HMA
Heads of Medicines Agencies

EMA
EUROPEAN MEDICINES AGENCY

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

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

An agency of the European Union

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Table of Contents

1. Executive Summary

"We are in the business of excellent clinical evidence. (…) Bigger, better, and more impactful clinical trials are one part of this while enabling the use and establishing the value of RWE is another. That is our vision, and we are on track to achieve it."

Peter Arlett, Big Data Steering Group co-chair, April 2024

Introduction

This report builds on the experience previously acquired during the period from September 2021 to February 2023 in conducting regulatory-led studies using real-world data (RWD) to support EU regulatory decisions (see previous report here). It covers the period from 8 February 2023 to 7 February 2024, which corresponds to year 2 of DARWIN EU and provides a review of the progress made in delivering on the vision of EU regulators to enable the use of RWE and establish its value for regulatory decision-making by 2025 (Arlett et al., 2022). This is in line with the European Medicines Regulatory Network (EMRN) strategy to 2025 as well as the Agency's Regulatory Science Strategy to 2025. The European Medicines Agency (EMA) alongside the EMRN is working towards the establishment of a framework to enable better integration of real-world data (RWD)/real-world evidence (RWE) alongside the gold standard of randomised controlled trials into regulatory decisions on the development, authorisation and supervision of medicines. The report follows the priority recommendations of the Big Data Task Force as implemented through the Big Data Steering Group and the fourth multiannual work plan (2023-2025).

Compared to the previous report (covering the period from September 2021 to February 2023), this time all studies conducted by EMA were considered, including those conducted in response to the Pharmacovigilance impact strategy or to inform vaccine safety and effectiveness as well as public health emergencies. In addition, information on the use of RWD by national competent authorities (NCA) was collected.

For studies conducted by EMA, all of the three RWE generation pathways available to the Agency were considered in the following order: (i) studies conducted via a DARWIN EU a federated network of data, expertise, and services; (ii) studies conducted in-house by a team within EMA of pharmacoepidemiologists and data scientists using six databases containing mainly primary care medical records from different European countries; and (iii) studies commissioned to one of eight research organisations and consortia via the Agency's research framework contract (FWC). A triaging system was applied, by which scope of the relevant service contracts, capacity and, most importantly, feasibility and fit-for-purpose considerations, including data relevance and timeliness, were considered. Further information on the process for requesting and conducting a study, the available RWE generation pathways and the type of research questions that can be addressed is available in a guide published on the Agency's website.

Main findings

Amongst the decision makers for whom studies were conducted are the Agency's scientific committees, namely the Pharmacovigilance Risk Assessment Committee (PRAC), the Paediatric Committee (PDCO), the Committee for Orphan Medicinal Products (COMP), the Committee on Herbal Medicinal Products (HMPC), the Committee for Advanced Therapies (CAT), as well as the Committee for Medicinal Products

for Human Use (CHMP) and its Scientific Advice Working Party (SAWP). In addition, national competent authorities, the Co-ordination group for Mutual recognition and Decentralised procedures (CMDh), the Executive Steering Group on Shortages and Safety of Medicinal Products (MSSG) and the Medicine Shortages Single Point of Contact (SPOC) Working Party as well as EMA functions (internal) could request a study. Beyond the EMRN, EMA furthermore collaborates with the wider spectrum of regulatory and decision-making bodies, including the health technology assessment (HTA) bodies and payers' organisation as well as European Centre for Disease Prevention and Control (ECDC).

During the 12 months covered by this report, a total of 60 new research topics were identified, translating into 25 new studies. In addition, 16 studies were either initiated or continued into the reporting period as a result of research questions detected prior to 8 February 2023. **Overall, 41 studies were conducted** of which 22 were completed (9 DARWIN EU studies, 9 FWC studies and 4 in-house studies), 18 studies were ongoing (10 DARWIN EU studies, 5 FWC studies and 3 in-house studies) and one in-house study was discontinued early in the process. All these studies are included in the HMA-EMA catalogue of RWD studies, which was launched in February 2024, replacing the former EU PAS register.

Most of the studies (63%) were descriptive cohort studies. The remaining studies were comparative with more complex analyses being performed. There was a trend to more complex studies being conducted, and a reason thereof might be that more simple analyses were perceived to be less impactful with regards to supporting regulatory decisions (although this hypothesis was not tested).

There was a broad range of study types including safety studies, drug utilisation studies, disease epidemiology studies, effectiveness studies and studies to inform the design and feasibility of clinical trials and clinical management.

The studies primarily addressed research needs of the PRAC, PDCO and CHMP in the context of safety signals, and applications for paediatric investigation plans as well as other regulatory procedures. The vast majority of studies (28/41, 68%) was however not linked to a specific procedure. These included studies to inform vaccine safety and effectiveness, including to address public health emergencies, conducted in collaboration with ECDC, the Agency's Emergency Task Force (ETF) and addressing the Vaccine Monitoring Platform (VMP) Research Agenda. Additional cases were pilot studies with other external stakeholders including HTAs/payers, methodological studies, as well as studies in the area of disease epidemiology, frailty and standard of care in older patients in line with the CHMP 2024 workplan to support the geriatric medicines strategy.

Notably, during the reporting period, two studies were requested by the HMPC, which is the first time EMA has explored feasibility of generating RWE to support the Agency's opinions on herbal substances and preparations. Similarly, EMA also initiated for the first time studies (2/60) to support the work of the MSSG and the SPOC Working Party in relation to the monitoring of supply and demand of critical medicines, shortages prevention and crisis preparedness.

Overall, there is an increased diversity of requesters and use cases compared to the previous reporting period.

The studies conducted concerned 11 different therapeutic areas (based on ATC classification), and most of them investigated anti-infectives, antineoplastic and immunomodulating agents, and alimentary tract and metabolism disorders.

With regards to the three RWE generating pathways, most of the 41 studies conducted during the reporting period were conducted via DARWIN EU (19 - 9 completed, 10 ongoing), followed by FWC studies (14 - 9 completed and 5 ongoing) and in-house studies (7 - 4 completed, 3 ongoing). When only looking at studies for which a request was received during the reporting period, again the majority of the studies that proceeded to analysis were conducted via DARWIN EU (16 - 6 completed, 10 ongoing). Fewer studies (5) were initiated in-house (3 completed, 2 ongoing) or via the FWC pathway (4 ongoing).

As it was expected in view of the increase in capacity of DARWIN-EU studies from year 1 to year 2 of its establishment, DARWIN EU has overtaken the in-house RWE generation route and become the main RWE generation pathway for studies to support regulatory decisions. In turn the proportion of in-house studies has decreased from 2022 to 2023 [see Figure 6, Section 3, Summary Statistics].

Similarly to 2022, the in-house pathway was also the fastest route for RWE generation in 2023 with a median duration for conducting studies and delivering the final report just above three months. This was followed by DARWIN EU with 8 months and the FWC route just above 2 years (25 months).

The pathways differ among each other mainly due to process related aspects (e.g., tender and contractor selection, which is specific for FWC; formal review of deliverables in DARWIN EU, which is expedited for in house studies).

Notably, within all three pathways, study duration varied a lot across individual studies, depending on the complexity of the study, the type of data access (direct access in-house, federated network in DARWIN EU, third party subcontracting for FWC) as well as whether or not ethical approval was required prior to releasing the data.

In this context it is worth to highlight that, during the reporting period, DARWIN EU was in its second year of establishment with work on the analytical pipelines and related processes still ongoing and other work just being initiated, e.g. on phenotypes. Yet, a lot of progress has been made in these and other regards, and this is further described in a dedicated section on DARWIN EU (see below). To better distinguish between factors influencing the study duration, future reviews should take into account the complexity of the studies, whether or not the study is conducted with a set deadline and stratify the duration e.g. time from study request to completion of the feasibility assessment, time from study initiation to study protocol and study report.

Regarding study feasibility, a study was not feasible[1] for about one third of the new research topics received during the reporting period. This was mainly because the outcome(s) and/or the medicinal product(s) of interest were not (adequately) captured in the available databases. This concerned mainly rare disease settings, as well as outcomes and medicines not recorded at primary or even secondary care level and for which a suitable specialised data source was not available.

The two study requesters mostly affected by non-feasible study requests were PDCO and SAWP. Despite several study requests having been received, only a few studies could be conducted to support the PDCO in the review of paediatric investigation plans (PIPs) and related waiver requests. Notably, however, amongst the studies deemed unfeasible, there were two cases concerning rare paediatric conditions for which only limited data was available and it was decided not to pursue the respective studies. However, the initial counts from the feasibility assessments in themselves were considered informative and provided an orientation on the frequency of the respective conditions and thus the feasibility of clinical trials in the respective (paediatric) target populations.

Similarly, none of the requests by the SAWP, for which feasibility had been assessed during the reporting period, could be conducted. This included four requests received in the context of the repurposing pilot initiated by EMA and the Heads of Medicines Agencies' (HMA) in 2021. Aside from the time constraints resulting from the short procedural timelines for scientific advice/protocol assistance and PIP reviews, this is explained by the fact that all research topics concerned (ultra) rare disease settings, very often in the area of oncology.

Notably, during the previous reporting period (September 2021 to February 2023) studies were more likely to be feasible in case of research questions for conditions and medicines used in the primary care

[1] By the end of the reporting period, eight feasibility assessments were pending.

setting, reflecting the available databases and main RWE generation route (in-house) at the time. With DARWIN EU becoming the primary pathway for studies and a broader range of types of data from different care settings being available, this has changed with the majority of studies using data from at least one non-primary care setting.

Finally, when seeking feedback from the recipients of the study results, including via a survey, two-thirds of the responders considered the results useful for their (future) assessment. One study using primary data collection (ongoing) is considered to be of substantial added value to inform the effectiveness and safety of the MVA-BN mpox vaccine. It was included in the risk management plan of the product and is complemented by evidence from a second study under this EMA-funded mpox research programme using US data sources. While mpox cases continue to be reported, this research continues to generate important RWE to inform potential further needs for regulatory and public health decision-making in public health emergency situations.

Another study on the association of GLP-1 receptor agonists and suicidal ideation in patients with type II diabetes mellitus contributed to the PRAC review of the related signal. The results did not support a causal association between the use of GLP-1 receptor agonists and this event, offering additional evidence that the risk is not increased in the treated population compared to an active comparator (PRAC meeting highlights, April 2024).

Further details on the research topics identified and the studies conducted are provided in Section 3. (Summary statistics) as well as Annex 1 (list of studies requested and/or ongoing/completed during the reporting period). In addition, the portfolio of use cases published alongside the previous report on the experience with regulatory-led studies has been expanded with new use cases arising in the present reporting period (see Annex 2).

Finally, Section 2. reflects on the learnings and recommendations resulting from this and the previous reports on the experience with conducting regulatory-led RWD studies. Specifically, we reflect on the progress made so far in the implementation of the recommendations and additional actions needed, e.g. for further development of DARWIN EU, in order to make better use and fully integrate RWE in EU regulatory decision-making by 2025.

Highlights

During the period covered by this report

- **DARWIN EU successfully completed its 2nd year** of establishment and has now entered the operational stage. The network expanded from 10 to 20 data partners, enabling access to data from approximately 130 million patients from 13 European countries. Further information on the development of DARWIN EU and related achievements is available in a dedicated section below.
- A total of **40 studies were completed (22) or ongoing (18)** supporting an extended range of decision-makers: six of the Agency's scientific Committees and working parties, national competent authorities, as well as a number of external stakeholders (ECDC, HTA/payers, and EC) and EMA internal functions, e.g. ETF.
- **13 studies to inform vaccine safety and effectiveness, including public health emergencies**, were conducted. Eight of these studies were commissioned in accordance with the Vaccine Monitoring Platform (VMP) Research Agenda, exploring: the effectiveness of bivalent COVID-19 vaccines (2 studies); background incidence rates of adverse events of special interest relevant for vaccine safety monitoring; age-specific incidence rates of RSV-related disease to inform later vaccine effectiveness studies once there is sufficient uptake; effectiveness of Human Papillomavirus vaccines against cervical cancer; effectiveness and safety of mpox vaccination in Germany and the US; and a

framework for the post-authorisation safety evaluation of vaccines in the EU, including readiness of data sources in Europe, characterisation of immunocompromised population in healthcare data sources, and evidence generation on incidence of flares of auto-immune conditions.

- The first two studies were initiated to support the MSSG and the SPOC Working Party in the monitoring of the **demand and stock levels of critical human medicines** as well as crisis preparedness and management. Specifically, the studies aimed to support the monitoring of prescription of medicines for public health emergencies at risk of shortages (antibiotics) as well as prescription of essential medicines administered in intensive care units.
- Two pilot studies to test the processes for carrying out RWD analyses for **HTA and payer organisations** were conducted. One was completed (Multiple myeloma patient characterisation) and another one was ongoing (Overall survival of patients with advanced or metastatic non-small cell lung cancer treated with immunotherapies). Building on this experience, additional studies will be initiated in 2024.
- In close collaboration with the **European Commission**, the EMA 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 initiated as part of the **HealthData@EU (EHDS2) Pilot**.
- In collaboration with PDCO, a proposal for a conceptual **framework for RWD to inform the possibility of adult-to-paediatric extrapolation** was developed. A pilot study was conducted in the area of juvenile dermatomyositis and polymyositis and provided useful information on the strengths of RWD (e.g. to inform on the prevalence and natural history) as well as on its limitations (e.g. low numbers of patients and absence of information on biomarkers) in supporting extrapolation claims in this disease setting.
- Together with HMPC, the first two **studies on herbal medicines** were explored for their feasibility via DARWIN EU to support the Agency's opinions on herbal substances and preparations. Both studies have been initiated in 2024 (Use of medicinal cannabis and use and safety of pelargonium radix in children).
- Two studies were requested and are explored in the area of disease epidemiology, frailty and standard of care in older patients in line with the CHMP 2024 workplan to **support the geriatric medicines strategy** (Frailty and polypharmacy among adults aged 65 and above with cancer at the time of diagnosis; Inappropriate prescribing in European people with recurrent falls).

Implementing DARWIN EU – year 2 of the establishment

The network has now completed its establishment two years after the DARWIN EU Coordination Centre was set up in February 2022.

During this period (year 1 and year 2), 22 RWD studies were initiated (13 completed, 9 ongoing). DARWIN EU studies are published in the HMA-EMA catalogue of RWD studies and can be found under the following link. In addition, by the end of year 2, feasibility was under assessment for ten more research requests received during the reporting period.

Furthermore, 20 data partners were onboarded and are now providing access to data, notably with the addition of three hospitals, 2 nationwide registries and 1 biobank in year 2. Compared to the first year, the geographical coverage was also expanded to new countries, namely: Croatia, Hungary, Denmark, Norway and Portugal. Some countries started to establish national nodes, such as FinOMOP which offer more data sources but act as a single data partner. Taken together, DARWIN EU now has access to data from approximately 130 million patients from 13 European countries (Figure 1).

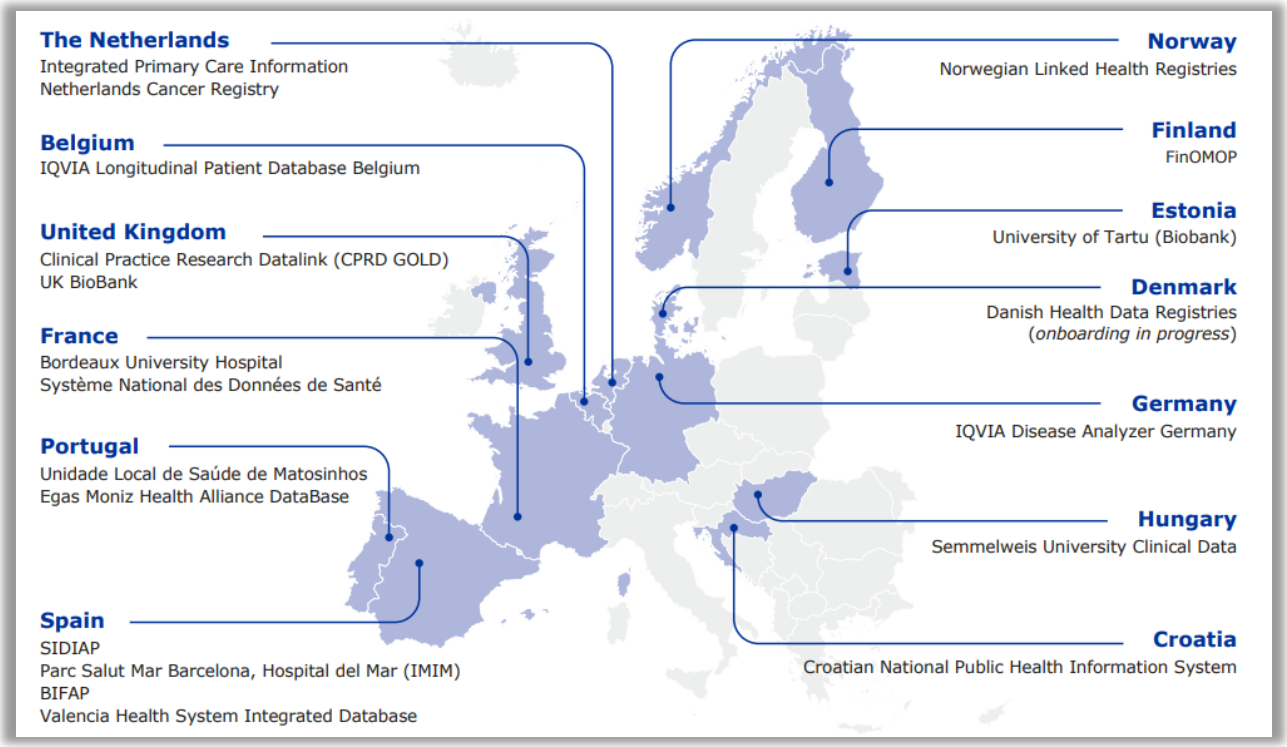

Figure 1. Overview of DARWIN EU data partners (1 June 2024)

Blanket protocols for a number of standardised, off-the-shelf type of studies were introduced for some of the data partners, expediting ethical and scientific approval and therefore study conduct. Furthermore, standard analytical pipelines were continuously developed to increase quality and speed and industry provided useful feedback on the Catalogue of Standard Data Analyses.

In agreement with the DARWIN EU Advisory Board, the process to inform or consult industry on complex studies investigating product related outcomes was agreed in 2022 and implemented in 2023.

A phenotyping process, including tools for phenotype creation and review were developed and tested in the network and it is now functional and described here. The aim was to increase the quality of phenotypes used during study conduct, which should be more standardized and reproducible but also to increase the speed of studies, this being a limiting step.

The feasibility assessment process was improved, by inclusion of more granular counts, with narrower categories and stratifications when needed, in order to have a more accurate picture of feasibility early on and avoid running unfeasible studies.

Finally, DARWIN EU continues to foster coordination and alignment with relevant European and EU Member State initiatives and policies. In 2023, DARWIN EU took part in the EHDS2 pilot with its use case on coagulopathy and COVID-19. EMA also continued to engage with the EHDS 'Joint Action' TEHDAS to ensure alignment.

Use of RWD at national level

To collect information on the use of RWD by NCAs, we conducted a survey (Annex 3) to explore the current access to RWD sources as well a capacity to conduct studies using these data.

Overall, eleven responses were received from Croatia, Czechia, Finland, France (veterinary), France (human), Germany (BfArM, BVL, PEI), Italy, Luxembourg, and Norway.

Amongst these, six responders (6/11) confirmed they have currently access to electronic health data for secondary use (research purposes), either directly (2) or indirectly (4), e.g. via external research organisation(s). Five responders replied that no such access existed at the time of the survey. Amongst those having access to data, three responders confirmed to have access to pharmacy dispensation records and patient registry data, respectively, followed by two NCAs having access to hospital records and other data sources (national public health information system in one case, not further specified in the other). One responder each confirmed access to primary care medical records, and claims data.

Only few responders (3) confirmed to have performed non-interventional studies at their own (NCA) initiative during the period covered by this report, and the capacity to conduct studies was also limited (1-2 studies reported by each of the three responders). The studies were conducted to explore drug utilisation, representativeness and validity of completed studies, disease epidemiology, safety, effectiveness, and impact research (effectiveness of risk minimisation measures).

Finally, when asked about priorities in order to further enable the use and establish the value of RWE in regulatory decision making (Figure 2), most responders (8/11) considered it important to build capability in the network for both generating and interpreting RWE, as well as to increase data quality and completeness. More than half of the responders also found it relevant to facilitate access to data from more EU countries (7/11), and to have better linkage between existing data sources (6/11). Building capacity for conducting studies (5/11), support to designs with randomisation and RWD (5/11), and helping the creation of networks of registries for rare diseases (4/11) was considered relevant by some responders.

It was considered less relevant to further accelerate the generation of RWE and to focus on repurposing of medicines. In addition, a suggestion was made to further explore and work towards a harmonised position amongst regulators on the usefulness and limitations of RWE in comparison to randomised controlled trials including different study types, datasets, effects of "unknowns" and investigator bias.

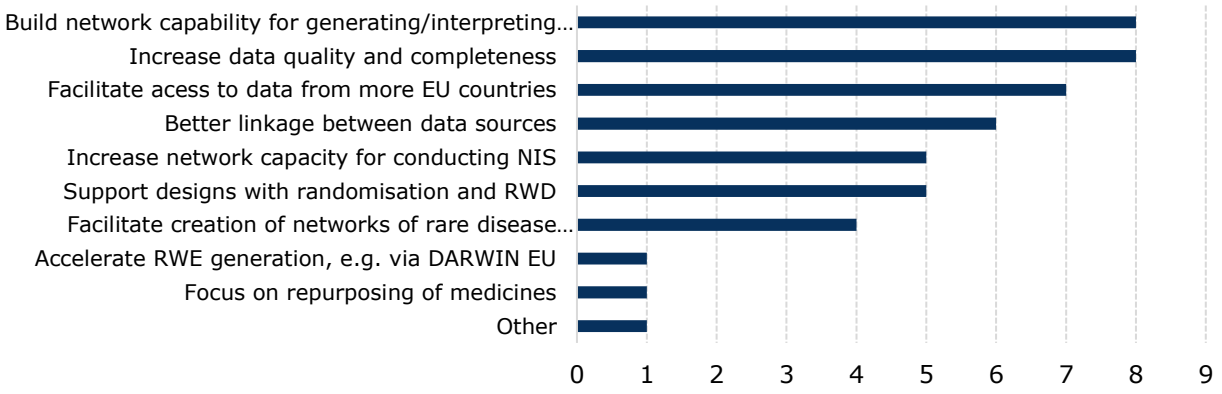

Figure 2. Survey on the use of RWD by NCAs: Priorities to further enable the use and establish the value of RWE in regulatory decision making.

Abbreviations: NIS = Non-interventional studies

2. Progress report on the lessons learned and recommendations

We previously reviewed the experience gained in conducting regulatory-led studies using RWD to support EU regulatory decisions (covering the period of September 2021 to February 2023, see report here). During this review, a number of lessons learned and recommendations for future improvements were identified.

Based on the additional experience gained in year 2 of DARWIN EU and as presented in this report, this section summarises how the recommendations have been addressed since the previous report and what further actions are being proposed. **NEW** lessons learned and related recommendations are also reflected here.

1. Suitability of available RWD sources and pathways		
Recommendation	**Implementation status**	**Further actions**
1) **Widen access to a larger range of diverse and complementary data sources** including secondary care databases (ideally with linkage to primary care data), biobanks, large claims databases, (networks of) registries, as well as data sources from **additional European countries** for broader geographical representativeness.	The network of data sources accessible via DARWIN EU increased from 10 to 20 data partners, covering now 13 European countries and over 130 million patients. The additional data types and settings covered are: Hospital electronic health records (EHR) (3), claims data (2), biobank (1), nationwide registries (2), primary care (2). In terms of geographical coverage, new countries covered include Croatia, Denmark, Hungary, Norway and Portugal. Of note that some countries established nodes of several data sources which act as a single data partner.	Continue the growth of DARWIN EU with additional relevant data partners, focusing on more specialised data sources including data in special populations such as paediatrics, as well as rare diseases and oncology. Strengthen the outreach to data/registry owners including in the EMRN to communicate needs and establish collaboration for secondary use of the data to support regulatory decisions.
2) Retain the availability of all three **RWE generation pathways** that come with different limitations but also advantages, e.g., short timelines for simple in-house	All three pathways have been maintained and, while DARWIN EU has overtaken the in-house RWE generation route and become the main RWE generation pathway for studies to support	Additional data sources to maximise in-house data analytics capability and capacity may be considered after the discontinuation of several previously accessible sources.

1. Suitability of available RWD sources and pathways		
analyses, expected increase in capacity and agility of DARWIN EU, and additional expertise and data sources provided through the framework contracts.	regulatory decisions, all three pathways have been utilised in accordance with the revised triaging system.	The current FWC 'Quality, efficacy and safety studies on medicines' (EMA/2020/46/TDA) is expiring in 2025. Options for a new contract should be explored.
3) Work with NCAs and stakeholders to **leverage complementary pathways** for RWE generation.	Collaboration with NCAs and other stakeholders were continued and strengthened including via the following means: • Two surveys were conducted amongst the EMRN to better understand (needs for) computing capability and RWD use. • First meeting of the Methodology European Specialised Expert Community's (ESEC) special interest area (SIA) on RWE held in November 2023. • Contact points established with a number of NCAs to explore available national data sources for potential partnership with DARWIN EU. • A joint HMA/EMA multi-stakeholder workshops on RWD quality and RWE use was held in June 2023.	The collaboration with NCAs should be further strengthened to maximise the use of both DARWIN EU and national data sets, as well as of analytical capability/capacity. The Agency will continue collaboration with other stakeholders such as academia and research organisations via ENCePP, the Methodology ESEC and RWD SIA and other relevant routes.

2. Regulatory context and timelines		
Recommendation	**Implementation status**	**Further actions**
1) Explore proactive approaches for **anticipation and early identification of**	The following proactive approaches to identify research topics (in addition to the screening of	Engagement with relevant EMA functions, committees and working party members should

2. Regulatory context and timelines		
RWD study needs (e.g., based on horizon scanning, business pipeline activities, screening of upcoming applications, engagement with EMA staff, committee and working party members).	new PRAC signals) have been initiated or are being explored: • Review of portfolio of upcoming initial marketing authorisation applications (on a 6-monthly basis) and pre-submission meetings (monthly basis). • Discussion initiated on the potential to identify research opportunities during periodic safety update report single assessments (PSUSAs) and conduct studies in support of future PSUR submissions. • Systematic involvement in EMA Portfolio and Technology meetings.	be continued to fully leverage the knowledge of upcoming and ongoing applications in order to identify potential research opportunities. Additional systematic screening options should be explored. Further review the experience with studies conducted outside a specific regulatory procedure to ensure timely review of the evidence and, if needed, regulatory action.
2) Consider additional **strategies to accelerate RWE generation** in order to generate results in time for incorporation into regulatory decisions, especially for short procedural timelines. This may include via DARWIN EU development of standard analyses, phenotype libraries, pre-computed, searchable dashboards, and increased automation of repeated tasks.	The phenotyping process (e.g., definitions for diseases and medicines capture) was built and tested in the DARWIN EU platform and it is now functional. Each study contributes to the expansion of the phenotype library, with, for example, a large addition of 40 phenotypes from the ongoing "Background rates of AESI" study. The catalogue of standard analytics is revised quarterly to implement new features and increase automation and comments from industry were implemented during 2023. The feasibility process was improved, by inclusion of more granular counts for the feasibility assessments, with narrower	It should be explored how the feasibility assessment can be further expedited, including an improved feasibility form submitted electronically and further refinements of the feasibility output in terms of stratification and age groups. Running analyses at partner level can benefit from further automatization and this is ongoing, as well as new data partners trainings in federated analytics. Reconsider for future reports the approach to analyse study duration, taking into account the different milestones and study phases as well as the level of study complexity, in order to identify potential bottlenecks and areas for

2. Regulatory context and timelines		
	categories and stratifications when needed. This should be always carefully balanced against patient privacy by not disclosing low cell counts. For urgent requests such as signal procedure, an expedited feasibility request is now possible. Blanket protocols for some standardised, off-the-shelf type of studies were introduced for some data partners, thereby expediting ethical and scientific approval and therefore study conduct.	improvement, e.g. time from study request to completion of the feasibility assessment, time from study initiation to study protocol and study report.
3) **NEW:** The EC proposal for a **revised pharmaceutical legislation** provides for the Agency the possibility to process personal health data, from sources other than clinical trials, for the purpose of improving the robustness of its scientific assessment or verifying claims of the applicant or marketing authorisation holder in the context of the evaluation or supervision of medicinal product. Although the proposal has yet not been adopted, it will be important to **prepare for the implementation** of the legislation as early as possible. The same applies to the **new Regulation on a European Health Data Space**, which was adopted in April 2024.		

3. Collaboration		
Recommendation	**Implementation status**	**Further actions**
1) Each study to have **at least one RWE sponsor identified** as an end-user of the study findings (EMRN or external stakeholder).	The EMA process for conducting studies to support regulatory decisions foresees involvement of at least one sponsor from the EMRN or other decision-maker (usually the requester of the study) as well as relevant EMA functions (e.g. relevant therapeutic area office) at all major milestones, i.e. formulation of the research question, feasibility assessment, protocol agreement and finalisation of the study report. Other potential interested parties were also systematically considered and offered to follow the study/ies.	Continue to review the experience linked to the involvement of Rapporteurs and other representatives of the EMRN and the extended group of decision-makers to ensure a balanced approach taking into account the effort needed to support a study throughout its conduct, as well as the expected benefit of the additional expertise to ensure that the study is fit-for-purpose.
2) Continue, and where relevant, intensify **regular interactions with the Committees, the SAWP, and the CMDh** in an efficient manner (e.g., quarterly plenary presentations and focussed discussions with the RWE liaison groups) to better understand research needs.	Quarterly updates on RWD related activities including relevant planned, ongoing or completed studies have been given to the CHMP, CAT, CMDh, PRAC, COMP, PDCO and SAWP. Regular interactions also took place with the RWE liaison groups in line with the respective 2023 and 2024 workplans. Presentations were also made to HMPC, the SPOC Working Party, the Patient's and Consumers' Working Party as well as the Healthcare Professionals Working Party.	By the end of 2024, the RWE pilots[2] with CHMP, CAT, PDCO, COMP and SAWP will close. The experience gained from these pilots will help to understand more precisely the research needs by Committee/Working Party. After the pilots, it will be important to ensure continuous engagement while implementing the routine RWE support, thereby ensuring that, with growing experience, the RWE generation framework is further adapted, as needed.

[2] See previous report on the experience with regulatory-led studies (September 2021 to February 20023) for further details on the pilot related activities.

3. Collaboration		
	Based on the experience today, research needs vary by requester, as do challenges encountered. Generally, for medicinal products (to be) approved via the centralised procedure, knowledge gaps appear to be more prominent in rare diseases including in the area of oncology and for special populations such as paediatrics.	
3) Consider creation of a **forum of RWE experts** from the EMRN to facilitate **knowledge sharing.**	In November 2023, the first meeting of the Methodology ESEC's RWE SIA took place.	It should be further explored how to best leverage the expertise in the RWE SIA for the purpose of knowledge sharing and capability building.

4. Building capability & capacity		
Recommendation	**Implementation status**	**Further actions**
1) 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 have been launched in December 2023, providing an introduction on RWE generation and training on data sources to EMRN members. By the time of this report, the curriculum has been further complemented by a new knowledge sharing event series (called Real-World Academy). Topics for the 2024 agenda were developed with input from the RWE liaison group members of the Agency's scientific committees. In addition, a spring	The release of additional modules of the curriculum on how to draft and review of study protocols and reports, statistical methods used in RWE generation and the process from RWD to RWE is foreseen throughout 2024 and 2025. Additional knowledge sharing events should be developed in 2024 and 2025 onwards to complement the curriculum, according to priorities identified by the EMRN. Similarly, additional trainings specifically on DARWIN EU will be needed to increase the awareness of

4. Building capability & capacity		
	school on DARWIN EU had been held, giving insights on the common data model used, data quality assessment, phenotyping and the standardise analyses, amongst other.	relevant processes, methods and analytical tools[3].

5. Usefulness for decision-making		
Recommendation	**Implementation status**	**Further actions**
1) Provide thorough **discussion of the study findings, the strengths** and **limitations** in all future study reports as this helps the **interpretation of the findings** and their **integration into regulatory decision-making.**	Dedicated fitness-for-purpose paragraphs are now added in the reports of DARWIN EU studies, to corroborate both the strengths and limitations of the study as well as suitability of the selected data sources.	Further collect feedback from the EMRN, EMA functions and other decision-makers to better understand the information needed to facilitate the interpretation of the study finding. Explore means to address these needs, e.g. sources of heterogeneity in the study results such as impact of differences in national healthcare systems within Europe on the use of medicinal products. Expand knowledge sharing, training and communication activities (see also recommendations section 4) to increase the confidence in the interpretation of study results.

[3] By the time of this report, a new knowledge sharing event series (called Real-World Academy) had been introduced for the EMRN and the first two events had been held in April (study use case) and July (data quality), respectively. Topics for the 2024 agenda were developed with input from the RWE liaison group members of the Agency's scientific committees. In addition, a DARWIN EU spring school was organised by the DARWIN EU Coordination Centre, giving insights on the common data model used, data quality assessment, phenotyping and the standardise analyses, amongst

6. Awareness and transparency		
Recommendation	**Implementation status**	**Further actions**
1) **Promote** the possibility to **request RWD studies** via the RWE framework.	Amongst other, the possibility of requesting studies was communicated: • As part of the RWE newsletter introduced in December 2023 and sent to relevant members of the EMRN and EMA. • As part of updates to the Agency's scientific committees and working parties including presentations on RWD/E at strategic review and learning meetings, as well as internal meetings with relevant EMA functions. • In dedicated meetings with NCAs on DARWIN EU and other RWD/E related topics. • During workshops and knowledge sharing sessions on regulatory-led studies. • By publishing on the Agency's Big Data website a guide on the process for requesting and conducting studies, the available RWE generation pathways and type of research questions to be addressed.	Continue to promote the use of RWE@ema.europa.eu for requesting studies and/or exploring research opportunities. Publish on the EMA website the process for requesting studies and relevant supporting information[4].

[4] By the time of this report, EMA published on the Agency's Big Data website a guide on the process for requesting and conducting studies, the available RWE generation pathways and type of research questions to be addressed.

7. Other process related aspects		
Recommendation	**Implementation status**	**Further actions**
1) Explore means to **systematically trigger reflections on knowledge gaps** that could be addressed by RWE and better engage Rapporteurs and EMA product teams in this process.	See also recommendation section 2 on regulatory context and timelines. Specifically, progress has been made in the area of reviewing portfolios of upcoming initial marketing authorisation applications (on a 6-monthly basis) and pre-submission meetings (monthly basis), as well as EMA Portfolio and Technology meetings and initial discussion on a potential process for providing support to PSUSAs.	Continue the effort to trigger reflections on research needs in suitable settings, by reviewing current activities and exploring new opportunities, e.g. by developing a set of criteria to help identify study opportunities at earlier stages or in anticipation of upcoming submissions.
2) Further **streamline and harmonise processes** and templates	The triaging system to choose between the different RWE generation pathways was adapted in view of the increase in capacity and agility to conduct studies via DARWIN EU. DARWIN EU is now the first pathways to be considered for all study requests, followed by in-house analyses (if not feasible via DARWIN EU) and FWC (if not feasible via DARWIN EU and in-house)	Further ensure alignment of relevant study templates and processes in case of updates and amendments, e.g. apply fit-for-purpose paragraph as implemented for DARWIN EU study reports also for in-house and FWC studies. In view of the expected increase in study capacity in 2024 and 2025, the process for conducting studies should be reviewed for potential efficiency gains, e.g. in the area of interaction with the DARWIN EU Coordination Centre, assignment of EMA study teams, and review of study deliverables. Publish on the EMA website the process for requesting studies and relevant supporting information[5].

[5] By the time of this report, EMA published on the Agency's Big Data website a guide on the process for requesting and conducting studies, the available RWE generation pathways and type of research questions to be addressed.

3. Summary statistics

Number and types of study topics by feasibility. From 8 February 2023 to 7 February 2024, a total of 60 new RWD research topics were identified (Figure 3). Amongst the potential studies, 31 (52%) were considered feasible, 21 (35%) were not feasible and in eight cases (13%), a feasibility assessment was not yet available by the cut-off date for this report. A total of 25 out of the 31 feasible studies (81%) were initiated during the reporting period, of which nine studies (36%) were completed and 16 (64%) were ongoing by the end of the reporting period. Of the remaining six feasible studies, two were on hold, awaiting the onboarding of additional data partners in DARWIN EU and four studies were offered by EMA to Rapporteurs/lead member states, but finally not considered useful to support the respective assessment and consequently not accepted.

In addition to the 60 new research topics, 16 studies were conducted as a result of research questions identified before the start date of the reporting period (Figure 4). Of these, 13 (81%) were completed, and two (13%) were ongoing. One study was discontinued early on (see further information below).

Finally, two additional research topics were identified before the cut of date of 8 February 2023 but a study to address the respective research questions was considered not feasible.

In total, during the 12 months covered by this report, 22 studies were completed (9 DARWIN EU studies, 9 FWC studies and 4 in-house studies), and 18 studies were ongoing (10 DARWIN EU studies, 5 FWC studies and 3 in-house studies).

For the full list of study requests and a portfolio of use cases (selected studies that present illustrative examples for RWE supporting regulatory decisions), please see Annex 1 and 2, respectively.

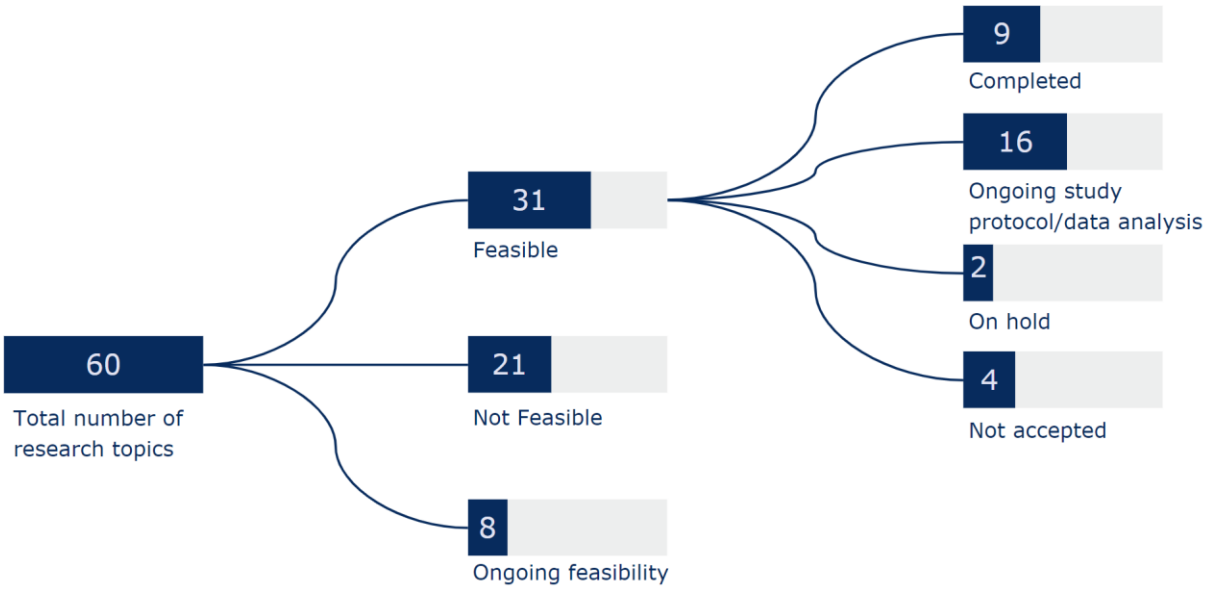

Figure 3. New research topics identified between 8 February 2023 to 7 February 2024.

Notes: (i) 'Not accepted' includes studies offered by EMA but that the respective Rapporteur/lead member state did not consider useful to support the assessment. (ii) 'On hold' includes research topics that need further discussion on the scope or design of the study.

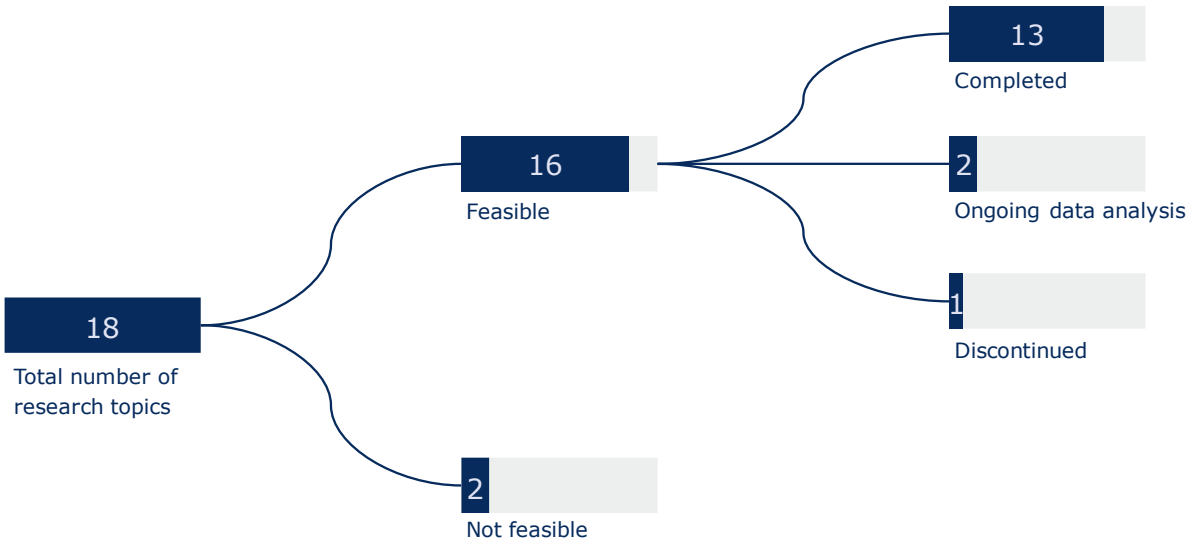

Figure 4. Research topics identified before 8 February 2023 and related ongoing/ completed/ discontinued studies between 8 February 2023 to 7 February 2024.

Amongst the 60 new research topics identified between 8 February 2023 to 7 February 2024, 38 (63%) were triaged via the DARWIN EU pathway, 16 (27%) via the in-house study pathway, and 6 (10%) via the FWC pathway (Figure 5).

A total of 19/38 (50%) of the DARWIN EU studies were feasible and of these 16 studies proceeded to analysis (six completed, 10 ongoing) during the reporting period. One research topic was not pursued as not perceived to provide added value compared to evidence already requested from the marketing authorisation holders (MAHs). Two studies were on hold pending onboarding of additional data partners. Eleven studies (11/38, 29%) were not feasible and for the remaining eight (21%) studies a feasibility assessment was not yet available by 8 February 2024.

Of the 16 research topics considered for the in-house pathway, half (8/16, 50%) were feasible, and half (8/16, 50%) were not feasible. Of the eight feasible studies, five were initiated during the reporting period of which three were completed and two were ongoing by the cut-off date for the report. The remaining three studies were offered to support signal assessments, but not considered needed in view of other evidence that was already available.

Finally, six studies were considered via the FWC pathway. Of these, four (67%) were feasible and proceeded to analysis (ongoing by 8 February 2024). The remaining two study topics were not considered feasible in view of doubts of the availability of suitable data. In one case (risk of cancer in the offspring of mothers taking hydroxyprogesterone), mother-child linkage would have been needed and exposure was expected to be very limited for the nationally approved products, and in the other case (natural history of amyotrophic lateral sclerosis), although relevant registries were identified during a market research, it was still unclear if the data sources would capture all needed information and the requester decided not to pursue the study.

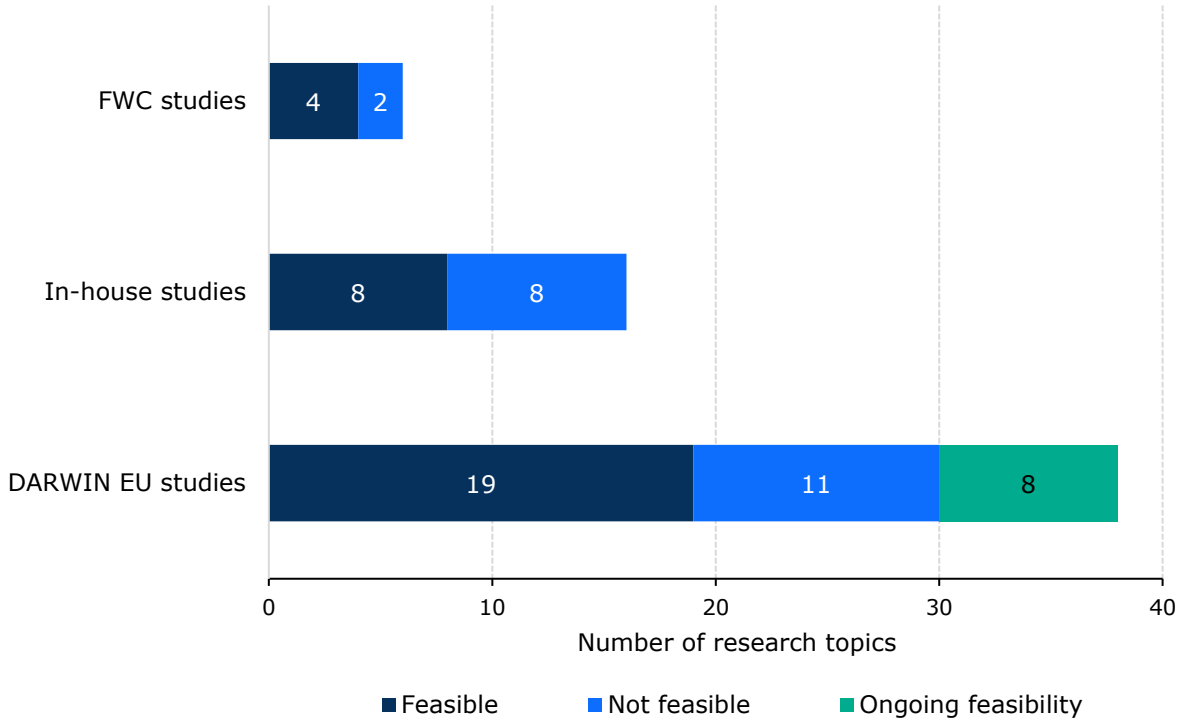

Figure 5. Number of new research topics identified between 8 February 2023 to 7 February 2024 by RWE generation pathway (n=60)

Of the 16 studies that were initiated before the start of the reporting period, ten studies were conducted via the FWC pathway, three studies via DARWIN EU and three studies in-house. Amongst the ten FWC studies, nine were completed and one was ongoing by the end of the reporting period. All three DARWIN EU studies were completed during the reporting period. Finally, of the three in-house studies, one was completed, one ongoing and the third was discontinued after an initial literature research indicated that there was insufficient information to select suitable comparators (prevalence validation study to compare prevalence estimates using RWD with the gold standard).

Number of studies over time. Starting from 2022, the number of research topics identified appears relatively stable with numbers ranging between 24 and 33 per six-month period (Figure 6). The same can be said about the number of studies initiated per six-month period in 2022 and 2023. However, there is a clear trend for an increase in the number of DARWIN EU studies and a decline in in-house studies, which was to be expected in view of the plans to upscale the capacity of DARWIN EU in year 2 of its establishment, thereby becoming the main pathway for EMA-led RWD studies.

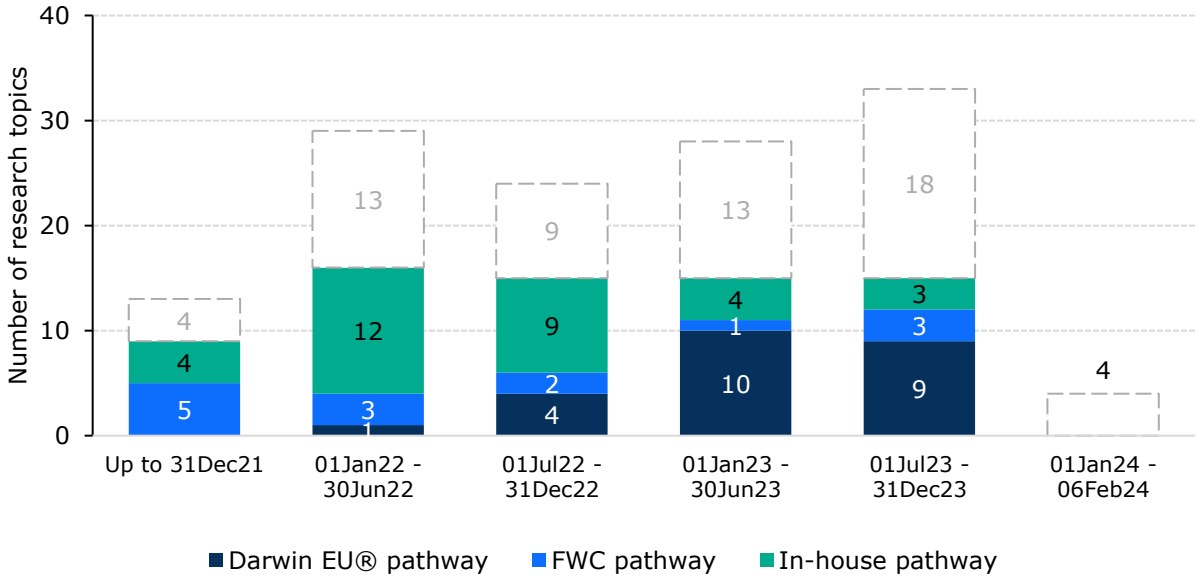

Figure 6. Number of identified research topics over time. The height of the bar reflects the total number of research topics identified in each semester. The coloured bars represent feasible studies (including studies that were ongoing, on hold or completed). The dashed bars illustrate research topics that were considered unfeasible, not accepted by requesters or whose feasibility assessment is still ongoing.

Use case categories/study types. Most of the studies that were ongoing or completed during the reporting period, were descriptive cohort studies (25/40, 63%). The remaining studies (15/40, 38%) were comparative with more complex analyses being performed.

Most of the new research requests received, aimed at generating evidence in relation to drug utilisation (18/60, 30%), followed by medicines safety (16/60, 27%), disease epidemiology (8/60, 13%) and topics to inform the design and feasibility of MAH/applicant studies (7/60, 12%) (Figure 7).

It is important to note that during this reporting period, six research questions on the effectiveness of medicines were received and four studies were initiated (three via DARWIN EU and one via the FWC route): two studies to explore effectiveness of COVID-19 vaccines, one to assess effectiveness of Human Papillomavirus Vaccines (HPV) to prevent cervical cancer, and one to measure overall survival of patients with advanced or metastatic non-small cell lung cancer treated with immunotherapies. Two of the requests were not feasible due to timelines being too short and unavailability of relevant outcome variables.

One drug utilisation study (with Janus kinase inhibitors) was explored to understand the impact of recent regulatory decisions that aimed to restrict the use of these products but, while feasible, the study was not pursued in view of evidence already requested from the MAHs.

When considering only the research topics deemed feasible or unfeasible (Figure 7), most of the disease epidemiology studies (5/6, 83%), safety studies (11/16, 69%), effectiveness studies (4/6, 67%) and drug utilisation studies (8/13, 62%) were feasible, whereas research topics on clinical management, and the design and feasibility of future MAH/applicant studies were more likely to be unfeasible with only 1/4 (25%) and 1/6 (17%) requests proceeding to studies (see reasons for non-feasibility below).

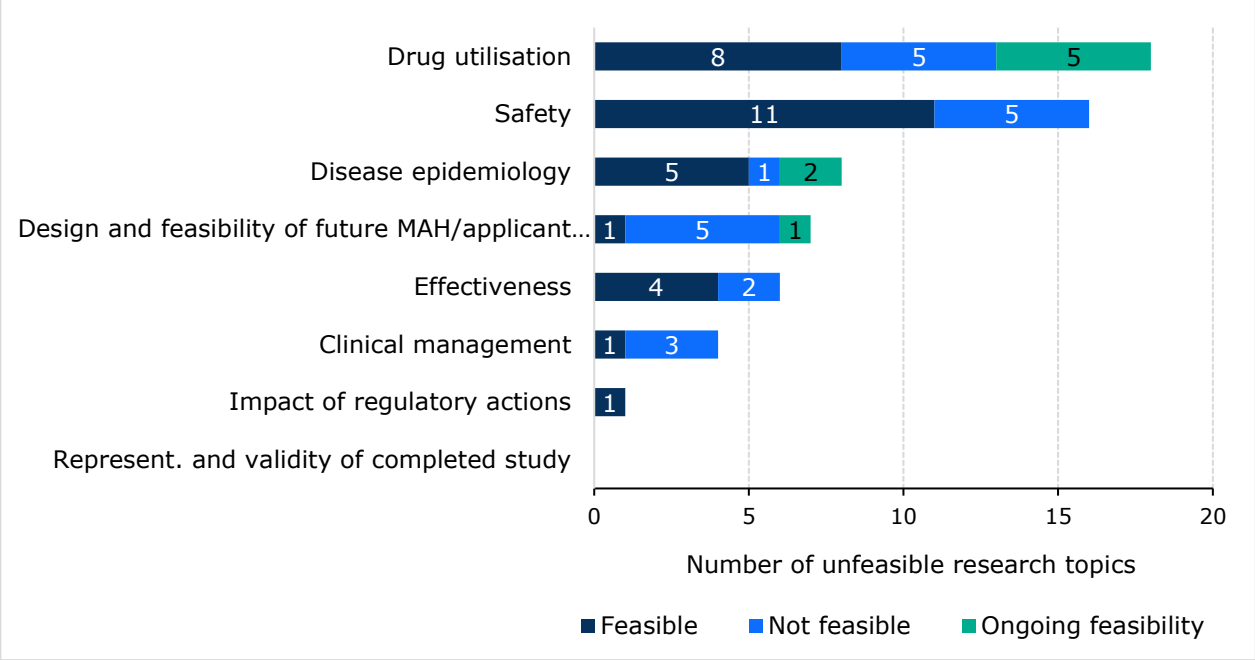

Figure 7. Type of research topic (new research questions identified during the reporting period) by use case and feasibility status (n=60).

Requester/sponsors. The majority of the new research topics identified during the reporting period emerged in the context of scientific assessments by the PRAC (16/60, 27%) and PDCO (9/60, 15%), as well as in relation to vaccine safety and effectiveness, including public health emergencies (ECDC/ETF, 9/60, 15%) (Figure 8). This was followed by study topics related to CHMP (6/60, 10%), SAWP (6/60, 10%) and internal EMA requests (5/60, 8%). The latter included primarily requests from the Agency's Pharmacovigilance office linked to signal detection activities, but also methodological studies exploring topics such as treatment-related intercurrent events or direct and indirect methods to estimate prevalence of diseases.

Few study requests originated in the context of procedures or topics of interest for other EMA scientific committees, namely CAT and COMP, as well as national competent authorities. Equally so, only few study topics were identified for the extended group of decision-makers such as the European Commission and HTA bodies and payers.

Notably, during the reporting period, two studies were requested by the HMPC, which is the first time EMA has explored feasibility of generating RWE to support the herbal committee. Similarly, EMA also initiated for the first-time studies (2/60) to support the work of the MSSG and the SPOC Working Party in relation to the monitoring of supply and demand of critical medicines, shortages prevention and crisis preparedness.

Research topics from PDCO (2 feasible study out of a total of 9 requests), and SAWP (5/6) were more often unfeasible than for other decision-makers, whereas most study requests by PRAC (12/16) and studies conducted in collaboration with ECDC/ETF (8/9) were feasible. This is partially explained by the fact that the majority of these studies were offered (10/16 PRAC topics and 6/9 ECDC/ETF topics) on the basis of some knowledge that relevant data would be available. In case of PDCO and SAWP, on the other hand, the requests received usually refer to rare diseases and/or situations with limited exposure. For

paediatric research, specialist databases which capture paediatric population comprehensively are still needed or not (yet) accessible in the network.

Finally, although only two studies could be conducted to support the PDCO, these studies informed efforts to develop a conceptual framework for RWD to inform the possibility of adult-to-paediatric extrapolation. Currently, RWD is rarely used to support paediatric extrapolation concepts. However, data on patient characteristics, existing treatments, and clinical management, amongst other, may help generate complementary information in relation to disease similarity and response to treatment. A pilot study was conducted in the area of juvenile dermatomyositis and polymyositis and provided useful information on the strengths of RWD (e.g. to inform on the prevalence and natural history) as well as its limitations (e.g. low numbers of patients and absence of information on biomarkers) in supporting extrapolation claims in this disease setting. The second study investigated treatment patterns of drugs used in adult and paediatric populations with systemic lupus erythematosus, showing that RWD can be used to explore similarities and differences between different age groups in this regard.

Overall, the range of decision-makers, for whom studies were conducted, increased compared to the last reporting period, from 7 to 12 different origins.

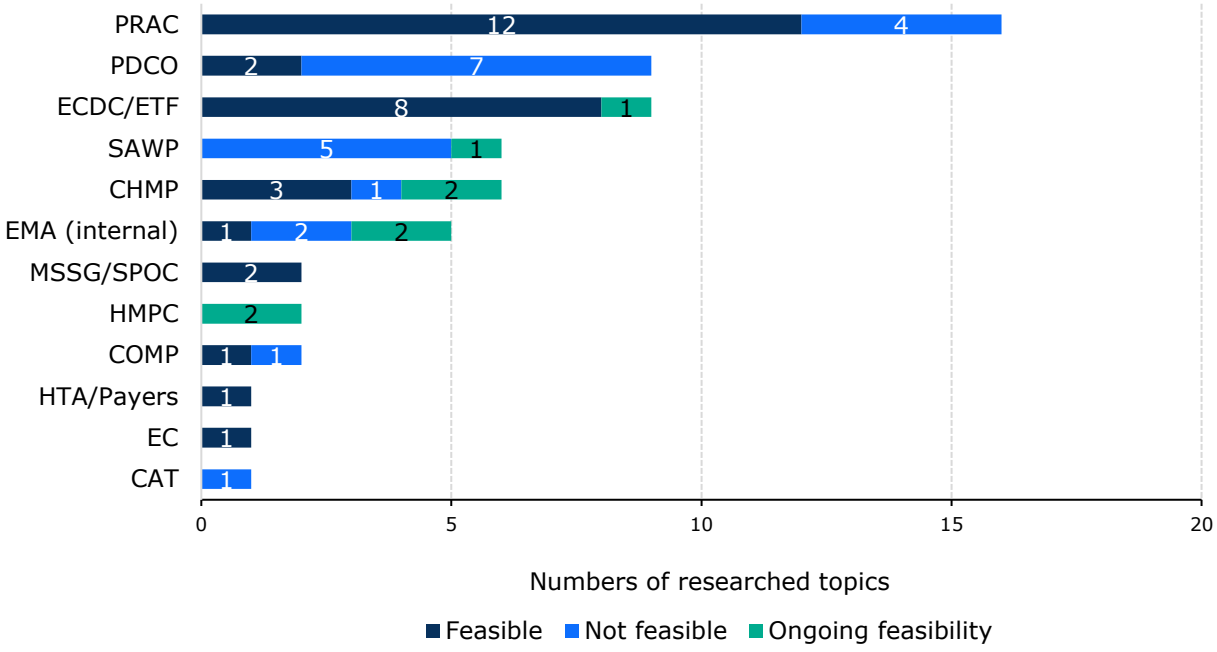

Figure 8. New research topics identified during the reporting period by requester and feasibility status (n=60)

Regulatory context. Most of the new research questions identified during the reporting period were not linked to a specific procedure (28/60, 47%) (Figure 9). These included studies to inform vaccine safety and effectiveness, including public health emergencies (ECDC/ETF), studies intended for the HMPC and the MSSG/SPOC, the latter in the context of shortage prevention and crisis preparedness. In addition, there were pilot studies with other stakeholders (European Commission and HTA bodies/payers), methodological studies, as well as studies in the area of disease epidemiology, frailty and standard of care in older patients in line with the CHMP 2024 workplan to support the geriatric medicines strategy. In addition, some studies were requested in areas of general interest and in anticipation of future applications/procedures.

From the research topics linked to a specific procedure (32/60, 53%), the majority emerged in the context of signals (12/32, 38%), requests for paediatric investigation plans (PIPs) (7/32, 22%), scientific advice (4/32, 12%) and initial marketing authorisation applications (4/32, 12%). Few study requests originated in the context of type II variations, referrals, and other post-authorisation procedures.

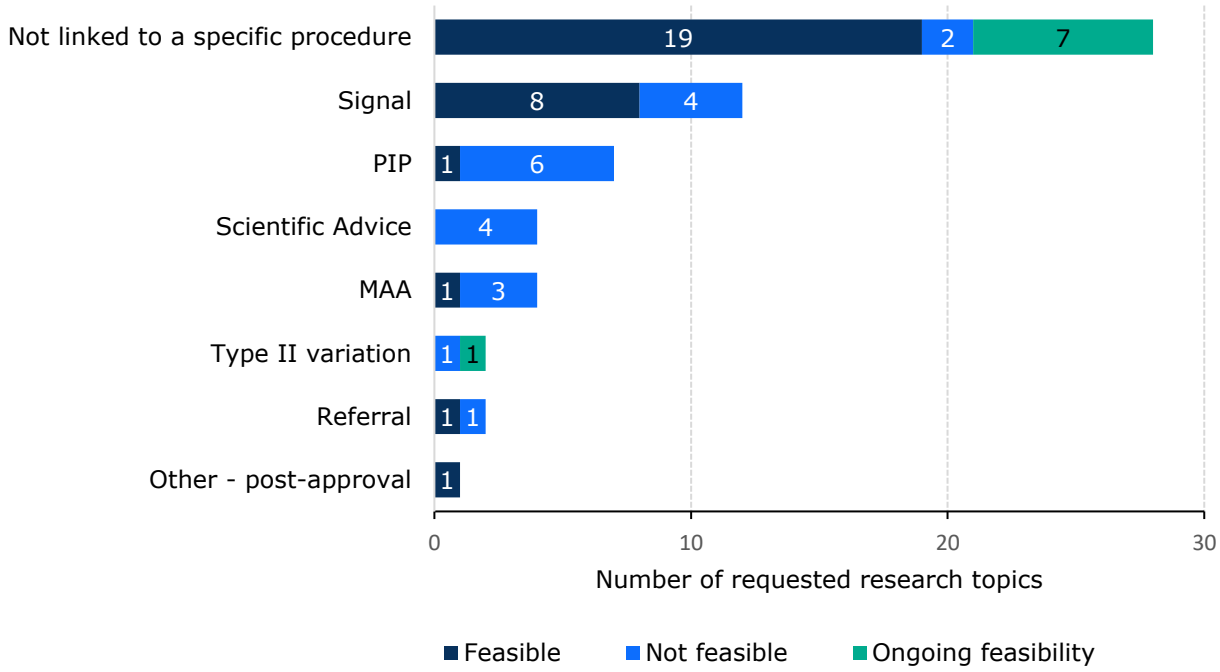

Figure 9. New research topics identified during the reporting period by regulatory procedure type and feasibility status (n=60)

Notes: For this analysis, scientific advice procedures also include requests for protocol assistance.

Abbreviations: PIP: paediatric investigation plan, MAA: marketing authorisation application.

Therapeutic and disease areas. Research topics were also classified based on the ATC classification system. The ATC main group was assigned to each research topic based on the medicinal product included in the regulatory procedure which triggered the research question (e.g., a study on background rates of interstitial lung disease was assigned to L (Antineoplastic and immunomodulating agents) group because the medicinal product under evaluation was a substance used for the treatment of cancer being investigated for a safety signal of ILD). However, there were 5 (out of 60) research topics related to medicines that have not yet been categorised in the ATC system or which comprises several medicinal products which were left unclassified and considered missing datapoints.

Thus, research topics requested during the reporting period were related to a total of 11 different therapeutic areas, of which antineoplastic and immunomodulating agents (15/55, 27%), anti-infectives (14/55, 25%), and alimentary tract and metabolism disorders (6/55, 11%) were the most requested areas for RWE generation (Figure 10). Notably all studies considered for medicinal products intended for use in alimentary tract and metabolism disorders were feasible, as well as the majority of the studies with anti-infectives. In contrast, less than half of the studies related to antineoplastic and immunomodulating agents could be conducted, which was mostly due to lack of relevant data as many research requests concerned (very) rare diseases for which not enough patients were captured and/or would have required specific variables that were not available in the currently available data sources.

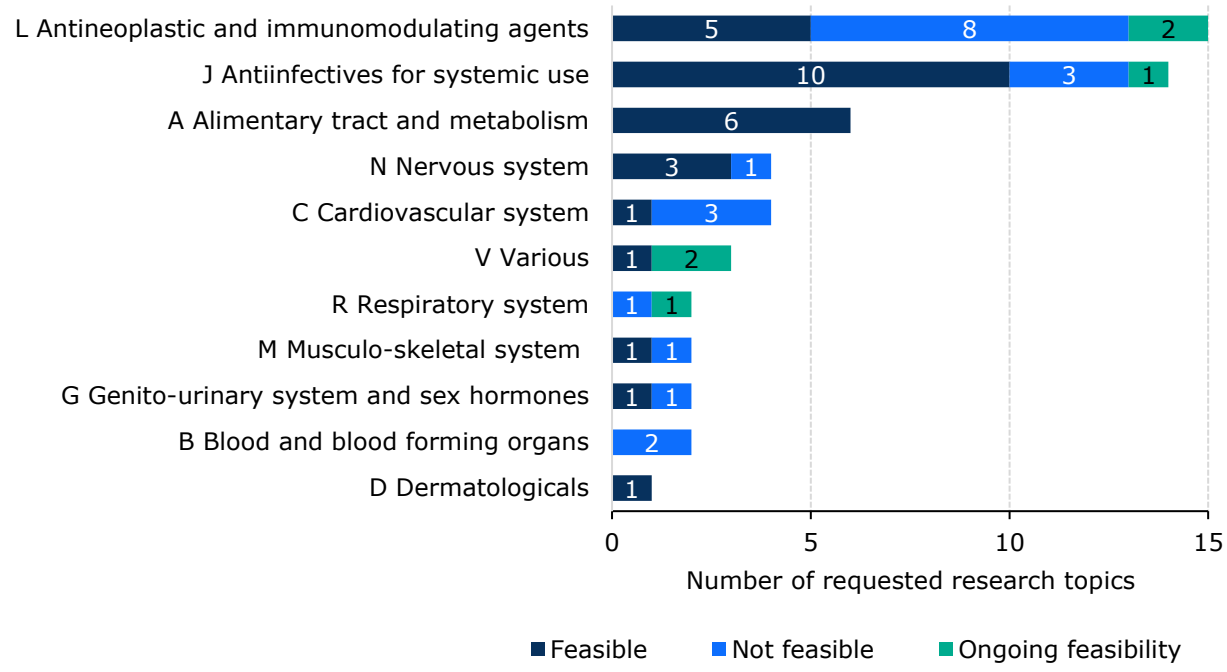

Figure 10. New research topics by Anatomical Therapeutic Chemical (ATC) classification (n=55).

Note: The ATC main group was assigned to each research topic based on the medicinal product under evaluation which triggered the research question. Missing data include research topics for which the medicine has not yet been classified in the ATC system and research topics which comprises several medicinal products.

Reasons for lack of feasibility. The most common reason for lack of study feasibility was that the outcome of interest (condition or adverse event) was not adequately captured in the available databases (11/21, 52%) (Figure 11). This included rare outcomes or outcomes not recorded at primary or even secondary care level and for which a suitable specialized data source was not available. This reason (outcome not being adequately captured in the databases) was the only reason for lack of feasibility of studies aiming to evaluate the design and feasibility of future MAH/applicant studies, which often concerned rare diseases.

Another frequent reason was the medicinal product (class) of interest was not prescribed in the database setting or not authorised/not used in the respective countries (4/21, 19%). Other reasons included the lack of granularity in the information contained in the databases (e.g., specific outcomes that are poorly captured by the coding system, or insufficient information on prescribing, dose, duration, and indication of medicines) (2/21, 10%), and timelines being too short to conduct the study (1/21, 5%).

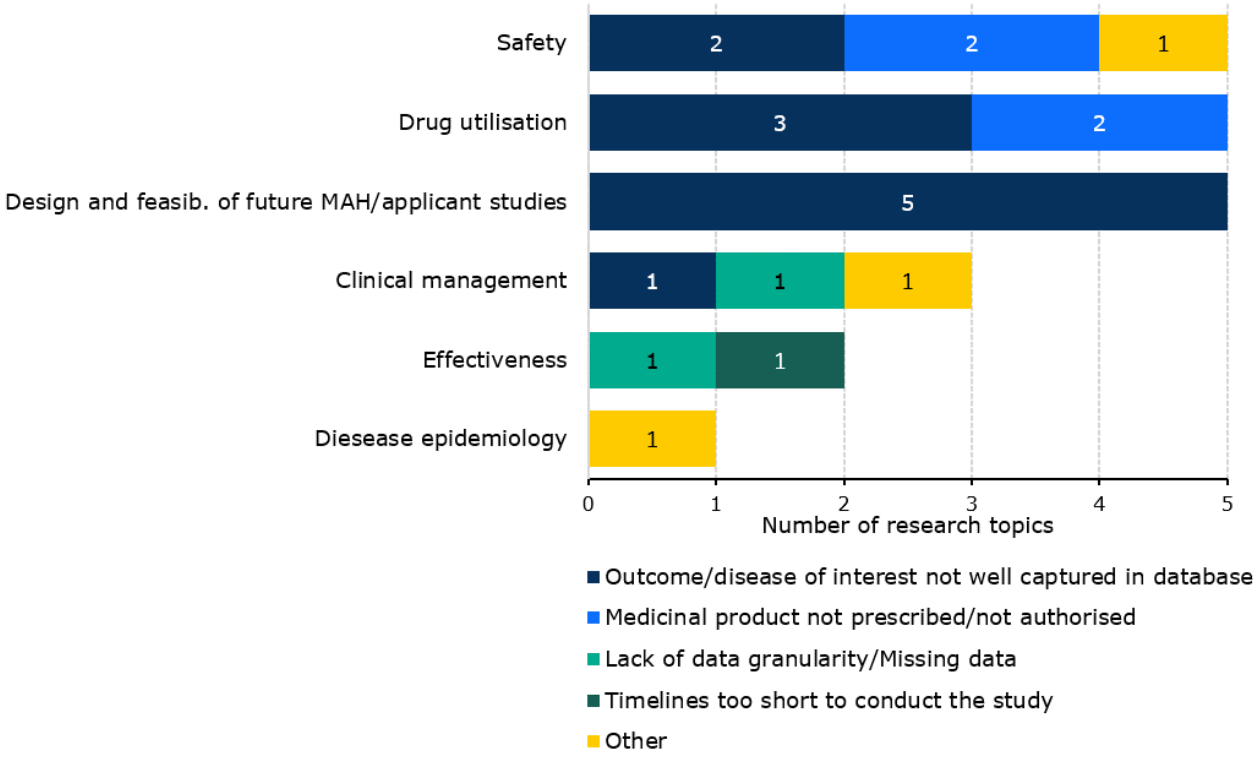

Figure 11. Reason for lack of study feasibility by use case (n=21)

Notes: Outcome/disease of interest not well captured includes cases due to the intrinsic rarity of the event or due to characteristics of the database, e.g., not captured in the type of setting covered by the database. Medicinal products not prescribed/authorised refers to medicinal products (class) that are not prescribed in the database setting or not authorised or not used in the respective countries. Lack of granularity refers to outcomes poorly captured by the coding system, or insufficient information on prescribing, dose, duration, and indication.

Conduct and timelines of RWD studies. To inform the performance of the RWD study process, we calculated the mean and median time from receipt of a research request to study completion (Table 1) by RWE generation pathway. For this specific analysis, we considered all 22 studies that were completed during the reporting period on any pathway.

The median number of calendar months required for conducting a study (from receipt of the research request to delivering a final report) was 8.0 for studies conducted via DARWIN EU, 3.2 for studies conducted via the in-house pathway and 25.0 for studies performed by research organisations that are part of the Agency's framework contract. Notably, for all three pathways, study duration varied a lot across individual studies, which is most notable for FWC studies with a range from approximately 10 months to 3.6 years.

The median number of calendar days from receipt of a research request to the feasibility assessment report was 31 calendar days (IQR: 16-56 days) for topics processed via DARWIN EU, and 9 calendar days (IQR: 0-28 days) for the in-house pathway[6].

[6] For FWC studies, there is no formal feasibility assessment.

An important determinant of study duration is the type of data access (direct access in-house, federated network in DARWIN EU, or third-party subcontracting for FWC) including the need for ethical approval from the data partner and the complexity of the study itself.

In DARWIN EU, an agreement was reached with some data partners to expedite data access approval if the studies to be conducted were aligned with previously submitted blanket protocols. There are still data partners for which ethical and/or scientifical approval for data access takes a longer time.

Other factors that impact the duration include:

- Studies conducted via the FWC pathway tend to consist of multiple research questions and may require exploratory work to set up a functional network and verify data quality, e.g. when accessing new data sources. This route also requires adherence to the Agency's procurement procedure (mandatory steps for re-opening of the competition), with awarding of the contract and monitoring of the contract deliverables that are quite time consuming.
- Specifically for DARWIN EU, it should be noted that in year 2 of its establishment, work on the analytical pipelines and related processes was still ongoing and other works to ease the study process were just initiated, e.g. on phenotypes. Yet, a lot of progress has been made in these and other regards, and this is further described in a dedicated section on DARWIN EU as part of the executive summary (see above).
- The vast majority of research topics identified during the reporting period was not linked to a specific (upcoming) regulatory procedure and in agreement with the requesters, who would eventually receive the study results, study timelines were agreed in a flexible manner, taking into account, amongst other aspects, available resources and capacity for conducting the studies across the year.

To better distinguish between factors influencing the study duration, future reviews should take into account the complexity of the studies, whether or not the study is conducted with a set deadline and duration should be reported per study phase, e.g. time from study request to completion of the feasibility assessment, time from study initiation to study protocol, time from study protocol to study report.

Table 1. Mean, median and interquartile range of time (calendar months) from receipt of a research request to study completion by RWE generation pathway (N=22)

Pathway	N[(i)]	Mean	Median	Min-max
DARWIN EU studies	9	9.4	8.0	5.9 – 17.7
In-house studies	4	3.3	3.2	1.8 – 4.9
FWC	9	22.7	25.0	9.9 – 43.0

(i) 3 DARWIN EU, 1 in-house and 9 FWC studies were completed during the reporting period (07/02/2023 to 06/02/2024) but requested before 07/02/2023.

Study complexity. Only studies in DARWIN EU are currently characterised in terms of complexity (Table 2) and this is driven mainly by the existence of DARWIN EU standardized analytics to answer a research question.

Table 2. Categories of studies according to DARWIN EU criteria

Category of observational analyses and studies	Description
Off-the-shelf studies	Studies for which a generic protocol is adapted to a research question • Estimate the prevalence, incidence or characteristics of exposures • Health outcomes • Describe population characteristics
Routine repeated analyses	Routine analyses based on a generic study protocol • Periodical estimation of drug utilisation • Safety monitoring of a medicinal product • Estimation of the incidence of a series of adverse events
Complex Studies	Studies requiring development or customisation of specific study designs, protocols and Statistical Analysis Plans (SAPs), with extensive collection or extraction of data • Etiological study measuring the strength and determinants of an association between an exposure and the occurrence of a health outcome considering sources of bias, potential confounding factors and effect modifiers
Very Complex Studies	Studies which cannot rely only on electronic health care databases, or which would require complex methodological work • Studies where it may be necessary to combine a diagnosis code with other data such as results of laboratory investigations, or studies requiring additional data collection

Bespoke studies are considered more complex not only for operational but also for scientific reasons. Most of the feasible studies in DARWIN EU during the reporting period were either off-the-shelf (OTS, 15/19) or complex (4/19) studies as per agreed classification above. To have routine repeated studies, first OTS or complex studies need to have been completed. None of the year 1 studies were yet repeated e.g. either with more recent data or additional data sources. Finally, no 'very complex' studies were planned per contract during the establishment phase of DARWIN EU.

In future reports, studies conducted via the other two RWE generation pathways would benefit to also be characterised in term of complexity, in analogy to the DARWIN EU categories, for better time and resource planning.

Usefulness of RWE generation. Finally, to better understand the usefulness of the study results, we reached out to the respective recipients (decision-makers) enquiring about the impact of the study results and whether they were helpful and taken into account for the decision making. Feedback was either received in writing or in response to a survey. Information on whether the study was reflected in the respective assessment report was also sought.

Overall, responses were received for 15 of the 22 completed studies. The findings are summarised below:

- The majority of the responders (10/15, 67%) confirmed that the study results were useful for their (future) assessment. Where an assessment report was available, the study results (either extracts or the full study report) were included.

  This included four cases where the study was not immediately linked to a regulatory procedure: (i) HTA/payer pilot study evaluating multiple myeloma patients' characterisation, treatments, and survival, (ii) study on treatment patterns of drugs used in adult and paediatric population with systemic lupus erythematosus conducted, (iii) study on the natural history of disease and treatment patterns of spinal muscular atrophy, and (iv) study on the use of erythromycin use as a prokinetic agent.

  The remaining 6 cases were linked to signals (3), MAAs (2) and a PIP (1). Of these, five were considered supportive for the assessment, exploring (i) the risk of pemphigus and pemphigoid with the use of COVID-19 vaccines, (ii) co-prescribing of endothelin receptor antagonists (ERAs) and phosphodiesterate-5 inhibitors (PDE-5is) in pulmonary arterial hypertension (PAH), (iii) confounding factors for thyroid cancer in users of GLP-1 receptor agonists, (iv) prevalence of juvenile

dermatomyositis and polymyositis in paediatric patients, and (v) risk of suicidal ideation in users of GLP-1 receptor agonists. This last study (on the association of GLP-1 receptor agonists and the risk of suicidal ideation in patients with type II diabetes mellitus) even featured in the PRAC meeting highlights, April 2024. Finally, one study was considered to have provided substantial added value, as it informed on the effectiveness and safety of the MVA-BN mpox vaccine and was included in the risk management plan of the product. While mpox cases continue to be reported, this EMA-funded research continues to generate critical RWE to inform potential further needs for regulatory and public health decision-making in public health emergency situations.

- Four studies were not used for decision making. In one case, the study was not considered to provide critical information needed for the decision, albeit being informative (drug utilisation study of prescription opioids). Another study was conducted to support a signal assessment. The report was included in the report but there was already sufficient evidence supporting a causal relationship and in view of the limitations of the study, it had no impact on the decision (incidence of phimosis and acquired phimosis in patients treated with dapagliflozin). A third study included very limited number of patients receiving the medicine of interest in a particular setting not well captured in primary care databases and therefore no reliable conclusion could be drawn (prevalence of use of take-home naloxone use for opioid overdose treatment). The experience with this study was used to further fine-tune and optimise the feasibility assessment process in DARWIN EU. Finally, a study exploring the exposure and use patterns of alternatives to ranitidine-containing medicines was conducted after the decision to suspend ranitidine containing medicinal products. The results of the study showed a switching pattern that was already known and hence the study did not provide additional relevant information.
- Finally, one study (characterisation of patients with chronic hepatitis B and C) was not linked to any immediate regulatory decision as it was requested by ECDC and consequently any impact was considered 'not applicable'.

It is also worth mentioning that amongst the studies deemed unfeasible via DARWIN EU or in-house pathways, there was one case each concerning rare paediatric conditions for which only limited data were available and it was decided not to pursue the respective studies. However, the initial counts from the feasibility assessments were considered informative by themselves as they provided an orientation on the frequency of the respective conditions and thus on the feasibility of clinical trials in the respective (paediatric) target populations.

Further information on selected use cases can be found in Annex 2.

Annex 1: List of EMA RWD study requests

This Annex is available in the Use of real-world evidence section (Report with regulator-led studies using real-world data) on the EMA's Real-world evidence webpage.

Annex 2: Portfolio of use cases

This portfolio lists illustrative examples of RWD studies conducted against the various use case categories during the period covered by this report.

The full portfolio with all use cases identified so far is available here.

PRAC – in-house – Association between exposure to GLP-1 receptor agonists and risk of suicide-related and self-harm-related events (EUPAS1000000052)	
Problem statement	A safety signal concerning a potentially increased risk of suicidal ideation and self-injurious ideation associated with the use of GLP-1 receptor agonists (GLP-1a) semaglutide and liraglutide was raised by the Icelandic Medicines Agency after the review of 3 individual case reports. Liraglutide and semaglutide are both authorized for controlling type-2 diabetes mellitus (T2DM) as well as for weight management in obese individuals, while other GLP-1a are only recommended for T2DM. Both T2DM and obesity are potential risk factors for depression and suicidality. The biological mechanism by which GLP-1a could modify the risk of self-harming/suicidal ideation is not clear. The PRAC requested MAHs to review available evidence for all members of the GLP-1a class. In parallel, the EMA conducted an observational new-user, active comparator cohort study to estimate the causal association between GLP-1a and the risk of self-harming and suicidal ideation in T2DM.
Research question	To compare the incidence of self-harming and suicidal ideation between a cohort of T2DM patients who initiated GLP-1a and a cohort of T2DM patients who initiated SGLT-2 inhibitors (SGLT-2i) without having used any drug from these classes previously.
Findings	The study used data from IQVIA™ Medical Research Data (IMRD) UK. The unadjusted analysis showed a ~60% higher incidence rate of self-harming /suicidal ideation among diabetic GLP-1a initiators compared to SGLT-2i initiators in both intention-to-treat analysis (where patients in both cohorts were followed regardless of discontinuing or switching the baseline treatment) and on-treatment analysis (where patients were censored at baseline treatment discontinuation or switch to the comparator treatment). The difference could be explained by a higher incidence of obesity and psychiatric disease history (including depression) among GLP-1a initiators, since after adjusting for baseline differences between treatment cohorts, the contrast dropped very close to the null (hazard ratio ~1.1, with a lower 95% confidence limit ~0.8). Several sensitivity analyses, where the definition for treatment discontinuation was changed and adjustment for post-baseline selection bias was applied, were consistent with the main analysis.
How was this useful?	The EMA study results were included in the signal assessment report and were mostly in line with other findings presented in the report. The conclusion of the report was that the combined evidence does not support an increased risk of self-harming/suicidal ideation associated with GLP-1a treatment and no update to the product information is warranted. See also PRAC meeting highlights, April 2024.

CHMP – DARWIN EU – Co-prescribing of endothelin receptor antagonists (ERAs) and phosphodiesterate-5 inhibitors (PDE-5is) in pulmonary arterial hypertension (PAH) (EUPAS106052)	
Problem statement	An application was submitted for a new marketing authorisation for a fixed-drug combination treatment of two therapies for pulmonary arterial hypertension (PAH). The applicant initially proposed a comparative effectiveness study based on their own registry datasets, but this was abandoned for technical reasons. However, the Rapporteur's team considered useful to try to perform a study in the DARWIN EU network. The objective was to describe the actual use of mono- and combined therapies in patients with PAH, specifically for combination of interest and also for the respective classes: endothelin receptor antagonists (ERAs) and phosphodiesterase-5 inhibitors (PDE-5Is).

	The final aim was to establish if a comparative effectiveness study could be done using DARWIN EU.
Research question	The purpose of the study was to estimate the proportion of PAH patients initiating treatment with ERAs or PDE-5Is (as monotherapy or in combination), duration of prescription and sequences of treatments and the proportion of treated patients experiencing specific outcomes(cardiovascular hospitalisation, all-cause hospitalisation, and death) after initiating treatment with ERAs and PDE-5Is.
Findings	A study was performed in 4 countries (Estonia, France, Germany and UK). 9,474 patients with incident PAH were characterised by age, sex, symptoms, comorbidity, co-prescribed medications and use of PDE-5is and ERAs. Monotherapy was most frequent therapy (either PDE-5is or ERAs) but there was some use of the combination of other ERAs (mostly bosentan) and PDE-5Is (mostly tadalafil) was identified. The specific combination of drugs of interest was not used/prescribed in the databases.
How was this useful?	The results of the study were included in the clinical efficacy section of the assessment report as supportive evidence to complement evidence provided by the MAH and from the literature.

HTA/Payers – DARWIN EU – Multiple myeloma: patient characterisation, treatments and survival in the period 2012-2022 (EUPAS105033)	
Problem statement	The rarity of multiple myeloma makes it challenging to have a clear picture across Europe of the characteristics of these patients at the time of diagnosis, the different therapies they receive in subsequent lines and their overall survival. The goal of this study was to inform these aspects, which are important from the point of view of HTA bodies and payers to provide context and help understand how new medicines may add value for patients.
Research question	This specific study aimed at describing demographic and clinical characteristics of multiple myeloma (MM) patients at the time of diagnosis, as well as therapies to treat MM (including combinations and sequences) and overall survival.
Findings	The study identified more than 30,000 newly diagnosed patients of MM in six databases from five different European countries (Estonia, France, Germany, The Netherlands and Spain). While the results varied across data sources, general findings included: *Characterisation at the time of diagnosis:* The median age was around 70 years, with approximately half of the patients being female. The most frequent co-morbidities were hypertension, renal impairment, and hyperlipidemia. In younger age groups, the most common ones were anxiety, depression and asthma. The most frequently used co-medications were medicines for acid related disorders, agents acting on the renin-angiotensin system, and lipid modifying agents. *Treatments received within one year of diagnosis:* More than 50% of patients received glucocorticoids, with dexamethasone and prednisone being the most prescribed. Other therapies included (in decreasing order of usage): proteasome inhibitors, chemotherapies, immunomodulatory imide drugs and monoclonal antibodies. *Survival:* Results were quite heterogenous, with 5-year survival rates ranging from 49% to 78% across different data sources.
How was this useful?	This is the first of two use cases for HTA bodies/ payers piloting use of RWE generated via DARWIN EU. The feedback received was positive, especially regarding the speed of study execution and large amount of useful data for a rare disease, allowing to better understand what data is available and which questions can be studied via the network. It also confirmed that some information may still need to be derived from RCTs.

PRAC – In-house – Incidence rates of pemphigus and pemphigoid following COVID-19 vaccines (EUPAS50715)	
Problem statement	During routine signal detection activities, cases of pemphigus and pemphigoid in close temporal association to the Comirnaty, Spikevax and Vaxzevria vaccinations were identified in EudraVigilance and the scientific literature. To

	support assessment of this signal, an in-house study was proposed to generate estimates on incidence rates for pemphigus and pemphigoid in the general and vaccine-exposed population across those electronic health record databases available within the Agency with data on COVID-19 vaccines.
Research question	This study aimed to describe: 1. Comirnaty, Spikevax and Vaxzevria vaccine exposure: overall and stratified by sex, age, and year; 2. Incidence rates of new onset pemphigus or pemphigoid in the general population: overall and stratified by sex, age, and year; 3. Incidence rates of new onset pemphigus or pemphigoid following exposure to Comirnaty, Spikevax or Vaxzevria vaccines stratified by number of doses. In an exploratory analysis, a Self-controlled Case Series (SCCS) design was used to investigate whether there is an association between exposure to COVID-19 Vaccines and pemphigus/pemphigoid.
Findings	Description of the vaccine coverage in Spain and the UK was in line with expectation. Differences in the post-vaccination standardised incidence rate for pemphigoid or pemphigus were observed in the UK but not Spain when compared to a historic background population for Comirnaty and Vaxzevria vaccines. An association between exposure to Comirnaty and increased relative incidence of pemphigoid or pemphigus was observed in just one sensitivity analysis. Similar associations were found for Spikevax in Spain and for Vaxzevria, but all results had wide confidence intervals.
How was this useful?	When considering the totality of the available evidence, the Rapporteurs concluded that that there was insufficient evidence to establish a causal association for all three vaccines. However, it was decided that further monitoring was warranted with ongoing reviews for all new emerging data on pemphigus and pemphigoid after all three COVID-19 vaccines. The in-house study offered supportive evidence that was highly appreciated.

ECDC/ETF – FWC – Association between COVID-19 vaccines and paediatric safety outcomes in children and adolescents aged 5-19 years in the Nordic countries (EUPAS48979)	
Problem statement	Following safety concerns about myocarditis and pericarditis with Comirnaty and Spikevax vaccines, PRAC concluded in July 2021 that these events can very rarely occur and recommended listing them in the Product Information (PI) of the two vaccines. Concerns regarding the risk of vaccine-associated thromboembolic events in adults were raised in relation to Vaxzevria and Jcovden: in April 2021, PRAC concluded that a causal relationship between both vaccines and thrombosis in combination with thrombocytopenia (TTS) was at least a reasonable possibility, resulting in the update of the PI. This study was initiated to better characterise the risk of these outcomes in children and adolescents, both after vaccination and after COVID-19 infection.
Research question	The purpose of the study was to assess the association between COVID-19 vaccines and paediatric safety outcomes in children/adolescents in the Nordic countries: myocarditis/pericarditis; thromboembolic and thrombocytopenic outcomes; autoimmune hepatitis, juvenile rheumatoid arthritis and Guillain-Barré syndrome juvenile rheumatoid arthritis, multiple sclerosis and type 1 diabetes.
Findings	The study included 5,098,625 subjects aged from 5 to 19 years from Denmark, Finland, Norway and Sweden between Jan 2021-Oct 2022. Myocarditis, pericarditis, and thromboembolic events were rare after vaccination with Comirnaty. An association between Comirnaty and myocarditis was observed in the 28-day main risk period after 1 dose (RR 2.75, 95% CI, 1.92-3.95), 2 doses (RR 2.81, 95% CI, 1.94-4.07), and 3 doses (RR 5.30, 95% CI, 2.24-12.53) in contemporary cohort analyses. An association with pericarditis was observed in the 28-day main risk period after 2 doses (RR 2.58, 95% CI, 1.44-4.63) and 3 doses (RR 6.24, 95% CI, 0.81-47.85). There was no robust association with new onset of autoimmune hepatitis, Guillain-Barré syndrome, or type 1 diabetes, as well as with flares of juvenile rheumatoid arthritis, multiple sclerosis and type 1 diabetes.

ECDC/ETF – FWC – Association between COVID-19 vaccines and paediatric safety outcomes in children and adolescents aged 5-19 years in the Nordic countries (EUPAS48979)	
How was this useful?	The study generated reassuring evidence on the safety of COVID-19 vaccination in children and adolescents, in which serious adverse events were very rare, and provided important methodological considerations to support the planning of future safety studies with immune-mediated outcomes and the evaluation of the evidence from such studies.

ECDC/ETF – FWC – Effectiveness of heterologous and booster COVID-19 vaccination in 5 European countries, in children and adults (EUPAS47725)	
Problem statement	At the time of this study, evidence from studies on heterologous vaccination suggested that the combination of mRNA and viral vector vaccines produces acceptable levels of SARS-CoV-2 antibodies and a higher T-cell response, compared to homologous vaccination. However, the use of two different mRNA vaccines was less well studied. Therefore, additional real-world evidence was needed on the effectiveness of heterologous vaccination in large populations.
Research question	What is the comparative VE of completed heterologous primary schedule of COVID-19 vaccination in preventing severe COVID-19 in the general adult population, compared to a completed homologous primary schedule? This study also includes other populations (adolescents), other comparisons (e.g., completed heterologous primary schedule vs. no vaccination; completed homologous primary schedule vs. no vaccination; completed primary schedule plus booster vs. completed primary schedule only), other outcomes (COVID-19 related death, non-severe COVID-19) and other time periods (to explore waning of effectiveness over time).
Findings	The study used data sources from Italy, Spain, the Netherlands and the United Kingdom. For the main research question, only Spanish data sources could be used. No difference was found between homologous and heterologous primary regimen regarding their effectiveness in preventing severe COVID-19 in the adult population. The confidence interval included 0 in both data sources (comparative VE in BIFAP was 9% (95%CI -137; +65) and 40% in SIDIAP (95%CI -102; +82)). Results of the other analyses (other populations, other comparisons, other outcomes, and waning) can be found in the report.
How was this useful?	The results of this study supported the effectiveness of mixing different vaccine brands in the primary schedule and contributed to the overall published body of evidence on the effectiveness of COVID-19 vaccination.

ECDC/ETF, PRAC, PDCO – FWC – Safety monitoring of COVID-19 vaccines in European countries (*Covid-Vaccine-Monitor - CVM*) (EUPAS39798, EUPAS42504, EUPAS42467)	
Problem statement	Large scale COVID-19 vaccination campaigns started to be rolled out across Europe in January 2021, triggering the need for comprehensive safety monitoring to complement routine pharmacovigilance activities and non-interventional studies conducted by Member States and vaccine manufacturers, as well as the need for readiness to address emerging safety concerns. This led EMA to support a large, 2-year COVID-19 vaccine safety research programme embedding: prospective and retrospective evidence generation; a framework for the assessment of safety signals including data sources across Europe; and methodological research.
Research questions	1) Cohort-event monitoring to generate incidence rates of solicited and unsolicited suspected adverse drug reactions (ADRs) reported by vaccinated persons through active prospective surveillance in general population and special populations (pregnant/lactating persons, children/adolescents, immunocompromised, people with history of allergy, people with prior SARS-CoV-2 infection) 2) Secondary use of EHR data from 9 data sources in 5 countries were used to evaluate the following issues:

ECDC/ETF, PRAC, PDCO – FWC – Safety monitoring of COVID-19 vaccines in European countries (*Covid-Vaccine-Monitor - CVM*) (EUPAS39798, EUPAS42504, EUPAS42467)	
	• Incidence of multi-inflammatory syndrome (MIS) pre/post COVID-19 vaccination in children • Association between COVID-19 vaccines and myocarditis/pericarditis (to contribute to signal evaluation/PRAC). • Incidence of COVID-19 disease by severity and vaccine uptake in paediatric populations (to support PDCO assessment of PIPs for therapeutic products for paediatric patients with COVID-19 symptomatic infections)
Findings	1) Cohort-event monitoring (primary data collection) Results provided safety evidence after primary and 1st booster vaccination, combining self-reported data from 642,632 vaccinees in 13 countries The proportion of reported serious ADRs and AESIs was low (<0.9%) across the different cohorts and vaccine brands. Solicited ADRs were common (reported in >50% of the population), especially injection site reactions. Results were in line with data from clinical development and confirmed the overall safety profile of the vaccines. 2) Secondary use of data a. The multisystem inflammatory syndrome(MIS) analyses included 650,731 children aged 0-17 years. For data sources lacking MIS information, Kawasaki disease (KD) codes were used. KD and MIS were both very rare, and no post-vaccination cases were observed in the study period Jan 2020-Oct 2021 (where only few children were vaccinated). KD incidence increased >10-fold after COVID-19 diagnosis. Results updated in 2023 confirmed the very rare incidence of MIS. It is recommended to combine KD and MIS codes due to the challenges of estimating MIS incidence with specific codes. b. Myocarditis/pericarditis: >35 million individuals were included (57,4% received at least one COVID-19 vaccine dose). Baseline incidence of myocarditis was low. Myocarditis incidence rate ratios(IRR) were elevated after vaccination in those aged <30 years, after both Pfizer vaccine doses (IRR = 3·3, 95%CI 1·2-9.4; 7·8, 95%CI 2·6-23·5, respectively) and Moderna vaccine dose 2 (IRR = 6·1, 95%CI 1·1-33·5). An effect of AstraZeneca vaccine dose 2 could not be excluded (IRR = 2·42, 95%CI 0·96-6·07). Pericarditis was not associated with vaccination in this analysis. c. COVID-19 in children/adolescents: the study population comprised 4,447,460 including 368,706 at-risk with comorbidities that increase the risk of COVID-19 severe illness. Incidence of non-severe COVID-19 was highest during Omicron in Dec. 2021/Jan. 2022 (27-143 cases/100 PY). In subjects without risk factors, incidence rates varied between 70-240 cases/100 PY and dropped substantially (0-1/100 PY) for severe COVID-19 (hospitalisation, intensive care unit admission, and death after COVID-19). Severe COVID-19 accounted for <1.5% of cases overall. Understanding of COVID-19 severity in this population may contribute to Paediatric Investigation Plans for COVID-19-related or other therapeutic products in at-risk children.
How was this useful?	The project demonstrated that large EU collaborations for vaccine safety monitoring at EU level are feasible. The cohort event monitoring study allows to obtain near real-time evidence directly from vaccinated subjects, which plays an important role during public health emergencies. The *ad hoc* studies using EHR data confirmed findings from independent research, including additional evidence such as on the role of COVID-19 infection for MIS and peri/myocarditis. Lessons learnt will support future pandemic preparedness and may also inform safety monitoring outside of public health emergencies

ETF/ECDC – FWC – Effectiveness and safety of MVA-BN vaccination against mpox in at-risk individuals in the United States (USMVAc) (EUPAS104386)	
Problem statement	After the 2022 mpox outbreak was declared a public health emergency by WHO in July 2022, the indication of the 3rd generation smallpox vaccine MVA-BN (Imvanex) was extended to the prevention of mpox in adults, based on limited clinical experience and evidence primarily derived from non-clinical data. Therefore, there was a need for effectiveness and safety data to support public health and regulatory decision-making. The USMVAc study was initiated in the US where the vaccine had large uptake (Jynneos, authorised for emergency use in August 2022).
Research question	To assess the effectiveness and safety of the MVA-BN vaccine against mpox among men-who-have-sex-with-men (MSM) and transgender women (the populations most affected by mpox) through secondary use of data aggregated from HealthVerity's administrative healthcare data between 1 April 2021 and 31 December 2022.
Findings	Fully vaccinated subjects (2 doses ≥28 days apart) were initially matched with five unvaccinated subjects on calendar date, age, US region, and insurance type using coarsened exact matching to assign an index date in the unvaccinated group. Subjects were followed from index date (14 days after the second dose) until death or data end to ascertain mpox occurrence. After propensity score adjustment, vaccine effectiveness against mpox disease was 89% (95% CI: 12%, 99%) among those fully vaccinated; 64% (95% CI: 40%, 78%) for any dose; and 70% (95% CI: 44%, 84%) for a single dose. No safety events were observed (in either vaccinated or unvaccinated comparator group) using the primary risk window of 14 days. One pericarditis adverse event was observed when the risk window was extended to 28 days. Results were consistent with existing US evidence, suggesting that completing the 2-dose schedule is associated with a reduced risk of mpox disease in MSM and transgender women.
How was this useful?	This study provided evidence to complement SEMVAc study and its additional analyses using retrospective target trial emulation (TEMVAc) once available. This combined approach is aimed at increasing the robustness of evidence generation, to ultimately contribute to the totality of evidence supporting the favourable benefit/risk profile of the MVA-BN vaccine, and support readiness in case of future mpox outbreaks.

CAT – FWC – Spinal muscular atrophy (SMA): natural history of disease and treatment patterns (EUPAS50476)	
Problem statement	The natural course of SMA, diagnostic criteria and standard of care are expected to have evolved significantly since the approval of disease modifying therapies (DMTs). Recent studies have reported disease trajectories that significantly differ from the known natural history of SMA. An update on natural history of SMA would help regulators with the assessment of new therapies in this area.
Research question	The study aimed to investigate SMA patients' course of disease and standards of care delivery over time in multiple European countries including the newly available disease-modifying therapies in real-world settings. The study used patient registry data from six SMA registries.
Findings	Among the 2,188 patients with SMA across all registries overall, the greatest number of patients were identified from the Germany and Austria registry (31.8%), and the lowest from Sweden (8.0%). The breakdown for the other registries was 18.0% in the UK and Ireland, 15.9% in Czech Republic, 14.6% in Spain and 11.7% in Belgium. Among the 2,188 patients, 1,321 were classified as treated, 847 were never treated. Overall, SMA type 1 represented 19.7% of patients, SMA type 2, 41.8% and SMA type 3, 35.6% of patients. There was an almost equal split between male (51.6%) and female (48.4%) patients in the overall SMA population. Registry time coverage varied with Germany, Austria registry, and UK and Ireland registries covering 15 years (2008 to 2023) while Belgium covering only 4 years (2018 to 2021). The observed duration of follow-up ranged from 42 months (in Czech Republic and Slovakia) to 104.5 months (Sweden). 1321 (61.3%) patients have been treated with at least one DMT. Among treated group, 75.9% treated

CAT – FWC – Spinal muscular atrophy (SMA): natural history of disease and treatment patterns (EUPAS50476)	
	at least once with Spinraza. Overall, 29.7% of patients were lost to follow-up; 55.9% being among never treated patients.
How was this useful?	Use of multiple registries in rare diseases provided complementary information and allowed analysis of an unprecedented number of SMA patients. The study showed a treatment uptake over time. Once the data were analysed, the extent of missing data was important for many variables and was notable among never treated patients. In never treated patients, it may suggest a less regular and accurate follow up and/or an under report of data in such patients, alongside the fact that 55.9% of those untreated were lost to follow-up. Improving the data accuracy and quality, reducing the missingness, identifying essential variables that are mandatory - e.g. registry entry date, diagnosis date, presymptomatic and others - could help greatly answering key questions for the SMA community and regulatory decision making. These different elements plead for a common dictionary for SMA Registries across Europe with Regulators.

PDCO – DARWIN EU – Treatment patterns of drugs used in adult and paediatric population with systemic lupus erythematosus (SLE) (EUPAS106436)	
Problem statement	PDCO noted that there are several products targeted to treat paediatric lupus in the pipeline and the conduct of clinical trials in the paediatric population is hampered by competitive recruitment. As an example, belimumab was recently authorised for treatment of SLE above 5 years but it is not yet clear what the uptake is in clinical practice. Besides it would be important to understand the overall current treatment patterns in paediatric SLE and how it differs from adults.
Research question	The study aimed to describe demographic and clinical characteristics of patients with SLE and also the treatment patterns after diagnosis, both in paediatric and adult population.
Findings	We included between 699 and 5,964 patients for the new diagnosis cohort, out of which between 13 and 255 paediatric patients. In the paediatric SLE cohort, 66% to 83% were female, with median age of 12 to 16 years. The most common comorbidities were asthma (6-15%), pneumonia (10-13%), anxiety (8-13%), and other autoimmune disease (3-16%). The most common medications prescribed in the year before SLE diagnosis were anti-inflammatory/anti-rheumatic products (35-38%) and systemic antibacterials (25-45%). In the adult SLE cohort, 80% to 88% were female, with median age of 49 to 54 years. The most common comorbidities were other autoimmune disease (9-35%), hypertension (15-27%), anxiety/depressive disorder (6-27%). The most common medications prescribed in the year before SLE diagnosis were anti-inflammatory/anti-rheumatic products (13-57%) and systemic antibacterials (8-53%). Among the paediatric cohort, the most frequent treatments within the first year of diagnosis were hydroxychloroquine (9-62%), glucocorticoids (12-62%), and mycophenolate mofetil (5-46%) across all databases. Among the adult cohort, the most frequent treatments within the first year of diagnosis were hydroxychloroquine (13-49%) and glucocorticoids (18-42%). In paediatric patients using hydroxychloroquine, median duration was 8 to 501 days, median initial daily dose ranged from 199 to 300 mg, median cumulative dose ranged from 20,000 to 116,600 mg. For prednisone/prednisolone, median duration was 13 to 246 days, median initial daily dose ranged from 10 to 60 mg. In adult patients using hydroxychloroquine, median duration was 4 to 485 days, median initial daily dose ranged from 13 to 400 mg, median cumulative dose ranged from 600 to 130,051 mg. For prednisone/prednisolone, median duration was 4 to 111 days, median initial daily dose ranged from 2 to 40 mg.

PDCO – DARWIN EU – Treatment patterns of drugs used in adult and paediatric population with systemic lupus erythematosus (SLE) (EUPAS106436)	
How was this useful?	The study confirmed that the characteristics of SLE patients in both paediatric and adult cohort were similar with respect to majority being female, and frequently used medications. As expected, the most frequent treatments were hydroxychloroquine and glucocorticoids in both groups, with a higher proportion of these treatments being used in paediatric patients, as adults were treated with a wider range of treatments such as methotrexate. The low number of paediatric patients with SLE and especially hospitalised patients with SLE precluded full details on treatment patterns and we had only limited insight into belimumab and rituximab use.

PDCO – DARWIN EU – Natural history of dermatomyositis (DM) and polymyositis (PM) in adults and paediatric populations (EUPAS107454)	
Problem statement	As part of paediatric investigation plans (PIP), the PDCO often needs to evaluate paediatric extrapolation plans. These plans outline the objectives, methodological approaches, and planned analysis of existing or to be generated data to inform decision-making on similarity of disease and response to treatment between paediatric and reference adult populations. The role of RWD to potentially generate additional evidence that informs and might help reduce uncertainty around the extrapolation framework is not well known. A study on the epidemiology, diagnostic criteria as well as drug utilisation in dermatomyositis and polymyositis and their juvenile forms was considered useful to help address that knowledge gap.
Research question	The overall objective of this study was to describe and characterise dermatomyositis (DM), polymyositis (PM) and their juvenile forms (JDM and JPM), in terms of prevalence, natural history of the disease, disease severity, and treatment patterns.
Findings	We identified 3,969 DM patients, 2,541 PM patients, 333 JDM patients and 32 JPM patients. Most of the patients for all the conditions were women, around 60-70% in most cases, with a median age of 50-60 years old across data sources for DM and PM. JDM median age of diagnosis across data sources was around 9-13 years old. Period complete prevalence of DM and PM in adults (>18 years old) increased or was stable over time in all databases. Prevalence of DM was slightly higher than PM for all databases and ranged from 7 per 100,000 in one database from Spain to 40 per 100,000 in another database from Estonia at the end of the study. Prevalence for PM at the end of the study ranged from 0.5 per million in the Spanish database to 3 per million in the Estonia database. Looking at juvenile forms, JPM was very rare, with prevalences of less than 0.05 per million children in primary care databases. JDM was slightly more frequent but still with lower incidence than adult forms, with prevalence estimates at the end of the study period ranging from 0.2 per million in a UK database (0.3 per million in a German database) to 1 per million in a French hospital database. Most of these cases of JDM occurred in patients aged 13 to 18. In most databases, biomarkers such as C-reactive Protein (CRP), Erythrocyte sedimentation rate (ESR) and aspartate aminotransferase (AST) showed higher testing in the months before and after diagnosis of DM and PM. Testing of specific auto-antibodies can be seen in hospital databases. As for clinical manifestations, the highest was the occurrence of muscle pain; 14% and 15% for DM and PM, respectively. For JDM and JPM, the number of individuals with clinical manifestations and complications was less than 5. Adult DM and PM showed similar patterns in treatment use. The most used drug class one month before cohort entry were glucocorticoids. Their use increased notably in the 3 months after the index date and decreased afterwards. Use of disease-modifying anti-rheumatic drugs (DMARDS) was low before index but increased in the months following diagnosis and for up to 3 years after. Some

PDCO – DARWIN EU – Natural history of dermatomyositis (DM) and polymyositis (PM) in adults and paediatric populations (EUPAS107454)	
	use of biologics and immunoglobulins was seen in databases with hospital information, especially in the 3 months to 3 years after diagnosis.
How was this useful?	The results of this study helped contextualise several aspects for the discussion and evaluation by the committee. Prevalence estimates for PM and DM were consistent with previous studies. The observed disease manifestations for both diseases (including muscle weakness/pain, dysphagia, and interstitial lung disease) aligned with the latest clinical criteria recognised by European and American guidelines (EULAR/ACR). Testing in contributing databases aligned with diagnostic criteria in these guidelines, including inflammation markers, liver and muscle enzymes, and specific autoantibodies observed only in hospital and biobank datasets. Treatments prescribed in European real-world data for PM/DM aligned with the recent recommendations.

Annex 3: Survey on use of RWD at national level

Survey on the use of real-world data (RWD) by national competent authorities (NCAs) for regulatory decisions

Fields marked with * are mandatory.

Survey on the use of real-world data (RWD) by national competent authorities (NCAs) for regulatory decisions

This survey is distributed amongst the Heads of Medicines Agencies (HMA). It aims at exploring the activities at national level in relation to real world evidence (RWE) generation to support regulatory decisions for medicinal products throughout their lifecycle. The outcome of the survey will be included in the Agency's next **report on the experience with regulatory-led RWD studies** to ensure a balanced representation of the network's capability and capacity. This report will cover the **period from 7 February 2023 to 6 February 2024** (corresponding to year 2 of DARWIN EU®) and will be published on the Agency's Big Data webpage. For your information, please see link to the first EMA review, which was published in June 2023.

We would appreciate your feedback by 7 June 2024.

The completion of the survey should not take more than 3-5 minutes.

Thanks for your participation.

* **Please provide the name of your country**

- ○ Austria
- ○ Belgium
- ○ Bulgaria
- ○ Croatia
- ○ Cyprus
- ○ Czechia
- ○ Denmark
- ○ Estonia
- ○ Finland
- ○ France
- ○ Germany
- ○ Greece
- ○ Hungary
- ○ Iceland
- ○ Ireland
- ○ Italy
- ○ Latvia
- ○ Liechtenstein
- ○ Lithuania
- ○ Luxembourg
- ○ Malta
- ○ Netherlands
- ○ Norway
- ○ Poland
- ○ Portugal
- ○ Romania
- ○ Slovakia
- ○ Slovenia
- ○ Spain
- ○ Sweden

Please provide the name of your Agency (in case there are more than one in your country)

* **1. Do you currently have access to electronic health data for secondary use (research purposes)?**

- ◉ Yes, direct access
- ○ Yes, indirect access (e.g. via external research organisation(s))
- ○ No

If answer is 'Yes', additional question 1.1.

* **1.1. What type of data do you have access to?**

- [ ] Primary care medical records
- [ ] Specialist care records
- [ ] Hospital records
- [ ] Patient registry data
- [ ] Claims data
- [ ] Pharmacy dispensation records
- [ ] Biobank data
- [ ] Other

Please provide the names of the data sources available

* **2. Did you perform*) non-interventional studies at your own (NCA) initiative during the period of interest (from 7 February 2023 to 6 February 2024)?**

- (•) Yes
- ( ) No

If answer is 'Yes', additional questions 2.1, 2.2 and 2.3.

* **2.1. How many studies have you performed during the period of interest (from 7 February 2023 to 6 February 2024)?**

- ( ) 1-2 studies
- ( ) 3-5 studies
- ( ) 6-10 studies
- ( ) More than 10 studies

* **2.2. What is (are) the scope(s) of the studies you have performed during the period of interest (from 7 February 2023 to 6 February 2024)?**

- [ ] Disease epidemiology
- [ ] Understanding the current clinical management
- [ ] Drug utilisation
- [ ] Support to design and feasibility of planned studies
- [ ] Assessment of representativeness and validity of completed studies
- [ ] Safety
- [ ] Effectiveness
- [ ] Impact research (effectiveness of risk minimisation measures)

2.3. Please list up to 3 studies completed during the period from 7 February 2023 to 6 February 2024 to be included in the HMA/EMA report on the national experience with regulatory-led studies.
(Please include link to the study report or to the RWD study catalogue and/or scientific publication)

* **3. What do you consider a priority in order to further enable the use and establish the value of real-world evidence in regulatory decision making?**
Maximum 5 selection(s)

- [ ] Facilitate access to data from more EU countries
- [ ] Build capability in the network for both generating and interpreting RWE
- [ ] Increase the capacity in the network for conducting non-interventional studies
- [ ] Accelerate the generation of RWE, e.g. via DARWIN EU
- [ ] Better linkage between existing data sources
- [ ] Increase data quality and completeness
- [ ] Facilitate the creation of networks of registries for rare diseases
- [ ] Focus on repurposing of medicines
- [ ] Support designs with randomisation and RWD (e.g., pragmatic trials, registry-based trials…)
- [ ] Other (provide answer in free text field)
- [ ] None of the above (please use free text field to expand)

European Medicines Agency

Domenico Scarlattilaan 6
1083 HS Amsterdam
The Netherlands

Telephone +31 (0)88 781 6000
Send a question www.ema.europa.eu/contact

www.ema.europa.eu

Real-world evidence framework to support EU regulatory decision-making:
2nd report on the experience gained with regulator-led studies from February 2023 to February 2024
EMA/180299/2024