DARWIN EU®:
How is RWE transforming regulatory decision making?

15 Nov 2024

Presented by Andrej Segec
European Medicines Agency, Data Analytics and Methods Taskforce – Real World Evidence

An agency of the European Union

Disclaimer

The presenter does not have any conflict of interests.

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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 -

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.

Jan. 2020

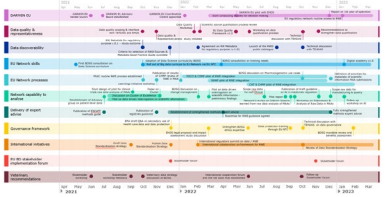
'Ten recommendations to unlock the potential of big data for public health in the EU'

May 2020

1st Big data steering group meeting in May 2020

Sep. 2020

Publication of the 1st BDSG workplan 2020/2021



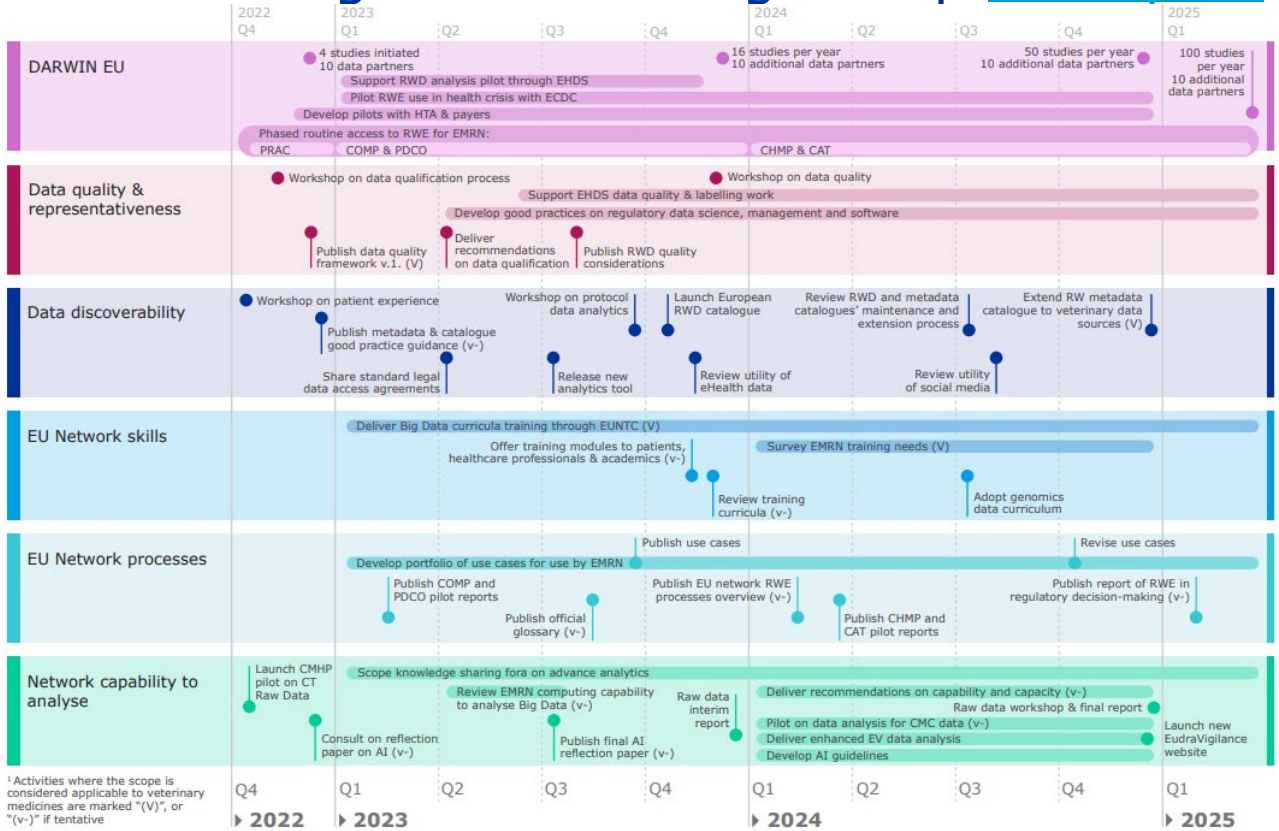
Aug. 2021

Publication of the 2nd BDSG workplan 2021/2023

Jul 2022

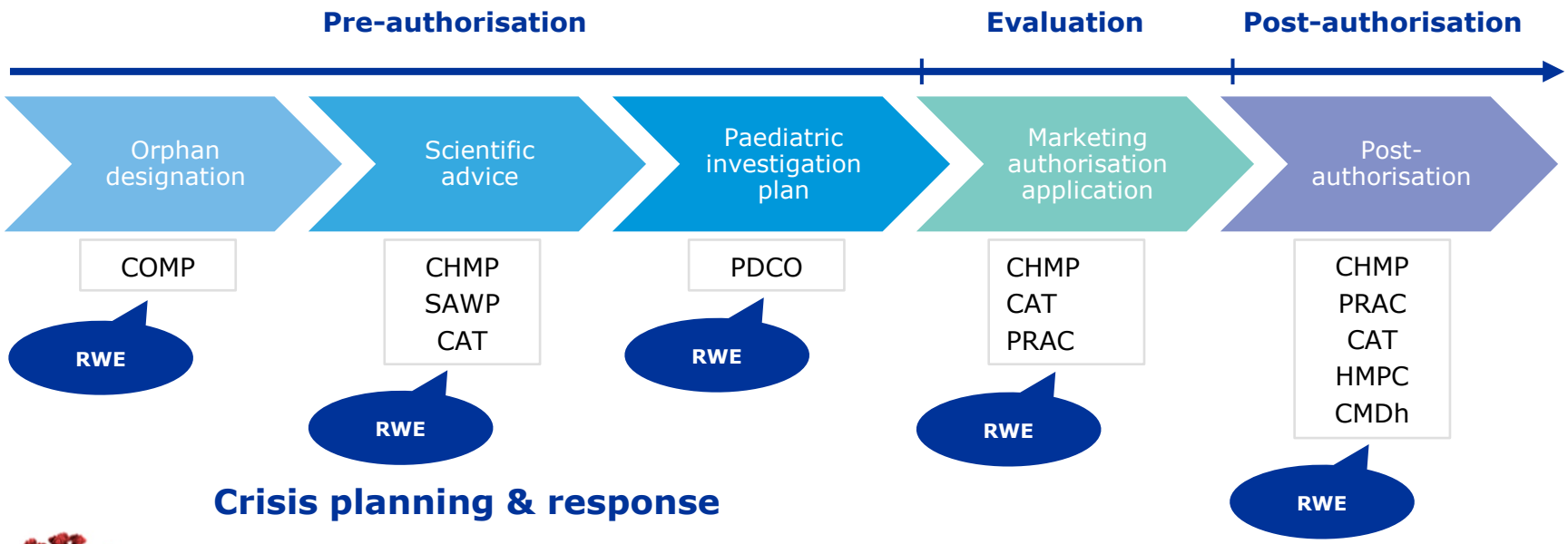
3rd BDSG workplan

HMA-EMA Joint Big Data Steering Group work plan

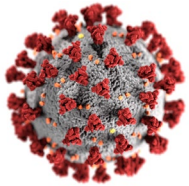


- Delivery of expert advice
- Governance framework
- International initiatives
- Stakeholder engagement
- Veterinary recommendations

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

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 of studies

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

3 Investigate associations and impact

- ✓ (Comparative) Effectiveness and safety studies
- Impact of regulatory actions

HMA
Heads of Medicines Agencies

EMA
EUROPEAN MEDICINES AGENCY

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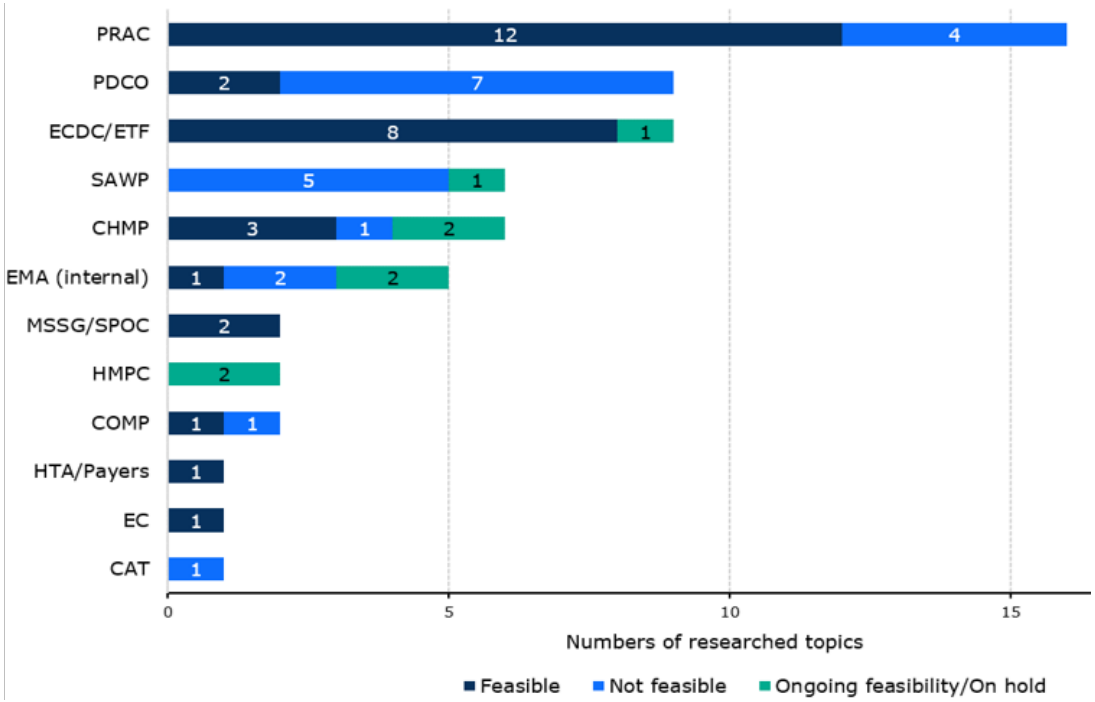
Real-world evidence framework to support EU regulatory decision-making

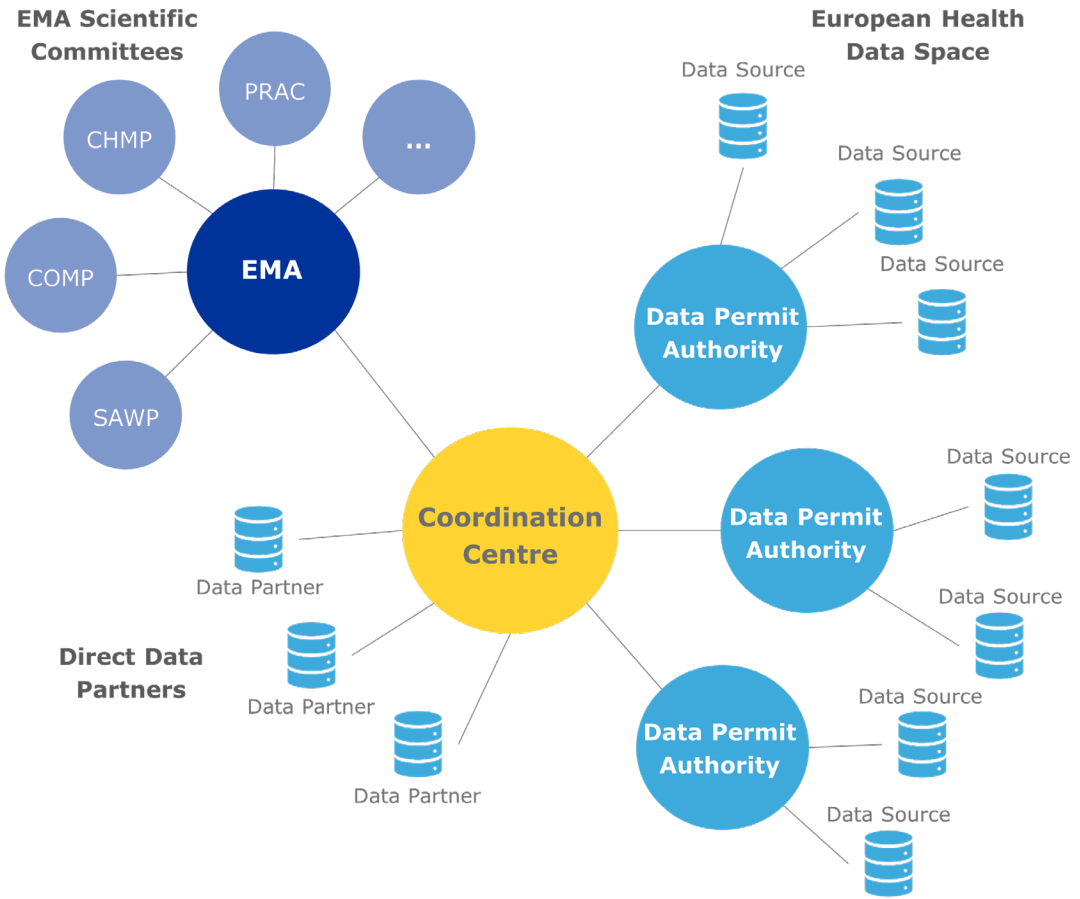
2nd report on the experience gained with regulator-led studies from February 2023 to February 2024

2nd report on RWE experience:

60 requests by:



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

Data Partners, n=20

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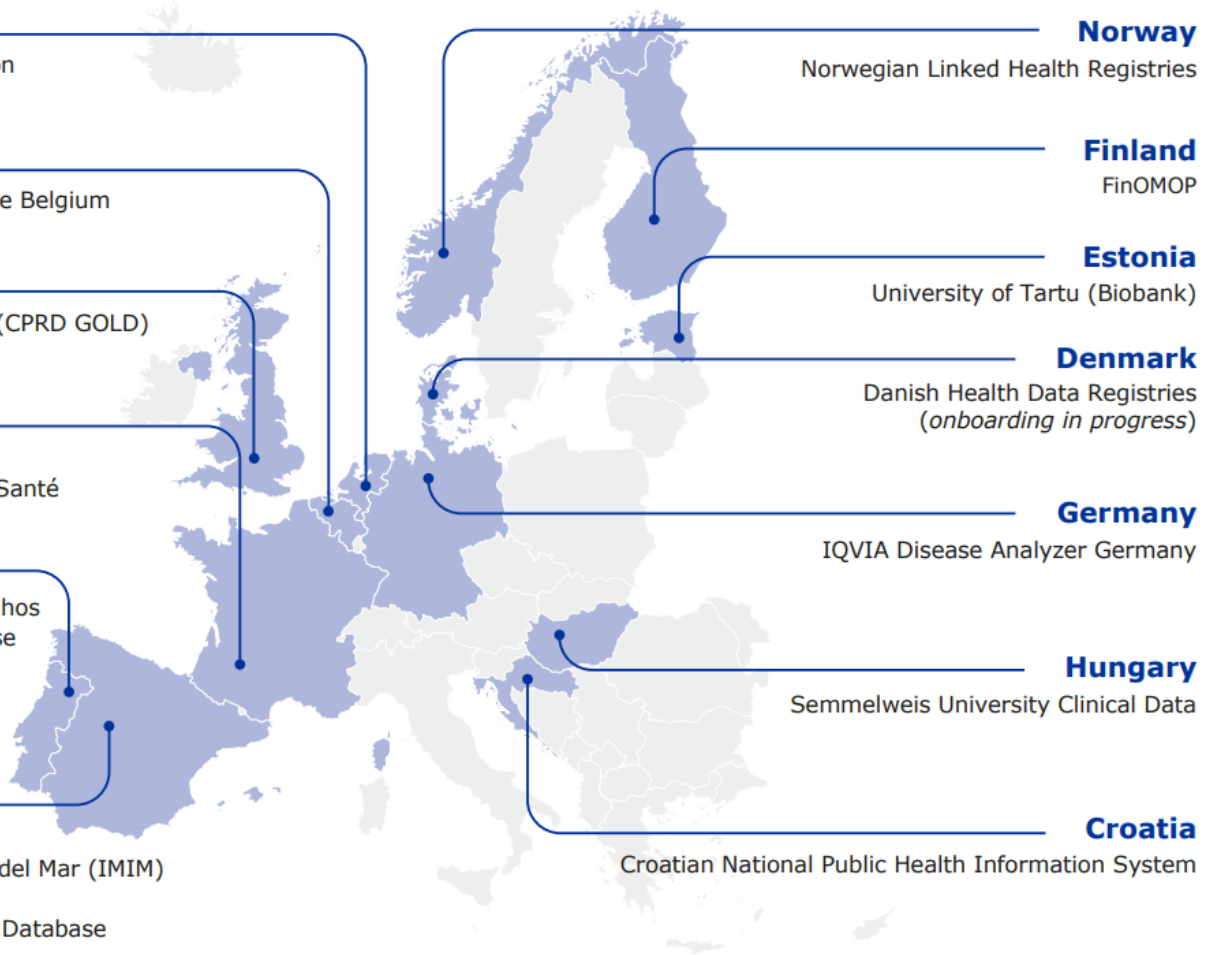


The Netherlands
Integrated Primary Care Information
Netherlands Cancer Registry

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

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 based on minimal inclusion criteria.

Complex

These are studies requiring development or customisation of specific study designs, protocol analytics, phenotypes. This includes studies on the safety and effectiveness of medicines and vaccines.

For complex studies, MAHs are consulted on study protocol

- Prevalent user active comparator cohort studies
- New user active comparator cohort

Studies comparing risk of health outcome in exposed vs unexposed cohorts

- Self-controlled case risk interval
- Self-controlled case series

Studies comparing risk of health outcome in exposed vs unexposed periods in cohort of cases

- Time series analyses and Difference-in-difference studies
- RMM effectiveness

Studies to assess the impact of restrictions in the use of medicines

Details in protocols + study reports in HMA-EMA catalogue of RWD studies

+shiny apps

Table of contents

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

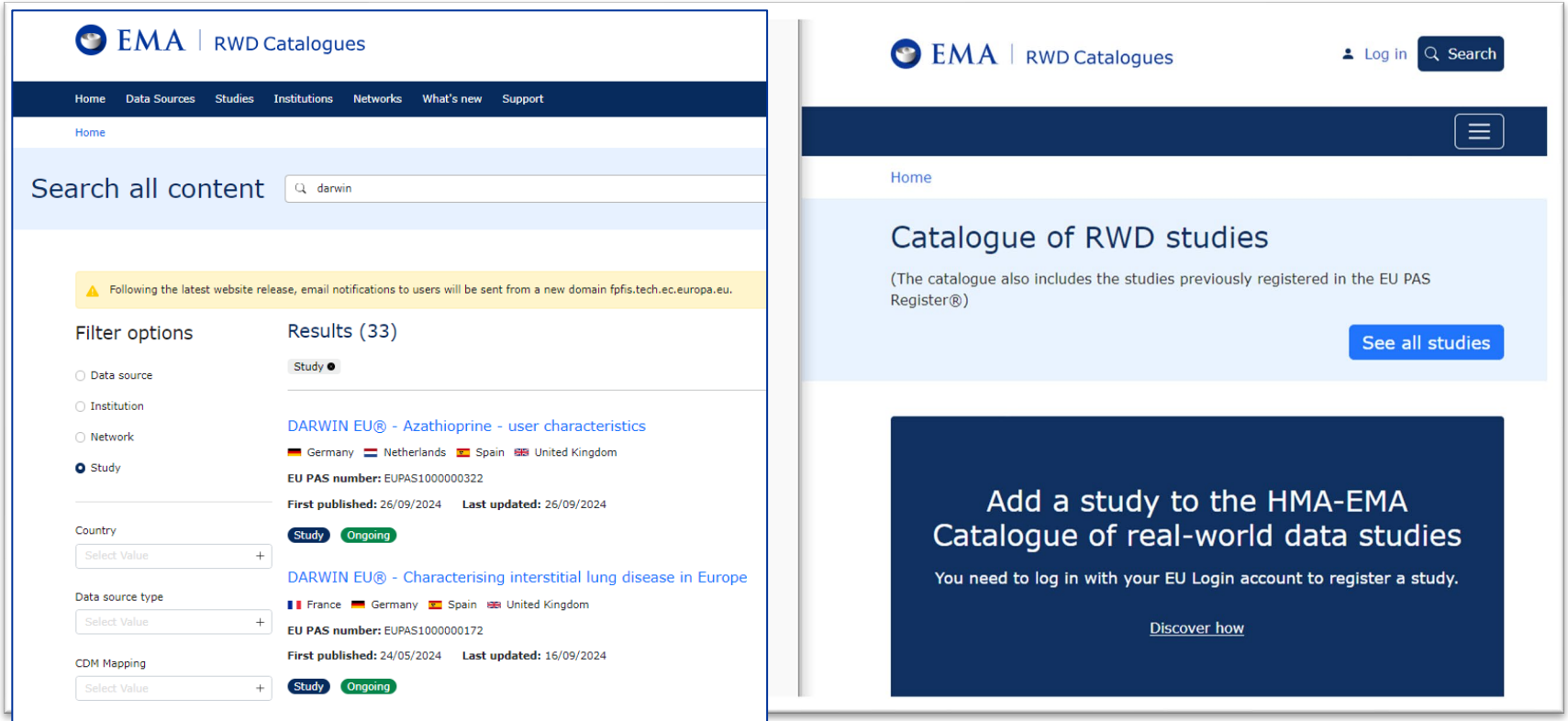
Version: v3.1

Dissemination level: Public

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

Study protocols and reports made public



Engagement with the industry

Via the DARWIN EU Advisory Board

Via regular events, workshops – upcoming Fifth EMA/HMA Big Data Stakeholder Forum | European Medicines Agency (EMA) (europa.eu) –28th Nov 2024

EMA-industry RWE focus group – inaugurated and 2nd meeting in Dec 2024

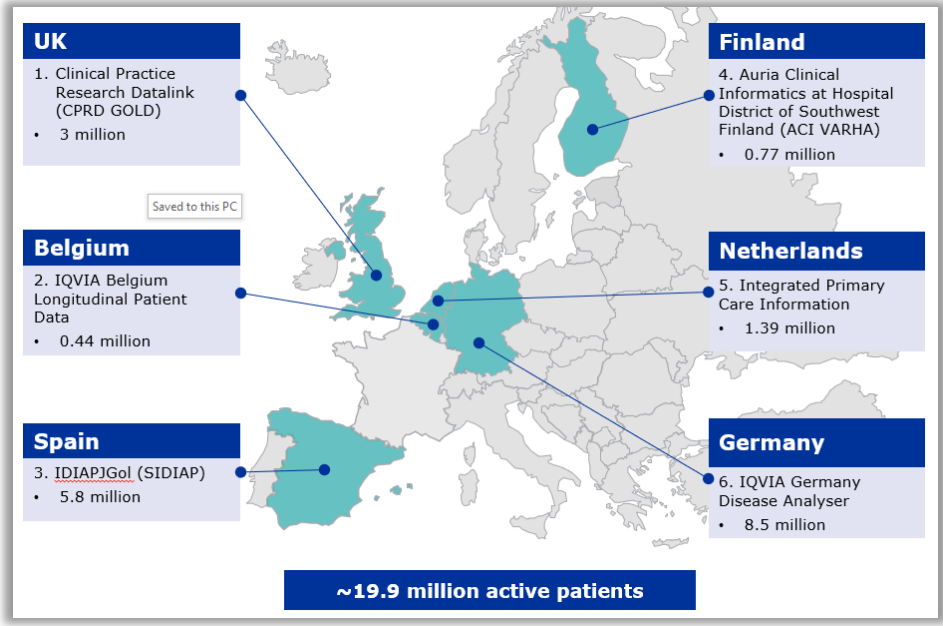
Consultation process for complex DARWIN EU studies:

- Per agreed process with the AB
- Notice to MAHs whose products are in scope (originator)
- Protocol (mature version) shared for comments – in one round, for 10 days
- EMA triages comments and implements for clarity/improvement where compatible with design
- Study report (final version) later shared for information and published

DARWIN EU® - Drug utilisation of valproate-containing medicinal products in women of childbearing potential

Objectives:

1. To estimate the ***prevalence and incidence of use of valproate*** containing medicines, and alternative antiepileptic therapies among women aged 12 to 55 years of age
   - Stratified by calendar year and age between 01/01/2010 and 31/12/2021 (population level analysis)
   - Prevalence was calculated as annual period prevalence. Incidence was calculated as new users of VPA
2. To ***characterise the use of valproate*** containing medicines among women aged 12 to 55 years of age
   - Stratified by **indication**, calendar year and age between 01/01/2010 and 31/12/2021 (patient level analysis)
   - Characterise indications, treatment duration and dose for new users of VPA



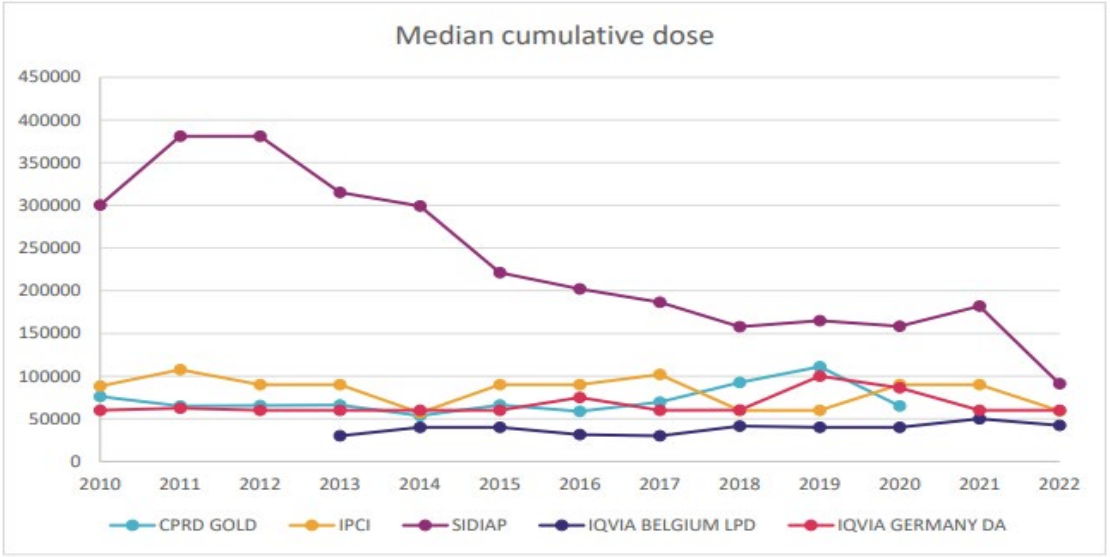
EUPAS50789

New user incidence in women 12 to 55 yrs (all databases)

Indication for VPA at initiation

Indication at index date often missing in some databases. Indication recorded any time before:

Database	CPRD GOLD	IPCI	SIDIAP	IQVIA BELGIUM	IQVIA GERMANY
Bipolar disorder	941 (14.7%)	57 (4.6%)	1531 (14.7%)	109 (11.5%)	416 (10.4%)
Epilepsy	1877 (29.3%)	276 (22.2%)	1399 (13.5%)	420 (44.4%)	2214 (55.3%)
Migraine	1660 (25.9%)	371 (29.9%)	1120 (10.8%)	382 (40.4%)	553 (13.8%)



Examples of possible DARWIN EU® studies

a. Drug utilisation study of prescription **opioids**. EUPAS105641

PRAC
OTS

b. Treatment patterns of drugs used in adult and paediatric population with **lupus**
EUPAS106436

PDCO
OTS

e. CGRP antagonists - Treatment patterns and users characteristics
EUPAS1000000240

PRAC
OTS

f. Background incidence rates of selected vaccine adverse events of special interest (AESIs) in Europe
EUPAS1000000254

PRAC
complex

c. Overall survival in patients with advanced or metastatic non-small cell lung (**NSCLC**) cancer treated with selected **immunotherapies as first line** of treatment.
EUPAS1000000112

HTA / Payers
Complex

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

HTA / Payers
OTS

g. Suicidality following exposure to doxycycline
EUPAS1000000280

PRAC
Complex

h. Azathioprine - user characteristics
EUPAS1000000322

PRAC
OTS

OTS = off-the-shelf study | **completed**

Closing remarks

- In EU medicines regulation, RWE use is being enabled and established across regulatory use cases → informing regulatory decision making on medicines across their lifecycle
- 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 and shorter timelines for studies

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

Coordination Centre website: www.darwin-eu.org

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

Subscribe here to receive future issues of the Big Data Highlights

Related, Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle just published

Thank you for your attention

Further information

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Backup slides

2nd report on RWE experience: Feb 23-Feb 24 Study requests

60

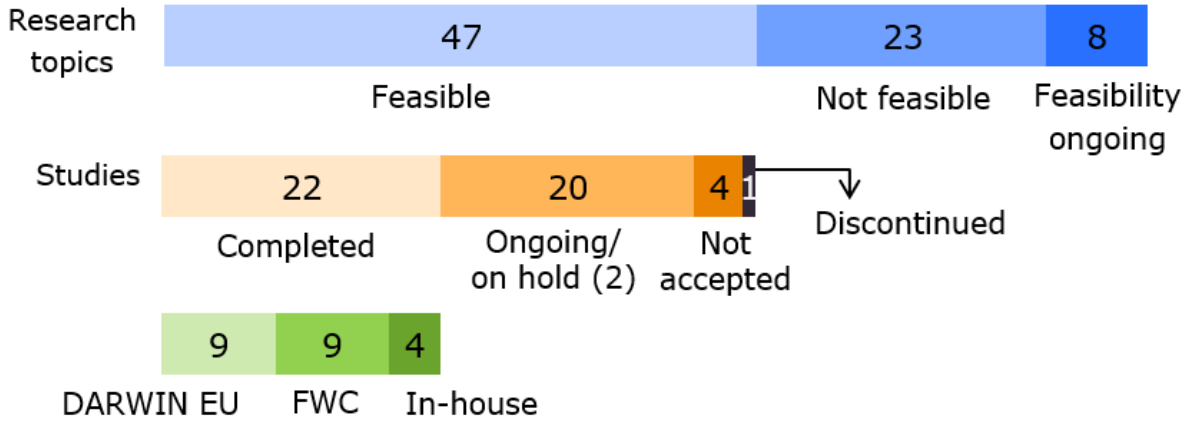
NEW research topics

(Feb '23 – Feb '24)

+18

Prior research topics

38	16	6
DARWIN EU	In-house	FWC



Three main areas of committees' decision-making for which RWE can be requested

Use case objective

1 **Support the planning & validity of applicant studies**

Use case category

Design and feasibility of planned studies

Representativeness and validity of completed studies

Inform recruitment in pre and post authorisation studies

- Number of incident and/or prevalent patients per year (for diseases and/or drugs)
- Geographical variation of incident and/or prevalent patients

Example – waiver or paediatric investigation plan modification

- Are clinical studies in young children with a rare haematological conditions feasible?

Examine impact of planned inclusion/exclusion criteria on

- Patient recruitment and its feasibility
- Composition of study population vs. real-world target population

Three main areas of committees' decision-making for which RWE can be requested

Use case objective

1

Support the planning & validity of applicant studies

Design and feasibility of planned studies

Use case category

Representativeness and validity of completed studies

Evaluate external validity

- Measure the representativeness of the CT population (treatment and control arm) vs. the real-world target population
  - Similar age distribution, gender, severity of underlying illness…
- Evaluate whether the standard of care used in the control arm of a CT is comparable with the current real-word standard of care

Three main areas of committees' decision-making for which RWE can be requested

Use case objective

2 **Understand clinical context**

Support the evaluation of incidence and prevalence of diseases

Example – prevalence for orphan designation or maintenance

- Do recent data and from a broader set of databases support the maintenance of an orphan designation?

Support better understanding of the disease and its progression

- Baseline factors at diagnosis and post-diagnostic characteristics

Use case category

Disease epidemiology

Clinical management

Generate evidence on the actual clinical standards of care and compare in different populations

- How are patients diagnosed and treated?
- Medicines used according to the authorised indication or off-label
- Treatment patterns

Drug utilisation

Three main areas of committees' decision-making for which RWE can be requested

Use case objective

2 **Understand clinical context**

Use case category

- Disease epidemiology
- Clinical management
- Drug utilisation

Characterisation of real-world drug use

- Incidence & prevalence of use
- Indication
- Amount and duration of exposure
- Switching of drug use over time

Example – contextualise risk of a possible contamination with a medicinal product

- What is the use of the medicinal product and how has it evolved over time?
- What other medicinal products are available, have they been used?

Three main areas of committees' decision-making for which RWE can be requested

Use case objective

3 **Investigate associations and impact**

Investigate the association between treatment exposure and either effectiveness or safety outcomes

- Characterise adverse events occurring in the treated population (incidence of events, time-to-onset, stratification by subpopulations)

Example - association between COVID-19 vaccine and the occurrence of thrombosis with thrombocytopenia syndrome (TTS)

- Proactively initiated a study to calculate background incidence rates; these were used to put into context the first cases of thrombosis events received
- This analysis allowed to investigate the potential signal and was central to the assessment of the committees

Use case category

Effectiveness and safety studies

Impact of regulatory actions

Monitor implementation of risk minimisation measures

- Changes in drug use with time

Monitor effectiveness of risk minimisation measures

- Changes in incidence of harmful event with time