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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

RWE in regulatory assessment and decision-making processes

A report on the experience with regulatory-led RWD studies

Multi-stakeholder workshop on Real World Data (RWD) quality and experience in use of Real World Evidence (RWE) for regulatory decision-making
27 June 2023

Presenter Stefanie Prilla, TDA

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Real World Evidence in regulatory decision making/at EMA

Enabling use & establishing the value of RWE

- Facilitating access
- Build business processes
- Set standards
- Validate methods
- Train/share knowledge
- Establish value across use cases
- Internationalise (build on ISPOR, ICMRA and ICH)

[EMRN strategy to 2025]

PERSPECTIVES

PERSPECTIVE

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

Peter Arlett[1]*, Jesper Kjaer[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, authorisation, 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 designs 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

[1]European Medicines Agency, Amsterdam, Netherlands; [2]Danish Medicines Agency, Copenhagen, Denmark; [3]BfArM, Bonn, Germany. *Correspondence: Peter Arlett (Peter.Arlett@ema.europa.eu)

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Big Data Steering Group workplan 2022-2025

Framework - to enable use of data and facilitate its integration into regulatory decision making

DARWIN EU

Data quality & representativeness

Data discoverability

EU Network skills

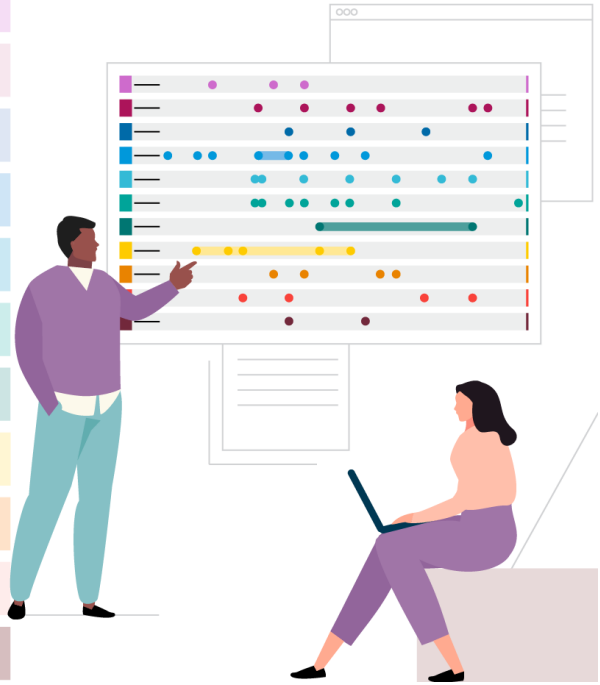
EU Network processes

Veterinary recommendations

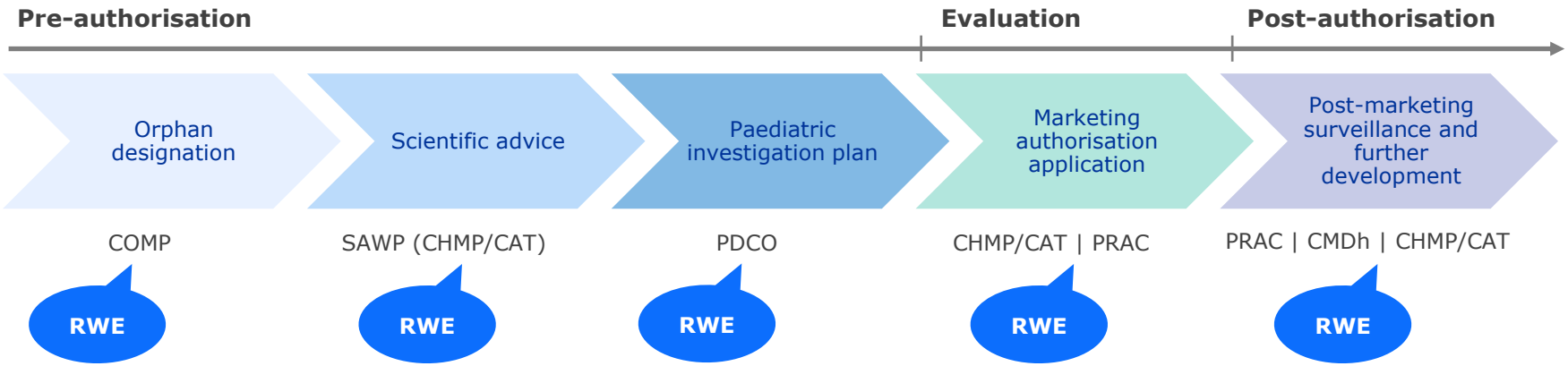
EU Network processes

Reports on pilot studies on the use of real world evidence (RWE) by EMA scientific committees will be published incrementally and concluded in 2025 with a report on RWE in regulatory decision-making. A portfolio of RWE use cases will be published to support uptake of RWE by the ERMN.

2023 - 2025	Develop portfolio of use cases for use by EMRN
Q1 2023	Publish COMP and PDCO pilot reports
Q3 2023	Publish official glossary (v-)
Q3 2023	Publish use cases
Q1 2024	Publish EU network RWE processes overview (v-)



Demand: RWE use across the medicinal product lifecycle



Demand: Three main areas for which RWD analyses can support committees' decision-making

1 Support the planning and validity of applicant studies

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

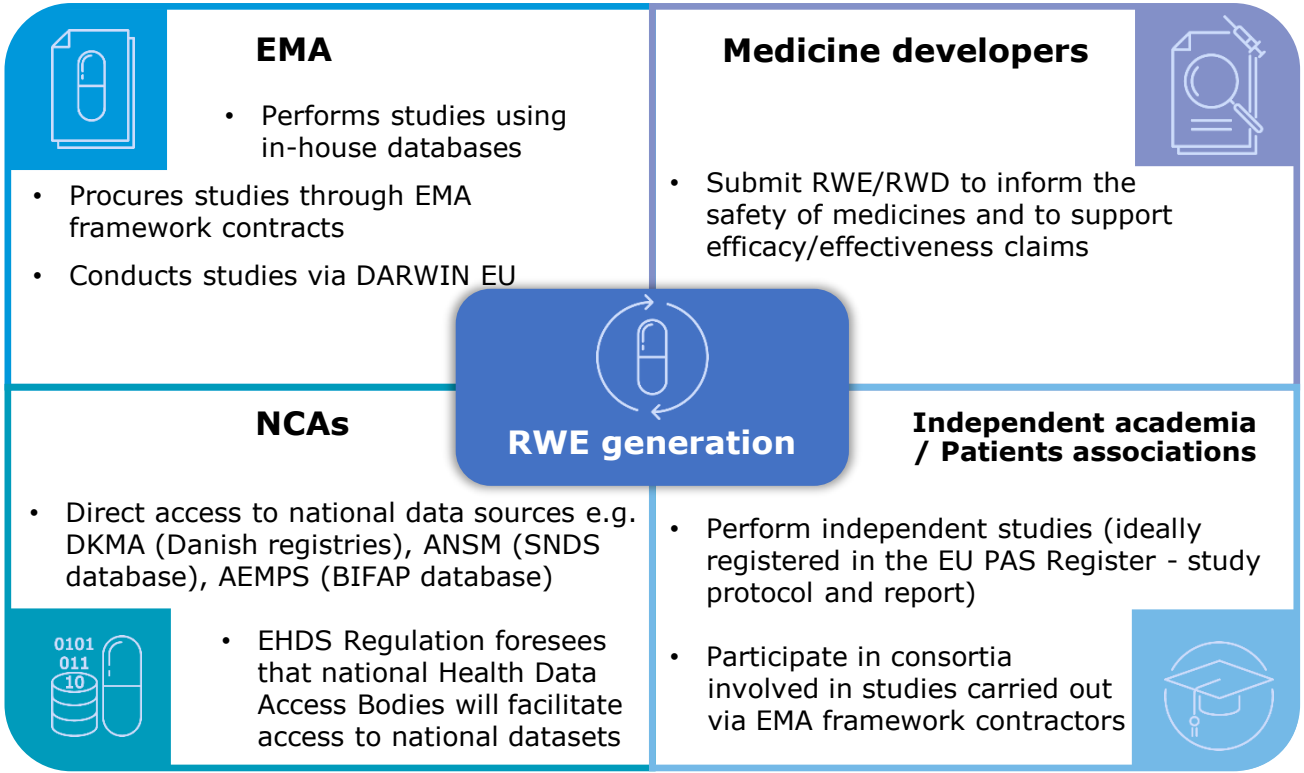
2 Understand the clinical context

- Disease epidemiology
- Clinical management
- Drug utilisation

3 Investigate associations and impact

- Effectiveness and safety studies
- Impact of regulatory actions

Supply: Real-world evidence



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Review of RWD studies: Introduction & objectives

Review published on Friday, June 23rd: Press release

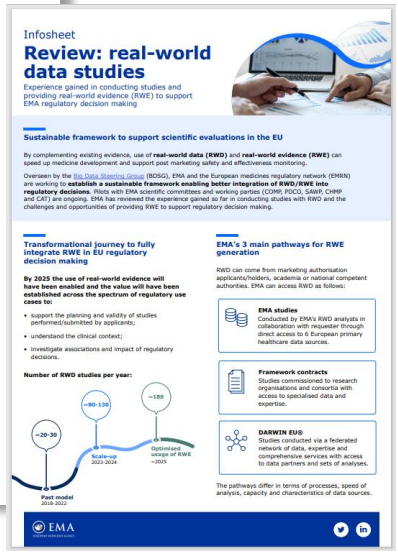
Big data | European Medicines Agency (europa.eu)

Use of real-world evidence (new)

New: A report is available on EMA's experience in using **real-world evidence** to support regulatory decision-making.

It is based on studies EMA conducted between September 2021 and February 2023, which focused on medicine **safety**, medicine use, disease **epidemiology**, design and feasibility of **clinical trials** and clinical management.

A list of research topics and a portfolio of use cases are also available.



Objectives of the review

Focus on studies conducted in addition to those performed in response to the COVID-19 public health emergency and the Pharmacovigilance impact strategy.

Take stock of the **experience with regulatory-led RWD studies** and evaluate the **opportunities and challenges in supporting regulatory decision making**

1. RWE needs

Understand:

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

2. Suitability of data sources

Understand:

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

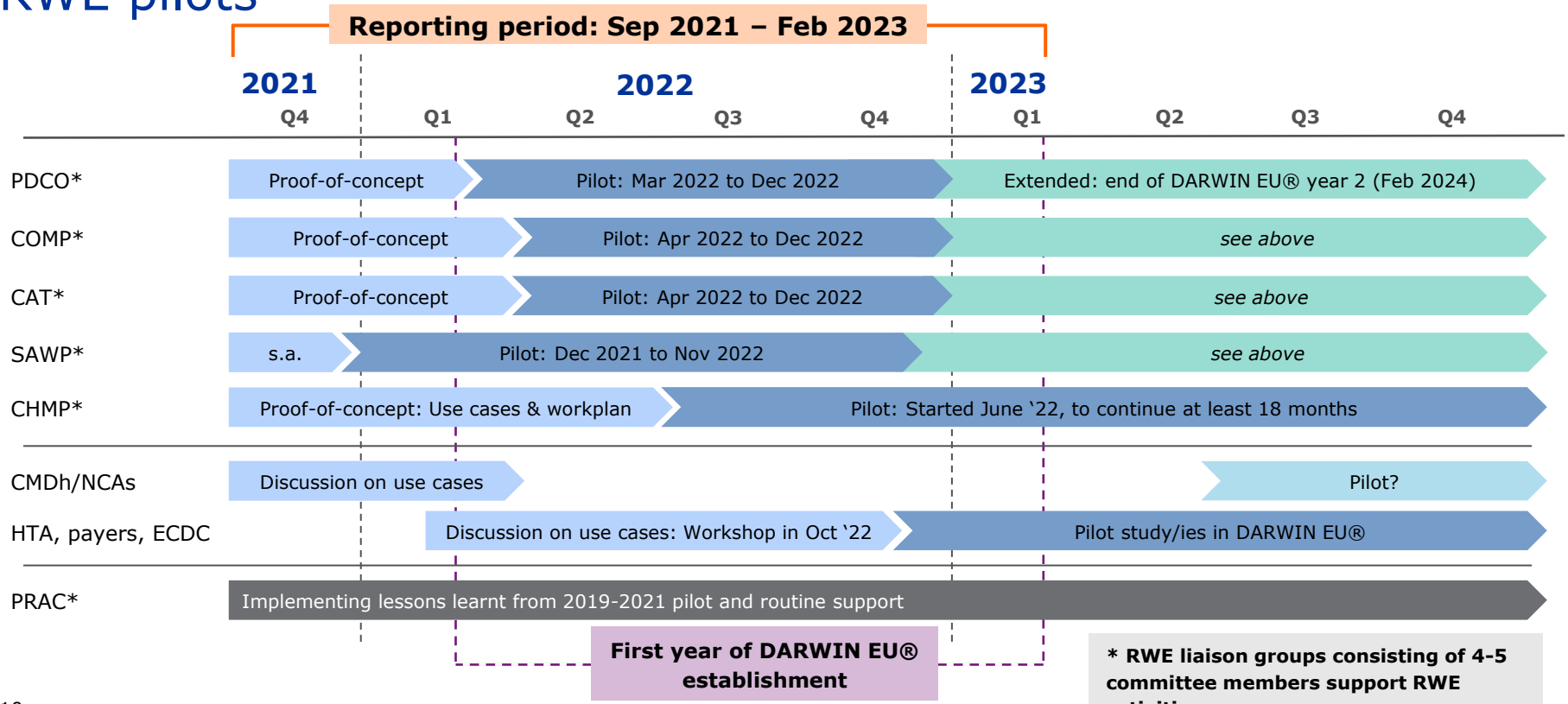
3. Process for RWE studies

Review the process for:

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

September 2021 – February 2023

RWE pilots



3 main pathways for generating RWE

EMA studies using in-house databases

- **Primary care** health records from the **France**, **Germany, UK, Italy, Spain** and **Romania**

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®

- 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 and 2024

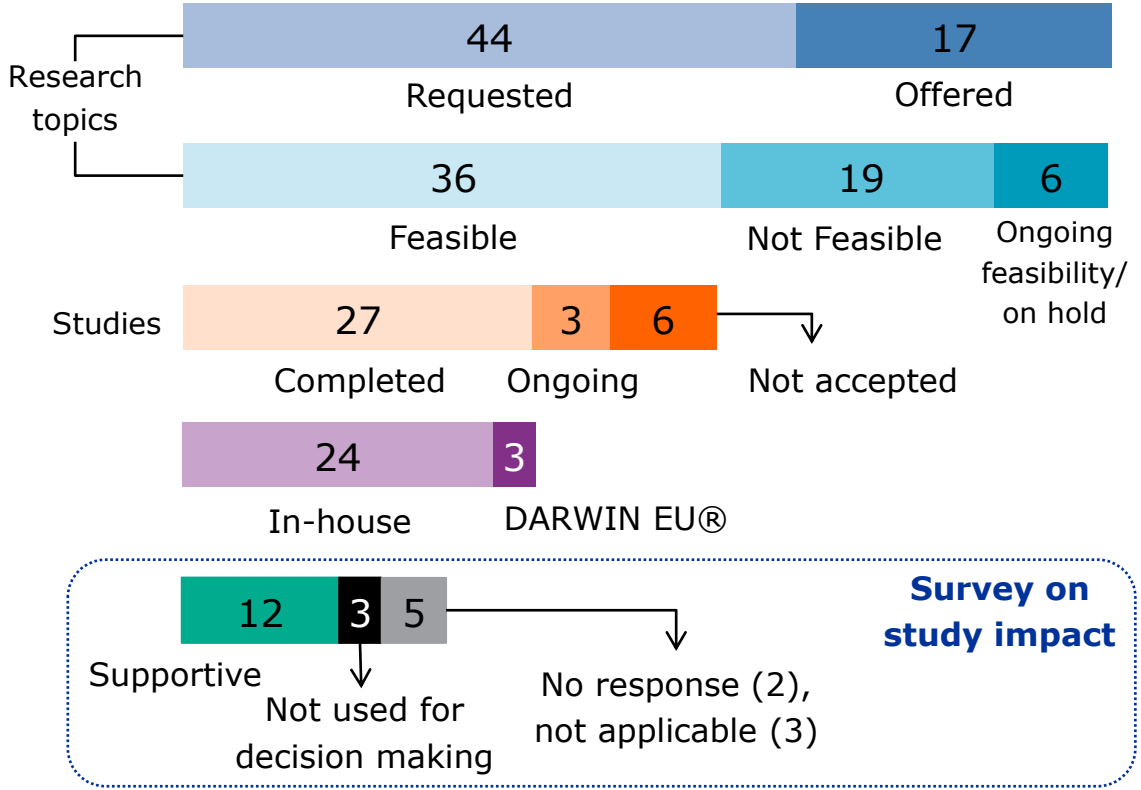
+ Regulatory authorities also have access to national databases e.g., Nordic registries, SNDS, BIFAP, …

Main results, learnings & recommendations

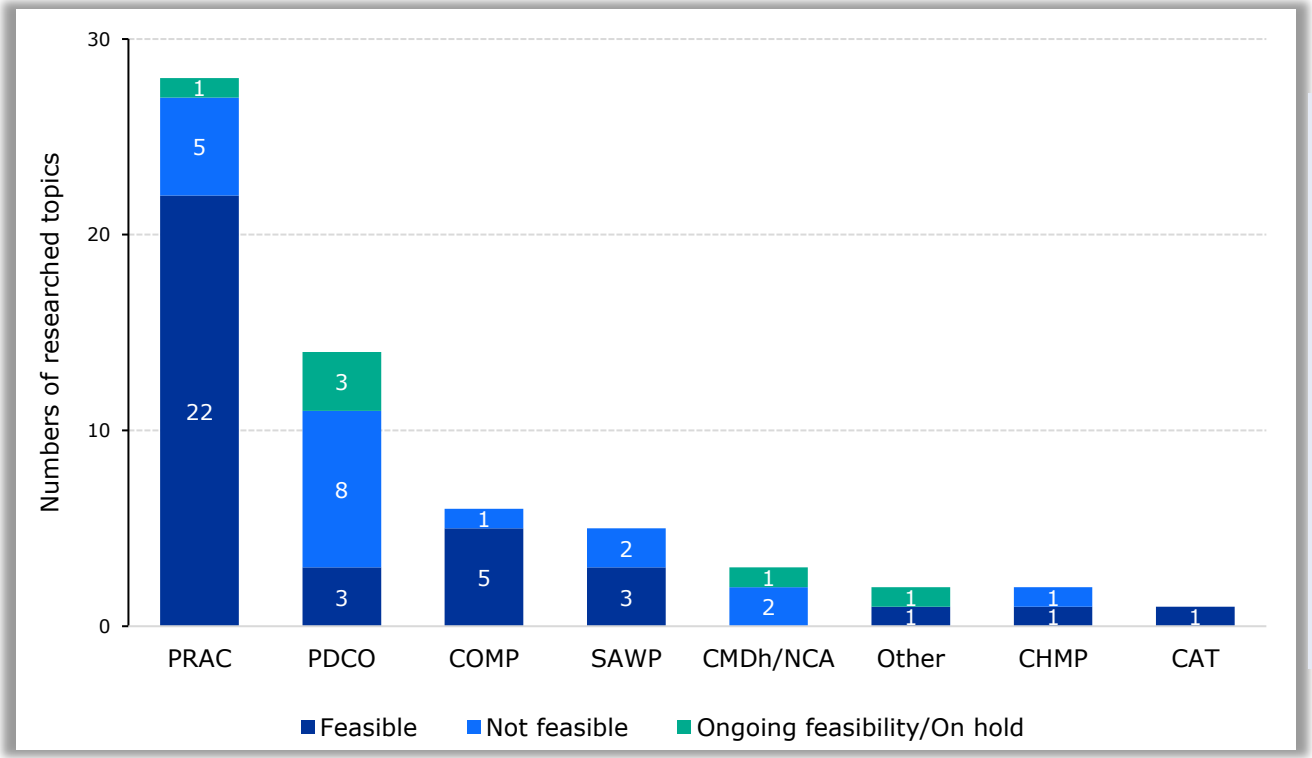
Main results – Overview of RWE studies

61
research topics

49	8	4
In-house	DARWIN EU	FWC

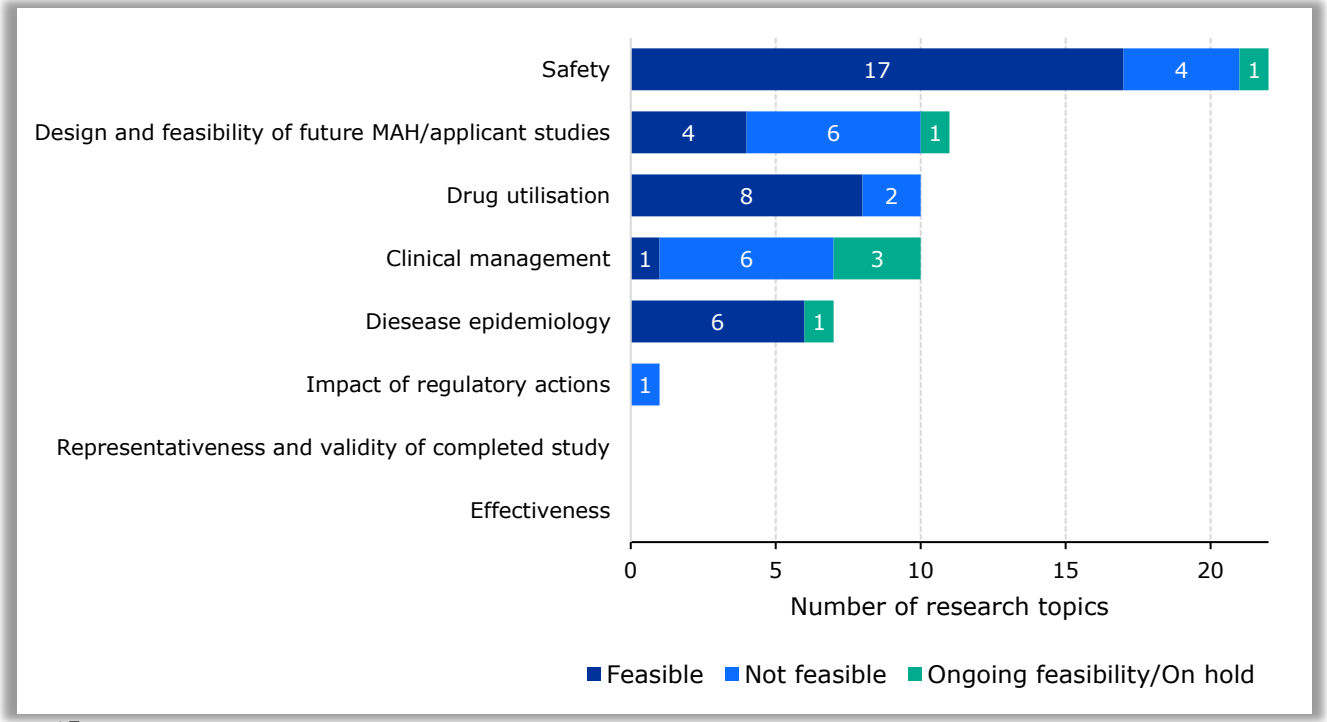


Research topics by committees/requester



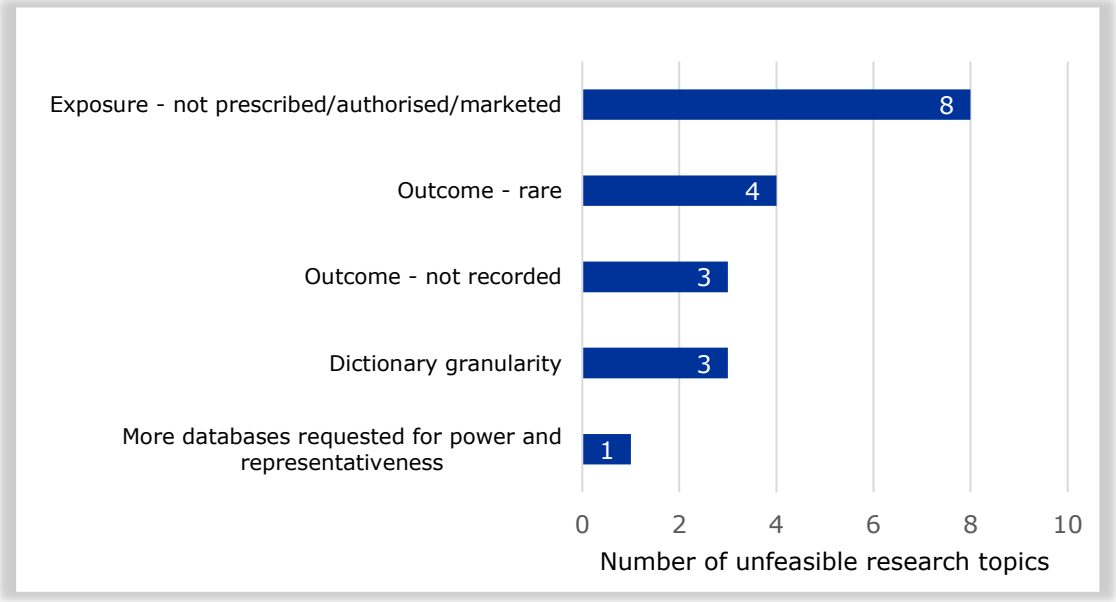
- The **majority of the research topics** emerged in the context of scientific assessments by the **PRAC** and **PDCO** followed by **COMP** and **SAWP**
- Research topics from PDCO (8 out of 11), SAWP (2 out of 5), and CMDh/NCA (2 out of 3) were more often **unfeasible** than for other committees

Use case categories



- Majority of research topics aimed at generating evidence on **safety of medicines**. Of these studies, **81%(17/22) were feasible**.
- No research topics were identified to generate RWE to inform "representativeness and validity of completed study" and "effectiveness"

Reasons for unfeasibility of studies (19)

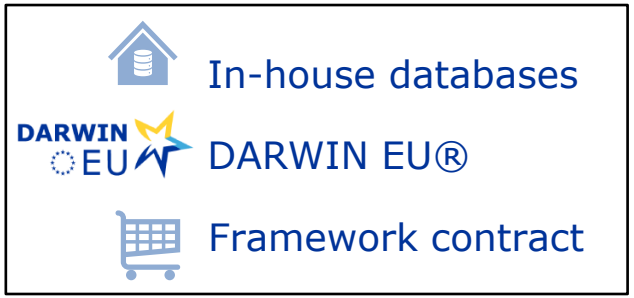


- Due to **time constraints** linked to the regulatory procedures DARWIN EU® and FWC pathways not considered for many of requests.
- The most common reason for lack of study feasibility was that the **medicinal product** (class) of interest was **not prescribed in the database setting** or **not authorised/marketed** in the respective countries (42.1%)

*** 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

Comparing the RWE generation pathway

Data sources used in studies



- In-house studies:
  - Most studies used **2 to 4 databases**
- DARWIN EU®:
  - Data sources from **8 European countries** were used in year 1 studies
  - **At least 5 data sources** (both primary and secondary care) used per study
- Framework contract:
  - Ongoing study uses **8 registries** (4 clinician-based and 4 patient-based) with data from **10 European countries**.

Conclusions – some of the main learnings

RWD studies were able to address **broad range of research questions and supported decision making** for variety of regulatory contexts, especially in **primary care setting**.

Most studies performed in-house, as **agile** pathway best suited in 2022 for tight procedural timelines/far advanced procedures - promise of **DARWIN EU® growing** in capacity and agility.

All 3 RWE generation pathways important with different strengths and limitations.

Still **many studies not feasible** especially if **conditions and medicines not in primary care, or medicines not prescribed in country, rare diseases** and in case of **tight procedural timelines**.

Collaboration with Committee sponsors/requesters (especially via **RWE liaison groups**) is key to ensure successful conduct of studies and implementation of RWE framework.

Main recommendations

Data sources!

Need for access to **more diverse and complementary data sources** incl. additional European countries & leverage **complementary RWE pathways** (NCAs, external stakeholders)

Regulatory context and timelines!

Explore possibilities for **early identification of RWE needs** & to **accelerate RWE generation**

Collaboration!

Interaction with decision-makers (especially via **RWE liaison groups** and **EMA product team/RWE community**) essential – continue & intensify

Building capability & capacity!

Educational and knowledge management tools needed
→ Big Data Steering Group's Pharmacoepidemiology curriculum

Use of RWE for decision-making!

Make available information on **data provenance, quality & completeness** to help interpretation of study findings (fit-for-purpose)

Awareness!

Promote possibility to request RWE studies via RWE framework and related processes (e.g. template email and RWE@ema.europa.eu)

Processes!

Trigger **systematic reflections of RWE needs** and further streamline processes

Portfolio of use cases – Annex 2

A portfolio of **use cases for RWE** is available in the Annex 2. Use cases are divided into the following **three categories**

Example:

Use case 3: PDCO – Prevalence of palmoplantar psoriasis (EUPAS104293)	
Problem statement	The PDCO received a request for a full PIP waiver in relation to a product intended for the treatment of palmoplantar psoriasis on the grounds that the disease does not occur in children. The PDCO asked for a study to estimate the prevalence of the condition in children in order to verify the applicant's claim.
Research question	The study aimed to describe the population level prevalence of palmoplantar and pustular psoriasis in children by age group during the last 10 years.
Findings	The prevalence of palmoplantar psoriasis in the two age groups (0-11 years and 12-17 years) was consistent across all the databases used, and typically being around 2 per 100,000 persons. The trend for prevalence of palmoplantar psoriasis over time in children seems to be stable or slightly increasing. The prevalence of pustular psoriasis was highly variable between databases with no consistency between countries, age group or across time. This is suggestive of variation in coding practice, changes in diagnostic criteria or diagnostic coding.
How was this useful?	The results informed PDCO and guided the decision making on the acceptability of a full product specific waiver for palmoplantar psoriasis. The PDCO also appreciated the analysis of the limitations of the RWE study which was helpful for the interpretation of the results.

Next steps

Next steps

- Implement recommendations
- Learnings and recommendations will feed into the work of the BDSG and the establishment of DARWIN EU®
- Pilot activities will continue until sufficient experience gained
- Review on RWE use in regulatory decision-making to be continued in coming years

[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

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Any questions?

Further information

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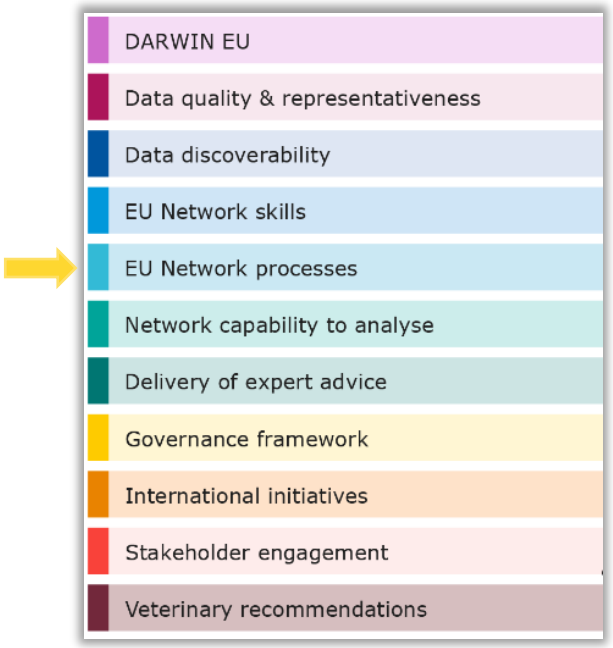
Backup slides

Big Data Workplan 2022-2025



EU Network processes

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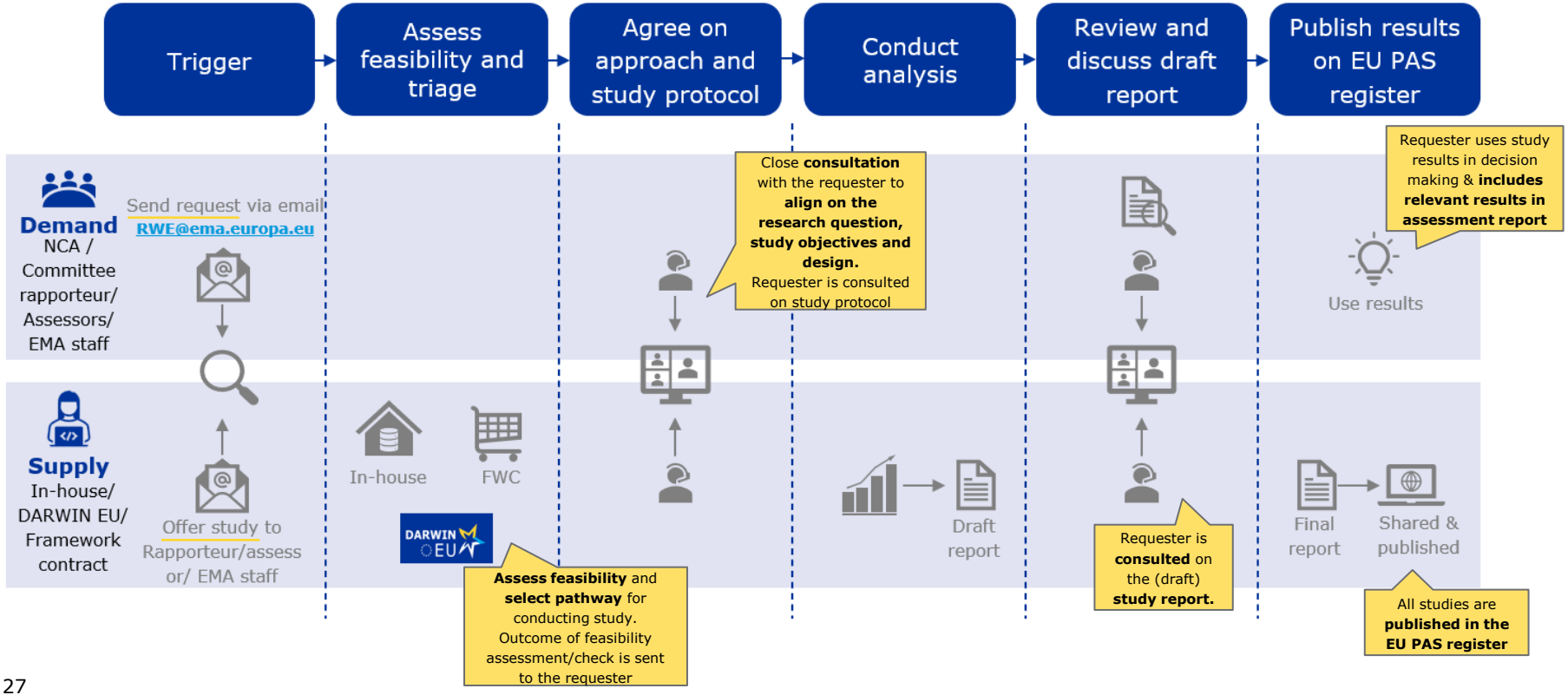
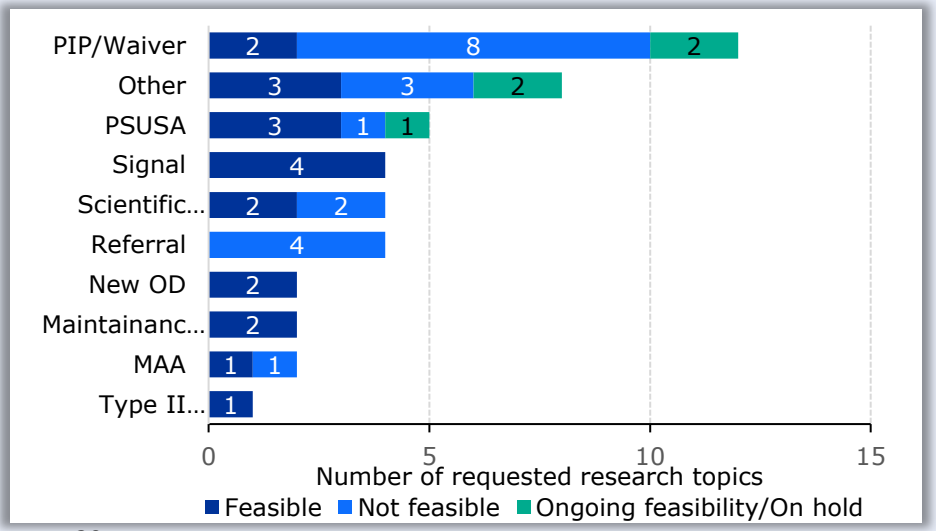
Process for conducting RWE studies

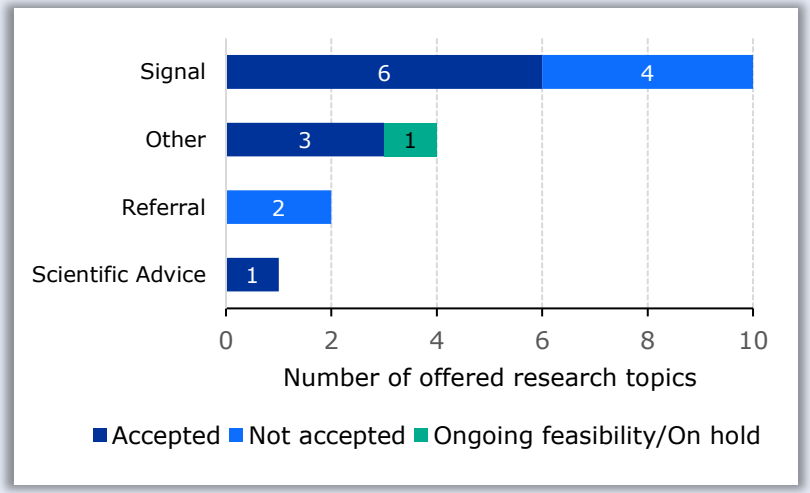


RWE in the context of regulatory procedures

Requested studies (44)

- Majority of requests in the context of **PIP and Waiver** applications
- Many were not linked to a specific procedure (category 'other')





Offered studies (17)

- Of the research topics offered, the majority were identified through **screening of new signals** in the PRAC agenda.
- Four were **not linked to procedures**
- **59% of offered studies** were **accepted** by rapporteurs/lead member states

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