DARWIN EU

PCWP and HCPWP, 15 November 2023

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An agency of the European Union

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The presenter does not have any conflict of interests.

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 -

Enabling use & establishing the value of RWE

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

- Facilitating access
- Build business processes
- Set standards
- Validate methods
- Train/share knowledge
- Establish value across use cases
- International collaboration:
  - build on ICMRA → RWE statement: 4 collaboration areas
  - ICH RWE reflection paper 'International harmonisation of real-world evidence (RWE) terminology, and convergence of general principles regarding planning and reporting of studies using real-world data, with a focus on effectiveness of medicines' →public consultation

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, 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.[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 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 medicine agencies

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

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

Countdown to 2025

Enabling use

Towards delivering the 2025 RWE vision

EMA studies using in-house databases

- **Primary care** health records from the **France**, **Germany, UK, Italy, Spain** and **Romania.** Some data sources include data on specialist.

Studies procured through EMA FWCs

- New framework contract (FWC) since September 2021: services of **8 research organisations** and academic institutes
- Access to **wide network of data sources**: 59 data sources from 21 EU countries
- Ability to leverage external **scientific expertise**

DARWIN EU

DARWIN EU®

- Coordination Centre launched February 2022
- Onboarded first **10 data partners**
- **First studies** finalised
- Additional 10 data partners are foreseen to **be added each year** for 2023-2025

RWE report published, with infosheet

61
research topics

49	8	4
In-house	DARWIN EU	FWC

RWE needs

- the **needs** for RWE of CxMP and SAWP;
- the **ability** and **capacity** of the current RWE framework;
- the **usefulness** of the RWE provided.

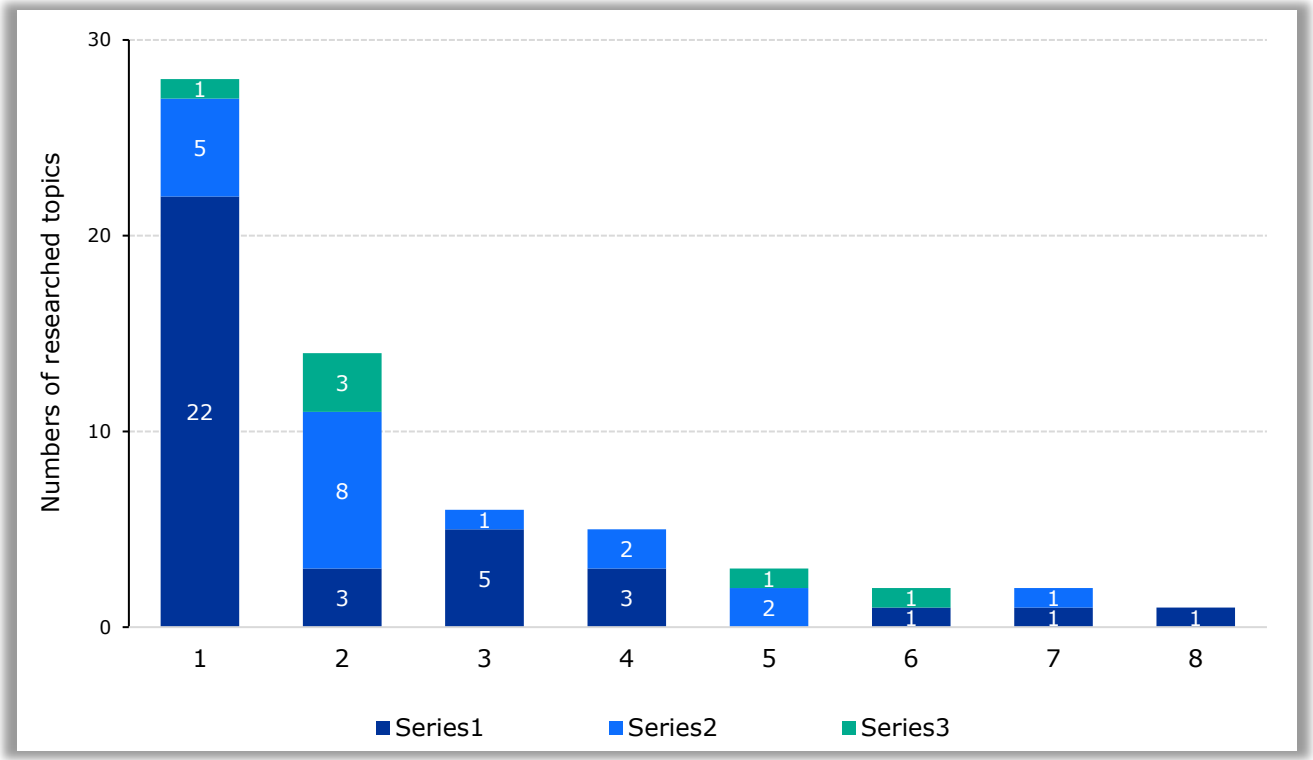
Suitability of data sources

- the **suitability** of available **RWD sources** and **pathways**;
- the **methodological challenges** of data collection, study design and reporting.

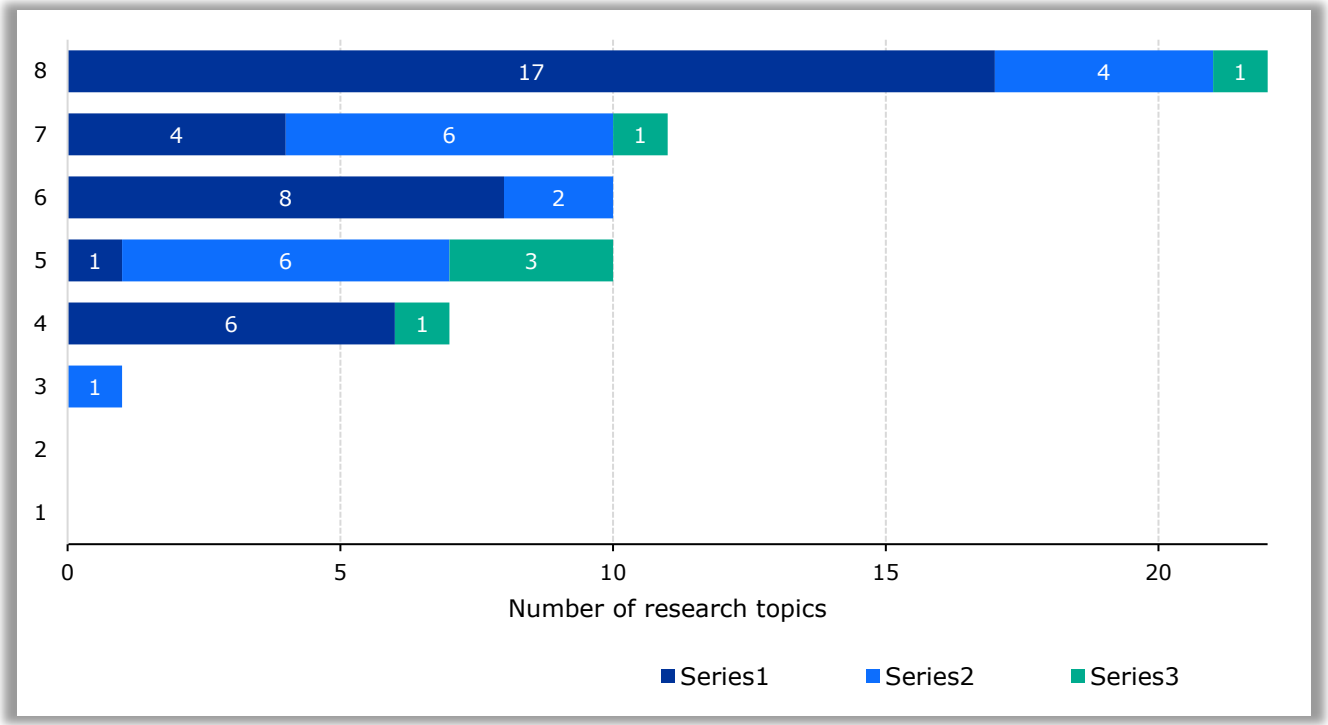
Process for RWE studies

- receiving **study requests**;
- **proactively offering** and **conducting** RWE studies;
- identify **opportunities for improvements.**

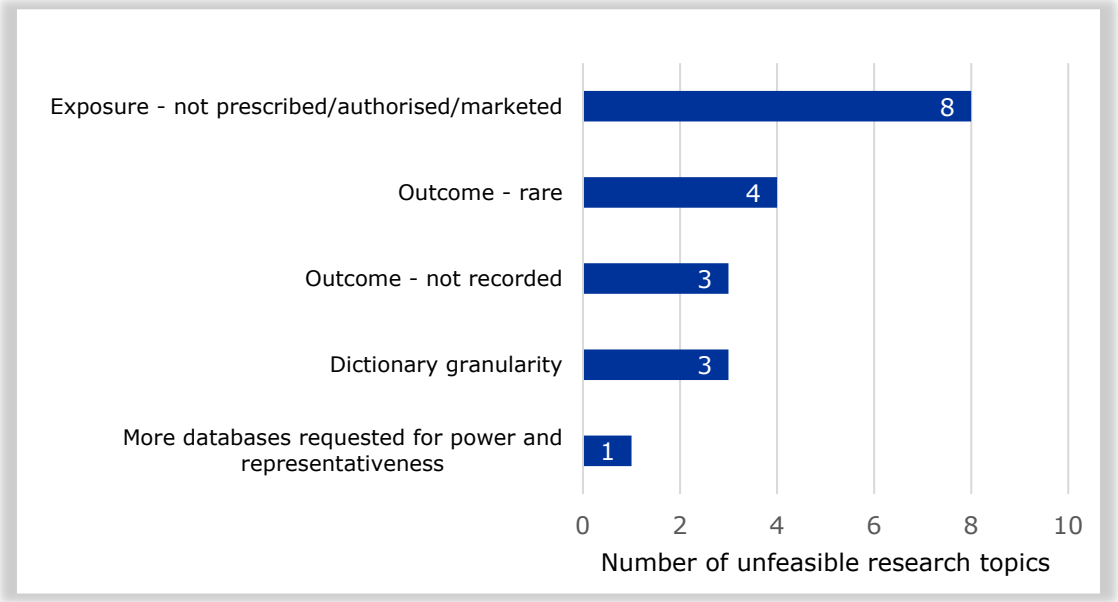
Research topics by committees/requester



Use case categories



Reasons for unfeasibility of studies (19)



*** Lack of granularity in the information contained in the databases** includes outcomes that are poorly captured by the coding system, or insufficient information on prescribing, dose, duration of use, and indication

Recommendations for enabling the use of RWE

The report provides a set of recommendations to address identified opportunities and challenges.

Access to data sources
Wider access to more diverse and complementary data sources

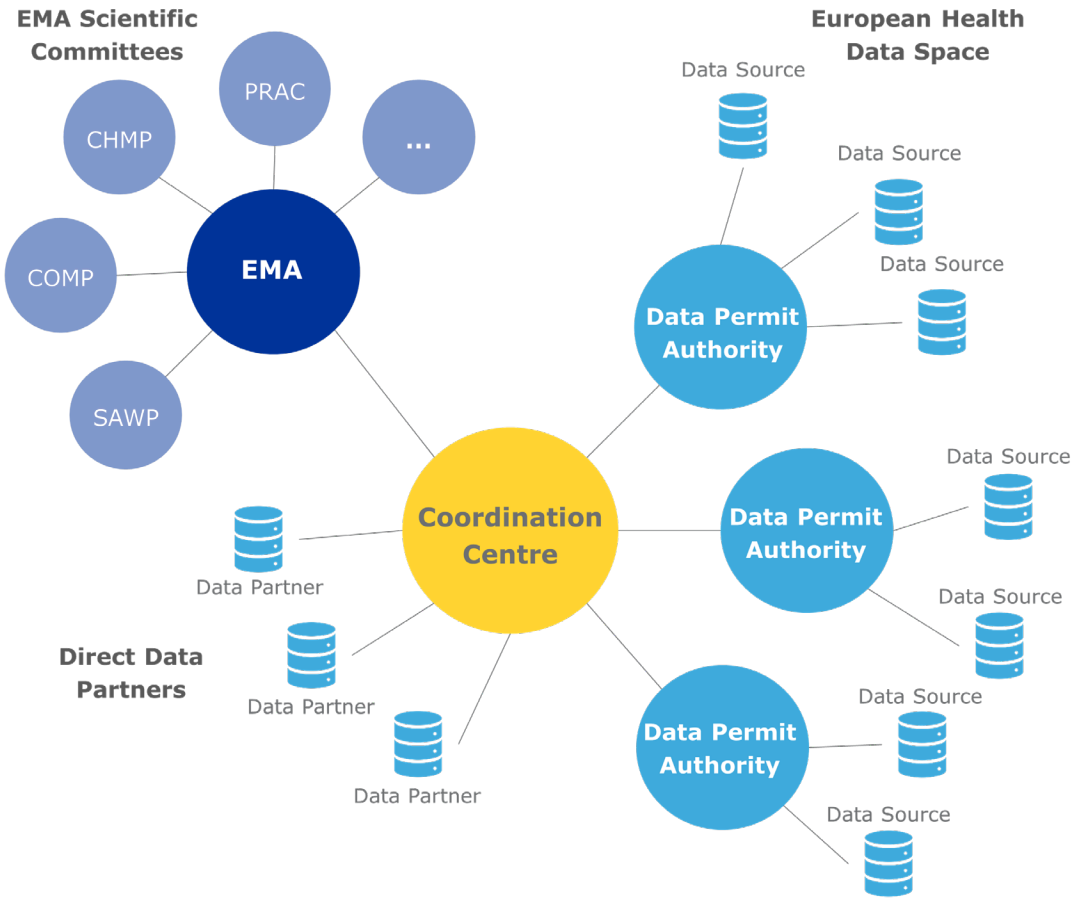
Accelerate
Strategies to further accelerate RWE generation

Regulatory context
Anticipate RWE needs of decision-makers by identifying research questions earlier

Capacity and capability
Develop educational and knowledge management sharing tools

Collaboration
Close collaboration with decision-makers and other stakeholders

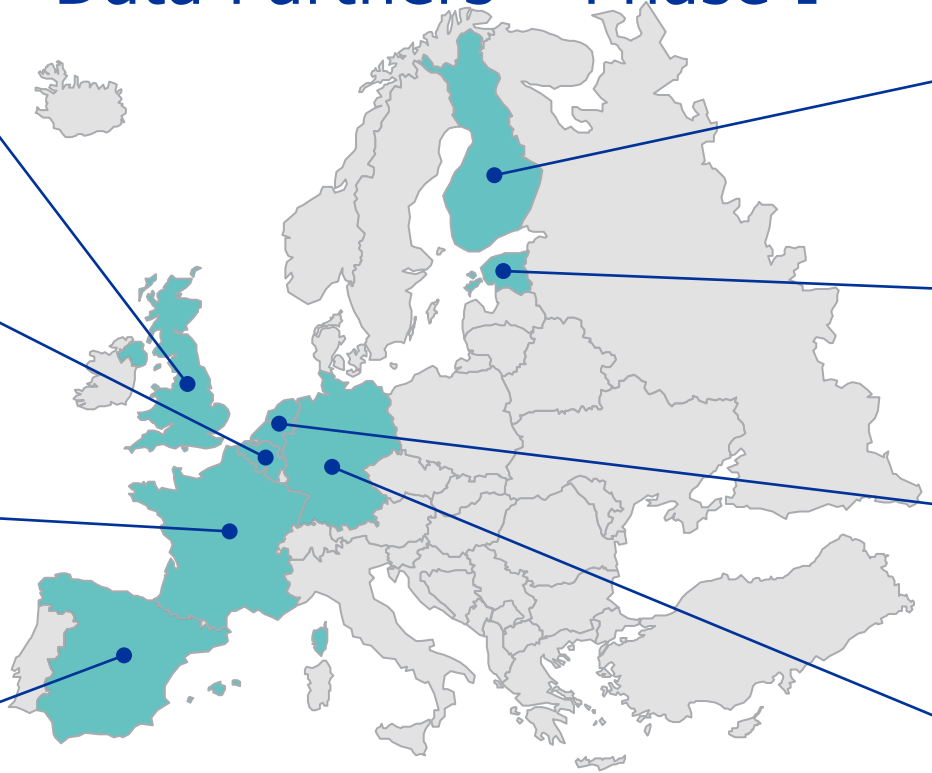
DARWIN EU® is a federated **network** of **data**, **expertise** and **services** that supports better decision-making throughout the product lifecycle by generating reliable **evidence from real world healthcare data**



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 – Phase I



UK

1. Clinical Practice Research Datalink (CPRD GOLD)

Belgium

2. IQVIA Belgium Longitudinal Patient Data

France

3. Bordeaux University Hospital

Spain

4. IDIAPJGol
5. Parc Salut Mar Barcelona, Hospital del Mar (IMIM)

Finland

6. Auria Clinical Informatics at Hospital District of Southwest Finland (HDSF)

Estonia

7. University of Tartu (Biobank)

Netherlands

8. Integrated Primary Care Information
9. Netherlands Comprehensive Cancer Organisation

Germany

10. IQVIA Germany Disease Analyser

~26 million active patients

Currently **onboarding Phase II DPs** after **open call for expression of interest**, then Phase III selection to follow

More detail in protocols + study reports in EU PAS Register

+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**

Ongoing studies

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

CHMP
Complex

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

HTA/Payers
OTS

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

PRAC
OTS

Naloxone use in treatment of opioid overdose. [EUPAS105644]

CHMP
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

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

NCA
OTS

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

ECDC/VMP
Complex

HPV vaccine effectiveness in preventing cervical cancer.

ECDC/VMP
Complex

DUS of medicines at risk of **shortages**

EMA TRS
OTS

OTS = off-the-shelf study

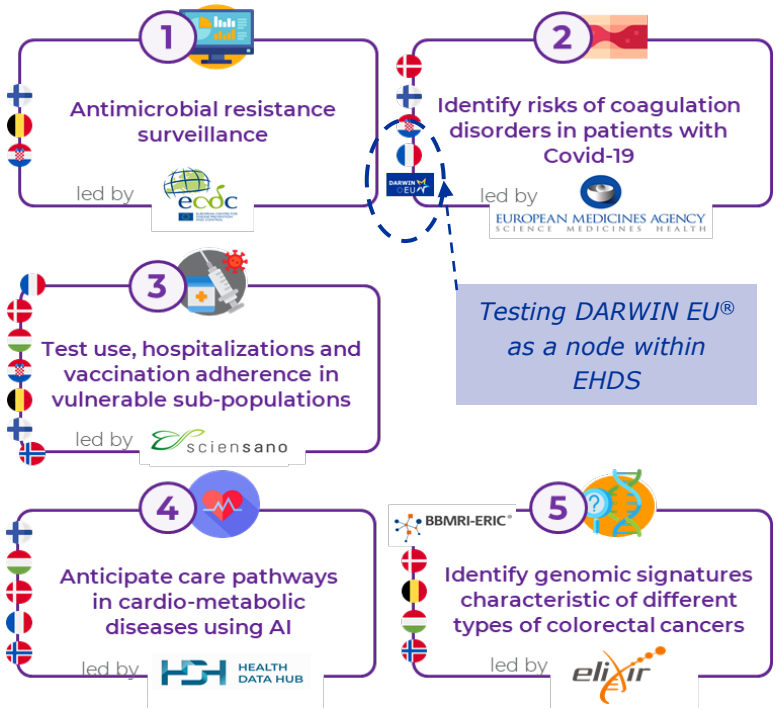
EHDS pilot (HDH coordinates)

European Health Data Space proposed in EC legislation to enable **effective use of health data**

- Primary use of health data for care (MyHealth@EU)
- Re-use or secondary use of health data (HealthData@EU)

Secondary use of data: 2-year pilot kicked off in Oct 22 (HealthData@EU pilot)

- **Five use cases** to inform design, development, and deployment of HealthData@EU frameworks
- EMA-led use case on blood clots in Covid-19 patients, testing **integration of DARWIN EU®**
- **Learnings** on governance, IT infrastructure, data quality, data availability and **data standardisation approaches**



EHDS pilot – COVID-19 thrombosis use case

Stakeholders

Use case leader

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Research teams

- DARWIN EU
- Denmark Health Data Authority, DK
- Health Data Hub, FR
- Croatian Institute for Public Health, HR
- Finnish Institute for Health and Welfare (THL), FI

Nodes

Findata, FI
HDH, FR
DHDA DK
CIPH, HR
DARWIN EU network

Objectives:

The use case will aim to address 5 research questions of increasing complexity - estimate the **incidence of venous and arterial thromboembolic events** among:

1. the general population;
2. patients with COVID-19;
3. patients with SARS-CoV-2 vaccination;
4. estimate 4/the impact of clinical risk factors and prior SARS-CoV-2 vaccination on the incidence of venous and arterial thromboembolic events among patients with COVID-19 and worsening of COVID-19
5. the incidence rate ratios for such events among patients with COVID-19 during the period when Omicron was the dominant variant and people vaccinated against SARS-CoV-2, compared to background rates as estimated in objectives. 1, 2 and 3.

→ Aggregated analysis of results from all nodes (in CDM or not)

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
- Current focus for DARWIN EU is its scale-up: Data Partners, studies, pilot use cases and developing standard analytical pipelines
- Paving the way to high study volume meeting the demand and shorter timelines in future years, once DARWIN EU establishment is completed

Upcoming events:

- **AI workshop**: 20/21 November
- BDSG/industry meeting: end of November TBC
- **Big data forum**: 4 December

- RWE workshop with HTA/payers – follow-up from Oct 2022 workshop – Dec 2023 TBC
- **Multistakeholder workshop on Patient Registries**: 12-13 February 2024

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

Any questions?

Further information

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Backup slides

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

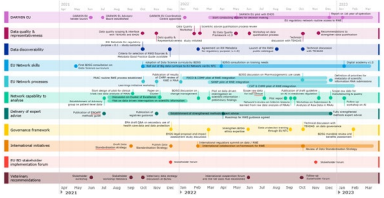
'Ten recommendations to unlock the potential of big data for public health in the EU'

May 2020

1st Big data steering group meeting in May 2020

Sep. 2020

Publication of the 1st BDSG workplan 2020/2021



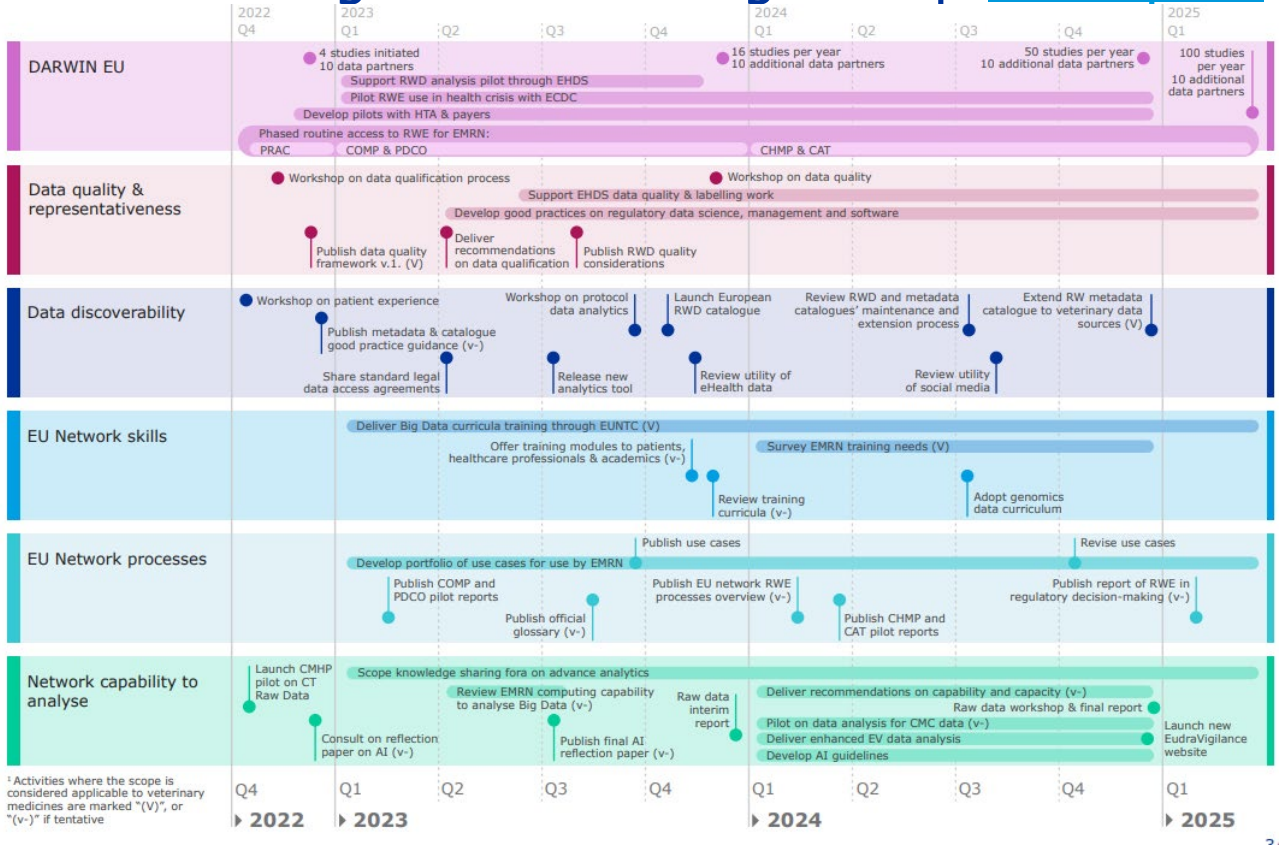
Aug. 2021

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

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?

Disease epidemiology

Support better understanding of the disease and its progression

- Baseline factors at diagnosis and post-diagnostic characteristics

Use case category

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

3

Use case objective

Investigate associations and impact

Use case category

Effectiveness and safety studies

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

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

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, protocols, analytics, phenotypes. This includes studies on the safety and effectiveness of medicines and vaccines.

- 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

First studies in 2022 (year 1)

Type	Studies	Data Partners	Planned RWE use
Off the Shelf	**Population level epidemiology** study on prevalence of **rare blood cancers** from 2010 EUPAS50800	NL, ES, UK, BE, DE	orphan designation decision making & background rates
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
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
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