EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

RWD/RWE

BioBridges 2023 – Prague, 21-22 Sep 2023

Presented by Steffen Thirstrup, 22 September 2023
Chief Medical Officer

Disclaimer

I have no conflict of interest to disclose.

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 one of its committees or working parties.

Clinical evidence 2030: Real world evidence

Real world evidence

- Establish value across use cases
- Build business processes
- Set standards
- Enable access
- Validate methods
- Train
- Internationalise (build on ICMRA and ICH)

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 medicines agencies

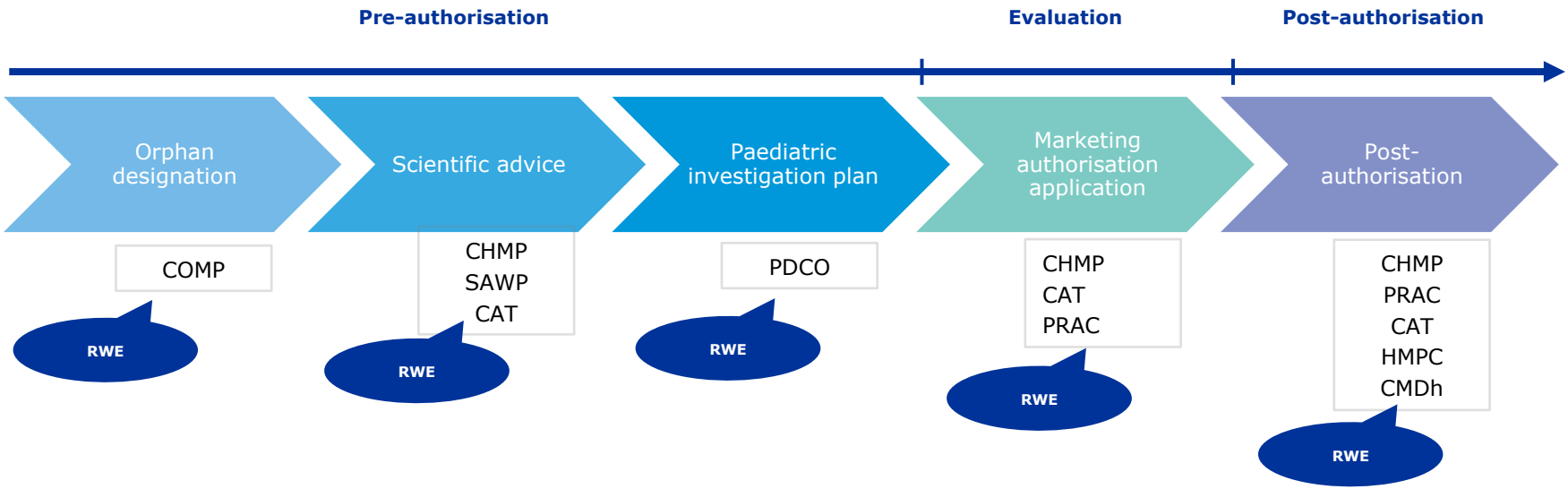
[1]European Medicines Agency, Amsterdam, Netherlands; [2]Danish Medicines Agency, Copenhagen, Denmark; [3]BfArM, Bonn, Germany. *Correspondence: Peter Arlett (Peter.Arlett@ema.europa.eu)

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

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

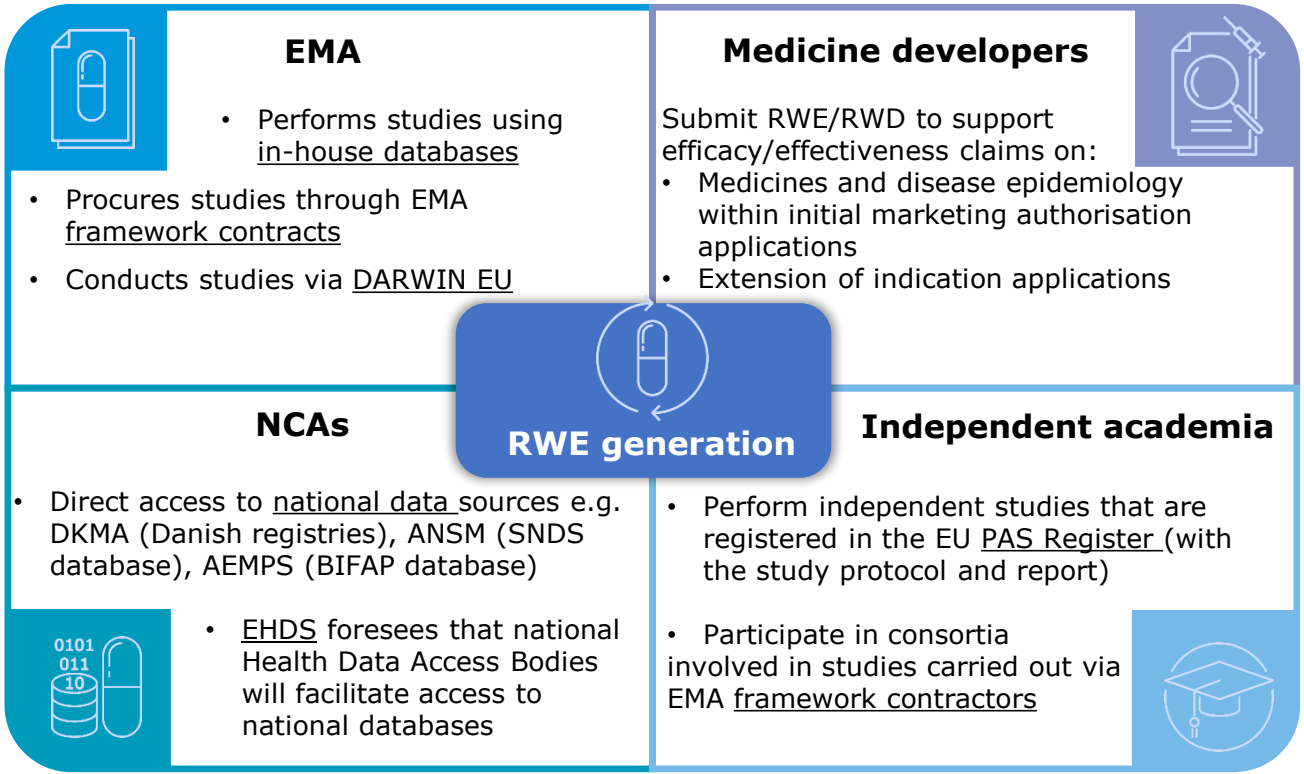
1 Understand the clinical context	2 Support the planning and validity of applicant studies	3 Investigate associations and impact
Disease epidemiology		
Clinical management and unmet need	Design and feasibility of planned studies	Effectiveness and safety studies
Drug utilisation	Representativeness and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

Demand: RWE use across the medicinal product lifecycle



Supply: Real-world evidence

EUROPEAN MEDICINES AGENCY



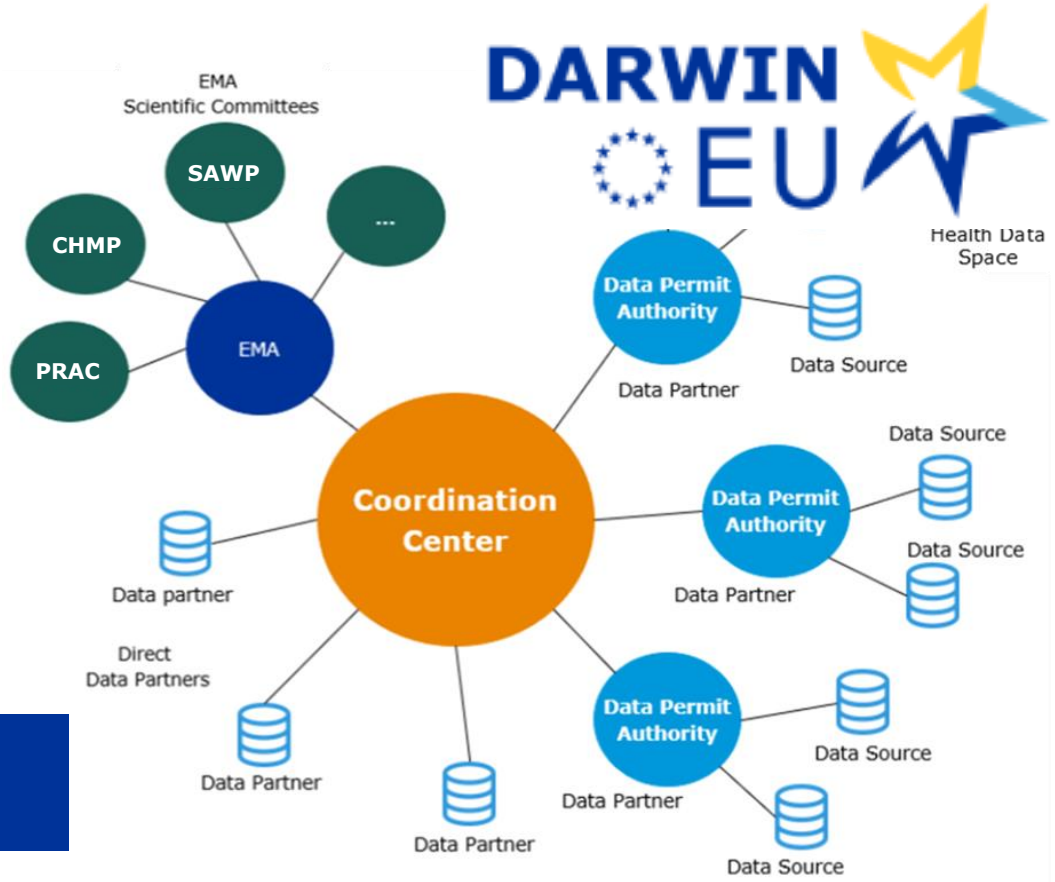
Data Analysis and Real-World Interrogation Network

EUROPEAN MEDICINES AGENCY

DARWIN EU® is a federated **network** of **data**, **expertise** and **services** that generates **evidence from real world healthcare data**

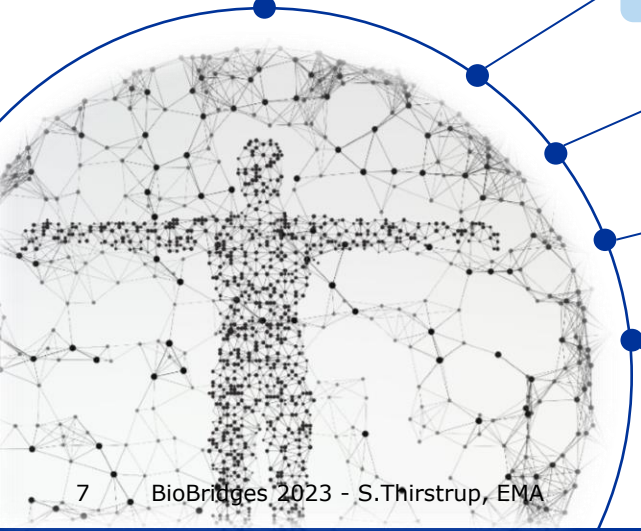
NETWORK PRINCIPLES

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



By 2025 DARWIN EU will deliver 150 RWE studies annually

What will DARWIN EU® do?



- Provide scientific expertise in formulating and executing studies and analyses
- Maintain & expand the federated network of data partners, assisting new data holders in conforming with required standards for usage in regulatory context
- Conduct scientific studies and analyses on behalf of the EMRN and EMA scientific committees
- Deliver training, governance, support of business services
- Enable the EMRN, EMA and the scientific committees to make use of the EHDS in the context of medicines regulation, acting as EHDS 'pathfinder'

Who will benefit from DARWIN EU®?

EUROPEAN MEDICINES AGENCY

EU medicines regulators

- Drug development – disease epidemiology, unmet need, historical controls, planning
- Authorisation – contribution to benefit-risk, controls, extrapolation to general and/or special populations
- Post-authorisation – benefit-risk monitoring, extension of indication, risk minimisation measures

DARWIN EU® will **increase the capacity** of the EMRN to undertake high-quality observational studies based on RWD and **reduce the time** per study

EU patients and healthcare professionals
Faster access to innovative medicines and safe and effective use

European Commission
Key use case for the European Health Data Space

National competent authorities
Support health policy and delivery of healthcare systems

HTA bodies and payers
Support better quality decisions including on cost-effectiveness

EU and international health agencies
Use cases specific for other EU Agencies such as ECDC

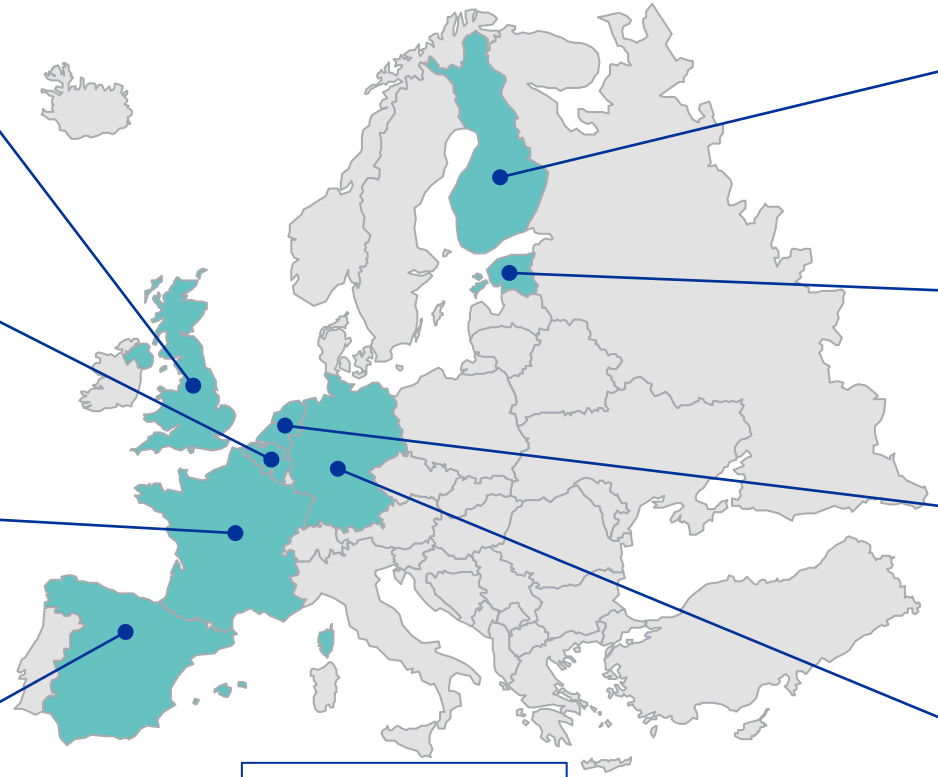
Academia and research organisations
Increase use of RWE, methodology development, and better data quality

Industry
Enable better evidence supporting decision-making, increase receptiveness for RWE in MA submissions, and reduce time & cost of drug development

Supply: DARWIN EU Data partners – Year 1

EUROPEAN MEDICINES AGENCY

10 data partners in year one: additional 10 in year 2



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

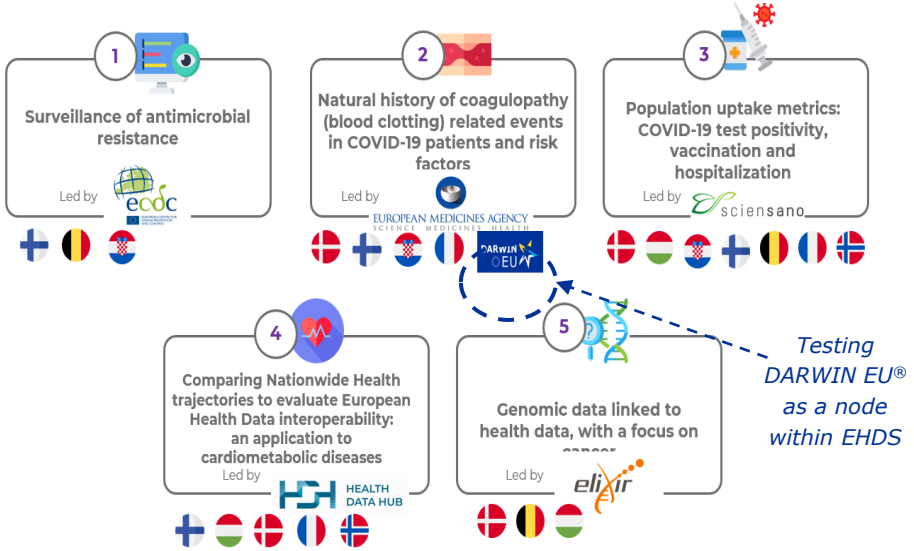
EHDS pilot: DARWIN EU use case

EUROPEAN MEDICINES AGENCY

- EC proposed legislation to establish a **European Health Data Space (EHDS)**: aims to enable the effective use of health data in the EU

Covers two aspects:

- ***Primary use*** of health data for care (MyHealth@EU)
- ***Secondary use*** of data: a pilot phase (HealthData@EU pilot) kicked off
- Five use cases selected to inform the design, development, and deployment of HealthData@EU
- DARWIN EU® - use case on blood clots in Covid-19 patients
  - Contributors: research teams and data nodes from Finland, France, Denmark and Croatia
  - Integration of DARWIN EU® will be tested



EHDS: we need **R**apid, **W**ide and **D**eep access to healthcare data

EUROPEAN MEDICINES AGENCY

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.

Catalogue of standard data analyses

EUROPEAN MEDICINES AGENCY

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

Studies – Examples, Year 1

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

CHMP
Complex

EHDS coagulopathy of COVID-19

EC/EHDS
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 on co-prescribing of **endothelin receptor antagonists** (ERAs) and **phosphodiesterate-5 inhibitors** (PDE-5is) in pulmonary arterial hypertension.

CHMP
OTS

Erythomycin use as prokinetic

NCA
OTS

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

HTA/Payers
OTS

Naloxone use in treatment of opioid overdose.

CHMP
OTS

Drug utilisation study of prescription **opioids**.

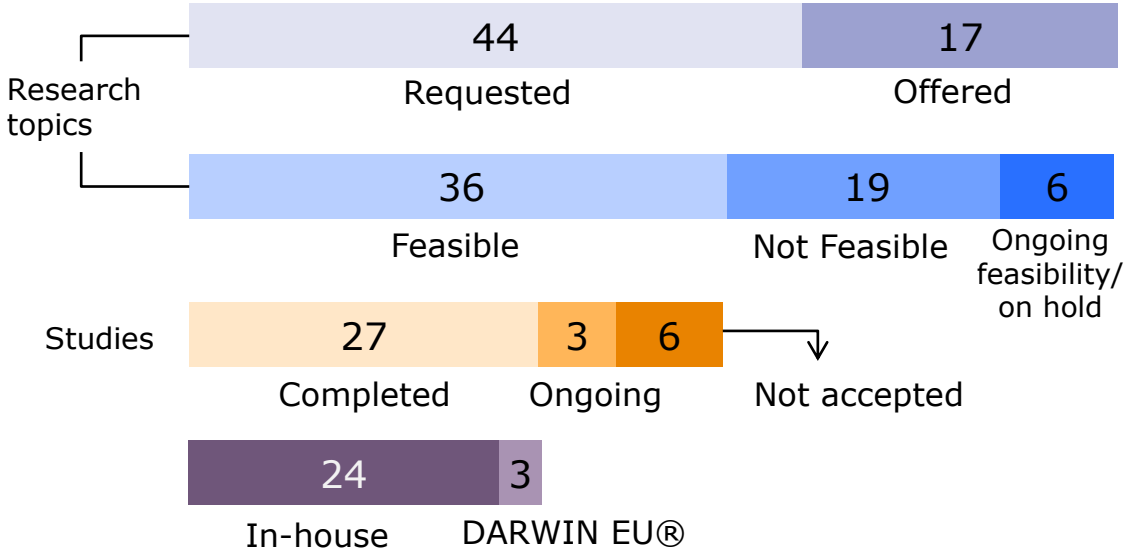
PRAC
OTS

OTS = off-the-shelf study

Main results – overview of RWE studies

61
research topics

49	8	4
In-house	DARWIN EU	FWC

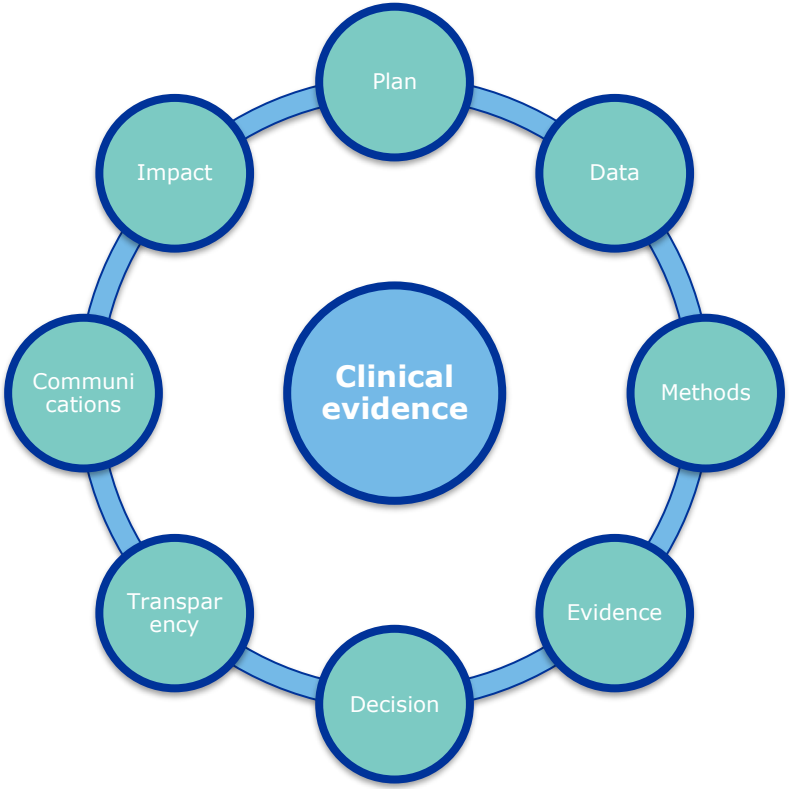


Clinical evidence: a vision for 2030

EUROPEAN MEDICINES AGENCY

"At the core of a successful MA dossier is excellent clinical evidence"

- Evidence generation is planned and guided by data, knowledge and expertise
- Research question drives evidence choice; embraces spectrum of data and methods
- Clinical trials remain core but are bigger, better and faster
- Real world evidence is enabled, and value is established
- The patient voice guides every step of the way
- Healthcare systems are supported in their choices
- High levels of transparency underpin societal trust



Any questions?

Further information

steffen.thirstrup@ema.europa.eu

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Telephone +31 (0)88 781 6000
Send us a question Go to www.ema.europa.eu/contact

Follow us on **@EMA_News**