HMA
Heads of Medicines Agencies

EMA
EUROPEAN MEDICINES AGENCY

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

3rd report on the experience gained with regulator-led studies from February 2024 to February 2025

An agency of the European Union

Table of Contents

"The healthcare landscape in Europe is evolving and the convergence of several factors now provides the opportunity for a stronger and more sustainable approach to clinical evidence generation."[1]

Executive Summary

This third annual report outlines the progress in integrating Real-World Evidence (RWE) into regulatory decision-making, aligned with the European Medicines Regulatory Network (EMRN) strategy to 2028. It comprises all three RWE generation pathways coordinated by the European Medicines Agency (EMA): DARWIN EU®, framework contract (FWC), and in-house EMA studies.

A total of 59 studies were conducted during the reporting period, with 33 completed and 26 ongoing, representing a 47.5% increase from the previous year. Of the 90 research topics whose feasibility was already assessed, 78% were deemed feasible for the RWD study, showing an improvement in feasibility compared to previous period. This is likely due in part to the fact that DARWIN EU® has expanded in 2024 to include 30 data partners across 16 countries, covering approximately 180 million patients, offering more opportunities.

The studies addressed a range of topics, including drug utilization (42%), safety (24%), and disease epidemiology (24%). The research topics were requested by a diverse range of regulatory and public health decision-makers: EMA scientific committees and working parties, EMA internal functions, European Centre for Disease Prevention and Control (ECDC), HTA bodies/payers and the European Commission (EC).

Considering the subject of studies, these included assessments of suicidality-related risks associated with doxycycline and GLP-1 agonists, of possible shortages of specific medicines as well as of effectiveness of mpox vaccination. The median duration for DARWIN EU® was four months, from protocol approval to final study results, which is much faster the traditional RWE approaches and supports timely integration into regulatory timelines.

In the last year, we improved the way we check the quality of the data and how these data are used to answer multiple questions, especially thanks to more consistent ways to define health and drug conditions as well as to analyse them. Use of pre-approved study protocols definitively helped to speed up the analysis of the data when possible.

Transparency efforts continued with the launch of the HMA-EMA RWD catalogues and improved communication of study results within the EU regulatory Network.

This report shows that thanks to the work done over the last 4 years the use of RWE is now enabled, and its value continues to be established across the full range of regulatory use cases.

[1] *Clinical Evidence 2030 in Clinical Pharmacology and Therapeutics*

List of Abbreviations

Acronyms/term	Description
ADHD	Attention-Deficit Hyperactivity Disorder
ATC	Anatomical Therapeutic Chemical classification
CDM	Common Data Model
CHMP	Committee for Medicinal Products for Human Use
COMP	Committee for Orphan Medicinal Products
DARWIN EU	Data Analysis and Real World Interrogation Network EU
DUS	Drug Utilisation Study
ECDC	European Centre for Disease Prevention and Control
EHDS	European Health Data Space
EHR	Electronic Health Record
EMA	European Medicines Agency
EMRN	European Medicines Regulatory Network
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EUPAS	European Union Post-Authorisation Study Register (study identifier prefix)
FWC	Framework Contract
GLP-1 RA	Glucagon-Like Peptide-1 Receptor Agonist
HIV	Human Immunodeficiency Virus
HMPC	Committee on Herbal Medicinal Products
HTA	Health Technology Assessment
MAA	Marketing Authorisation Application
MPXV	Monkeypox Virus
MSSG	Medicines Shortages Steering Group
NCR	Netherlands Cancer Registry
NNRD	National Neonatal Research Datasource
NSCLC	Non-Small Cell Lung Cancer
OMOP	Observational Medical Outcomes Partnership
PDCO	Paediatric Committee
PRAC	Pharmacovigilance Risk Assessment Committee
PSUSA	Periodic Safety Update Single Assessment
RMMs	Risk Minimisation Measures
RWD	Real-World Data
RWE	Real-World Evidence
SAWP	Scientific Advice Working Party
SPOC	The Medicine Shortages Single Point of Contact Working Party
VMP	Vaccine Monitoring Platform
VTE	Venous Thromboembolism

Highlights

- **DARWIN EU successfully completed its 3rd year**. The network expanded from 20 to 30 data partners, enabling access to data from approximately 180 million patients from 16 European countries.
- A total of **59 studies were conducted** (33 completed and 26 ongoing) during the period, representing a 47.5% increase compared to the previous reporting period.
- **DARWIN EU** capacity was scaled up, becoming the main evidence generation pathway for EMA-led studies with an almost threefold increase in completed studies compared to the previous reporting period.
- The proportion of feasible studies addressing initial requests increased from the previous reporting period (78% vs. 60%).
- The **median duration for DARWIN EU studies was 4 months** (inter-quartile range (IQR): 3.0-5.8 months) from protocol approval to study results. This speed of evidence generation makes studies more suited for integration into regulatory procedures' timelines.
- The research topics were requested by a **diverse range of regulatory and public health decision-makers**: EMA scientific committees and Working Parties, EMA internal functions, European Centre for Disease Prevention and Control (ECDC), HTA bodies/payers and European Commission (EC).
- Nineteen studies were conducted to support **PRAC** (a steep increase compared to the last period), mostly linked to signal and Periodic Safety Update Single Assessment (PSUSA) procedures, referrals or were studies on the impact of risk minimisation measures. Five studies were conducted to support **CHMP**: one study linked to an initial marketing authorisation application (MAAs) and four studies to support the geriatric medicines strategy. Seven studies were conducted to support EMA's work on shortages via the Medicines Shortages Steering Group (**MSSG**) and the Medicine Shortages Single Point of Contact (**SPOC**) Working Party in the monitoring of the demand and stock levels of critical human medicines, investigating the following medicines or class of medicines at risk of shortages: antibiotics (2 studies), medicines administered in ICUs, ADHD medicines, GLP-1 receptor agonists, salbutamol and therapeutic alternative inhalation products. At the end of the observation period two studies in collaboration with **HTA bodies and payer organisations** were ongoing in the area of oncology.

1. Introduction and scope

Clinical Evidence 2030 envisions a future where evidence generation is more patient-centred, efficient and impactful. By 2030, the process of evidence generation should be guided by 6 principles: patient-centred evidence generation, leveraging of existing data and knowledge, formulating clear research questions, embracing the full spectrum of data and methods, early and collaborative planning, and maintaining high levels of transparency. Supported by the reforms in the pharmaceutical legislation, the integration of RWE in the regulatory framework should complement the value of the evidence generated by clinical trials.

This report is the third annual report on the experience acquired with RWE generation, spanning the period from 8 February 2024 to 7 February 2025, which also corresponds to year 3 of DARWIN EU, first operational year following establishment in 2022-2024 (see previous reports here). As with previous reports, this report focuses on RWE generation via EMA's three RWE generation pathways: DARWIN EU, studies commissioned via the framework contracts for scientific studies (FWC) and in-house studies performed by experts at European Medicines Agency (EMA). The report also covers the value of EMA-generated RWE for regulatory decisions, progress made on operational aspects since the last report, as well as methodological advice on the use of real-world data (RWD) and methods within regulatory submissions. Research topics originate from the scientific assessment of EMA committees and divisions or EMA's collaborative work with other EU network stakeholders (e.g., Health Technology Assessment (HTA) bodies, European Centre for Disease Prevention and Control (ECDC)). The report does not cover RWE generated at the national competent authority level or by other EU agencies without EMA involvement or those submitted by industry.

This report illustrates the progress made in delivering the vision of EU regulators to enable the use of RWE and establishing its value for regulatory decision making. It also highlights how RWE aligns with the updated European Medicines Regulatory Network (EMRN) strategy to 2028, which has six main themes, with RWE playing a key role particularly:

- *Accessibility*: create strong scientific evidence to support regulators, HTA bodies, and payers.
- *Leveraging data, digitalisation, and AI:* ensure data interoperability, standardisation, and quality while addressing biases and ethical issues, incorporating DARWIN EU evidence into decision making processes.
- *Regulatory science, innovation and competitiveness*: focus on generating high-quality evidence, supporting innovation, and improving clinical trials and data generation.
- *Availability and supply of medicines*: identify and prevent shortages of human and veterinary medicines.

This report is structured into four sections: 1) RWE generated for the EMRN and other stakeholders, 2) value of RWE, 3) methodological RWE advice, and 4) progress made since the last report.

2. Real-world evidence generated for the EMRN and other stakeholders

A total of 107 research topics were assessed, out of which 79 (74%) were identified in the reporting period from 8 February 2024 to 7 February 2025, (i.e., 'new research' topics), and 28 (26%) were identified before 8 February 2024 and carried over (i.e., 'carried over' topics). The new research topics increased by 32% (from 60 to 79) compared to the previous reporting period.

Out of 90 research topics whose feasibility was already assessed, 70 (78%) were deemed as feasible. Of note, the feasibility was still ongoing at the end of the review period for 17 research topics (Figure 1). These led to 33 studies completed (25 via DARWIN EU, 4 via FWC and 4 in-house) and 26 ongoing studies (21 via DARWIN EU, 4 via FWC studies and 1 in-house) by 7 February 2025. In addition, some research topics assessed as feasible were not initiated (9) or have been discontinued (2) by the requester.

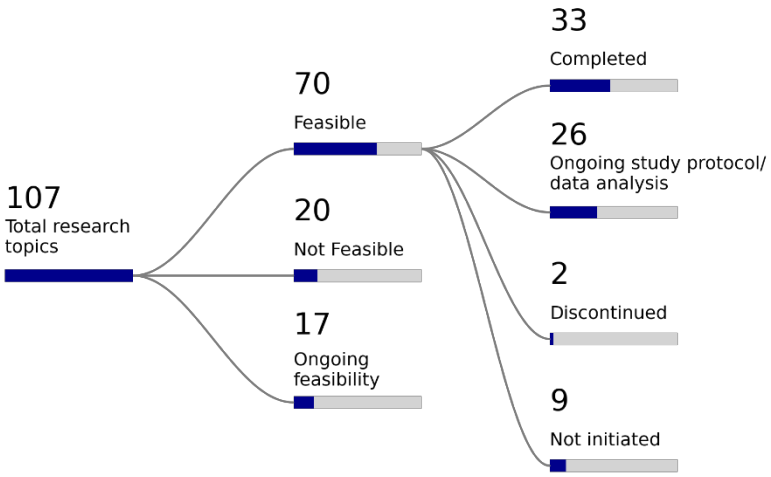


Figure 1. Research topics identified or addressed during the reporting period.

This flowchart includes research topics identified during the reporting period (8 February 2024 to 7 February 2025) or addressed during the reporting period but identified before 8 February 2024. 'Not initiated' are studies that were feasible, however after additional discussions with the requester were not considered needed at the moment.

Eighty-nine research topics (83.2%) were triaged via the DARWIN EU pathway (Figure 2), which is more than double compared to the previous reporting period. Nine (8.4%) research topics were triaged via the in-house pathway, marking a decrease compared to the last reporting period (16 research topics), and nine (8.4%) research topics were triaged via the FWC pathway (previously six topics).

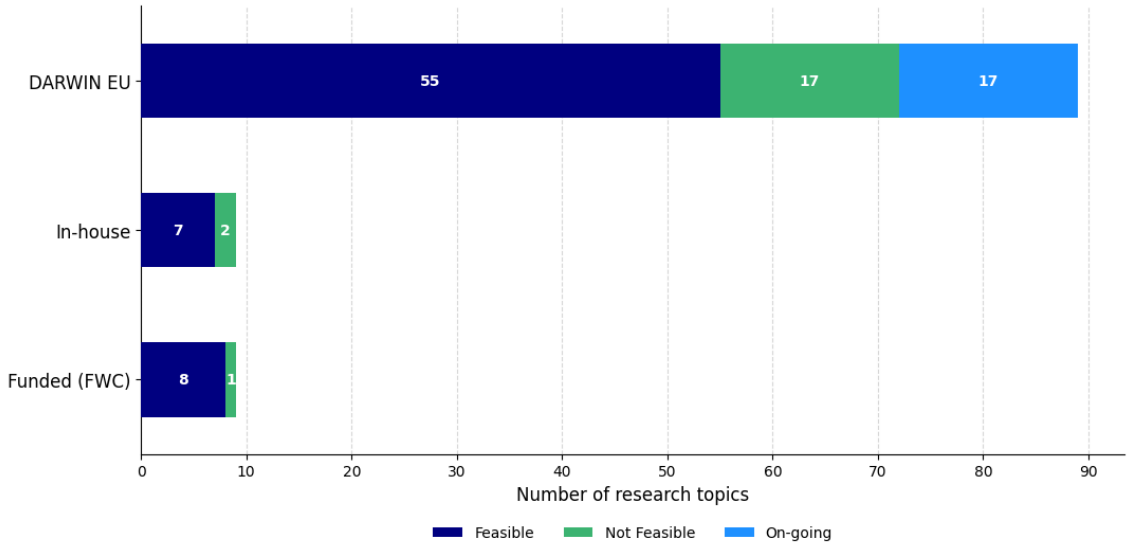


Figure 2. Number of research topics addressed (n=107) during the reporting period by RWE generation pathway.

The increase in studies performed via DARWIN EU compared to the other RWE generation pathways was expected due to the upscaled capacity of DARWIN EU in year 3 of its establishment, thereby becoming the main pathway for EMA-led RWD studies.

2.1. Feasibility of research topics

Feasibility of research topics was higher than during the previous reporting period (78% across all pathways and 76% in DARWIN EU only vs. 60% and 63%, respectively).

Considering only the new research topics identified in the reporting period (N=79), 18 were deemed unfeasible and did not proceed to the study conduct phase. The most common reason for lack of feasibility was that the medicinal product or class of interest was not prescribed/ captured or not authorised/ not used in the data sources/ countries assessed (N=8, 44.4%). The second reason was the short timelines (N=4, 22.2%), followed by the outcome of interest not being adequately captured in the assessed data sources (N=3, 16.7%) (Figure 3).

The largest change between the period covered by the second and third reports was the reduction in research topics deemed unfeasible due to inadequate capture of the outcomes of interest in the available data sources. In the previous period, most research topics (63.6%) were considered unfeasible for this reason and by 2024, this figure has decreased to 16.7% (Figure 3).

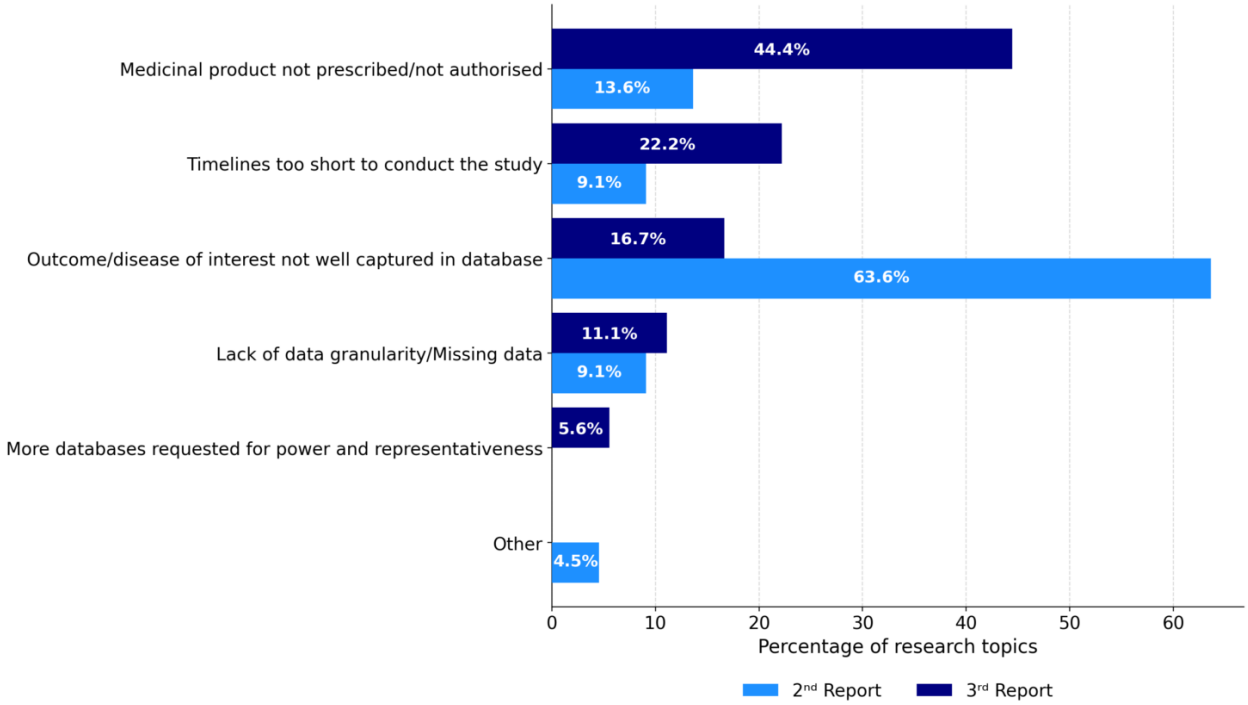


Figure 3. Reasons for lack of feasibility in 3rd (n=18) vs 2nd (n=22) report

Medicinal products not prescribed/authorised refers to medicinal products (class) that are not prescribed/ captured or not authorised/ not used in the data sources/ countries assessed. Outcome/disease of interest not well captured includes cases due to the intrinsic rarity of the event or due to characteristics of the data sources assessed Lack of granularity refers to outcomes poorly captured by the coding system, or insufficient information on prescribing, dose, duration, or indication.

It is worth noting that for most requesters, more than 50% of the research topics were feasible, except for Paediatric Committee (PDCO), which had the highest percentage of unfeasible requests, similar to last year findings (Figure 4). This challenge is not unique to DARWIN EU network and it is due to the rarity of these diseases in children, the small population size, and limited sources specialised in paediatrics, among other contributing factors. To address the low feasibility of paediatric research topics, one paediatric specific data source was onboarded in DARWIN EU (National Neonatal Research Datasource (NNRD)) during the reporting period (See section 6).

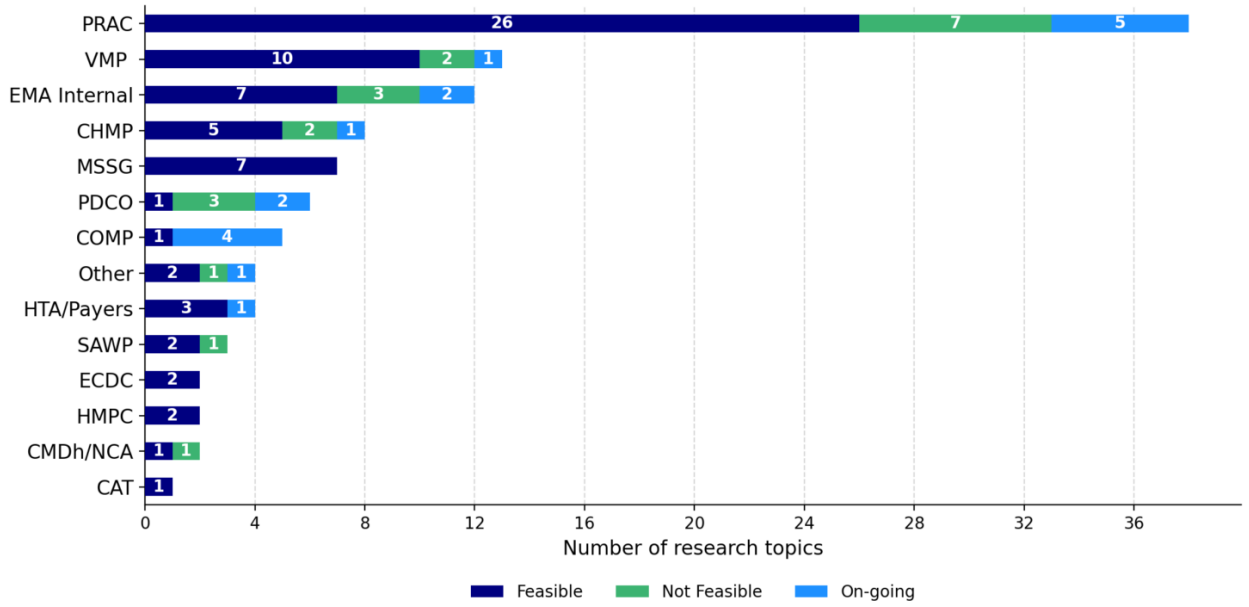


Figure 4. Feasibility of research topics by requester (n=107)

During the reporting period, research focused on 14 therapeutic areas. The most common were anti-infectives (22 studies, 21%), antineoplastic and immunomodulating agents (19 studies, 18%), and nervous system treatments (17 studies, 16%) (Figure 5). As in the previous report, anti-infectives and antineoplastic/immunomodulating agents remained the top two areas. However, research on the alimentary tract and metabolism declined, while studies on the nervous system increased.

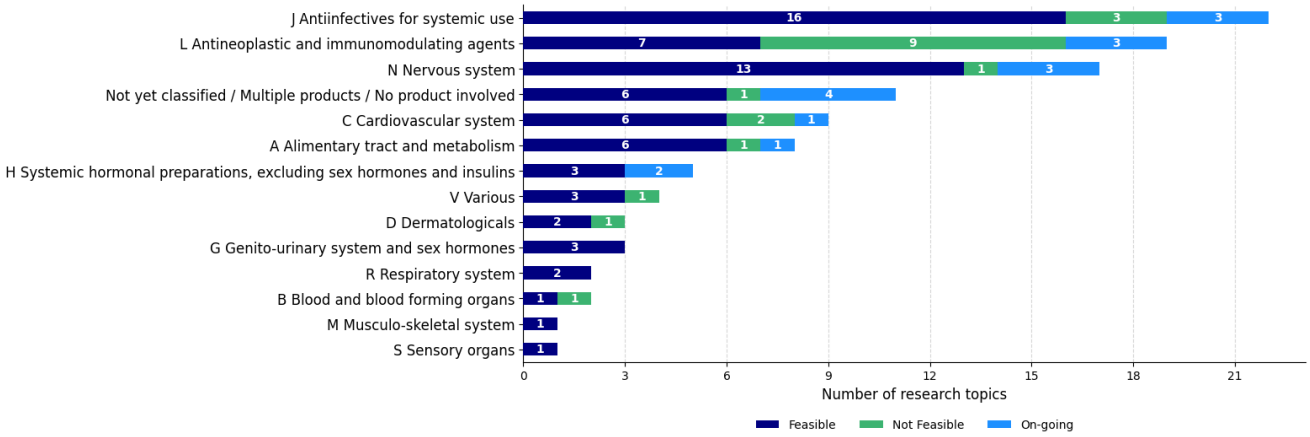


Figure 5. Feasibility of research topics by Anatomical Therapeutic Chemical (ATC) classification (n=107)

The ATC main group was assigned to each research topic based on the medicinal product under evaluation which triggered the research topic, or the substance studied in the study if there is no procedure applicable. 'Not yet classified/Multiple products/No product involved' category includes research topics for which the medicine has not yet been classified in the ATC system, the research topics which comprises several medicinal products or research topics which do not include medicinal products (e.g., disease epidemiology studies).

2.2. Study requesters and the regulatory context

The diversity of study requesters (N=14) already observed in the previous reporting period was maintained including seven of the Agency's scientific committees and Working Parties, national

competent authorities, ECDC, HTA bodies/payers, EC and EMA internal functions. This demonstrates the diverse uptake of RWE in the regulatory and public health landscape (Figure 6).

Most of the new research topics during the reporting period were requested by PRAC (N=32, 40.5%), EMA internal teams (N=10, 12.6%) and PDCO (N=6, 7.6%), a similar picture to last reporting period, with a steep increase in PRAC requests.

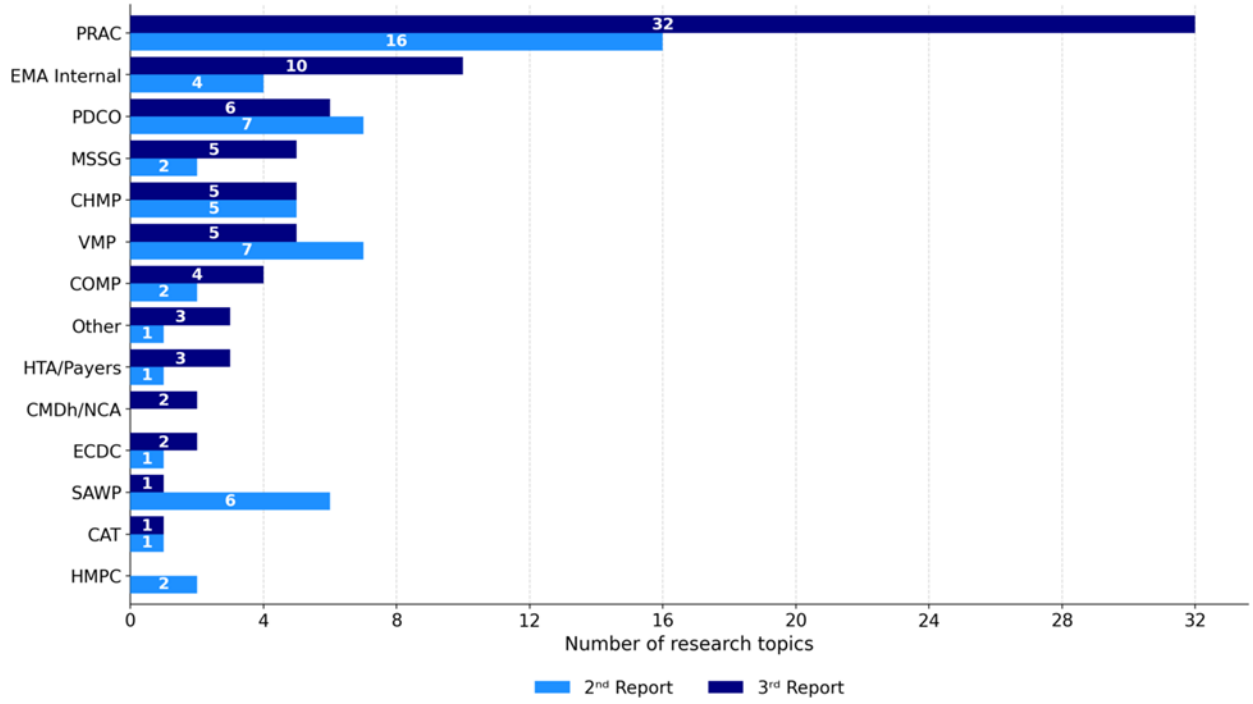


Figure 6. New research topics by requester, comparison between 2nd and 3rd reports

The demand for RWE from EMA internal teams, particularly the Human Medicines division, also increased over the last year (Figure 6). This includes requests in relation to preparedness for upcoming MAAs and for extension of indication, and from the Pharmacovigilance office linked to signal detection activities and impact of Risk minimisation measures (RMMs). Two of these were methodological studies, one focused on the characterisation of pregnancy and mother-child linkage data in the DARWIN EU data partners network, and the other on the use of target trial emulation and estimand framework in effectiveness and safety studies (TARGET-EU). The latter is being conducted in collaboration with the EMA Methodology workstream.

New research topics destined to inform CHMP remained stable (5 studies per year) in comparison to the previous reporting period. The EMA RWE team implemented the review of the portfolio of upcoming initial marketing authorisation applications (MAAs) on a 6-monthly basis, which led to the identification of seven research topics, of which four were feasible: prevalence of hypertrophic cardiomyopathy and obstructive hypertrophic cardiomyopathy in Europe, epidemiology of type I diabetes, treatment patterns in postmenopausal women in Europe, and treatment patterns and epidemiology of BCG-resistant non-invasive bladder cancer patients.

The requests from SAWP decreased from 6 to 1 (Figure 6). The only research topic received was on natural history and treatment patterns in acute myeloid leukaemia. SAWP members recommended to rerun the feasibility assessment of previously requested studies to assess if some of these previously

non feasible studies would now be feasible thanks to the expansion of the DARWIN EU data partners network over last year.

The number of MSSG requests and topics related to medicines shortages increased compared to last year (from 2 to 5), as part of the network's strategy for improving the availability of medicines through prediction of shortages and identification of factors contributing to shortages.

Studies commissioned to inform the Vaccine Monitoring Platform (VMP) research agenda had a slight decreased number of requests compared to last year (Figure 6). These studies were aimed at strengthening regulatory preparedness for public health emergencies by completing projects initiated during the previous review period such as setting up a framework for vaccine safety evaluation, assessing the effectiveness of COVID-19 vaccines and exploring opportunities for the generation of brand-specific seasonal influenza vaccines to support the annual assessment by EMA of seasonal influenza vaccines.

COMP requests increased from two to four (Figure 6), which was partly driven by the onboarding of additional data partners to the DARWIN EU network (e.g., nationwide registries and cancer registries), knowing that the requested studies were mostly within the scope of the oncology area.

Although demand remains limited, research requests to inform HTA bodies/payers increased from 1 to 3, all in the area of oncology (Figure 6).

One study was conducted in collaboration with ECDC, namely the monitoring of use of antibiotics of the WHO AWaRe classification, the second research topic although feasible was not accepted.

Regarding regulatory procedures, safety signal evaluation was by far the most common procedure which triggered studies, followed by PSUSAs (Figure 7). The latter increased markedly due to a collaborative effort between PRAC and EMA to establish a process to request studies during this procedure. The number of studies to inform other procedures such as paediatric investigational plan (PIP) waivers and upcoming MAAs remained stable compared to the previous reporting period (Figure 7).

Thirty-nine of the new research topics (49.4%) were requested outside of an ongoing procedure, in the context of vaccine safety and effectiveness monitoring (5), shortage prevention and crisis preparedness (4), EMA geriatric strategy (4), preparedness for future applications/procedures (3), methodological studies (3) among others. It is worth noting that the use of RWE goes beyond immediate procedures, with timely evidence often needed to prepare for future procedures, monitor shortages, enhance agency collaboration within the EU regulatory network, or for methodological improvements.

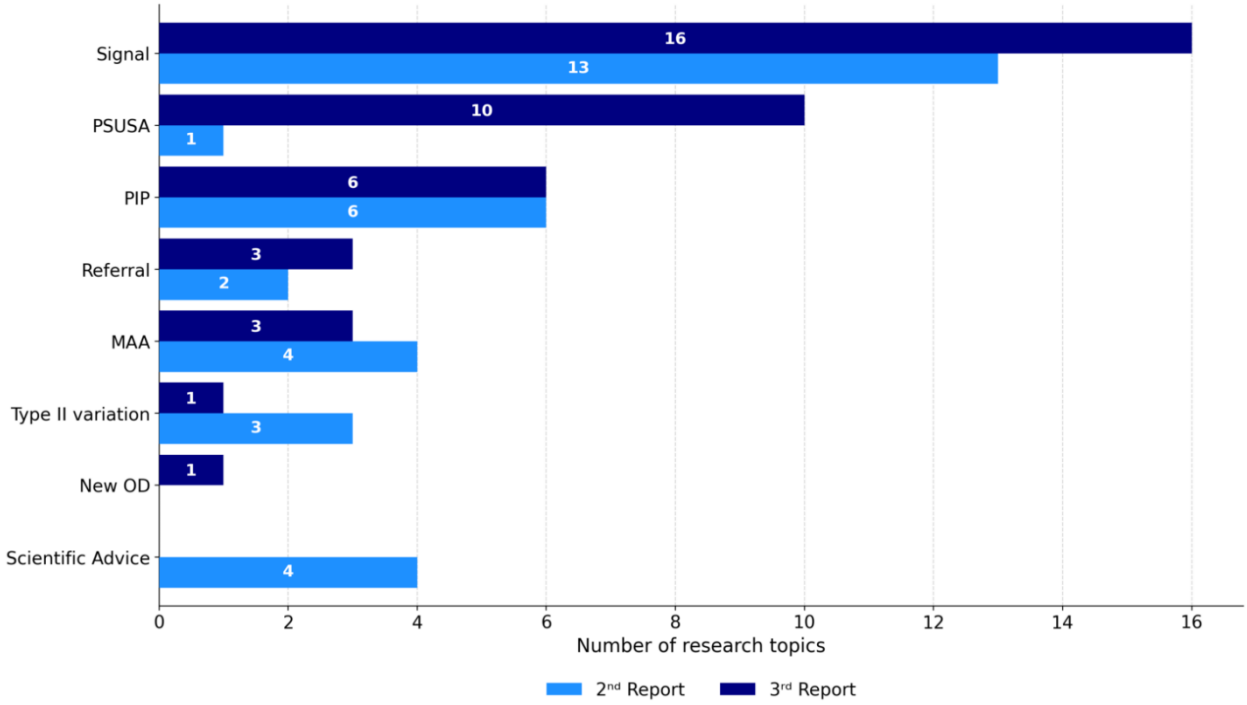


Figure 7. New research topics identified during the reporting period, by type of regulatory procedure, comparison between 2nd and 3rd reports

2.3. Completed and ongoing studies

A total of 59 studies were conducted during the reporting period, across all pathways (33 completed and 26 ongoing), representing a 47.5% increase from the last report. Of the completed studies, 25 were conducted in DARWIN EU, an almost three-fold increase compared to the last reporting period (9 studies).

The number of ongoing or completed studies during the reporting period were classified according to predefined use cases. Most studies aimed at generating evidence in relation to drug utilisation (N=25, 42%), followed by medicines safety (N=14, 24%), and disease epidemiology (N=14, 24%) (Figure 8). This distribution is similar to the previous reporting period, except for studies related to effectiveness which increased.

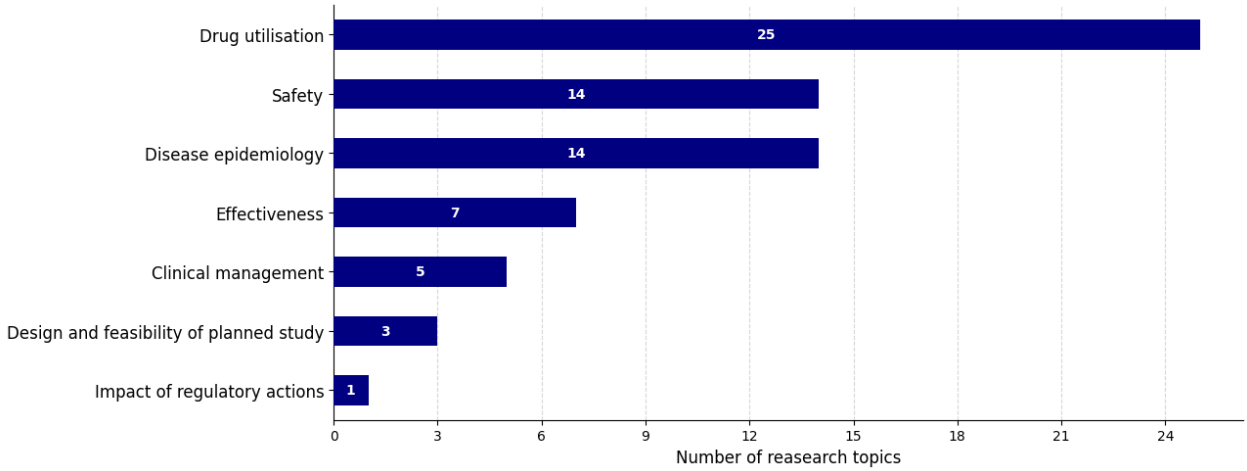


Figure 8. Number of conducted studies (n=59) by use case type during the reporting period

Depending on the scope, a research topic may be assigned to one or more categories (e.g., a study aiming to describe incidence of a disease and prevalence of related prescribed treatments could represent both categories: disease epidemiology and drug utilisation). Therefore, the values presented in the bars sum up more than 59.

In contrast to the previous report, where only studies in DARWIN EU were characterised in terms of complexity, this dimension is now applied by extrapolation to all pathways, to enhance comparison and for improved resource planning. The number for complex studies performed in DARWIN EU increased from four in the previous period to 18 in the current period. In addition, 14 complex studies were conducted via other pathways in the same period.

To inform the performance of the RWD study process, the time from protocol acceptance to study completion was estimated, stratified by RWE generation pathway. The median study duration in DARWIN EU was around 4 months (IQR: 3-5 months), while managing increased demand (Table 1). The current speed makes DARWIN EU suitable for integration into the timetable of most regulatory procedures, thanks to adequate planning.

The median time to conduct a FWC study was 6 months (IQR: 5.2-6.2 months), excluding the time needed for tender launch and contract signature which can be significant in some cases, while an in-house study was significantly faster with a median duration of one month. However, both these pathways had a small number of studies.

Table 1. Mean, median and interquartile range of time (calendar months) from protocol approval to study completion by RWE generation pathway

Pathway	Count	Mean	Median	IQR
DARWIN EU	25	4.8	4.0	3.0 - 5.0
Funded (FWC)	4	5.5	6.0	5.2 - 6.2
In-house	4	1.5	1.0	0.8 - 1.8

3. Value of RWE

To understand the value of the evidence generated, requesters were enquired about the impact of the study results, whether they were helpful and taken into account for decision making. Feedback has been received either in writing, verbally during dedicated meetings, or in response to a survey with an overall response rate of 76%, higher than during the previous reporting period (68%). Study results were considered supportive in 12 cases, and substantial in 4 cases. In addition, results from 14 studies were included in the respective assessment reports.

The following 3 studies provided substantial evidence for regulatory assessments (see section 4.1):

- Risk of suicidality with doxycycline
- Risk of suicidality with GLP-1 agonists
- Emulated Target Trial to Estimate the Safety and Effectiveness of MVA-BN vaccination against MPXV infection in at-risk individuals in Germany

In addition, results from the following study were included in the HealthData@EU report whose aim is to inform the European Health Data Space (EHDS) implementation:

- Natural history of coagulopathy in COVID-19 patients and persons vaccinated against SARS-CoV-2 in the context of the OMICRON variant

A brief description of the ongoing and completed studies during the reporting period by requesters is provided below.

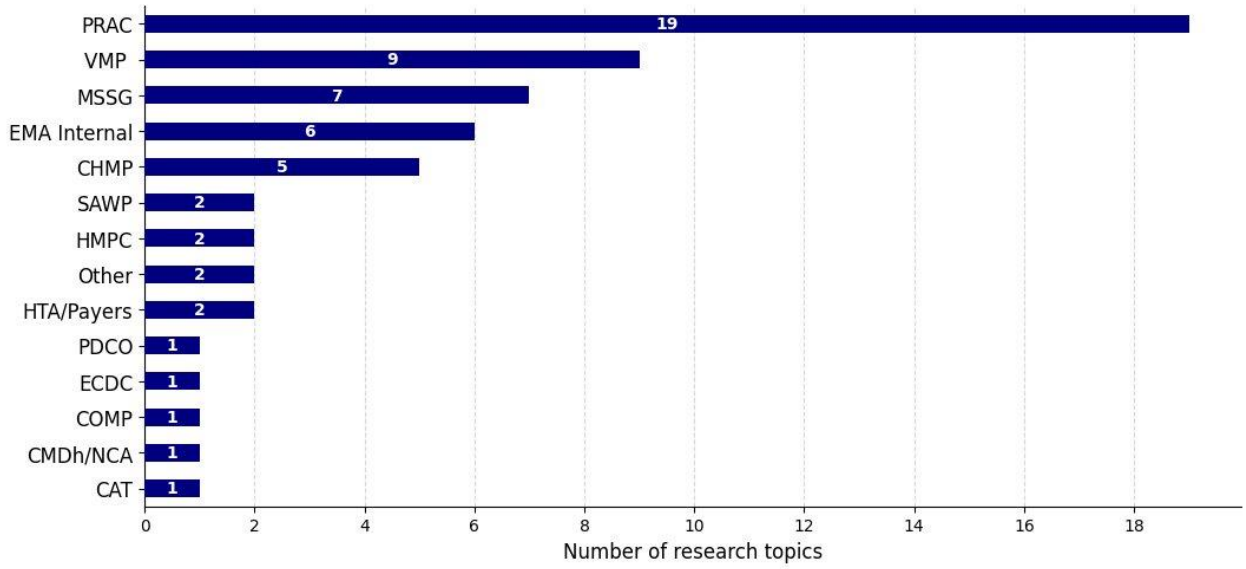


Figure 9. Number of ongoing or completed studies (n=59) during the reporting period by requester.

EMA Committees

PRAC: During the reporting period, **nineteen** ongoing or completed studies (Figure **9**) were conducted to support PRAC assessments, of which nine were related to safety signal procedures, four conducted in the context of PSUSAs, one evaluating the impact of risk minimisation measures, and one contributing to a referral (suicidality after exposure to finasteride and dutasteride). The other four studies were not

linked to an ongoing procedure. The main change during this period compared to the previous reporting period was that the process for both signal and PSUSA related studies was formalised, with study initiation decision made by the PRAC plenary, results then published once approved, and the concerned company/-ies informed about the results during the procedure. Due to the short timeliness for signal procedure (four months on average), it is still challenging to complete etiological studies; however, in various cases, background incidence rates and patient characterisation studies are informative and helped decision making.

CHMP: Within the context of **CHMP** activities, five studies were ongoing or completed (Figure **9**), one linked to an initial upcoming MAA and four studies to support the **geriatric medicines strategy**. Of these four, two examined antipsychotic prescribing trends in Europe, with one focusing on older adults in the general population and the other on those with dementia. The third study explored the link between frailty and polypharmacy in older adults with cancer, while the fourth study investigated the prevalence of potentially inappropriate medications (STOPP criteria) in older adults experiencing falls. The ongoing study supporting an initial MAA aimed at estimating the prevalence of hypertrophic cardiomyopathy and obstructive hypertrophic cardiomyopathy in six European countries. In addition, two studies were ongoing in the context of SAWP.

PDCO: In collaboration with **PDCO,** one study was ongoing (Figure **9**), studying the use of antiretroviral therapies in paediatric patients.

HMPC: In collaboration with HMPC, the first two pilot **studies on herbal medicines** (Figure **9**) to test the possibility of DARWIN EU to support the Agency's opinions on herbal substances and preparations were completed. Both studies (Use of medicinal cannabis, and use and safety of pelargonium radix in children) were considered supportive evidence. In addition, these two pilot studies provided valuable insight to HMPC members to understand the potential value of electronic healthcare record data, its advantages and limitations, and how RWE could be used for regulatory purposes in this specific context. These two pilot cases also highlighted challenges in terms of mapping herbal medicines to a common data model (i.e., OMOP), which triggered further investigation and correction to the mapped data, that will ultimately lead to improved data quality for future studies.

Other stakeholders

VMP: Nine studies (out of which eight completed) were conducted (Figure **9**) to inform **vaccine safety** and **effectiveness** topics identified in the VMP Research Agenda and to address both routine vaccine monitoring and preparedness for public health emergencies. The studies investigated: the effectiveness of COVID-19 vaccines against severe outcomes and selected components of long COVID, background incidence rates of adverse events of special interest and of flares of chronic diseases relevant for vaccine safety monitoring, age-specific incidence of RSV-related disease to prepare for vaccine effectiveness studies, effectiveness of human papillomavirus vaccines against cervical cancer, effectiveness and safety of mpox vaccination in Germany, and characterisation of immunocompromised populations in healthcare data sources as part of the framework for the post-authorisation safety evaluation of vaccines in the EU, including readiness of data sources in Europe, started in the previous review period. The VMP was also exploring opportunities for the generation of robust brand-specific influenza vaccine effectiveness data to support vaccine manufacturers and inform the annual assessment of seasonal influenza vaccines in a fragmented EU influenza vaccine market.

MSSG: Seven studies (out of which four completed) were performed in 2024 (Figure **9**) to support the MSSG and the SPOC Working Party in monitoring the **demand and stock levels of critical human medicines**. These requests focused on various aspects of drug utilisation and include examining trends in the use of ADHD medications, GLP-1 receptor agonists, and salbutamol inhalation products and their alternatives. Additionally, monitoring of prescription of essential medicines in intensive care units (ICUs) and medicines likely to be used during public health emergencies were investigated. These efforts aim

to monitor availability and effective management of critical medications in different healthcare settings. Most of these studies will be regularly rerun to continuously inform the team on utilisation trends and upcoming shortages in Europe.

HTA bodies/Payers: In collaboration with HTA bodies and payer organisations, two studies were ongoing (Figure **9**). One study aimed at estimating the overall survival in patients with advanced or metastatic non-small cell lung cancer (NSCLC) treated with selected immunotherapies as first line of treatment. The other was a study on characterisation of patients with multiple myeloma, including treatments and survival, initially conducted during the second year of DARWIN EU with limited data availability, now repeated using six data sources for a more complete picture.

European Commission: In close collaboration with the **European Commission**, the EHDS use case study (natural history of coagulopathy in COVID-19 patients and persons vaccinated against SARS-CoV-2 in the context of the Omicron variant) was completed as part of the **HealthData@EU (EHDS2) Pilot**. The use case involved data partners from DARWIN EU along with non-DARWIN EU data nodes from Croatia, Denmark, Finland and France. The objective of the EMA use case was to inform about elements needed to be addressed by EHDS for secondary use of health data, to test the potential of data permit authorities acting as health data access bodies for running studies, and to demonstrate the potential impact of an interoperable re-usable network, such as DARWIN EU, for RWE generation. The use case had objectives focused around estimating incidence rates of arterial thromboembolism and venous thromboembolism among different cohorts, namely a background pre-pandemic population, a COVID-19 omicron infected cohort, and vaccinated cohorts, as well as investigating risk factors for arterial thromboembolism and venous thromboembolism among COVID-19 omicron patients. The use case highlighted different approaches to data selection, the benefits of using a structured feasibility assessment and metadata catalogue to select data partners, differences in data availability and accessibility. The use case also demonstrated the utility of using a common data model (OMOP) for federated analytics and highlighted challenges in terms of mapping to the common data model, and technical limitations regarding hardware and software infrastructure to ensure interoperability between data nodes, issues which have been summarised in the final report that will inform EHDS implementation.

3.1. Illustrative use cases

CGRP antagonists (PRAC request to support 3 signal evaluations - insomnia, erectile dysfunction, increased blood pressure)

CGRP antagonists are new drugs approved for migraine prophylaxis which were discussed by PRAC, on a potential association between the use of these drugs and three safety signals: insomnia, erectile dysfunction, and increased blood pressure, all based on spontaneous case reports.

The assessments of these signals were challenging due to limited exposure to date, suspected presence of confounding by indication, and all events having a multi-factorial aetiology. No association studies on these topics were identified.

Therefore, a study was conducted which aimed at evaluating the extent of confounding by indication by calculating the background rates of the events of interest in the population newly diagnosed with migraine as well as characterising the existence of other risk factors. The findings from this study contributed to reach a conclusion regarding the three different signals and led to a faster regulatory decision, with all signals being closed at the end of the procedure.

Association between doxycycline use and risk of suicidality and incidence of suicidality in patients with specific chronic skin conditions (PRAC request to support signal assessment)

There were spontaneous reports on a potential association between use of doxycycline and suicide. By means of a self-controlled case series and an active comparator cohort study, the DARWIN EU study aimed to assess the association between use of doxycycline and suicidality events.

The study results provided evidence which did not confirm an association between use of doxycycline and risk of suicide related events in individuals with acne.

In a second, complementary, DARWIN EU disease epidemiology study that evaluated suicidality-related events in patients with acne, psoriasis, and in the general population in UK, the Netherlands, Spain, and Croatia, it was observed that acne patients consistently had a higher incidence of suicidality-related outcomes, particularly among younger females, when compared to the general population. This suggests a potentially strong effect of confounding by indication. Considering these findings, the signal was closed with no product information update warranted.

Respiratory Syncytial Virus (RSV) epidemiology (CHMP request to support discussion on unmet medical need)

Accurate information about RSV burden of disease in high-risk groups is essential for decision-making to support the continuous assessment of the benefit/risk profile of approved RSV vaccines. This study aimed to explore the feasibility of capturing adequate RSV-specific endpoints in the DARWIN EU data sources (including for example, availability of laboratory testing data) to support the development of effectiveness studies once the vaccines are deployed and along their lifecycle. This study confirmed that RSV is a highly prevalent respiratory pathogen that poses a significant public health burden, particularly among infants and older adults. The study showed that these vulnerable populations are disproportionately affected by RSV infection, experiencing a higher incidence of hospitalisation, longer hospital stay, intensive care unit admission, and mortality. In addition, data concerning RSV hospitalisation for the 50–59-year-old age group - for which an extension of indication was requested by the MAH - was provided. These data were used as evidence to support the argument of unmet clinical need for this age group. This study will also support preparation for vaccine effectiveness studies.

Safety and Effectiveness of mpox MVA-BN vaccination in at-risk populations (requested by VMP)

This research using the FWC pathway included two studies, in Germany and the US. The German study (SEMVAc/TEMVAc) received EMA funding under the exceptional circumstances of the 2022 mpox public health emergency of international concern, and EMA and ECDC's committed to collaborate under the VMP as the vaccine had been approved based on limited clinical evidence of efficacy. The SEMVAc study was listed as a specific obligation in the Imvanex RMP to assess vaccine effectiveness, inform the safety profile of the vaccine, and describe sexual behaviours, human immunodeficiency virus (HIV) status, PrEP use, and history of smallpox vaccination in a cohort of men who have sex with men and transgender persons. This cohort study was conducted in 31 HIV and infectious disease clinics in Germany using primary data collection. TEMVAc was a complementary retrospective cohort analysis using target trial emulation in the SEMVAc centres, triggered by the decreasing number of cases in the SEMVAc study period. SEMVAc/TEMVAc findings were shared with the MAH and the study was removed from the RMP upon completion in December 2023.

The similarity of vaccination strategies in the US and Europe triggered the design of a complementary US study (USMVAc), which included additional populations of immunocompromised and HIV patients.

In addition to generate evidence on vaccine effectiveness, the two studies confirmed the positive safety profile of the vaccine, including in relation to adverse events of special interest (myocarditis, pericarditis, encephalitis, and anaphylaxis). Both studies showed the benefits of combining primary data collection (direct patient involvement in Germany) and secondary use of data (from large healthcare data sources in the US) to inform response to, and preparedness for future public health emergencies.

Trends in utilisation of Attention-Deficit Hyperactivity Disorder (ADHD) medicines (requested by MSSG/SPOC)

The ADHD medications are prone to shortages due to a combination of increased demand, manufacturing issues, and regulatory challenges. This study aimed to characterise the use of ADHD medications in the period of 2010 to 2023 in five European countries part of the DARWIN EU network. An increase in prevalence of any ADHD medication used was observed over the period; however, there was a lot of heterogeneity between data sources. Understanding the utilisation of ADHD medications can provide useful information in monitoring use, as well as for anticipation and planning to minimise potential shortages. Therefore, this study will be repeated regularly in order to monitor the use.

Determinants for shortage of GLP1 receptor agonists (requested by MSSG/SPOC)

Glucagon-Like Peptide-1 receptor agonists (GLP-1 RA) are a group of medicines authorised to treat type 2 diabetes mellitus and for weight management in people with obesity. Since 2022, a shortage of some of these medicines has been ongoing in several European Union/EEA countries. This DARWIN EU study looked at long-term prescription patterns of five GLP-1 RAs in five European countries; while also characterising the users as regards to their indication for use, BMI and comorbidities. During the study period, the use of exenatide and lixisenatide decreased, while the use of semaglutide and dulaglutide increased (with these two substances becoming the most prevalent ones); liraglutide use showed a varying pattern. Most users had type 2 diabetes with or without obesity. This study is expected to be repeated in the future, to allow monitoring of use of this therapeutic class, considering the increasing demand for diabetes and obesity treatments.

4. Methodological advice on relevance of RWD sources and methods within regulatory submissions

Another activity of EMA, linked to RWE use, is to provide methodological advice on the relevance of RWD sources to answer specific research questions, on non-interventional study designs, and on analytical methods within regulatory submissions (e.g. scientific advice, qualification of novel methodologies, PRIME procedures). In this context, the EMA RWE team is involved in the review of requests on the use of RWD for regulatory purposes raised by marketing authorisation applicants/ holders or non-for-profit organisations.

The aims of this activity are:

1) to guide applicants in the preparation and submission of their data packages to ensure all the relevant information and evidence are provided, for EMA committees/working parties to deliver an informed regulatory response
2) to provide tailored feedback to questions from applicants in the frame of innovative task force and portfolio and technology interactions, and
3) to support EMA committees/working parties in their evaluation of regulatory applications through peer-review processes.

For the latter, members of EMA committees/ working parties and national competent authority' assessors could seek EMA's methodological input across all stages of product development and evaluation, across all procedures and therapeutic areas. Examples of support offered may include the exploration of existing RWD sources and their fitness-for-purpose in a specific context, comparison against data sources known to EMA, discussion on the feasibility of a study proposed by an applicant in view of a particular design or exchanging views on a protocol/ report of a study leveraging RWD.

Between February 2024 and January 2025, the team was involved in the review of 26 scientific advice[2] requests for which at least one question related to the use of RWD was raised, and 10 portfolio and technology meetings[3]. For example, these included cases where historical data was used as benchmark for clinical trials endpoints, or where patient registry data were used as comparator in an externally controlled clinical study. The portfolio and technology meetings addressed recurring topics such as the use of RWD to inform benefit-risk of medicines, use of artificial intelligence and machine learning models in medicinal product development, innovative study designs and methodologies including pragmatic trials and target trial emulation. Figure 10 shows the number of methodological advice requests by ATC classification.

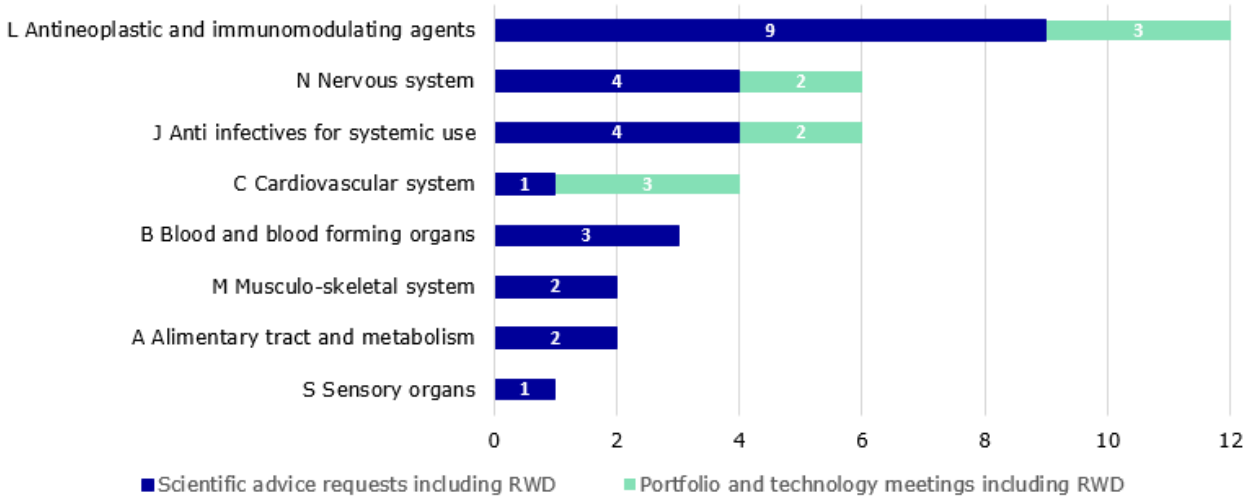
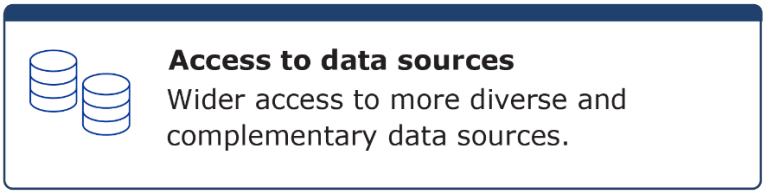


Figure 10. Number of requests for methodological advice by Anatomical Therapeutic Chemical (ATC) classification (n=36)

[2] Scientific advice and protocol assistance | European Medicines Agency (EMA)
[3] Portfolio and technology meetings | European Medicines Agency (EMA)

5. Progress report

This section reports on the progress made so far in the implementation of the recommendations made since the last report in five key areas as listed below.



- **Widen access to a larger range of diverse and complementary data sources** as well as data sources from **additional European countries** for broader geographical representativeness

The DARWIN EU® network expanded from 20 to 30 data partners during the reporting period. Currently, the network operates with public or private institutions from 16 European countries covering over 180 million patients from sources such as hospitals, primary care, health insurance, registries and biobanks.(see Figure 11) The list of new data partners is:

- Health Data Warehouse of Assistance Publique - Hopitaux de Marseille (France)
- Cancer Registry of Norway (Norway)
- HARMONY Big Data Platform (International)
- InGef Research Database (Germany)
- Papageorgiou General Hospital (Greece)
- Research Repository Fondazione Ca' Granda Ospedale Maggiore Policlinico (Italy)
- Health Data Research Platform of the Balearic Islands (Spain)
- The National Neonatal Research Database (United Kingdom)
- Health Impact - Swedish Population Evidence Enabling Data-linkage (Sweden)
- Fundación para la Investigación Biomédica del Hospital Universitario 12 de Octubre (Spain)

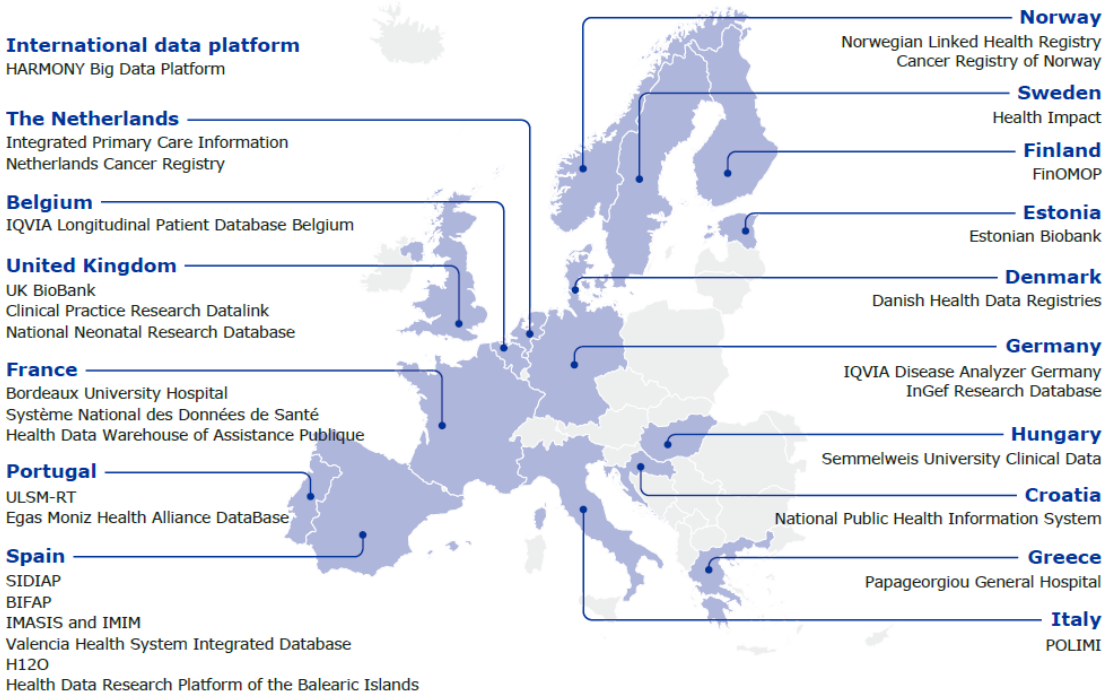


Figure 11 DARWIN EU Network as of February 2025

Two cancer registries and one dedicated paediatric data source (neonatal registry) were onboarded to address specific needs from PDCO, COMP and SAWP.

- **Next steps**

  In line with the recommendation from the Advisory Board, the fourth and last wave of data partners will focus more on specific clinical areas of interest (oncology, metabolic and cardiovascular areas) and relevant populations of interest such as paediatrics. We will also explore large data sources in countries outside EU and Europe, if relevant, representative enough, and adding incremental value to the existing network.

- Increase **transparency** on **data source description and justification for data source selection** for RWD studies

  To streamline processes and improve transparency, **data source descriptions** including data quality metrics, **were standardized and aligned with the Data Quality framework (DQF)** and will be regularly updated.

  A section on **justification for data source selection** (the relevance component of the DQF) is under development to be incorporated in protocols and reports, to increase transparency on feasibility and fit-for-purpose processes and help interpretation of results.

  Public consultation on the Chapter on Data Quality Framework for EU medicines regulation: applications to Real-World Data was closed, and the document is currently under finalisation. This guideline sets out the criteria for a more consistent and standardised approach to the assessment of quality of data used in medicine regulation.

Accelerate

Strategies to further accelerate RWE generation.

- Implement **standardised phenotypes** that can be reused for different studies

  The phenotyping process (e.g., definitions for diseases and medicines capture) that was built and tested in the DARWIN EU platform, became functional during the previous reporting period, and continued with the creation of curated and standardised phenotypes of outcomes of regulatory interest that can be reused for different studies. Each new study contributes to the expansion of the phenotype library.

- **Revise periodically and improve the standard analytical pipelines**

  Increased analytical quality and speed are the key enhancements developed during the reporting period, with the following notable additions: improvements in descriptive epidemiology pipelines, enhancements in drug utilisation analytics including improved treatment patterns analysis, and efforts to generate standardised outputs, including graphics.

- **Streamline, harmonise and improve processes and templates**

  The feasibility assessment process has been enhanced by simplifying the template and adding a more detailed fitness-for-purpose section. This is now supported by direct surveys to data partners, which provide insights into data availability and quality, complementing the automated assessments.

  Internal reviews of DARWIN EU templates for study protocols and reports have begun, aiming to improve clarity (e.g., by limiting redundancies), conciseness, and transparency. Although the discussion sections in reports have been strengthened, feedback suggests that contextualisation and interpretation of findings still need improvement.

- **Obtain faster ethical/scientific approvals for standardised and repeated analyses**

  Over the last years, blanket protocols for some standardised, off-the-shelf (descriptive) type of studies have been introduced for some data partners, thereby expediting ethical and scientific approval and therefore evidence generation. This effort has been continued during the reporting period with two additional data partners in DARWIN EU that have obtained 'blanket' approval for the execution of standardised analyses, and three pending approvals. This helps to reduce timeframes from 2-3 months to 0.5-1 month for data access.

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

- Review of portfolio of upcoming **initial marketing authorisation applications and pre-submission meetings**

  The review of portfolio of upcoming initial marketing authorisation applications and pre-submission meetings initiated during the last reporting period has continued on a 6-monthly basis and generated new research topics, some of which were feasible and translated in studies. This process is now considered as part of the routine processes.

- Create a process for identification of research opportunities during **PSUSAs and signal assessment**

  After initiation of discussions on the potential to identify research opportunities during PSUSAs and to conduct studies in support of future PSUR submissions during the last reporting period, the process of requesting a study in context of yearly PSUSA or in the context of signal assessment procedure was formalised together with PRAC during this period.

- Involve the EMA RWE team in **EMA Portfolio and Technology meetings**

  The team is now systematically involved in Portfolio and Technology meetings. This became standard practice during this reporting period.

- Monitor and enhance **the value** of RWD studies in the regulatory decision-making processes

  The impact of studies is monitored through periodic feedback from the requesters at study end including assessment on how many study results are used in assessment reports.

  Although direct immediate regulatory impact in ongoing procedures is important, the value of RWE goes beyond immediate procedures, being also used to prepare for future procedures, to monitor shortages, to enhance collaboration with other stakeholders, or for methodological improvements.

Capacity and capability
Develop educational and knowledge management sharing tools.

- Execute and promote the **Big Data Steering Group's data science and pharmaco-epidemiology curricula,** including development of educational material and tools specifically designed for regulatory decision makers

  The first two modules of the BDSG curriculum related to pharmacoepidemiology and RWE were launched in December 2023, providing an introduction on RWE generation and training on data sources to EMRN members. Two additional modules were launched in November 2024, covering aspects of the study process and statistical methods applied to RWE generation.

The Real-World Academy event series set up in 2024, continued during this reporting period after positive feedback from participants, with the aim of sharing and building knowledge on important areas of RWE generation in order to increase the collective understanding of (and trust in) RWD/E and facilitate the interpretation and use of study results for regulatory decisions.

A spring and an autumn DARWIN EU school sessions were organised internally to give insights on the different types of analyses conducted through the DARWIN EU network. Attendees involved members of the EU regulatory network.

- Improve knowledge on the use of RWE in the regulatory decision-making process for external stakeholders

  Three RWE-related multi-stakeholder workshops were held during the reporting period. The topics of the workshops covered the use of patient registries in the regulatory decision-making process, RWE methods, and pharmacogenomics.

  The Reflection paper on use of real-world data in noninterventional studies to generate real-world evidence for regulatory purposes was under finalisation after public consultation at the end of the reporting period. This paper discusses methodological aspects of non-interventional studies using RWD in order to generate RWE for regulatory purposes.

  Future developments in the guidance area for RWE use are mentioned in the Journey towards a roadmap for regulatory guidance on real-world evidence.

- Work with national competent agencies (NCAs) and stakeholders to **leverage complementary pathways** for RWE generation

  During the reporting period, NCAs helped to explore available national data sources for potential partnership with DARWIN EU by offering information about existing data sources in their country, establishing contacts or providing access to data themselves. So far, three national agencies are data partners of the DARWIN EU data partners' network.

  Additionally, NCAs requested two studies during the reporting period.

Collaboration and Communication
Close collaboration with decision makers and other stakeholders.

- Continue and, where relevant, intensify **regular interactions with the Committees, the SAWP, and the CMDh** in an efficient manner to better understand research needs

  Regular, tailored interactions with the Committees and Working Parties became a standard practice to update on RWD related activities including relevant planned, ongoing or completed studies. This led to increased interaction and participation in both studies as well as data acquisition for the network.

  An RWE newsflash is circulated quarterly to the network, highlighting trainings, publications, guidance development, workshops and studies of interest.

- **Increase communication on study results and their value** in the regulatory decision-making process, beyond the immediate request

Enhanced communication of specific study results to relevant stakeholders was carried out during Committee plenaries, EMA assemblies, and other key forums.

- Creation of a **forum of RWE experts** from the EMRN to facilitate **knowledge sharing**

  The Methodology European Specialised Expert Community (ESEC) introduced a special interest area (SIA) dedicated to RWD to provide a forum for stakeholders' interactions, and a platform for knowledge transfer, information sharing and communication. The first meeting of the RWD SIA was held in November 2023. Regular meetings with the Methodology ESEC SIA on RWD were held during 2024 and included more specifically topics on DARWIN EU and studies.

- Launch of the **HMA-EMA Catalogues of real-world data sources and studies**

  The HMA-EMA Catalogues were launched in February 2024, replacing the previous EU PAS Register and ENCePP Resource Database. We continued to disclose work done on studies, with each study conducted by one of the 3 pathways having an entry in the Catalogue of studies, and protocols and results being published shortly after approval. To date, 247 data sources, 3074 studies, 785 institutions and 180 networks have been registered in the different catalogues.

Annex 1 List of EMA-led RWD studies initiated in the period

Topic	Pathway	Study Requester	Study Status	Procedure	HMA/EMA Catalogue identifier
DUS of Antibiotics of the WHO AWaRe classification of antibiotics for evaluation and monitoring of use	DARWIN EU	ECDC	Ongoing - Protocol	Not linked to an ongoing procedure	To be published
Incidence rates of venous thromboembolic events in patients with selected cancers	DARWIN EU	EMA Internal	Ongoing - Results	Signal	EUPAS1000000440
Antipsychotic prescribing in the general population in Europe: a descriptive analysis of trends and patient characteristics	DARWIN EU	CHMP	Completed	Not linked to an ongoing procedure	EUPAS1000000330
Trends in utilisation of Attention-Deficit Hyperactivity Disorder (ADHD) Medications	DARWIN EU	MSSG	Ongoing - Results	Not linked to an ongoing procedure	EUPAS1000000219
Association between genetic polymorphisms of interest and risk of myopathy among statin users	DARWIN EU	PRAC	Ongoing - Results	Not linked to an ongoing procedure	EUPAS1000000369
Signal Risk of Suicidality with doxycycline	DARWIN EU	PRAC	Completed	Signal	EUPAS1000000280
Association of venous thromboembolism with non-steroidal anti-inflammatory drug use in women 15-49 years using hormonal contraceptives	DARWIN EU	PRAC	Ongoing - Results	PSUSA	EUPAS1000000443
Utilisation of commonly used benzodiazepines during pregnancy and the incidence of pregnancy losses	DARWIN EU	PRAC	Ongoing - Protocol	PSUSA	EUPAS1000000536
Paracetamol prescribing and paracetamol overdose in Europe: a descriptive analysis of trends and patient characteristics	DARWIN EU	PRAC	Completed	Not linked to an ongoing procedure	EUPAS1000000329
CAR T-Cell Therapy - feasibility and fitness for purpose study - ROC26	Funded (FWC)	CAT	Ongoing - Protocol	Not linked to an ongoing procedure	To be published

Topic	Pathway	Study Requester	Study Status	Procedure	HMA/EMA Catalogue identifier
Drug Utilisation Study on GLP-1 Receptor Agonists	DARWIN EU	MSSG	Completed	Not linked to an ongoing procedure	EUPAS1000000223
Incidence of suicidality in patients with specific chronic skin conditions	DARWIN EU	PRAC	Completed	Signal	EUPAS1000000294
CGRP antagonists - treatment patterns and users characteristics	DARWIN EU	PRAC	Completed	Signal	EUPAS1000000240
Characterisation of exposure to acitretin and purpura and related conditions	DARWIN EU	PRAC	Ongoing - Results	PSUSA	EUPAS1000000429
Impact of risk minimisation measures related to the risk of meningioma in women using nomegestrol and chlormadinone	DARWIN EU	PRAC	Ongoing - Results	Not linked to an ongoing procedure	EUPAS1000000455
Brand-specific influenza vaccine effectiveness in the Nordic countries	Funded (FWC)	VMP	Ongoing - Results	Not linked to an ongoing procedure	EUPAS1000000481
Azathioprine - user characteristics	DARWIN EU	PRAC	Completed	Signal	EUPAS1000000322
Drug Utilization of salbutamol products for inhalation and therapeutic alternative inhalation products	DARWIN EU	MSSG	Ongoing - Results	Not linked to an ongoing procedure	EUPAS1000000403
Prescription trends of ketamine and esketamine	DARWIN EU	Other	Ongoing - Results	Not linked to an ongoing procedure	EUPAS1000000436
Prevalence of hypertrophic cardiomyopathy (HCM) and obstructive hypertrophic cardiomyopathy (oHCM) in six European countries	DARWIN EU	CHMP	Ongoing - Results	MAA	EUPAS1000000430
Incidence of myoclonus in heart failure: a descriptive analysis in patients treated with sacubitril/valsartan and other treatments	DARWIN EU	PRAC	Completed	Signal	EUPAS1000000351

Topic	Pathway	Study Requester	Study Status	Procedure	HMA/EMA Catalogue identifier
Use of antiretroviral therapies in paediatric patients	DARWIN EU	PDCO	Ongoing - Results	PIP	EUPAS1000000545
Suicidality incidence rates in adult male patients and in patients treated with finasteride and dutasteride	DARWIN EU	PRAC	Completed	Referral	EUPAS1000000423
Antipsychotic prescribing in people with dementia in Europe: a descriptive analysis of trends and patient characteristics	DARWIN EU	CHMP	Completed	Not linked to an ongoing procedure	EUPAS1000000382
Exposure to NOMA/CMA in men in IMRD UK and IQVIA Germany	In-house	EMA Internal	Completed	Not linked to an ongoing procedure	To be published
DUS and patient characterisation of statin usage	In-house	EMA Internal	Ongoing - Results	Not linked to an ongoing procedure	To be published
Monitoring prescription of essential medicines administered in ICU	DARWIN EU	MSSG	Ongoing - Protocol	Not linked to an ongoing procedure	EUPAS1000000089
Comparative effectiveness and safety studies using the target trial emulation and estimand frameworks (TARGET-EU)	Funded (FWC)	EMA Internal	Ongoing - Protocol	Not linked to an ongoing procedure	EUPAS1000000539
Eye disorders in women with breast cancer treated with anastrozole, letrozole or tamoxifen	DARWIN EU	CMDh/NCA	Ongoing - Protocol	PSUSA	EUPAS1000000599
Monitoring prescription of medicines for public health emergencies at risk of shortages	DARWIN EU	MSSG	Ongoing - Results	Not linked to an ongoing procedure	EUPAS107932
Feasibility of studies of AML in DARWIN EU network	DARWIN EU	SAWP	Ongoing - Protocol	Not linked to an ongoing procedure	To be published
Clozapine and the incidence of agranulocytosis over time	DARWIN EU	PRAC	Ongoing - Protocol	Signal	EUPAS1000000549

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Real-world evidence framework to support EU regulatory decision-making:
3rd report on the experience gained with regulator-led studies from February 2024 to February 2025
EMA/115547/2025