Update on DARWIN EU®

ENCePP plenary
1 Dec 2023

Presented by
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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

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.

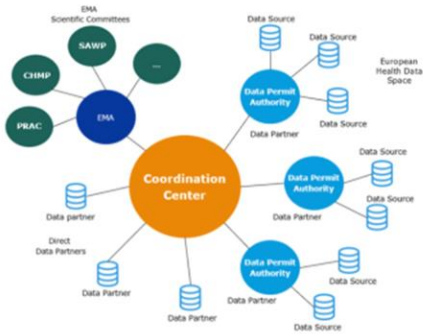
- European Medicines Regulatory Network (EMRN) strategy to 2025 -

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



Use cases: How RWE can support decision-making?

1 Understand the clinical context	2 Support the planning and validity	3 Investigate associations and impact
Disease epidemiology	Design and feasibility of studies	Effectiveness and safety studies
Clinical management	Representativeness and validity of completed studies	Impact of regulatory actions
Drug utilisation		

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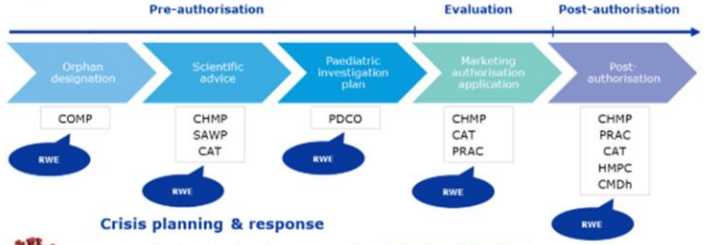
Demand: RWE use across the medicinal product lifecycle



Crisis planning & response

- Monitoring the use of medicines to predict demand and shortages
- Understanding the disease natural history → development of vaccines and therapeutics
- Provide evidence for repurposing existing medicines
- Monitor the safety and effectiveness of vaccines and therapeutics post-authorisation

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What analyses and studies will DARWIN EU® deliver?

Category of observational analyses and studies	Description
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
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
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

13 Dr Sabine Haubenreisser - Use of Real-World Evidence pre- and post-authorisation

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
		18			

Data Partners – Phase I and II

CONFIDENTIAL

Onboarding work in progress

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

NCA
OTS

DUS of medicines at risk of **shortages**

EMA TRS
OTS

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

CHMP
OTS

EHDS coagulopathy of COVID-19

EC / EHDS
Complex

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

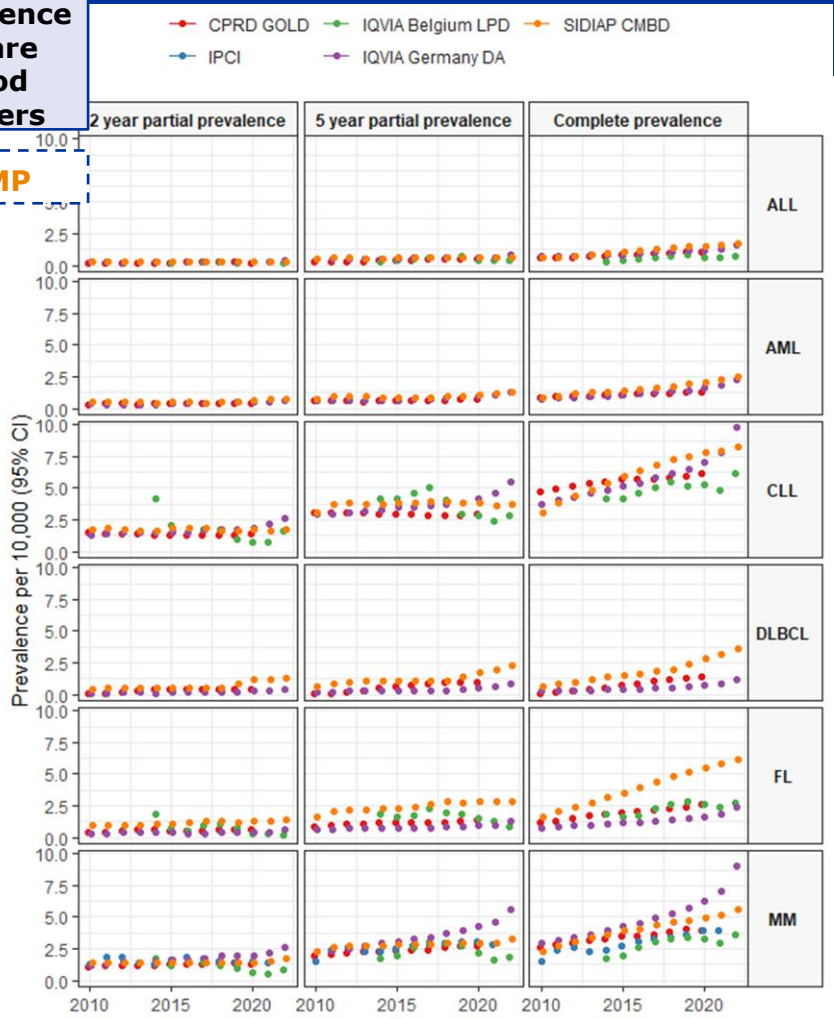
HTA / Payers
OTS

OTS = off-the-shelf study

completed

Prevalence of rare blood cancers

COMP

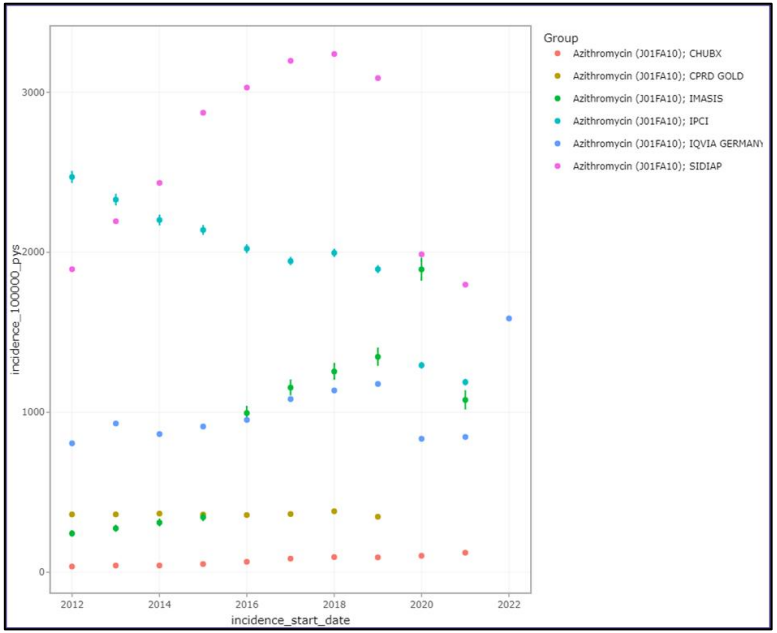


DUS of antibiotics

PRAC/CHMP/EMA

EUROPEAN MEDICINES AGENCY

Incidence rates of azithromycin



Ref. EUPAS50800
and EUPAS103381

Catalogue of standard data analyses - General aspects

- Analytical pipelines developed/under development to address common research questions using RWD
  - The goal is to be able to run studies end-to-end in a matter of weeks
- Code is written using R language - Pipelines built in a modular way (R packages)
- Input and output of pipelines is standardised
  - Detail in protocol, study report and shiny apps
- Catalogue is publicly available - Quarterly updates foreseen
- Industry consultation in 2023 and comments received on standard analyses => catalogue (website) update in Q1 / Q2 2024

https://darwin-eu.org/index.php/methods/standardised-analytics

Off-the-shelf studies

These are mainly characterisation questions that can be executed with a generic protocol. This includes disease epidemiology, for example the estimation of the prevalence, incidence of health outcomes in defined time periods and population groups, or drug utilization studies at the population or patient level.

- Patient-level characterisation
- Patient-level DUS analyses

Cohort of newly diagnosed patients or new users of a medicine followed over time. Studies used to characterise disease patients or use of medicines

- Population-level DUS analyses
- Population-level descriptive epidemiology

Used for incidence/prevalence studies. All subjects in the database are eligible subject to minimal inclusion criteria

Industry involvement
Agreed with DARWIN EU® Advisory board

Studies use standardised analytics and have short timelines

(Very) Complex studies investigating the use, safety or effectiveness of one or several substances	Off-The-Shelf / Routine Repeated studies (as per category of observational analyses and studies)
EMA will **consult** concerned MAH(s)	EMA will **inform** industry
Industry to provide comments on the protocol (consolidated feedback across MAHs if possible) and via the Assessment Report	Industry to be informed using existing processes such as the Assessment Report, committee agenda and minutes, publication in EU PAS register

Protocols available in EU PAS for completed studies

International harmonisation work on RWE

2022 ICMRA RWE statement

ICH M14 Guideline on non-interventional pharmacoepidemiological studies for safety assessment of medicines → Public consultation Q4 2023/early 2024, establishment Jan 2025

ICH Reflection Paper for convergence on RWE terminology, format of study protocol and report, and study transparency

More Information

Data Analysis and Real World Interrogation Network (DARWIN EU) | European Medicines Agency (europa.eu)

Coordination Centre website

- For questions to the Coordination Centre, please contact: enquiries@darwin-eu.org

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Thank you for your attention

Further information

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Studies completed in 2022 (year 1/ phase I)

Additional 19 studies started in 2023 (Phase II) – including HTA/payers, ECDC, EHDS2 pilots

Off the Shelf	**Population level epidemiology** study on prevalence of **rare blood cancers** from 2010 EUPAS50800	NL, ES, UK, BE, DE	Support COMP in orphan designation decision making & useful as background rates for other committees	COMP
Off the Shelf	Patient level **drug utilization** study of **valproate-containing medicinal products** in women of childbearing potential from 2010 EUPAS50789	NL, ES, UK, BE, DE, FI	Assess the use of valproate after safety referral	PRAC
Off the Shelf	Patient level **drug utilisation** study of **antibiotics** on the Watch list of the WHO AWaRe classification, 2010-2021 EUPAS103381	NL, FR, ES, DE, UK	Inform PRAC/CHMP decision making, AMR strategy	PRAC – CHMP AMR strategy CMDh
Complex	Background all-cause **mortality rates in patients with severe asthma aged ≥12 years** old EUPAS103936	NL, ES x2, UK, EE	Support CHMP post-authorisation inform future decision making	CHMP