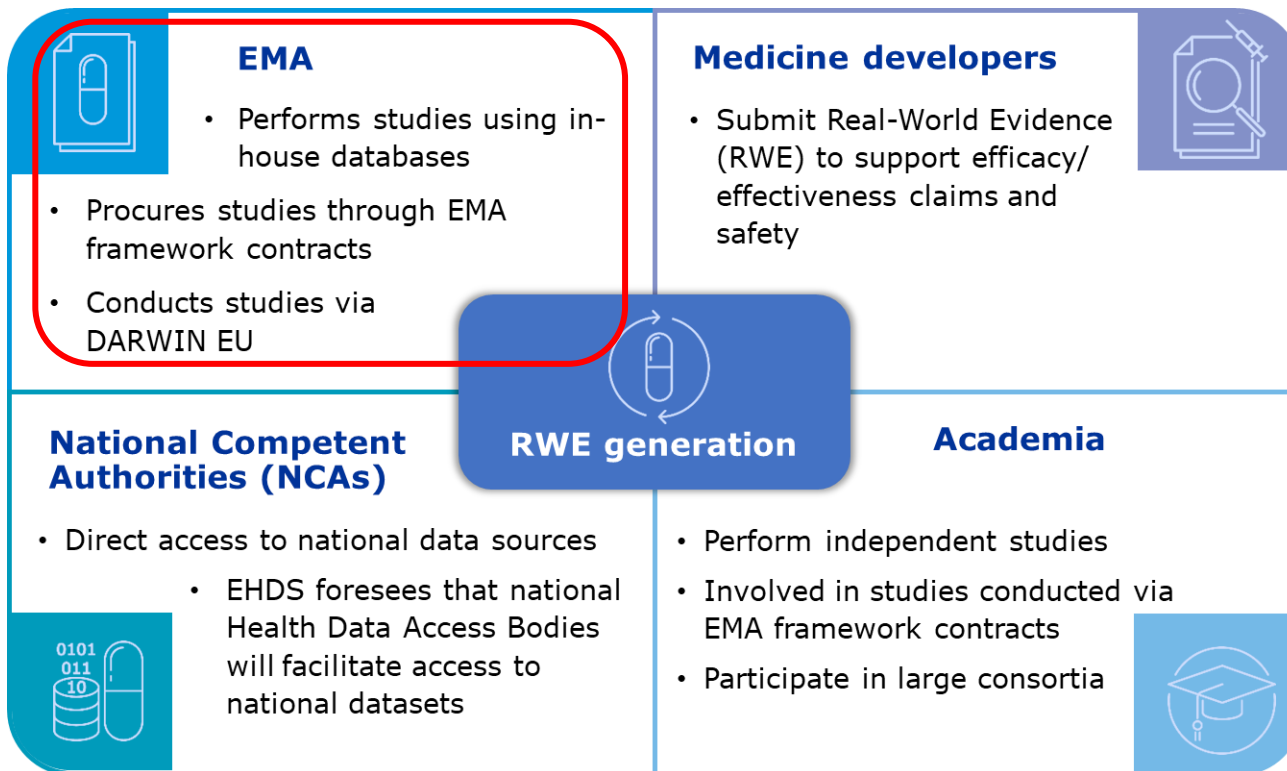


HMA / EMA Big Data Steering Group

The European Medicines Agency (EMA) and Heads of Medicines Agencies (HMA) set up a joint task force to describe the big data landscape from a regulatory perspective and identify practical steps for the **European Medicines Regulatory Network to make best use of big data in support of innovation and public health** in the European Union (EU). This led to the creation of the Joint HMA/EMA Big Data Steering Group and Big Data Steering Group Work Plan.



Who delivers RWE for regulatory purpose in the EU?



How EMA generates Real-World Evidence



EMA studies using in-house databases

Primary care health records from the **UK and Germany**



Studies procured through EMA FWCs

New framework contracts (FWC) 2021-2025

Lot 5 Pharmacoepidemiology provides services of 8 research organisations and access to wide network of data sources.

Ability to leverage external scientific expertise



DARWIN EU®

Data Analysis and Real-World Interrogation Network

Coordination by Erasmus University Medical Centre Rotterdam, responsible for setting up the network and managing its day-to-day operations.



DARWIN-EU®

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

FUTURE ACTIONS

Continue the growth of DARWIN EU, focusing on more **specialised data sources** including data in special populations, rare diseases and oncology

Strengthen the **outreach to data/registry owners** to facilitate access to data for secondary use

The Netherlands

Integrated Primary Care Information
Netherlands Cancer Registry

Belgium

IQVIA Longitudinal Patient Database Belgium

United Kingdom

Clinical Practice Research Datalink (CPRD GOLD)
UK BioBank

France

Bordeaux University Hospital
Système National des Données de Santé

Portugal

Unidade Local de Saúde de Matosinhos
Egas Moniz Health Alliance DataBase

Spain

SIDIAP
Parc Salut Mar Barcelona, Hospital del Mar (IMIM)
BIFAP
Valencia Health System Integrated Database

Norway

Norwegian Linked Health Registries

Finland

FinOMOP

Estonia

University of Tartu (Biobank)

Denmark

Danish Health Data Registries
(onboarding in progress)

Germany

IQVIA Disease Analyzer Germany

Hungary

Semmelweis University Clinical Data

Croatia

Croatian National Public Health Information System



1st report on the experience gained with regulator-led studies* to support regulatory decision

* Focus on ongoing RWE pilot activities (incl CHMP, SAWP, CAT, PDCO, COMP, HTA/payers, ECDC) and routine RWE support to PRAC

Period covered: Sep 2021 to Feb 2023

Published in June 2023 on [EMA Big Data site](#)

Published in July 2024 in Clinical Pharmacology & Therapeutics: [Prilla et al., 2024](#)

Infosheet

Review of real-world data studies

Experience gained in conducting real-world data (RWD) studies and providing real-world evidence (RWE) to support EMA regulatory decision making since September 2021



Sustainable framework to support scientific evaluations in the EU

Overseen by the [Big Data Steering Group](#) (BDSG), EMA and the EU network are working to **establish a sustainable framework enabling better integration of RWD/RWE into regulatory decisions**. EMA has reviewed the experience gained so far in conducting studies with RWD and in providing RWE to support regulatory decisions made by its scientific committees and working parties.

The experience is summarised in two reports, covering the periods from September 2021 to February 2023 and from February 2023 to February 2024.

Ways to deliver RWE for regulatory purposes in the EU

RWE can come from marketing authorisation applicants/holders, academia or national competent authorities. EMA can generate RWE thanks to:

EMA studies
Conducted by EMA's experts in collaboration with the requester through direct access to European healthcare data sources.

Framework contracts
Studies commissioned to research organisations and consortia with access to specialised data and expertise.

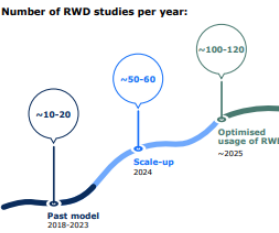
DARWIN EU®
Studies conducted by data partners via a federated network of data, expertise and comprehensive services.

The pathways differ in terms of processes, speed of analysis, capacity and characteristics of data sources.

Transformational journey to fully integrate RWE in EU regulatory decision making

By 2025, the use of real-world evidence will have been enabled and the value will have been established across the full spectrum of regulatory use cases to:

- support the planning and validity of studies performed/submitted by applicants;
- understand the clinical context;
- investigate associations and impact of regulatory decisions.

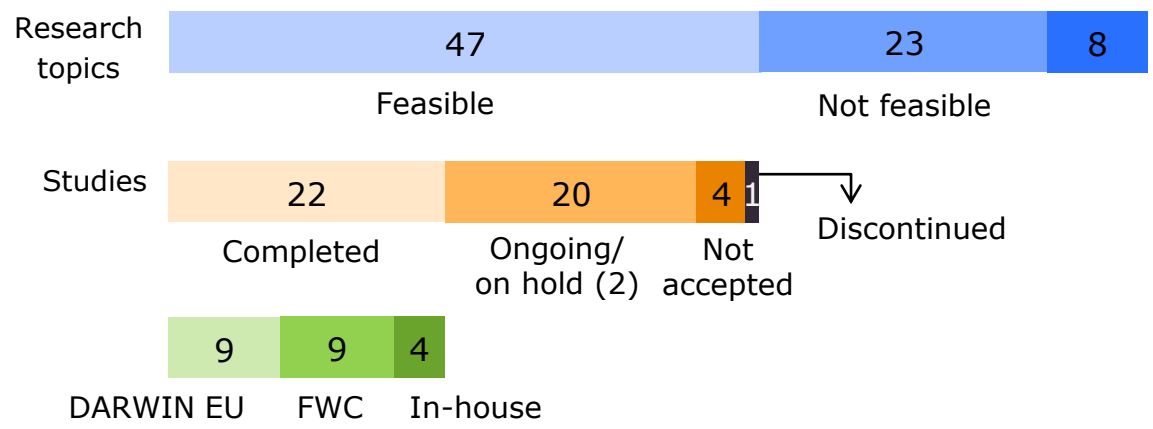


Second report – reporting period from Feb 2023 to Feb 2024

60
NEW research topics
 (Feb '23 – Feb '24)

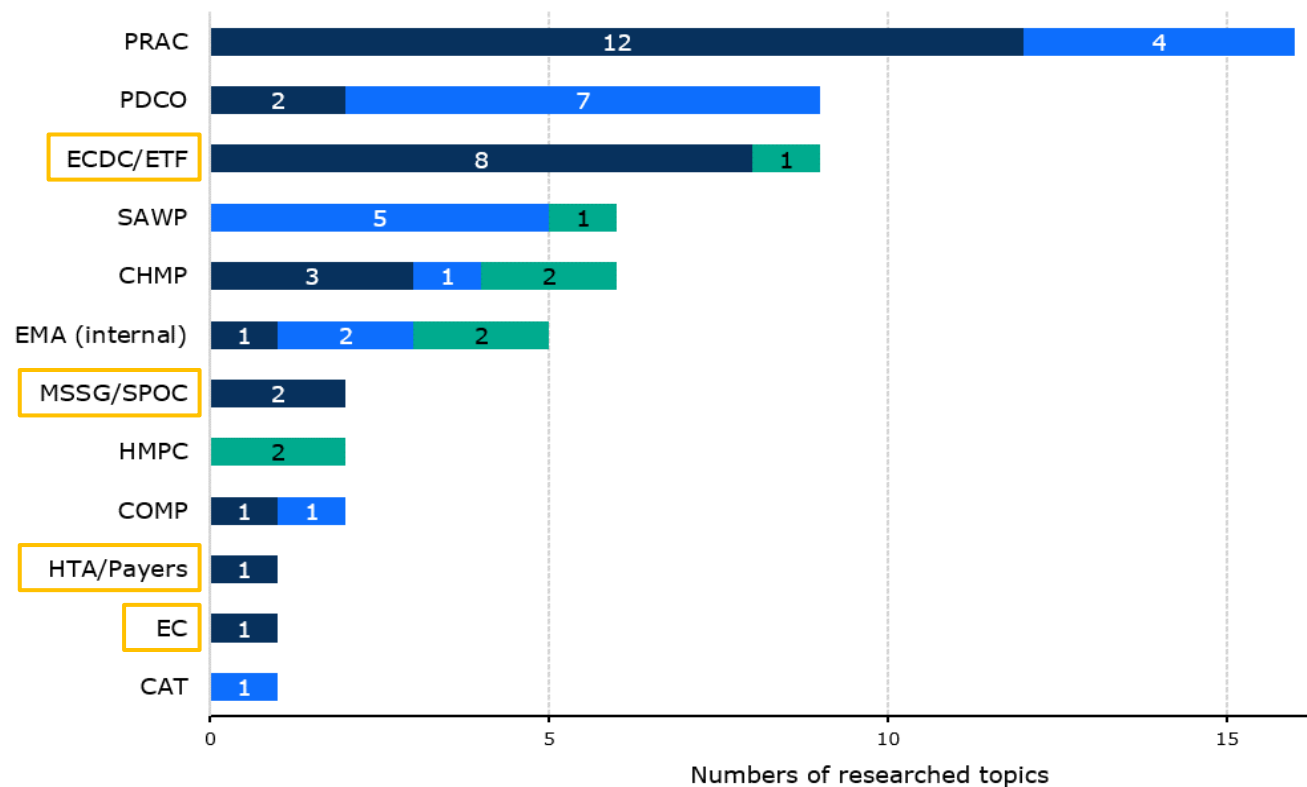
38 DARWIN EU
16 In-house
6 FWC

+18
 Prior research topics





NEW study topics (n=60) by 'decision-maker'



■ Feasible ■ Not feasible ■ Ongoing feasibility/On hold

Classified as internal/staff & contractors by the European Medicines Agency



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How much can we trust the results of a RWD study?

- Non interventional data:
 - 10% research data – data collected *primarily* for research
 - 90% secondary data – data used *secondarily* for research (EHR, administrative data, etc.)
- Main issues:
 - **Quality** of the data used in the study
 - **Methodological** aspects: study design and methods



Data quality

- Reliability:
 - Foundational:
 - What is the primary purpose of data collection in the data source?
 - Are data representative for inferential purposes?
 - Peer-review publications of the data source? Participation in studies?
 - Intrinsic:
 - Good values in metrics capturing intrinsic aspects will increase confidence in the data source
- Relevance:
 - Description of key data elements available in the data source that justify its inclusion in the study



Study design and methods

- Study Design choice independent of data source, but driven by research question
- Variable definitions and analysis of a study may depend on data quality
- Data quality framework and metrics can inform fit-for-purpose assessment of data source for specific question



Landscape of EU RWE guidance (list not exhaustive)



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

Guideline on registry-based studies



HMA
Heads of Medicines Agencies

15 February 2024
EMA/563896/2022
European Medicines Agency



List of metadata for the HMA-EMA Catalogues of real-world data sources and studies



HMA
Heads of Medicines Agencies

30 October 2023
Data Analytics and Methods Task Force
EMA/326985/2023

Data Quality Framework for EU medicines regulation



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1 September 2022
EMA/787647/2022
European Medicines Agency

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



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15 April 2024
EMA/CHMP/150527/2024
Committee for Human Medicine Products (CHMP)

Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence
Draft



HMA
Heads of Medicines Agencies

9 October 2017
EMA/813938/2011 Rev 3*

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





Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence – main features

- The **use of NISs** to assess medicines efficacy is hindered by **methodological limitations**, including absence of randomisation, uncontrolled conditions, non-standardised treatment and uncertainties regarding data quality
- The increasing ability to capture electronic healthcare data and data from registries provides **new opportunities to generate RWE**, including:
 - Post-marketing monitoring, investigate safety concerns, evaluate effectiveness of risk-minimization measures
 - Describe patterns of drug utilization
 - Characterise disease epidemiology
 - etc...



Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence – main features (2)

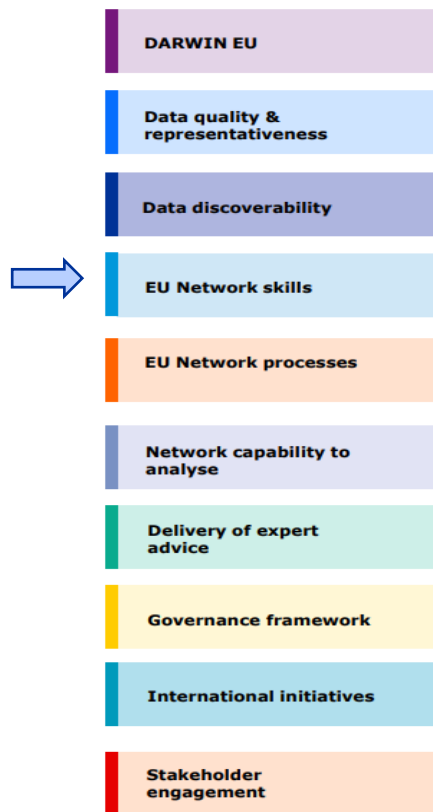
- **Feasibility assessments** to ensure data sources included are fit for purpose, i.e. they have good quality – assessed with a DQF
- Distinction made between **studies with descriptive objectives** and **studies with causal objectives** given different implications for the study design
 - Use of the **target trial emulation approach** for studies with causal objectives, with the **estimands framework** used to specify the target trial
- Considerations given to appropriate pharmacoepidemiological and statistical methods applied to transform and analyse the data



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Recommendation 4 – Develop EU Network skills



Goal: Develop a big data training curriculum



By increasing the level of expertise within the European medicines regulatory network (EMRN), it is expected that:

- ❑ There will be *more contribution from regulators* to the definition of research questions, study protocols and interpretation of study results, as well as informed advice on strengths and weaknesses of using certain types of data sources for post-authorisation studies (both safety and effectiveness)
- ❑ The general *level of expertise on pharmacoepidemiological methods* will be increased throughout Europe
- ❑ The EU Network will act as a *reference for data-driven regulation*



Big Data Training Curriculum

- The Big Data training curriculum includes the following curricula:
 - **Pharmacoepidemiology/Real World Evidence**
 - Data Science
 - Biostatistics & Clinical trial methodology
 - Clinical Trials
- Target audience:
 - European medicines regulatory network
 - EMA



Pharmacoepidemiology/Real World Evidence

- Objective: **provide knowledge** on **core principles of pharmacoepidemiology** to increase EMRN's capacity in the use of RWD to generate real-world (observational) evidence for regulatory purposes
- Training modules:
 1. Introduction to Real-World Evidence (available through EU NTC)
 2. Real-World Data sources (available through EU NTC)
 3. Study protocol (published in Q4 2024)
 4. Statistical methods applied to RWE (published in Q4 2024)
 5. The journey from real-world data to real-world evidence (published in 2025)
 6. Practicals: assessing and interpreting results of observational studies (published in 2025)



Any questions?

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