HMA
Heads of Medicines Agencies

EMA
EUROPEAN MEDICINES AGENCY

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

Report on the experience gained with regulator-led studies from September 2021 to February 2023

An agency of the European Union

Executive Summary

Overseen by the Big Data Steering Group (BDSG), EMA and the European Medicines Regulatory Network (EMRN) are working to establish a sustainable framework to enable the use and establish the value of real-world evidence (RWE) across different regulatory use cases (Arlett et al., 2022).

While the majority of RWE for regulatory use is generated by pharmaceutical companies, the added value of regulator-led studies has been demonstrated over the last few years by the use of real-world data (RWD) to monitor the safety and effectiveness of COVID-19 medicines. Nevertheless, further work is needed to better integrate RWD/RWE into regulatory decision making alongside the evidence coming from more established sources (notably randomised controlled trials)[1].

In 2021, EMA completed a pilot with the Pharmacovigilance Risk Assessment Committee (PRAC) to test the Agency's ability to conduct rapid analyses in a number of databases containing electronic health records in order to address knowledge gaps arising in the context of PRAC scientific assessments. From September 2021 onwards, the pilot activities were expanded to explore opportunities for generating RWE in order to also support the scientific evaluations of other committees and working parties, including the Paediatric Committee (PDCO), the Committee for Orphan Medicinal Products (COMP), 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).

While these pilot activities are still ongoing in 2023, in line with the BDSG second multiannual work plan (2022-2025) this report takes stock of the experience gained to date in conducting RWD studies[2] aiming at addressing needs of EU regulators as well as external stakeholders including health technology assessment (HTA) bodies and payers' organisations. It focuses on studies conducted in addition to those performed in response to the COVID-19 public health emergency and the Pharmacovigilance impact strategy. All of the three existing pathways available to EMA for RWE generation were considered: (i) 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; (ii) studies conducted via a DARWIN EU® a federated network of data, expertise, and services initiated in February 2022 which has access to a growing list of data partners; and (iii) studies commissioned to one of eight research organisations and consortia via the Agency's research framework contracts.

[1] In line with the European Medicines Regulatory Network (EMRN) strategy to 2025 as well as the Agency's Regulatory Science Strategy to 2025.
[2] This report focuses on studies requested and conducted in the context of the RWE platform pilot activities. Studies conducted in response to the COVID-19 public health emergency and Pharmacovigilance impact studies were not included in the main analyses.

The report covers the time period from the receipt of the first pilot study requests (September 2021) up to the end of year 1 of DARWIN EU® (7 February 2022). During this period, a total of 61 RWD research topics were identified (in addition to research questions related to the COVID-19 public health emergency and the Pharmacovigilance impact strategy). This includes 44 (72%) study requests received from members of EMA's scientific Committees, SAWP, national competent authorities (NCAs), or external stakeholders or EMA functions. The remaining 17 studies (28%) were offered to Rapporteurs and lead member states mostly as a result of proactive screening by EMA of certain new/upcoming regulatory procedures (e.g. signals and referrals).

For more than half (36) of these topics, a study was considered feasible in terms of the availability of relevant data and the timeframe, and, while six study offers from EMA were refused by the Rapporteur/lead-member states as considered to be of limited value, a total of 30 studies proceeded to execution. Most of these studies were descriptive cohort studies and some were comparative with more complex analyses performed. The studies primarily addressed research needs of the PRAC, PDCO, COMP, and SAWP in the context of safety signals, periodic safety update report single assessments, applications for paediatric investigation plans and waivers, (maintenance of) orphan designations as well as scientific advice. There was a broad range of study types including safety studies, drug utilisation studies, disease epidemiology studies, and studies to inform the design and feasibility of clinical trials and clinical management.

By the end of the reporting period, 27 studies had been completed and three were ongoing. Reflecting the status of the three pathways during the review period, most of these studies were conducted via the in-house pathway (24 completed, 1 ongoing) in a rapid manner with the majority of study reports (19/24, 79%) being delivered within less than 90 days from receipt of the initial request. Most of these studies used data from Germany, France and UK.

Noting that the first DARWIN EU® data partners were onboarded only in the Autumn of 2022, an additional four studies were conducted via DARWIN EU® (in line with the pre-defined capacity for studies in year 1) and one study was commissioned to a research organisation via the Agency' framework contract[3].

Studies via DARWIN EU® and the framework contract were less frequent compared to in-house studies. A key driver for this was the fact that these pathways cannot (yet) deliver results within the time constraints of the regulatory procedures in the context of which the research questions arose, especially if the procedure is already far advanced. For the framework contract pathways, this is a general limitation due to the requirements of the procurement process. However, DARWIN EU® is expected to become a more agile pathway with increased capacity and speed based on the onboarding of at least 40 data partners by 2025, the use of a common data model and the building of a suite of analytical tools that allow fast conduct of studies of similar nature.

[3] During the reporting period, framework contract studies were also performed in response to the COVID-19 public health emergency (7 completed, 4 ongoing) and the Pharmacovigilance impact strategy (4 completed, 3 ongoing).

For about one third of all research topics, a study was not considered feasible[4], mainly because the medicinal product(s) and/or the outcome(s) of interest were not adequately captured in the available in-house databases in combination with the fact that alternative RWE generation pathways could not be used in view of procedural time constraints. This concerned mainly studies in therapeutic areas not covered at primary care level, medicines used in specialised settings, as well as rare diseases.

In a survey of RWE sponsors (recipients of the study results involved at all relevant milestones of the study conduct) to ascertain the usefulness of the completed studies, two-thirds (12/18) of the network responders considered the results supportive for their assessment. In the remaining cases, the data were either not considered critical for the assessment (as compared to other available evidence) or there were study limitations which hampered the interpretability of the findings.

Since the initiation of the RWE pilots in 2022, there has been a good level of requests especially by PDCO (14 research topics), COMP (6 topics), and SAWP (5 topics). However, fewer research topics were identified for CHMP and CAT and in areas in which use of RWD is less established (e.g. no request for studies on effectiveness). Consequently, the experience is still limited, which led to the decision in 2023 to continue the pilots longer-term. In 2023, pilot studies are also foreseen for external stakeholders including HTA bodies and payers' organisation and European Centre for Disease Prevention and Control (ECDC).

Overall, our review shows that the current RWE framework with its three evidence generation pathways is able to address a broad range of research questions and help support decision-making in a variety of regulatory contexts and procedures. In 2022, this was particularly true for research topics concerning conditions and medicines used in the primary care setting, which constituted half of all queries received. In order to be able to also cover other settings (secondary and tertiary care, rare diseases, etc), **wider access to additional, more diverse and complementary data sources**, including hospital, claims and registry data, is needed. Similarly, data sources from additional European countries would be desirable for broader geographical representativeness.

The report also highlights the need to look to **accelerate the generation of RWE**, especially when a study is not feasible via the in-house pathway. As already foreseen for DARWIN EU®, this may be achieved by: further use of a common data model, the development of a catalogue of standard data analyses that can be readily executed, establishing phenotype libraries, and, using analytical packages and precomputed dashboards. Of equal importance is the **early identification and better anticipation of possible research questions** which will allow for the conduct of more complex and thus time-consuming analyses despite strict procedural time constraints. Better ways of anticipating RWD needs, even ahead of a regulatory submission, should be explored, building on the Agency's horizon scanning and business pipeline activities and making use of expert input from the EMRN and the EMA secretariats.

[4] By the end of the reporting period, 6 feasibility assessments were pending.

RWD research poses unique challenges and requires a good understanding of associated methods, terminologies as well as deep knowledge of data source characteristics and of the healthcare system organisation in the respective countries. The same is true for the interpretation of study findings. Consequently, RWE sponsors welcomed if the strengths and the limitations of a study were thoroughly discussed in the study report. Further efforts to make available relevant **information on data sources, data quality and methodological aspects**[5] of the studies should help achieve a better understanding and acceptance of RWE supporting regulatory decisions, and such efforts are foreseen in the BDSG workplan. Generally, **educational and knowledge management tools** are needed to further build capability and capacity within the network, such as via the Big Data Steering Group's Pharmacoepidemiology curriculum to be developed throughout 2023 and 2024.

Further efforts will need to be made to help the identification of potential research topics in areas for which the use of RWE is less established. To this end, **close collaboration with decision-makers and other stakeholders** should be continued as has shown to be crucial, not only for the successful conduct of studies, but also for the implementation of a fit-for-purpose RWE framework. Especially, the interactions with the committee RWE liaison groups (consisting of Committee members with a special interest in RWE) have provided an opportunity for flexible engagement and in-depth discussion of committee specific needs. Furthermore, EMA recently established an internal RWE community as a forum for knowledge sharing and it should be explored if a **forum of RWE experts** from the EMRN could be formed as part of the Methodology Working Party's European Scientific Expert Communities (ESECs) for the same purpose.

The following table provides an overview of the **learnings and recommendations** arising from this review. These will inform future improvements of the RWE framework including the further development of DARWIN EU® in order to make better use and fully integrate RWE in EU regulatory decision making.

[5] This may be partially addressed by the RWD source catalogue (see list of metadata) and the data quality framework currently being developed by EMA, as well as available ENCePP guidance.

	Learnings	Recommendations
Suitability of available RWD sources and pathways 	• The available RWD sources enabled the **generation of RWE to complement evidence from clinical trials** and other sources, thereby supporting EU regulatory decision-making. • Most **feasible studies** addressed research questions for conditions and medicines used in the **primary care setting** given the available databases.	• **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. • 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 analyses, expected increase in capacity and agility of DARWIN EU®, and additional expertise and data sources provided through the framework contracts. • Work with NCAs and stakeholders to leverage complementary pathways for RWE generation.
Regulatory context and timelines 	• Knowledge of the **regulatory context** and the **precise evidence gap** is important to inform choice of data and adequate study design. • **In-house studies** can generate RWE **rapidly** and are currently best suited to address research questions with **tight procedural timelines**.	• Explore proactive approaches for **anticipation and early identification of 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). • 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.

	Learnings	Recommendations
Collaboration 	• Close **collaboration and frequent interaction with the RWE sponsor** from the network are crucial for a successful study conduct. • The **Committee RWE liaison groups** are an important forum for flexible engagement to discuss both general and more study-specific aspects of RWD research.	• Each study to have **at least one RWE sponsor identified** as an end-user of the study findings (EMRN or external stakeholder). • 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. • Consider creation of a **forum of RWE experts** from the EMRN to facilitate **knowledge sharing.**
Building capability & capacity 	• **Knowledge of RWD and RWD research concepts**, methods, and terminologies is key to the understanding and acceptance of RWE.	• Execute and promote the **Big Data Steering Group's data science and pharmaco-epidemiology curricula,** including development of educational material and tools specifically designed specifically for regulatory decision makers.
Usefulness for decision-making 	• **Most RWD studies were considered supportive** for scientific assessments in a variety of regulatory contexts. • Knowledge of **relevant data source characteristics** helps understanding of the study strengths and limitations, as well as place and value of RWE.	• 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.**
Awareness and transparency 	• **Awareness** of the possibility to request and generate RWE as well as the related process is still **limited**.	• **Promote** the possibility to **request RWD studies** via the RWE framework.

	Learnings	Recommendations
Other process related aspects 	• Implementation of a **harmonised approach** for the conduct of RWD studies through **agreed processes, templates**, and **standard procedures** helps to generate RWE in an efficient and timely way.	• Explore means to **systematically trigger reflections on knowledge gaps needs** that could be addressed by RWE and better engage Rapporteurs and EMA product teams in this process. • Further **streamline and harmonise processes** and templates.

Table of Contents

Main report

1. Introduction

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. While established in the safety monitoring of medicines, there is less experience in using RWD/RWE in addressing evidentiary gaps at earlier stages of the lifecycle of medicines including pre-authorisation and for evaluating the effectiveness of medicinal products. Further work is needed to make full use of its potential. Consequently, EU regulators have recently set out their vision to have enabled the use of RWE and established its value for regulatory decision-making by 2025 (Arlett et al., 2022). This vision is embedded in the wider EU policy context, in particular the European Commission's proposal for a European Health Data Space as well as with a view to the Agency's commitment towards international collaboration to overcome common challenges in using RWD/RWE for regulatory decisions (Global regulators call for international collaboration to integrate real-world evidence into regulatory decision-making | European Medicines Agency (europa.eu)).

In this context, EMA together with the EMRN are building a RWD study framework to support the Agency's Scientific Committees as well as national competent authorities (NCA) and relevant external stakeholders in their scientific assessments. A pilot to test the framework with the Pharmacovigilance Risk Assessment Committee (PRAC) has been completed in 2021 [see PRAC pilot executive summary report published in the EU catalogue of observational studies (EU-PAS register], informing on a number of improvements to optimise the RWE support to PRAC as well as next steps in expanding the RWD study framework to other relevant Committees and Working Parties. This pilot was largely based on studies conducted with electronic health records (EHR) accessible to EMA at the time (also referred to as 'rapid analytics' in the report) aiming to address research questions arising from PRAC assessments. Since 2021 the number of accessible in-house data sources has increased to six EHR databases covering mainly primary care data. Furthermore, the Data Analytics and Real World Interrogation Network (DARWIN EU®) was launched as a federated network of RWD in Europe early in 2022 and, by the time of this report, has reached its first year of establishment and has onboarded 10 data partners.

Since the completion of the PRAC pilot in 2021, EMA has been providing routine RWE support to the PRAC. From September 2021 onward, opportunities for RWE to support the scientific evaluations of other Committees and Working Parties have been explored, including the Paediatric Committee (PDCO), the Committee for Orphan Medicinal Products (COMP), 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). Initial proof of concept interactions were followed by dedicated RWE pilots starting in Q2 2022. All pilots are continuing in 2023.

With this report, we take stock of the experience gained in the conduct of RWD studies since the launch of the proof-of-concept interactions with PDCO, COMP, CAT, CHMP and SAWP in September 2021 up until the end of year 1 of DARWIN EU® (7 February 2023), i.e., approaching a total of nearly 1.5 years of experience. The report follows the priority recommendations of the Big Data Task Force as implemented through the Big Data Steering Group and the second multiannual work plan (2022-2025), which foresees the publication of pilot reports for COMP and the PDCO in 2023. For a comprehensive picture, the report also summarises the routine support provided to PRAC.

The experience with COVID-19 effectiveness and safety studies conducted in response to the public health emergency as well as impact studies under the remit of the PRAC Impact Strategy to inform on the effectiveness of risk minimisation measures is also briefly summarised, but these studies were not taken into account for the main analyses conducted in this review.

Specifically, this report aims to **consolidate the acquired experience with the conduct of regulator-led RWD studies** in response to Committee and NCA needs, and to **evaluate the opportunities and challenges of providing RWE to support regulatory decision making**.

The specific objectives are:

- To understand the **needs for RWE of EMA's Scientific Committees and Working Parties**, the **ability and capacity of the current RWD study framework** to respond to these needs as well as the **usefulness of the RWE** provided;
- To understand the **suitability of available RWD sources and pathways** as well as the **methodological challenges** of data collection, study design and reporting and how they can be improved/expanded;
- To **review the process** for receiving study requests, proactively offering and conducting regulator-led RWD studies and to identify opportunities for improvements.

2. Piloting a platform for regulator led RWD studies – processes and background information

The following section sets out the process for identifying research questions and conducting RWD studies (Figure 1) within the EMA RWE pilots (see section 2.1. for details).

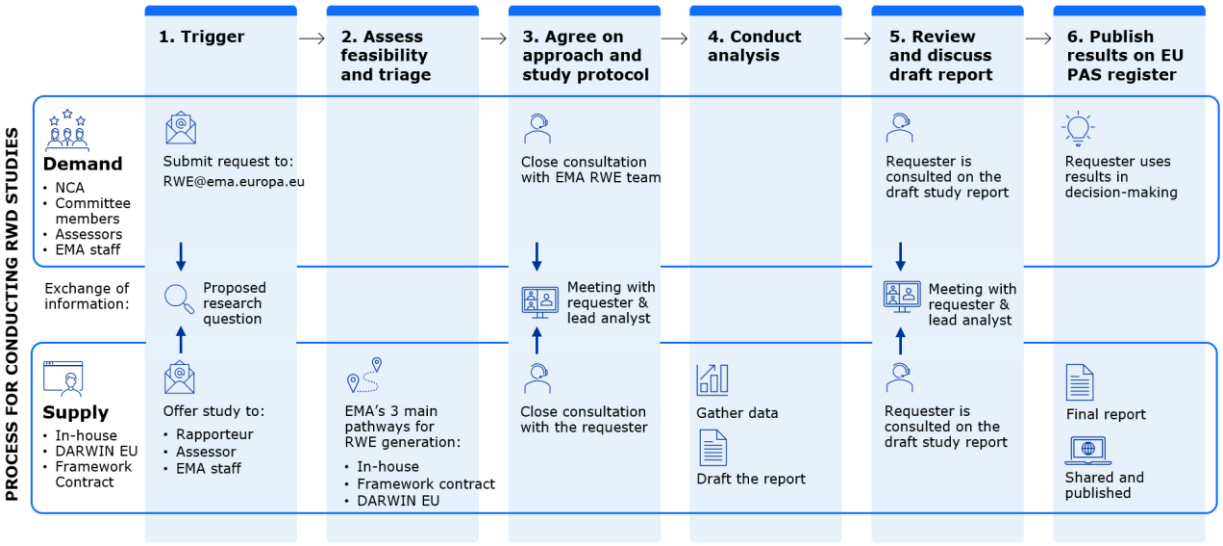


Figure 1. Overview of the process from identification of RWE research question to study conduct and publication

2.1. Committee pilots

From September 2021 onwards, following the experience of the PRAC pilot, EMA initiated proof of concept discussions with other scientific Committees, the SAWP as well as the Co-ordination group for Mutual recognition and Decentralised procedures (CMDh) to explore the need for and usefulness of regulator-led RWE generation to support regulatory decisions. This resulted in pilots being initiated with SAWP (from December 2021), PDCO (from March 2022), COMP (from April 2022), CAT (from April 2022), and CHMP (from June 2022) (Figure 2). In addition, a workshop with health technology assessment (HTA) bodies and payers' organisation was held in October 2022 to identify pilot studies to be conducted via DARWIN EU®.

Figure 2. EMA RWE proof-of-concept and pilot activities from 2021 to 2023

All ongoing pilots will continue into 2023 and at least until the end of year 2 of DARWIN EU® to ensure sufficient experience is gained before moving towards routine RWE support. The pilots and related activities are captured in the respective Committee workplans (CHMP Work Plan 2023; CAT Work Plan 2023; PDCO Work Plan 2023; COMP Work plan 2023).

In support of the pilot activities, **RWE liaison groups** were established including members of each participating Committee and the SAWP. The groups facilitate the interaction between the respective Committees/SAWP and the EMA RWE team with a view to implementing the RWD study framework, by providing input on potential research areas of interest and sharing experience with the process of requesting and conducting RWD studies, as well as how the results could inform decision-making. In addition, for selected studies including the first DARWIN EU® studies, members of relevant liaison groups were consulted on study related deliverables such as protocols and reports.

2.2. Identification of research questions

A study can be requested or offered.

- **Requested study:** Research topics for RWD studies could be directly identified by Committee members, CMDh and NCA representatives as well as SAWP members and members of the EMA product team. The topics could be in relation to ongoing procedures (Box 1) or be submitted outside and in anticipation of future procedures.

Box 1. Research topics for RWD studies

Research topics can emerge from regulatory procedures including:

- Initial marketing authorisation applications
- Periodic safety update reports (PSURs) single assessment procedures
- Safety signals
- Referrals
- Variation applications
- Scientific advice requests
- Applications for a paediatric investigation plan or waiver
- Applications for (maintenance of) an orphan designation

  In order to better understand the respective RWE needs, colleagues were encouraged to submit research topics regardless of any consideration of feasibility or timelines via a dedicated email address and email template with instructions on the information to be provided.

- **Offered study:** The EMA RWE team may also propose a RWD study, e.g., based on proactive screening of scientific advice requests, or by screening of meeting agendas and/or minutes of certain committees. Proactive screening of PRAC plenary meeting agendas for new safety signals and opportunities for RWE to complement the data from EudraVigilance and evidence provided by marketing authorisation holders (MAHs) has proven useful during the previous PRAC pilot. It has consequently been implemented as part of the routine RWE support to PRAC (see section 4.2.6.). For all offered studies, the Rapporteur/lead member state would decide on whether or not to pursue the study idea/proposal in view of its anticipated usefulness in supporting the evaluation.

2.3. Triaging of research requests and feasibility assessment

Upon receipt of a research request, the EMA RWE team aimed to respond within seven days and either request further information, discuss specific details of the research need and/or share information on the feasibility of the proposed study.

Triaging of research requests

Once sufficient information on the research question was available, the **best pathway to perform the study** was assessed, choosing between **three options** (see also Figure 3):

- **In-house studies**: As of February 2023, EMA has access to six databases containing electronic health records (EHR) from six different European countries (see Annex 3). The databases collect patient encounters from primary care, mostly general practitioner data and some also cover information from specialists. The data analyses for these studies are run by EMA RWE team.
- **DARWIN EU® studies**: In February 2022, DARWIN EU® was established, and by the end of year 1, the first 10 data partners have been onboarded with access to real world data from various sources such as hospitals, primary and secondary care, registry, and an EU biobank. (see Annex 4 for a list of data partners available for studies during the period covered by this report). At least ten additional databases are foreseen to be added each year.
- **Studies procured through the EMA framework contract (FWC)**: A FWC available from 2020 enables access to the scientific expertise of eight research organisations and academic institutions for performing RWD studies. Via this mechanism, a wide network of 59 data sources in 21 European countries is available for RWD studies. See section 3.4. for further information on FWC studies and Annex 5 for a list of the contractors.

Any study proposal with timelines below 10 weeks from the date of the receipt to the provision of results was only considered via the in-house pathway (see Figure 3).

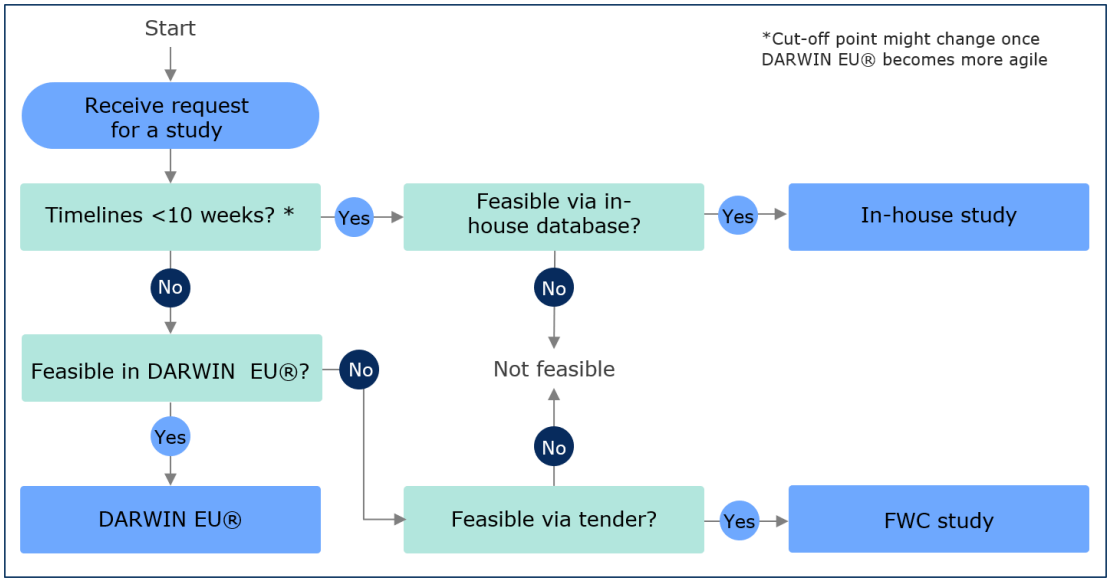


Figure 3. Flowchart for the triage of pathways to conduct a RWD study

Both DARWIN EU® and the FWC pathways were not suitable to conduct studies within such short timelines as the procedures and analytical pipelines for DARWIN EU® were still being established in 2022 and FWC studies required a time-consuming tender process. In absence of restricted timelines,

DARWIN EU® was considered a possible pathway as of Q3 2022, once the first data partners had been onboarded. If not feasible in-house or via DARWIN EU®, the option of a FWC study was also explored.

Feasibility assessment

Once all relevant information on the research request was available, a feasibility assessment was conducted considering all relevant elements to the research question including, if the study could be performed on the study population of interest (i.e., geographical and temporal coverage) and if enough data (exposures and/or outcomes) could be sourced. All potential pathways were considered[6]. The requester of the RWD study was informed of the outcome of the feasibility assessment including any reasons for non-feasibility and, occasionally, a proposal for an alternative study design if the original study was not possible. On the basis of the feasibility assessment and recommendations by the EMA RWE team, the requester decided if the study should be pursued in view of its potential to address the evidentiary gap and to inform the related assessment.

2.4. Study conduct and publication

The precise steps for the conduct of RWD studies varied depending on the pathway chosen. However, the main steps/deliverables were the same and consisted of

- the preparation of a study outline (DARWIN EU® only) and the study protocol, and
- the conduct of the study according to an agreed protocol and preparation of the study report.

If a study was to be conducted via the FWC route, there would be one additional step prior to the preparation of the study protocol in order to select the research organisation who would carry out the study. This selection process consisted of: (a) the development of technical specifications outlining the research question, study objectives, methods requirements, deliverables and timelines, and (b) the review of the tender proposals submitted by the research consortia.

Regardless of the origin of the request or the pathway for addressing it, an effort was made to identify at least one RWE sponsor from the Committees, CMDh/NCAs or SAWP (usually the requester and, if different or if study offered, the Rapporteur/lead member state) as well as the EMA product team to be involved in all steps of the study conduct. Both the draft study protocol and the report were shared with the identified sponsor(s) for comments prior to finalisation. For DARWIN EU®, in case of product specific complex studies, the relevant MAH(s) or applicant(s) were also consulted on the study protocol.

Regardless of the pathways, the final study protocol and the report would always be published in the EU PAS Register, after removal of confidential information. For in-house studies, EMA was responsible for the publication. For DARWIN EU® and FWC studies, the studies were registered by the Coordination Centre or the research organisation that conducted the study, respectively. If deemed informative and in agreement with the requestor/Rapporteur/lead member state, the EMA RWE team may have presented the study during the Committee plenary meetings.

[6] For in-house studies the EMA RWE team conducted the feasibility assessment, whereas for DARWIN EU® studies, the this was done by the Coordination Centre. Feasibility assessments are not routinely performed for FWC studies, but there is a possibility of performing a survey with the FWC contractors prior to reopening of the competition.

3. RWD studies conducted from September 2021 to February 2023

3.1. General overview

Number and types of study topics by feasibility. From 1st September 2021 to 7th February 2023, **61 RWD research opportunities** were identified for RWE generation to support regulatory decision-making. In response to these research topics, 36 studies (59%) were considered feasible, whereas a study was not considered feasible in 19 (31%) cases. Six requests (10%) were either on hold (i.e., further discussion is needed to define the scope or design of the study) or the feasibility assessment was ongoing by February 7th (Figure 4). Of the feasible studies, 27 (75%) were completed, and three studies (8%) were still ongoing. The remaining six studies (17%) had been offered to Rapporteurs/lead member states but were not accepted.

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.

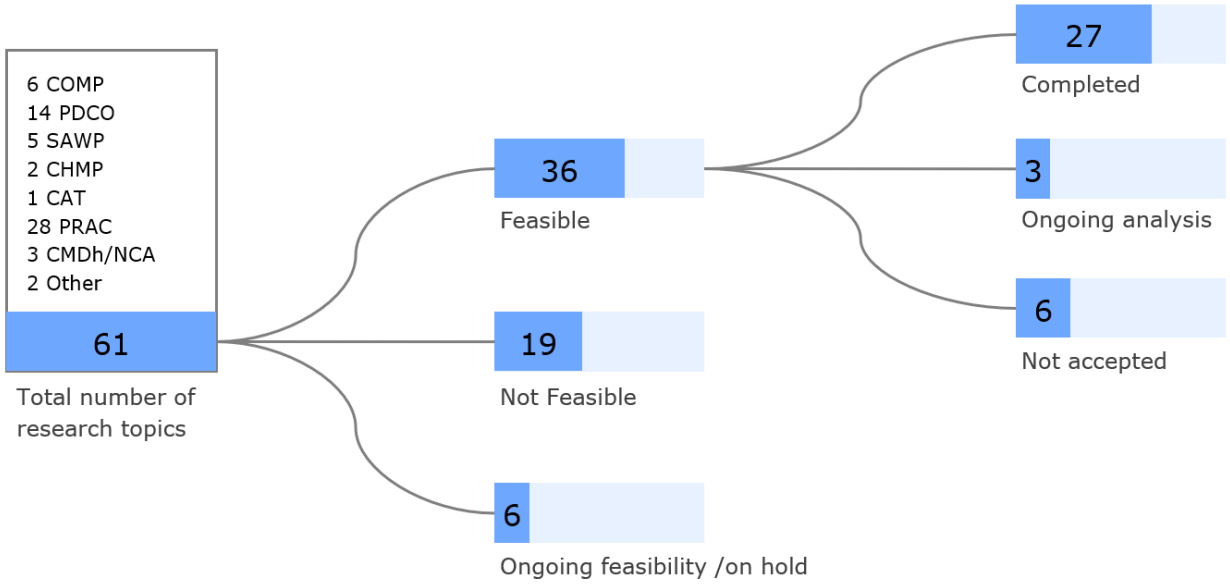


Figure 4. Number of research topics (and their statuses) for evidence generation to support decision-making

***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.*

Amongst the 61 research topics, 49 (80.3%) were considered via the in-house study pathway, eight (13.1%) via DARWIN EU® and four (6.6%) via FWC (Figure 5). A total of 31/49 in-house studies were feasible but only 25 studies proceeded to analysis (24 completed and one ongoing). The remaining six research topics were offered to Rapporteurs/lead member states but not accepted. One more study was considered via in-house pathway which was pending feasibility assessment by February 7th. Of the eight DARWIN EU® research topics, four studies were initiated (and three completed) during the reporting period and four were pending feasibility to be assessed in year 2. Only one study was initiated via the FWC pathway. This study is ongoing. Three more FWC studies were considered, two of which were considered unfeasible and one was pending further discussion with the requester by the end of the reporting period.

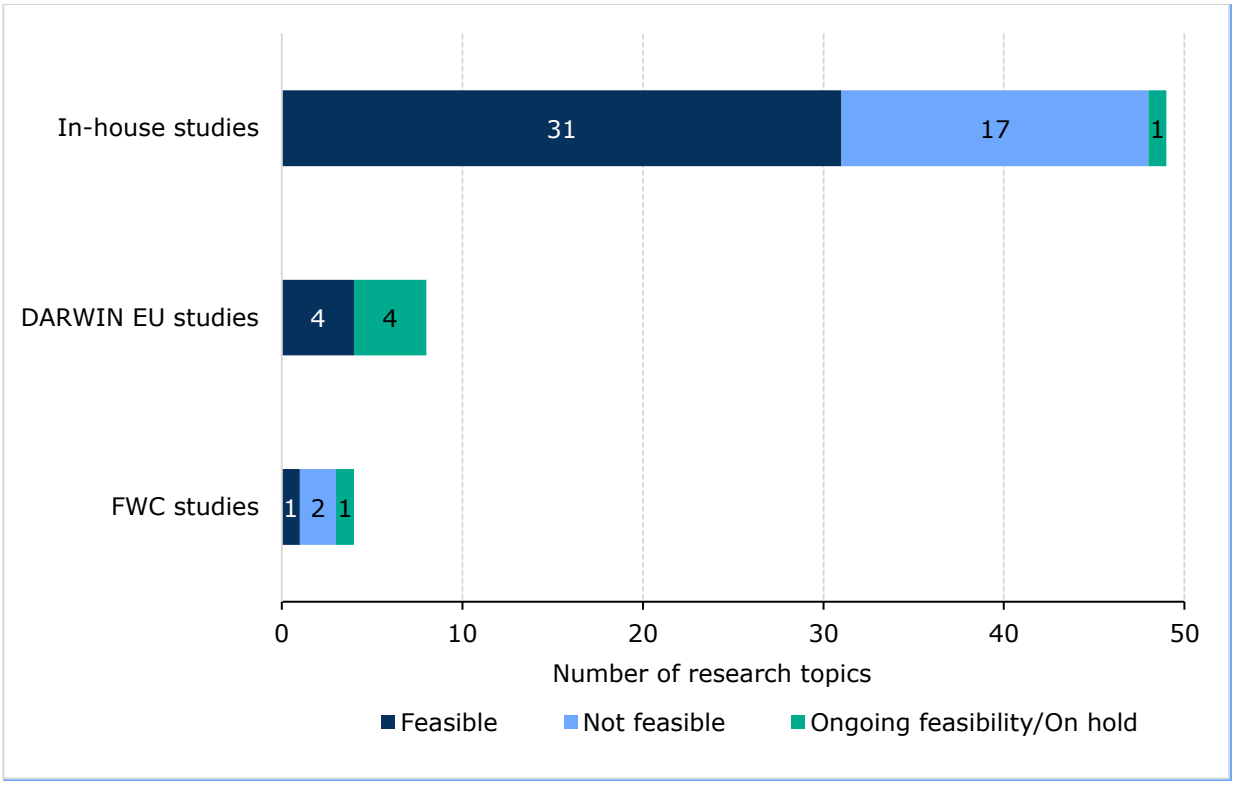


Figure 5. Number of research topics by RWE generation pathway (n=61)

Out of the 61 research topics, 44 (72%) were requested by members of the scientific Committees, the SAWP, CMDh/NCAs, external stakeholders or members of the EMA product teams. A total of 17 (28%) studies were offered by the EMA RWE team.

Research requests were mostly received via e-mail, but only 19 (43%) used the RWE mailbox. Few (5, 11%) requests were received via other means such as discussion during meetings.

Number of requested and offered studies over time. More research topics were received between January to June 2022 in comparison to the second part of the year (22 versus 12), and the opposite is true for offered studies, i.e., more research topics were offered by the EMA RWE team between July to December 2022 (10 versus 4), see Figure 6. This might be a chance finding, but it could also reflect changes in the strategy of promoting the conduct and use of RWE during the reporting period. For instance, by the end of 2021 and in the first half of 2022 the proof-of-concept and pilot interactions were initiated and there were more presentations at Committee plenary meetings.

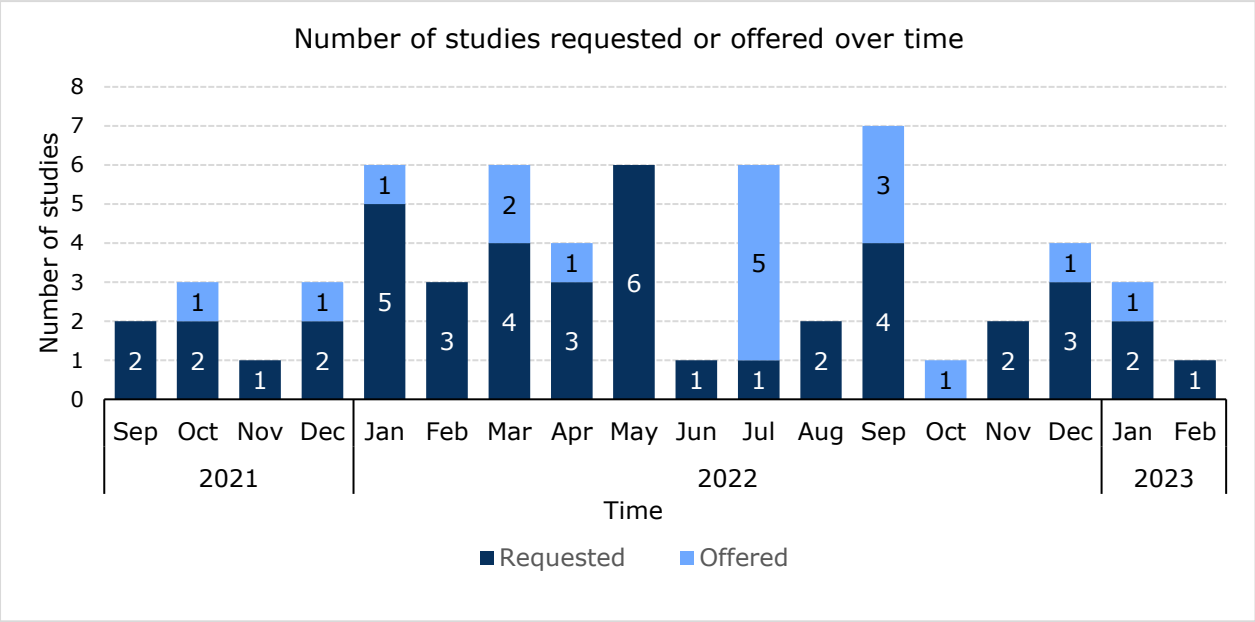


Figure 6. Number of research topics requested or offered over time (n=61)

The **number of studies completed per month** slightly increased towards the second half of 2022 (Figure 7) which may be explained to some extend by the time taken to perform the studies started in the previous months, but it may also at least partially reflect more efficiency of the EMA RWE team after the implementation of additional standard operating procedures (SOP) and other tools, e.g., timetable for conducting in-house studies to support signal assessments.

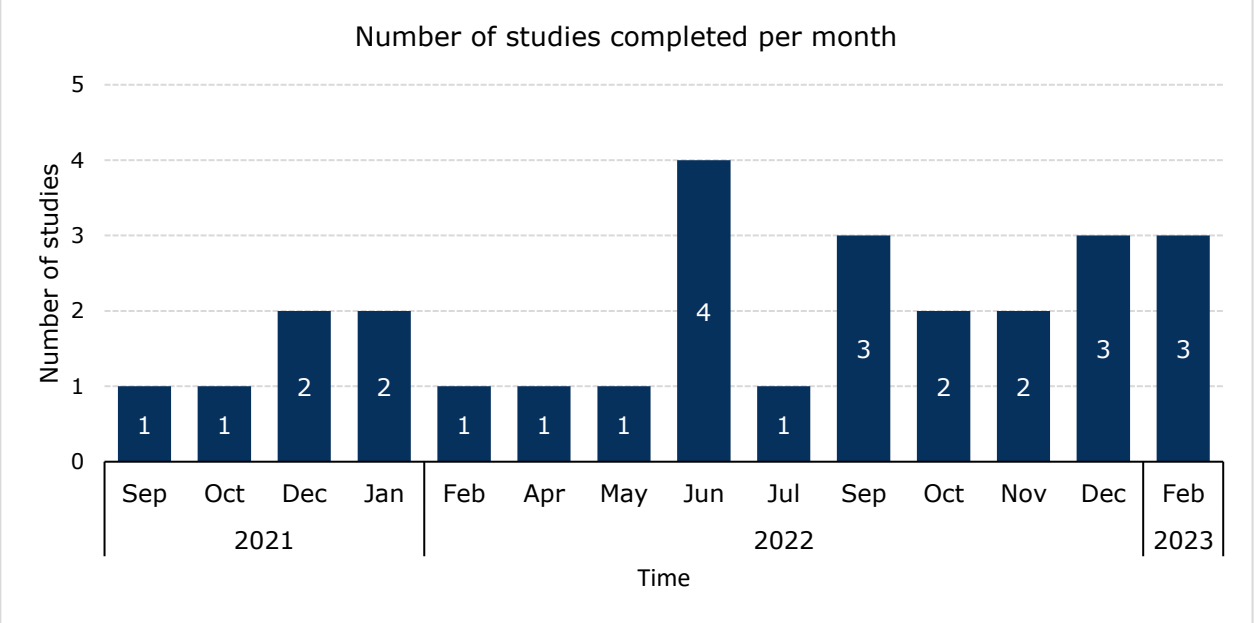


Figure 7. Number of completed studies over time (n=27)

Use case categories/study types. Most of the research requests aimed at generating evidence on drug/vaccine safety (22, 36.1%), followed by topics to inform the design and feasibility of

MAH/applicant studies (11, 18%), drug utilisation (10, 16.4%), clinical management (10, 16.4%) and disease epidemiology (7, 11.5%). We received one request for the assessment of the impact of regulatory actions (1, 1.6%). For other use case categories identified as potential areas of need for RWE, including 'representativeness and validity of completed studies' and 'effectiveness', no requests were received (Figure 8).

When considering only the research topics deemed as feasible or unfeasible (Figure 8), most of the safety studies (17/21, 81%), drug utilisation (8/10, 80%) and disease epidemiology studies (6/6, 100%) were feasible, whereas research topics on the design and feasibility of future MAH/applicant studies and clinical management were more likely to be unfeasible with only 4/10 (40%) and 1/7 (14%) requests proceeding to studies (see reasons for non-feasibility below).

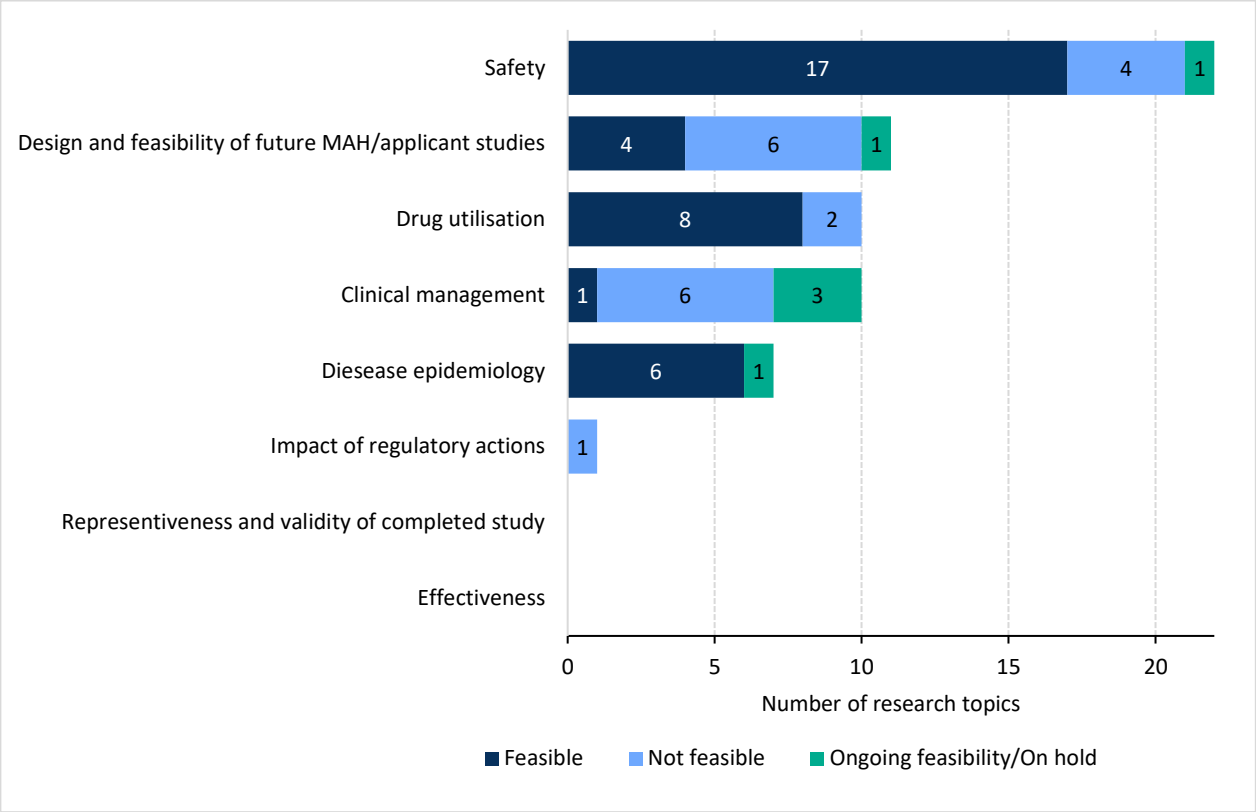


Figure 8. Type of research topic by use case and feasibility status (n=61).

Notes: *'On hold' includes research topics that need further discussion on the scope or design of the study.*

Requester/recipient. The majority of the research topics emerged in the context of scientific assessments by the PRAC (28/61, 45.9%) and PDCO (14/61, 22.9%), followed by COMP (6/61, 9.8%) and SAWP (5/61, 8.2%). Few study requests originated in the context of procedures or topics of interest for other decision-makers and external sponsors, i.e., CHMP, CAT, CMDh/NCA, HTA/ payers' organisations (Figure 9). When considering only the research topics deemed as feasible or unfeasible, research topics from PDCO (8 out of 11), SAWP (2 out of 5), and CMDh/NCA (2 out of 3) were more often unfeasible than for other RWE sponsors. For an in-depth discussion by Committee please see section 4.2.

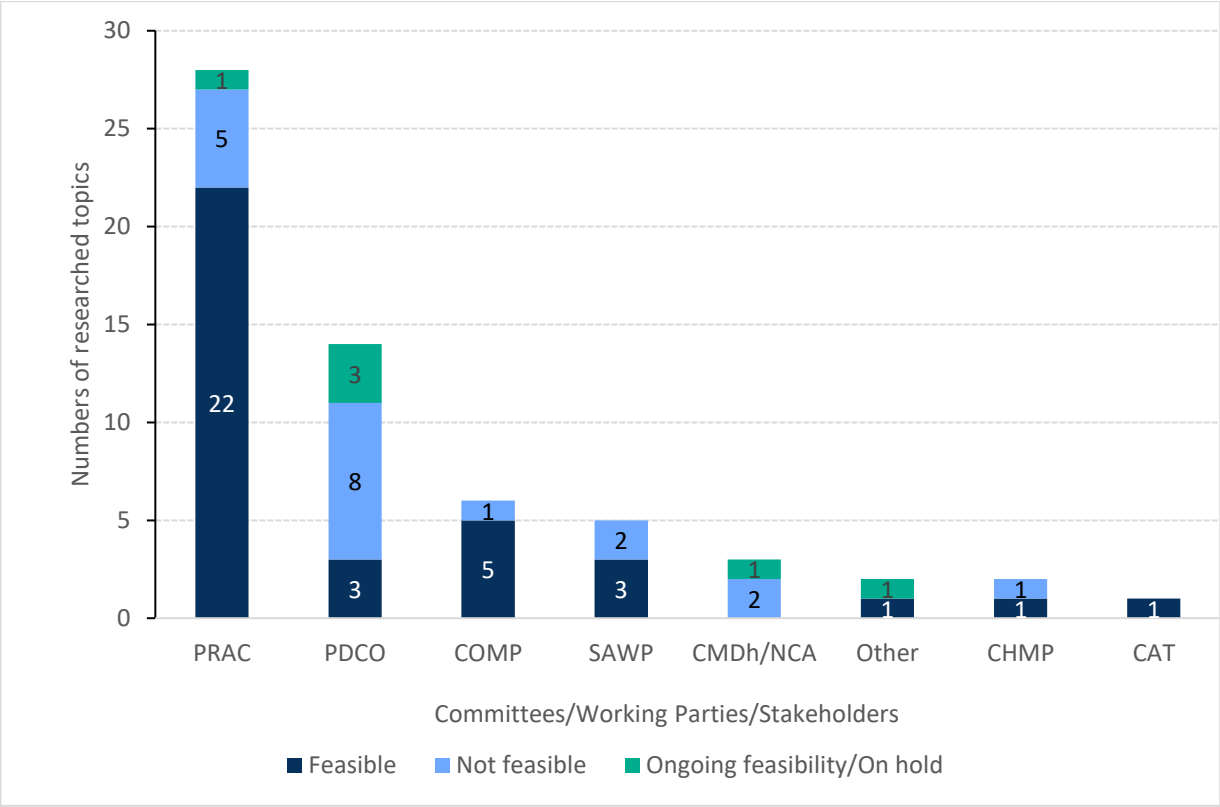


Figure 9. Research topics by requester/recipient and feasibility status (n=61)

Notes: *'On hold' research topics that need further discussion on the scope or design of the study.*

The vast majority of RWE research topics concerned centrally authorised medicinal products/products intended to be submitted via the centralised procedure (43/61, 71%). Still, every fifth study topic was related to a nationally authorised product (13/61, 21%) and some concerned both nationally and centrally authorised products (5/61, 8%) (Figure 10).

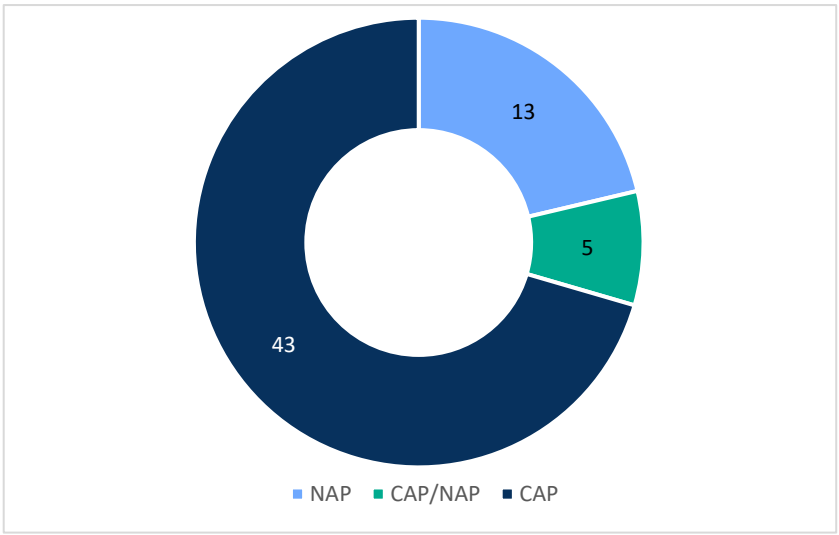


Figure 10. Number of research topics by centralised (CAP) or national (NAP) procedure.

Regulatory context. Of the research topics requested by members of the scientific Committees, the SAWP, CMDh/NCAs, external stakeholders or members of the EMA product teams (44), the majority emerged in the context of requests for paediatric investigation plans (PIPs)/waivers (12, 27.3%) or were not linked to a specific procedure (category 'other') but relate to an area of general interest or an anticipated future application/procedure (8, 18.2%). This is followed by periodic safety assessment report single assessment (PSUSAs, 5, 11.4%), signal assessments, scientific advice requests, and referrals (4, 9.1% each). Few study requests originated in the context of requests for new or for maintenance of orphan designation, marketing authorisation application (MAA) and type II variation (Figure 11).

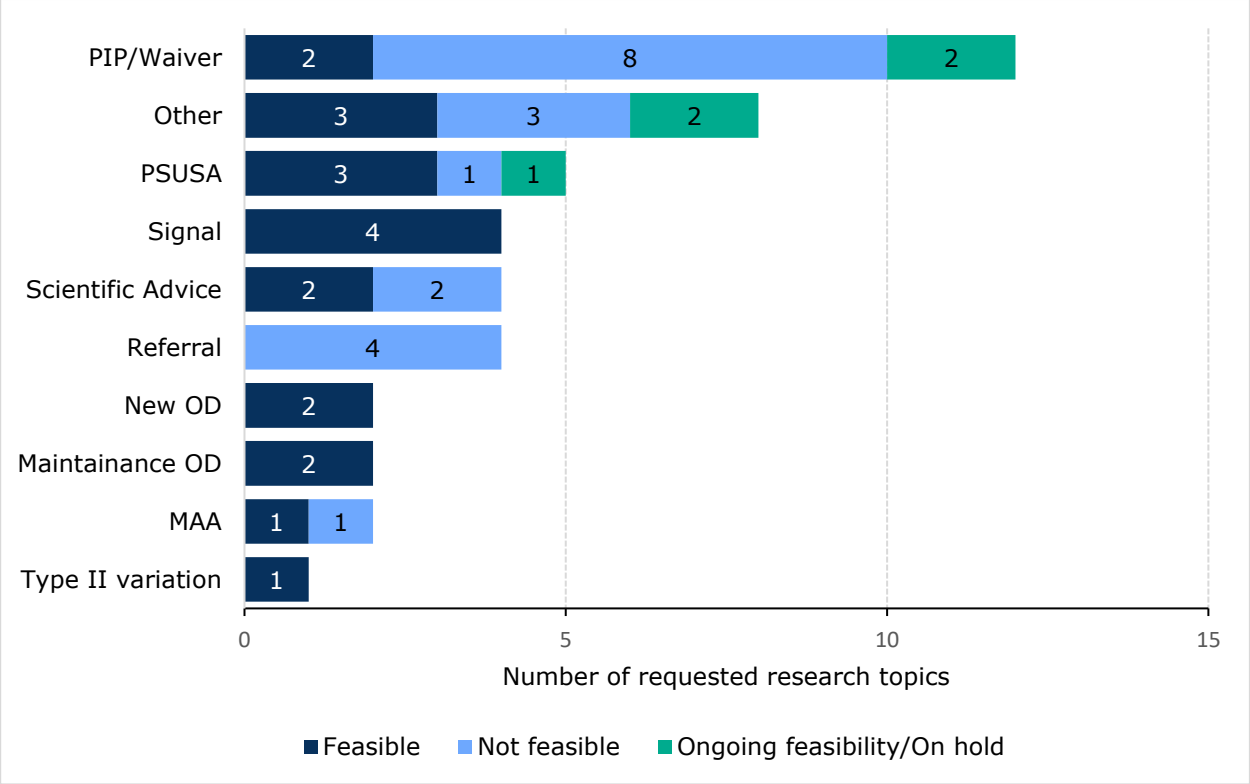


Figure 11. Requested research topics by regulatory procedure type and feasibility status (n=44)

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

***Abbreviations:** PIP: paediatric investigation plan, PSUSA: Periodic Safety Update Report Single Assessment, OD: orphan designation, MAA: marketing authorisation application.*

Of the **research topics offered** by the EMA RWE team (17), the majority emerged in the context of signal assessments (10, 59%), four were not linked to a specific procedure (23.5%), and few research topics originated in the context of referrals (2, 11.8%) and scientific advice request (1, 5.9%) (Figure 12). More than half of the offered studies (10, 59%) were accepted by Rapporteurs/lead member states.

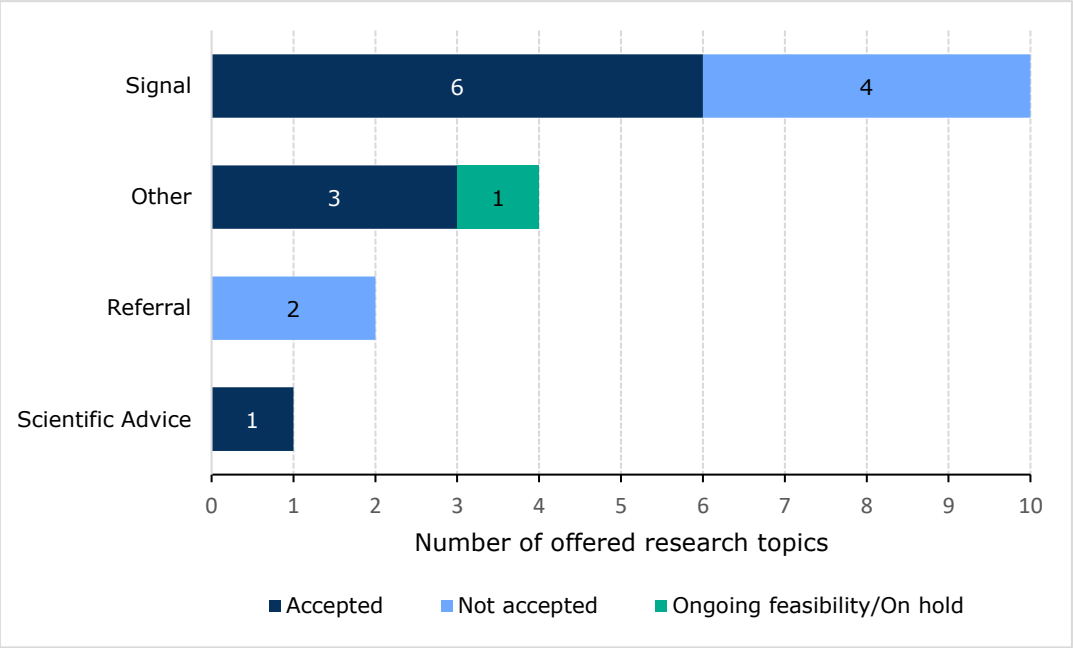


Figure 12. Offered research topics by procedure and feasibility status (n=17)

Notes: *For this analysis, SA also includes protocol assistance, i.e., the procedure when SA is provided for orphan medicinal products.*

The most common **reason for lack of study feasibility** was that the medicinal product (class) of interest was not prescribed in the database setting or not authorised/not used in the respective countries (8, 42.1%). Another frequent reason was the outcome of interest (condition or adverse event) not being adequately captured in the databases. This included rare outcomes or outcomes not recorded at primary care level (7, 36.8%), see Figure 13. Other reasons included the lack of granularity in the information contained in the databases (e.g., outcomes that are poorly captured by the coding system, or insufficient information on prescribing, dose, duration, and indication), lack of power and/or representativeness.

Outcomes not being adequately captured in the databases were the main reason for lack of feasibility of studies to evaluate the design and feasibility of future MAH/applicant studies (4 out of 6), as well as clinical management (3 out of 6). This was also the main reason why research topics concerning the PDCO could not be pursued, while medicinal products not being prescribed in the database setting/not authorised/not used was the main reason for lack of feasibility of requests originating from PRAC. See also section 4.2. for a more detailed discussion by Committee.

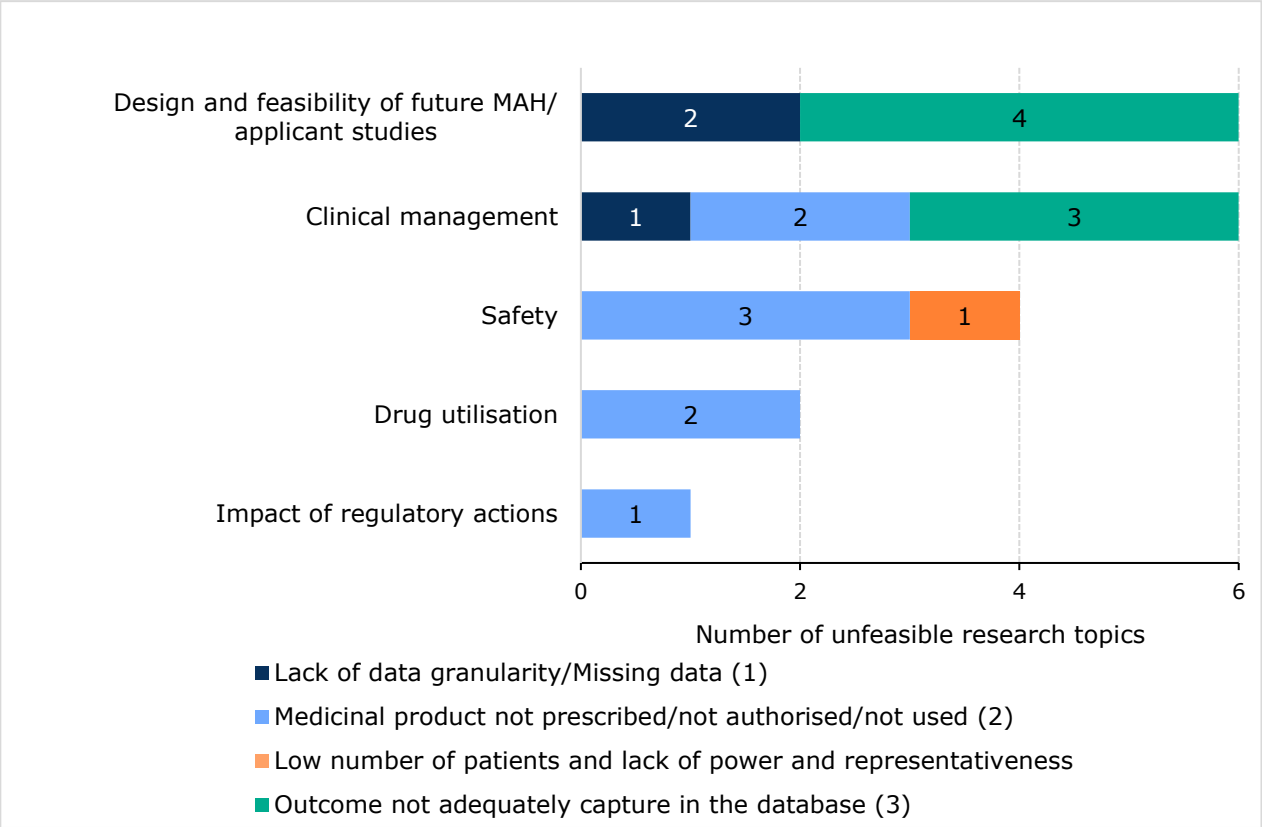


Figure 13. Reason for lack of study feasibility by use case

Notes: *(1) Outcomes poorly captured by the coding system, or insufficient information on prescribing, dose, duration, and indication. (2) Medicinal products (class) that are not prescribed in the database setting or not authorised or not used in the respective countries. (3) Outcomes not captured, e.g., 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.*

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 first response, to conduct of the feasibility assessment and to study completion (Table 1) by RWE generation pathway. Notably, the analysis for FWC and DARWIN EU® studies is informed by a very small number of studies only. Furthermore, all DARWIN EU® studies were conducted in the first year of the network's establishment with the initial set of data partners being onboarded in late 2022. Therefore, the time calculated from receipt of the study request to study completion in this analysis includes inactive periods and consequently overestimates the actual time needed to conduct the studies.

Upon receipt of a research request, a reply was usually sent within less than 3 days (median 2.5 days, interquartile rage, IQR: 0 - 4.5). In all but three cases (8 days), the response was sent within seven calendar days.

The median number of calendar days from receipt of a research request to conduct of the feasibility assessment was 11 calendar days (IQR: 4-27 days) for in-house pathway, 40 calendar days for topics processed via DARWIN EU® and 108 calendar days for topics processed via the Agency's FWC.

Of the requested research topics processed via the in-house pathway, the feasibility assessment was carried out within seven calendar days for 49% (17 out of 35) requests, within eight to 30 calendar days for 28% (10 out of 35) requests, and more than 30 calendar days for 23% (eight out of 35) requests. Research topics that required longer time for the assessment of feasibility were cases when

various discussions (via email exchanges, meetings) took place to clarify and redefine the research question, or when due to the complexity of the research question (e.g., requiring development and validation of phenotyping algorithms[7]) an initial exploration was required to understand better the opportunities/limitations of conducting such a study and consequently select the most adequate pathway for conducting it.

The average number of calendar days required for conducting a study and delivering a final report was 51 for studies conducted via the in-house pathway and 217 for studies conducted via DARWIN EU®. However, as previously highlighted, the figure for DARWIN EU® is impacted by a number of factors including the onboarding of data partners in late 2022. Notably, from study protocol until final report, the process took a median of 131 days (interquartile range: 84–131).

No study conducted via the FWC pathway had been completed by the time of this report[8]. One FWC study has been ongoing for a total period of 17 months.

Table 1. Average, mean, median and interquartile range of time (calendar days) from receipt of a research request to first response, time until conduct of the feasibility assessment and time to study completion

Pathway	N	Mean	Median	Interquartile range (IQR)[(i)]	Min-max
Time from receipt of a study request to first response					
Research topics	44	2.6	2.5	0 – 4.5	0 – 8
Time from receipt of a study request to feasibility assessment					
Requested in-house studies	35[(ii)]	15.5	7	4 - 23	0 - 68
DARWIN EU® studies	4[(iv)]	70.5	40	23.5 - 118	22 - 181
FWC studies[(iii)]	3[(ii), (iv)]	148	108	51 - 284	51 - 284
Time from study request/offer to study completion (study report)					
In-house studies (requested and offered)	24	56.4	51	22.5 – 80.5	6 - 211
DARWIN EU® studies	3[(iv)]	215	217	207 - 220	207 - 220

[(i)] Interquartile range (25th-75th percentiles)

[(ii)] The feasibility assessment was still ongoing by 7 February 2023 for one in-house study and for one FWC study.

[(iii)] There was no formal feasibility assessment for FWC studies. However, in two cases, a survey was sent to contractors/data partners regarding the availability of key variables in their databases to conduct a study, and in one case, discussions on suitable data sources only took place between the EMA RWE team and the requester.

[(iv)] The analyses are based on few studies only and additional limitations apply to DARWIN EU® studies.

Considering the 24 studies conducted in-house and completed during the reporting period, 10 (41.7%) were completed within 30 calendar days, nine (37.5%) were completed within 31-90 calendar days and five (20.8%) were completed in more than 90 calendar days (Figure 14). In-house studies that

[7] A phenotyping algorithm (or phenotype) is the collection of observable and measurable patient characteristics in electronic databases [note, not just EHRs] that defines a population of interest, e.g., any codes used to record diabetes mellitus or age > 65.

[8] This analysis only considered framework contract studies requested and conducted in the context of the RWE platform pilot activities, i.e. studies conducted in response to the COVID-19 public health emergency and Pharmacovigilance impact studies were not included – see sections 3.4.2. and 3.4.3. for a short summary of these studies.

took 90+ calendar days for completion where cases considered complex studies given that they required the development and validation of phenotyping algorithms to identify populations of interest, performing a forecasting model of disease prevalence, or modelling the association between the exposure and the occurrence of health outcome considering source of bias explored through various sensitivity analyses.

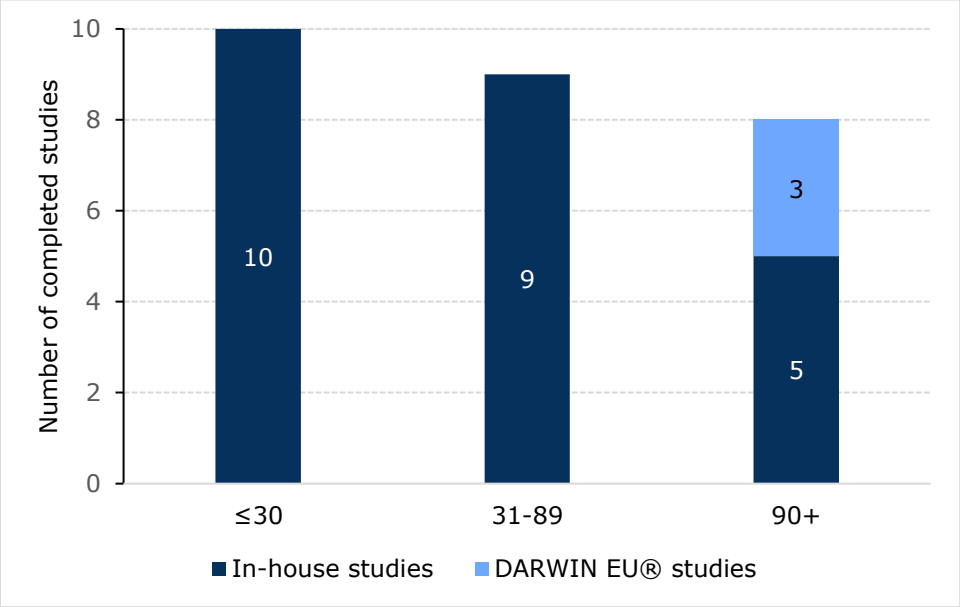


Figure 14. Total of calendar days to completion of studies by pathway (n=27).

Of the 24 completed in-house studies, 75% (18) were completed within the pre-defined timelines (+3 days), four studies were completed 5-9 days after deadline and only two studies took more than a month after deadline to be completed. Of these two studies, one was considered a complex study which required a forecasting model of disease prevalence and the other involved inclusion of the six databases available at EMA and redefinition of the health outcome after preliminary results were presented. All three studies conducted via DARWIN EU® were completed within the pre-specified timelines (i.e., within year 1 of the establishment).

3.2. In-house studies

The majority of research topics received during the reporting period were addressed via the in-house RWE generation pathway. Consequently, descriptive results presented in section 3.1.1 (i.e., general overview) are mostly driven by the research topics addressed via in-house pathway. Therefore, we only discuss the use of the available in-house databases in this section.

As mentioned before, EMA has direct access to RWD in the form of patient medical records which can be used to provide RWE and facilitate the assessment of regulatory submissions and inform regulatory decision-making. These consist of six databases containing EHR from primary care settings from six different European countries (see Annex 3 for further details) as follows:

- IQVIA™ Medical Research Data (IMRD) UK (available since January 2022),
- IQVIA™ Disease Analyzer Germany and France (available since 2018),
- The Health Improvement Network (THIN®) Italy, Spain, and Romania (available since June 2022)

Of these databases, IQVIA™ Germany and THIN® Spain also contain data from specialist care settings.

Of the feasible research topics processed in-house (31), six were offered to Rapporteurs/lead member states but not accepted. The remaining 25 topics resulted in studies of which 24 were completed and one was still ongoing as of 7 February 2023. Of these, only one study used one database, 11 studies (44%) used two databases, six studies (24%) used three databases, four studies (16%) used four databases and three studies (12%) included five to six databases. While most studies (6/9, 67%) included two databases until May 2022, the number of databases used by study increased after the acquisition of the THIN® databases (used since June 2022), see Figure **15**.

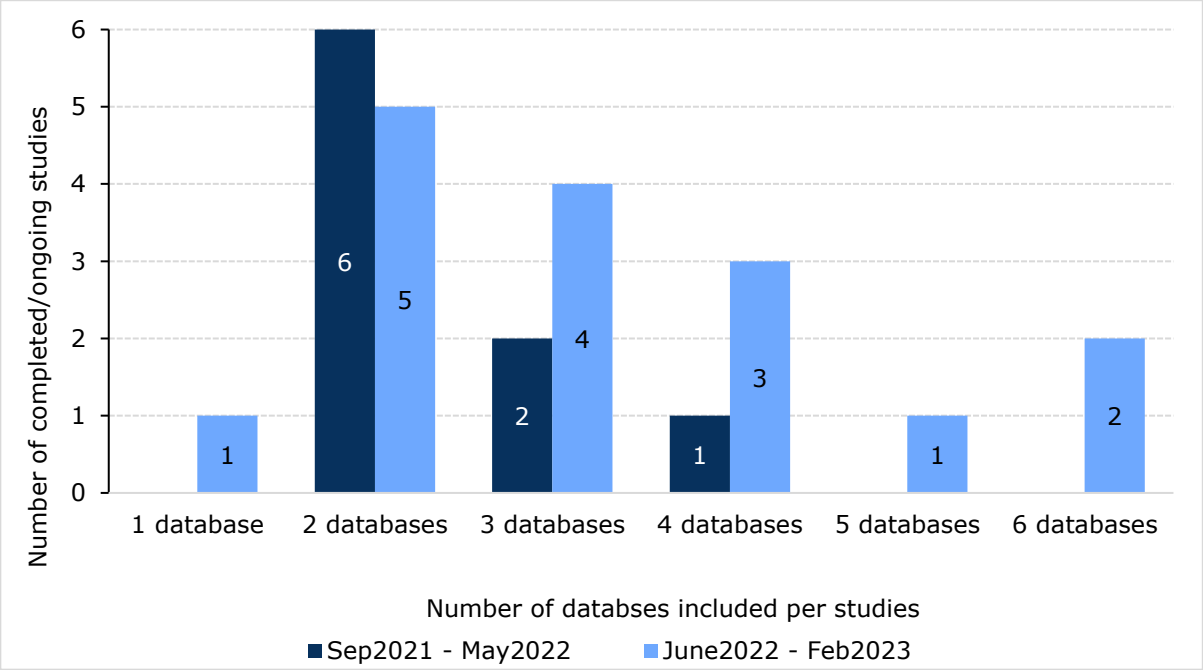


Figure 15. Number of databases included per completed/ongoing in-house study (n=25)

Notes: *IMRD UK database was used from January 2022 and THIN® databases from June 2022. From September 2021 to May 2022, only three databases were used for conducting the studies (IQVIA™ Disease Analyzer Germany and France and IMRD UK database). In addition, one study included publicly available data from Nordic countries.*

IQVIA™ Germany and France were the most frequently used databases even after the acquisition of additional databases in January and June 2022, respectively. The use of IMRD UK increased substantially over time (Figure 16). Disparities in the frequency of use of databases over time are both explained by the differences in the time of acquisition and time needed for EMA data analysts to get familiar with the use of the databases. In addition, the fact that IQVIA™ Germany and THIN® Spain also contain data from secondary care settings explains why studies with these databases were more often feasible than with other IQVIA™ or THIN® databases.

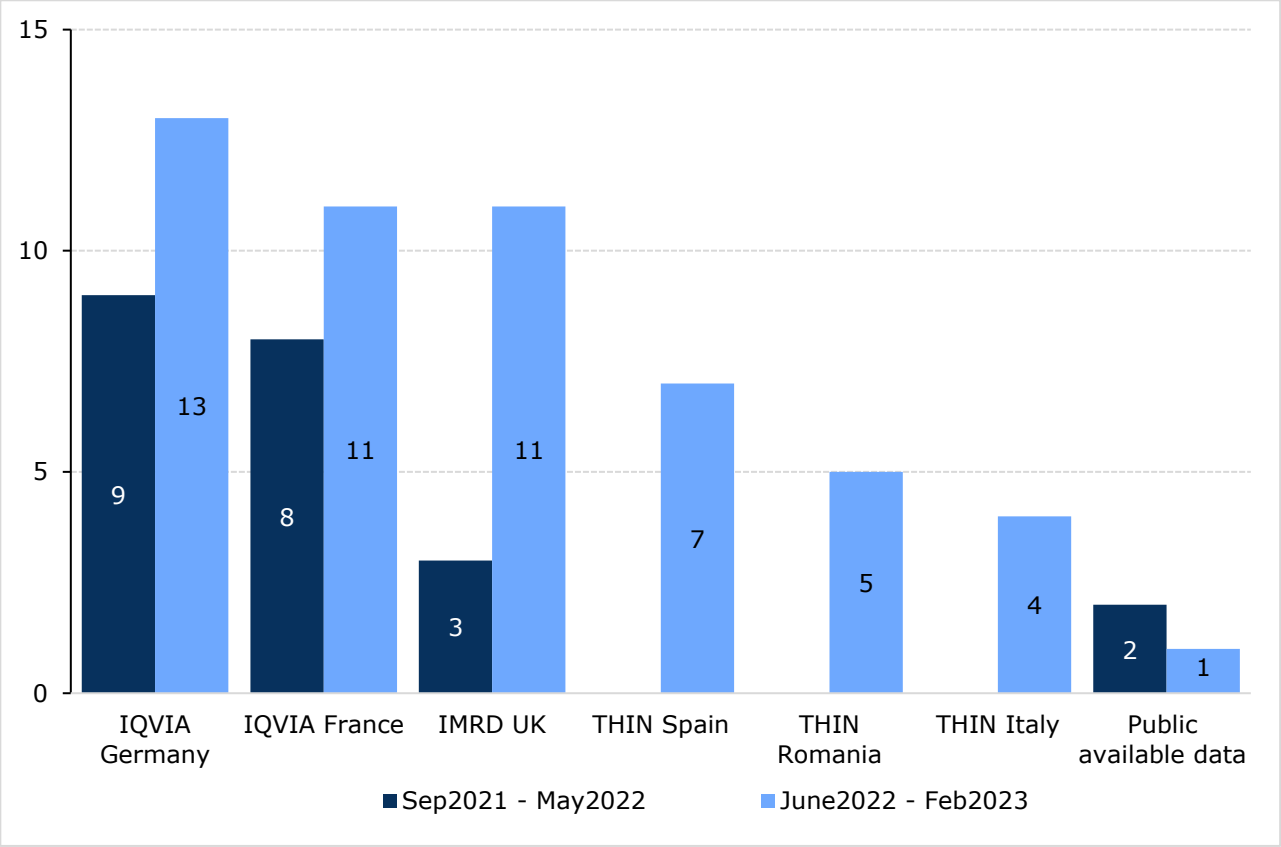


Figure 16. Frequency of use of each database in completed/ongoing in-house studies (**n=25**)

N.B.: IMRD UK database started to be used from January 2022 and THIN databases from June 2022.

Learnings:

- **In-house studies can generate RWE to support committee decision-making in a rapid manner** (in 56 calendar days on average), provided suitable data sources exist. While limited in their capability of addressing research questions for conditions/medicines used in specialist settings or very rare disease, more than half of the research questions were feasible via the available primary care data sources.
- Research requests with **short to medium timelines can currently only be accommodated via the in-house RWE generation pathway**. However, the DARWIN EU® network is expected in the future to become more agile and enable delivery of study results also in time for short and advanced regulatory procedures. In particular, it is anticipated to progress in the development of their analytical pipeline and in the standardisation of study documents (protocols, reports), library of phenotypes, and blanket ethical approvals for specific study types.
- **Close collaborations with requesters and the Committee RWE liaison groups** have proven to be crucial to better understand the regulatory needs, optimise the research question definition, and identify evidence gaps and emerging areas of interest for Committees in an efficient manner.
- Implementation of **standard processes and timetables** aligned with regulatory procedural timelines enables the generation of RWE in an efficient and timely manner.

Recommendations:

- Further efforts are needed to **promote regulator-led RWD studies** and their use to support regulatory decisions across the life cycle of a medicinal product. Similarly, efforts should be made to **increase awareness of the Agency's capacity to conduct RWD studies** and the related processes for requesting RWE (e.g., use of RWE mailbox) and for conducting the studies.
- There is a need to **expand the access to diverse and complementary data sources** (e.g., hospital health records, registries) that are:

    a) **suitable for addressing research questions on rare diseases, or conditions treated, and medicines prescribed at secondary care level,** and

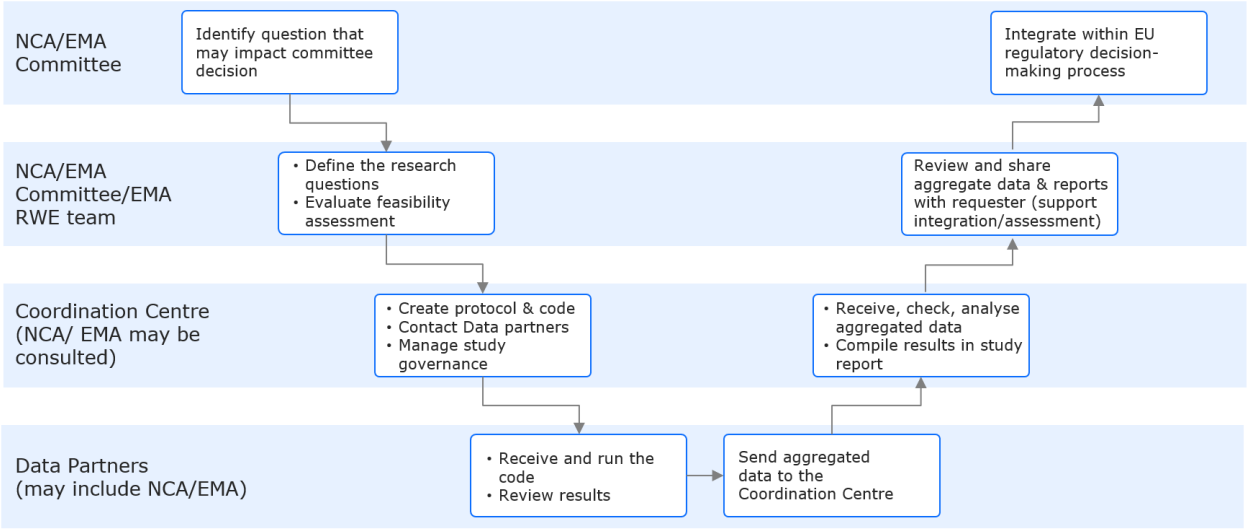
    b) with enough granularity to have access to the relevant information to fill the current evidence gaps.

    The onboarding of new data sources may also occur through different pathways than the in-house route, including DARWIN EU®.

3.3. DARWIN EU® studies

The Data Analysis and Real World Interrogation Network (DARWIN EU®) is a federated network of data, expertise and services that supports better regulatory decision making throughout the medicinal products' lifecycle by generating reliable evidence from analysis of real world healthcare data. In February 2022, following a tender, the contract was awarded to Erasmus University Medical Centre (EMC) Rotterdam who now constitutes the Coordination Centre. In November 2022, DARWIN EU® completed the onboarding of the first set of data partners with access to real-world healthcare data from sources such as, primary care, secondary care, health insurance, registries and biobanks. By the end of year 1 of its establishment, DARWIN EU® had 10 data partners from across Europe. A list of data partners available for studies during the period covered by this report can be found in Annex 4.

The process for studies conducted via DARWIN EU® is portrayed in Figure 17. This process considers the actions of the NCAs/EMA committees, the EMA RWE team, the Coordination Centre, and the relevant data partners involved in the study.



Completed RWD studies and impact on decision-making:

In the first year of establishment of DARWIN EU® (8 February 2022 – 7 February 2023), four RWD studies have been initiated. These studies were conducted outside a specific regulatory procedure, but were instead informed by previous procedures and/or requests for RWE.

Three of these studies have been completed by the end of the reporting period. The fourth and only complex study accepted this year was ongoing at the time of reporting. in terms of use case categories there was one disease epidemiology, two drug utilisation, and one safety studies.

A notable example of a RWD study conducted via DARWIN EU® is showcased below. Further DARWIN EU® use cases are available in the portfolio of use cases (Annex 2).

DARWIN EU®: Use of Antibiotics in the 'Watch' category of the WHO AWaRe classification (EUPAS103381)	
Problem statement	The inappropriate use of antibiotics can lead to the development of antimicrobial resistance (AMR). The WHO "Watch list" includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine and/or antibiotics that are at high risk of selection of bacterial resistance. These

DARWIN EU®: Use of Antibiotics in the 'Watch' category of the WHO AWaRe classification (EUPAS103381)	
	medicines should be prioritized as key targets of stewardship programs and monitoring.
Research question/ Objectives	The objectives of this study were to investigate the incidence and prevalence of use of antibiotics (from the WHO Watch list) and to explore duration of antibiotic use as well as indication for antibiotic prescribing/dispensing.
Findings	This study included five data sources from the Netherlands, United Kingdom, Spain, Germany and France. Amongst the listed antibiotics, 78 were prescribed in at least one of the data sources during the study period. Of the prescribed antibiotics, few had an incidence rate > 100/100,000 person-years (PY). Those antibiotics with the highest incidence rates were the same within the databases with, for instance, high prescribing (amongst top 3) of ciprofloxacin in all 4 primary care databases. Other drugs frequently prescribed in primary care were clarithromycin, fosfomycin and azithromycin with some variation amongst the data sources. In secondary care, higher use of ceftriaxone, vancomycin and meropenem was observed. In some databases, an increase in incidence rate over time was observed for ceftriaxone, cefuroxime, piperacilline-tazobactam and vancomycin. For azithromycin, different patterns were observed by database with an increase in IMASIS (ES) and SIDIAP (ES) up to 2018 and 2020 respectively, a decrease in IPCI (NL) and stable use in CPRD GOLD (UK) and CHUBX (FR). A decrease or steady state in incidence rate was observed for the fluoroquinolones. Other antibiotics for which the incidence rate clearly decreased over time were pheneticillin, oxytetracycline, erythromycin and clarithromycin. The prevalence analysis was in line with the incidence rates with highest use for azithromycin, ciprofloxacin, clarithromycin, and fosfomycin. Antibiotic use was lower in children than in adults and use increased with age. For some of the antibiotics, use was also high in children or young adults such as macrolides, second generation cephalosporins and tetracyclines. In primary care databases, the median duration of treatment ranged around a week and was shorter in hospital databases. With regards to the indication of use, there was a high proportion of prescriptions/dispensing with unknown indication (i.e., presence of a disease code but not belonging to any of the infection classes that had been generated) or missing indication (no disease code around the prescription/dispensing).
How was this useful?	The study provides important data on the long-term trends in utilisation of many antibiotics at risk of AMR, spanning primary and secondary care settings in five European countries over 10 years. The analysis can be repeated with an accelerated timetable with additional antibiotics and additional data sources, as and when necessary to inform regulatory decision making. PRAC welcomed the utillity of the results as additional evidence from European countries in the monitoring of antibiotics use as part of the work on antimicrobial resistance, allowing supervision of antibiotics across healthcare settings and countries. PRAC considered these results in the context of the ongoing review of the EMA commissioned impact study on fluroquinolones use after the referral (EUPAS37856) see section 3.4.4. In addition, the CMDh, the Infectious Diseases Working Party (IDWP), and members of the joint inter-agency antimicrobial consumption and resistance analysis (JIACRA) showed great interest in the study results and possible future repititions.

Recommendation: The results highlighted a high percentage of **unknown and missing indications** for a number of antibiotics. Refining the code list to improve the capture for these indications will be paramount to ensure the study results are more complete and can be better interpreted for regulatory decision making. Together with the DARWIN EU® Coordination Centre, a **phenotyping working group** will be set up to ensure codes to be developed are of high-quality, well documented, accessible, traceable, interoperable, and reusable. Moreover, active input will be sought from Member State experts to ensure all codes are correctly and appropriately defined to adequately retrieve the necessary data.

Prevalence of rare blood cancers in Europe. The first DARWIN EU® study was a study on estimating the prevalence of rare haematological cancers in Europe which included five data sources from the Netherlands, Spain, United Kingdom, Belgium, and Germany enabling broad representativeness (EUPAS50800, see also portfolio of use cases in Annex 2). This study was the first disease epidemiology study conducted via DARWIN EU® using standardised analytical pipelines for population-level descriptive epidemiology[9]. These pipelines can be reused in the conduct of future studies estimating disease incidence/prevalence to inform potential future orphan designation or maintenance of orphan designation, as well as PIP or waiver assessments, and background rates for safety assessments.

The results of this study were presented to various committees including COMP and PDCO. While the availability of several prevalence estimates were in principle considered useful, showing that partial prevalence underestimates the disease burden for chronic conditions[10], the COMP considered that the use of partial 5-year prevalence as main outcome, with additional analyses investigating 2-year prevalence and complete prevalence was not ideal. Further learnings included the selection of data partners which should be based on the most suitable sources available (e.g. IPCI, the Dutch primary care database, only reported on one type of haematological cancer (multiple myeloma)) as well as EU representativeness. The committee also highlighted the need to discuss the study results in view of data provenance, quality and completeness (including follow-up of patients over time) as well as any other important data source characteristics, especially in case of any misalignments with generally accepted prevalence values, e.g. as described in relevant scientific publications.

Recommendation: Future disease epidemiology studies intending to inform COMP opinions on (maintenance of) orphan designations should report on **complete prevalence** as the primary analysis for chronic diseases.

Other important points to be considered include **EU representativeness** of the results, as well as ability of selected/proposed data source to capture relevant **information accurately and completely** (e.g., cancer diagnosis in primary care), and ensuring the ability to **follow-up** individuals over a long period of time. Inclusion of **registry data** would be beneficial as these will capture more detailed information on rare disease. A comprehensive cancer registry from the Netherlands has now been onboarded within DARWIN EU®, and additional registries will be considered for future onboarding.

[9] See catalogue of standardised analytics to accommodate all the requested study designs: Standardised Analytics (darwin-eu.org)

[10] See also COMP Points to consider on the estimation and reporting on the prevalence of a condition for the purpose of orphan designation (EMA/COMP/436/01 Rev. 1)

Use of valproate-containing medicinal products in women of childbearing potential. The drug utilisation study of valproate-containing medicinal products in women of childbearing potential included six data sources from Belgium, Finland, Germany, Netherlands, Spain, United Kingdom enabling broad representativeness (EUPAS50789, see also portfolio of use cases in Annex 2). This study was the first drug utilisation study conducted via DARWIN EU®, which enabled the establishment of the analytical pipelines for future population and patient level drug utilisation studies[9]. Such studies will support the monitoring of medicines use, and can be repeated over time for continued monitoring ('routine repeated' study[12]), for example with additional data sources. PRAC welcomed the results of the study as additional evidence from several European countries in the ongoing monitoring activities for valproate.

Learning: One key learning from this DARWIN EU® study is the importance of understanding both the **context of how data are captured** and the **clinical practice of specific countries** to allow contextualisation and better assessment of study results e.g., in some countries, anti-epileptic drugs other than valproate are reimbursed only if the person was first prescribed valproate. In clinical practice, a valproate prescription is therefore issued in many cases only to bypass this rule. Thus, many patients never actually start valproate, but move on to the next treatment right away. This prescription practice increases incidence rates and bias results upwards.

Similar to the drug utilisation study for antibiotics, there was only limited **information on indications as well as contraceptive use** (see recommendation above). Both would have been informative in view of recent risk minimisation measures having been implemented.

DARWIN EU® year 1. In year one of the establishment phase of DARWIN EU®, the study capacity was limited to four studies. Year one also consisted of developing the services of the Cooridnation Centre, study analytics and processes. Additionally, the onboarding of data partners was only finalised in the later part of 2022, making early study requests received in Q1-Q2 not feasible via DARWIN EU®. Consequently, only few studies were conducted via DARWIN EU® during the reporting period. Lastly, given that 2022 was the first year of establishment for DARWIN EU®, many analytical pipelines had to be established. This meant that studies took significantly longer time than anticipated for the operational phases of DARWIN EU®. Study requests with relatively short timelines were considered unfeasible through DARWIN EU®, as was anticipated and reflected in the study triaging process outlined in section 2.3. Lastly, the phenotyping development also hindered the feasibility of complex study requests that were received (e.g., development of an algorithm to identify relevant populations) in year one.

Learning: DARWIN EU® has **successfully delivered the first RWD studies**. While mainly inspired by research questions of general interest or past procedures, and hence conducted outside specific regulatory procedures, the studies have shown the ability of the network to produce comprehensive results, presented with the help of interactive and user-friendly web applications (Shiny Apps[11]). The studies have been well received throughout, with some strengths and limitations for regulatory application. The experience of these three studies will help improve the study process in the future.

Furthermore, the first studies helped to **build and test DARWIN EU® analytical pipelines and processes**. Equally so, the experience was useful to **build and test engagement pathways** with decision-makers (e.g., RWE liaison groups) and external stakeholders.

[11] See Shiny applications for each completed DARWIN EU® study: Prevalence of rare blood cancers (darwin-eu.org); Valproate drug utilisation (darwin-eu.org); Antibiotics drug utilisation (darwin-eu.org)

Recommendations:

- All DARWIN EU® studies were conducted outside specific regulatory procedures. While work on the establishment of analytical pipelines and phenotype algorithms is ongoing, **early/proactive identification of research questions** to be addressed via the generation of RWE even ahead of the submission of a regulatory application, e.g., in pre-submission meetings, will help the conduct of future DARWIN EU® studies within the often demanding procedural timelines.
- The experience so far highlights the importance of **liaising and involving the requester/RWE sponsor early in the study process** to support defining the research question, scope and objectives to ensure the needs are met. Future studies outside the context of a specific procedure should always be allocated to **at least one Committee sponsor** (e.g., RWE liaison group member or Rapporteur/Coordinator/lead member state) to be involved from initiation to completion of the study, thereby making sure that the study objectives meet the needs of committees and can support regulatory decision making albeit outside the context of a procedure. This will also ensure ownership and help increase the trust in DARWIN EU® studies.
- **Educational work** is needed to support decision-makers and relevant external stakeholders to familiarise themselves with RWD/ RWE concepts and terminology, as well as data sources and analytical approaches, including how data partners collect their data. This will help Committees to better interpret and integrate the results into their assessments.
- Decision-makers have also expressed interest in **external validation studies** to support reliability of data.

Ongoing studies:

At the time of this report, one DARWIN EU® study was ongoing. This is a complex[12] study on background rates of serious adverse events to contextualise safety data from clinical trials and non-interventional studies in adolescent and adult patients with severe asthma (EUPAS103936) using data from five data sources, located in four European countries (United Kingdom, Spain, Estonia and The Netherlands). This study was requested in May 2022, in relation to an initial marketing authorisation application. It was deemed unfeasible in-house and via DARWIN EU® due to the unavailability of relevant data sources and strict timelines. Upon onboading of data partners in DARWIN EU®, and further discussions with CHMP, the study was initiated to inform potential future decision making. This marked the first study initiated for CHMP as part of the RWE pilot.

As this study request originated from a procedure, the concerned MAH was consulted on the study protocol. This allowed to test the processes for consulting industry on DARWIN EU® studies, and establish some key learnings which will be translated into a Question & Answer document in 2023.

Recommendations: The first MAH consultation for a DARWIN EU® study allowed to test the process and revealed the need for **streamlining of the consultation procedure** and the **need for guidance and clear communication** on the scope and intention of the review. To this end, EMA will develop a Question & Answer document. An efficient process is also necessary in view of the increase in capacity for conducting studies in the coming years and the strict timelines for the conduct of studies.

[12] The studies that DARWIN EU® will deliver are grouped by their anticipated level of complexity and frequency. See also: Studies (darwin-eu.org)

Future studies:

In year two of DARWIN EU®, approximately 16 studies will be conducted, varying in complexities and use cases. These studies will mark the rapid ramp-up in the number of studies to support regulatory decision making throughout the medicine lifecycle. By 2025, DARWIN EU® aims to deliver approximately 145 RWD studies per year. In this context, a number of pilot studies will continue to be initiated this year, including studies for HTA/Payers, the European Centre for Disease Prevention and Control (ECDC) and, in close collaboration with the European Commission, the EMA use case (Natural history of coagulopathy in COVID-19 patients and persons vaccinated against SARS-CoV-2 in the context of the Omicron variant) within the HealthData@EU (EHDS2) Pilot.

One of these studies is the DARWIN EU® study on multiple myeloma patient characterisation, treatments and survival in collaboration with HTA and payers' organisations. This study is currently undergoing feasibility assessment. In addition to addressing a number of research questions, the study will test the processes for carrying out RWD analyses for stakeholders beyond the EMRN. EMA will consult HTA and payers' organisations throughout the study conduct. Various other parties have expressed interest in the study, including EMA scientific committees and patient organisations.

During the period covered by this report, three studies were in the early stages of the feasibility assessment:

- a drug utilisation study requested by a NCA on the use of erythromycin as a pro-kinetic drug in children and adults;
- a disease prevalence study of tardive dyskinesia in the paediatric population for PDCO, and;
- a patient characterisation and treatment patterns study for PDCO focusing on paediatric extrapolation which is currently on hold while additional exploratory work is being performed.

Recommendations: To inform the **shortlist of future studies** for DARWIN EU®, EMA will closely collaborate with the EMRN and beyond. **Processes ensuring adequate consultation** during the various stages of the study conduct (e.g., feasibility assessment, outline, protocol, and report) and **dissemination of the study results** will be put in place. This is especially important in view of the rapid ramp-up of studies to be performed via DARWIN EU®in coming years.

Quarterly presentations are currently a key mechanism to inform relevant Committees, the SAWP and CMDh/NCAs of ongoing and finalised studies. In the operational phases, an additional feature will make use of an **automation function for informing on the study publication in the EU PAS Register**, by means of an alert function for interested parties to 'subscribe' to new publications**.**

3.4. Framework contract (FWC) studies

Through a public competition (reopened in 2020[13]) EMA has selected eight public and private organisations and consortia to conduct RWE research (see Annex 5). Via these eight contractors, a wide network of 59 data sources in 21 European countries can be accessed for pharmacoepidemiology studies.

The FWC route of conducting studies has been in use since 2014. Through the FWC route, data sources can be accessed which are not available in-house or via DARWIN EU®. In addition, primary data collection is possible if necessary and it can also leverage access to expertise not available in house. Depending on the research question, studies conducted via this route usually take several months and sometimes more than a year from the opening of competition to awarding of the contract, study initiation, conduct and provision of final report.

RWD studies conducted via the Agency's FWCs can be requested through different routes. In this report, we focus on the experience gained from:

- Study requests received in the context of the RWE platform pilot activities and as a result of the triaging process described in section 2.3. (section 3.4.2);
- FWC studies conducted in response to the COVID-19 public health emergency (section 3.4.3.);
- Pharmacovigilance impact studies conducted within the remit of the PRAC Strategy on Measuring the Impact of Pharmacovigilance Activities (PRAC Impact Strategy, section 3.4.4.).

3.4.1. Overview of FWC RWD studies conducted

Overall, since 2014, more than 40 pharmacoepidemiology studies have been commissioned via previous and the ongoing FWC.

During the period covered by this report, 11 FWC RWD studies intended to support EU regulatory decision-making have been completed. Nearly two thirds of these studies were conducted in relation to the COVID-19 pandemic (seven (64%), see section 3.4.2.) and four (37%) were studies investigating the impact of regulatory actions (see section 3.4.3.).

On average, from the time of contract signature to the provision of the final study report, it took a median of 18 months (IQR: 5-38 months). COVID-19 studies conducted in response to the health emergency were generally faster with a median of 10 months (IQR: 5-30 months) for completion.

3.4.2. FWC studies considered in the context of the RWE platform pilot activities

During the proof-of- concept and pilot period covered by this report (September 2021 to 7 February 2023), four RWD study requests received via the RWE platform pilot were considered for being conducted via the FWC pathway (see Annex 1 for a list of all study requests, which can be filtered by pathway).

One disease epidemiology study (natural history of disease and treatment patterns of spinal muscular atrophy) was requested by the CAT in September 2021. The study is currently ongoing with a total duration of 17 months to date.

[13] Lot 5 (pharmacoepidemiological research) of the framework contract 'Quality, efficacy and safety studies on medicines' (EMA/2020/46/TDA)

CAT use case #1 – Spinal muscular atrophy (SMA) - natural history of disease and treatment patterns (EUPAS50476)	
Problem statement	With the recent approval of disease modifying therapies, the natural course of SMA, diagnostic criteria and standard of care are expected to have evolved significantly. Recent studies have reported disease trajectories that significantly differ from the known natural history of SMA.
Research question/ Objectives	The study aims 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 uses patient registry data from seven SMA registries.
Findings	The study is ongoing. The study report is expected in Q3 2023.
How is this expected to be useful?	This study will inform future study designs and contextualise clinical data of new developments in this area. The results will also support the long-term post-authorisation efficacy and safety follow-up of advanced therapy medicinal products (ATMPs) and help to better understand the added benefit of a new therapy and its place in current practice.

This study is based on disease specific registry data from four SMA clinician-based registries (Belgium, Sweden, Switzerland and Czech Republic/Slovakia) and three SMA patient-based registries (Spain, Germany & Austria, and UK & Ireland) and represents an opportunity to assess whether the information collected in registries designed before the existence of treatments can be leveraged to provide insightful information on SMA progression over time, and to identify potential challenges of working with registries to generate evidence that can be used for regulatory purposes.

Learnings: Despite the willingness to collaborate, the process has been challenging, mostly due to the limited resources on registries' side, leading either to the non-participation of some of the registries, or too long timelines for feedback that caused further delays in the feasibility assessment and therefore to enrolment in the study.

Recommendation: Amongst the Committee sponsors for this study, the involvement of patient representatives made sure that throughout the design and conduct of the study the interests and experiences of patients were heard and reflected. **Involvement of patients should be systematically considered.**

The three remaining study requests considered via the FWC included:

- One disease epidemiology study for the PDCO to estimate incidence and prevalence of Duchenne muscular dystrophy per paediatric age ranges, and the phenotypes associated in Europe is on hold, pending further discussions with the requester on the precise research question and suitable data sources.
- Two study requests were not pursued. In one case (treatment patterns and patient outcomes for refractory or relapsed multiple myeloma), the condition was eventually considered too complex in view of the diverse treatment history of patients and the relevant outcome measures being not well captured in the available EHRs and hospital databases. A study in the area of rare haematological cancers was however later pursued via DARWIN EU® (see section 3.3.). In the other case (clinical practice for treatment of overdose), a survey with the FWC

contractors showed a high degree of heterogeneity and lack of complete and structured data, rendering the study infeasible.

3.4.3. FWC studies conducted in response to the COVID-19 public health emergency

During the COVID-19 pandemic, several RWD studies were conducted to enrich the real-world monitoring of the safety and effectiveness of COVID-19 therapeutics and vaccines.[14, 15] Since the start of the pandemic a total of 12 studies were commissioned to consortia specialising in observational research, of which eight were completed (all but one, which was completed in 2020, during the period covered by this report) and four were ongoing as of 8 February 2023. Four out of these studies started during the period covered by the report and eight started before September 2021.

FWC studies in response to the COVID-19 pandemic were conducted in the following areas:

- **Readiness:** Through the ACCESS (vACcine Covid-19 monitoring readinESS) project background incidence rates for adverse events of special interests (AESIs) were generated. In addition, study protocol templates for vaccine coverage, safety and effectiveness studies were made publicly available in the EU PAS register for use by marketing authorisation holders and research organisations to support the assessment of upcoming safety signals (EUPAS37273, EUPAS39370, EUPAS39361, EUPAS39289).
- **Safety studies**: As soon as the vaccination campaigns started, an early safety study was coordinated by the same research consortium that led ACCESS to complement spontaneous reporting in several Member States. It included primary data collection in six MS (BE, HR, FR, DE, IT, NL) and the UK, using apps (patient-reported outcomes), and parallel cohort monitoring of AESIs and COVID-19 diagnoses pre/post COVID-19 vaccination in large electronic healthcare databases (EUPAS39798, EUPAS40404). This early study transitioned into a larger, 2-year safety study with an overlapping period between July-Nov 2021. The monitoring of special populations in the primary data collection part (pregnant women, immunocompromised, former COVID-19, history of allergies) was complemented by a EHR component (nine data sources in five countries) reinforcing the framework to address emerging safety concerns (EUPAS42504, EUPAS39798, EUPAS42467).

  Additional studies were commissioned to better characterise emerging safety signals. For example, a study on the association between thrombosis with thrombocytopenia syndrome (TTS) or thromboembolic events and COVID-19 vaccines was initiated in Q3 2021 to further support the evaluation of safety signals, examine risk factors[16] and characterise genetic variants potentially associated with venous thromboembolism (VTE)[17] (EUPAS44469). Observational studies also helped to better characterise the occurrence of cases of myocarditis and pericarditis after vaccination with mRNA vaccines.
- **Drug utilisation**: The E-CORE project (Evidence for COVID-19 Observational Research Europe) was the result of an international collaboration with the US Food and Drug

[14] Durand et al. Safety monitoring of COVID-19 vaccines: perspective from the European Medicines Agency

[15] Report on pharmacovigilance tasks from EU Member States and the European Medicines Agency (EMA), 2019-2022

[16] Li et al. Comparative risk of thrombosis with thrombocytopenia syndrome or thromboembolic events associated with different covid-19 vaccines: international network cohort study from five European countries and the US

[17] Xie et al. Genetic risk and incident venous thromboembolism in middle-aged and older adults following COVID-19 vaccination

Administration (FDA) and other regulatory agencies and explored COVID-19 drug use patterns, safety and effectiveness. It has established cohorts of patients in a number of EU and non-EU countries, using a common protocol or an established common data model.

- **Impact of regulatory measures for COVID-19 vaccines:** The impact study of EU label changes and regulatory communication on SARS-CoV-2 adenovirus vector vaccines in the context of TTS was set up in late 2021 to provide a qualitative assessment of these actions, defined as the level of awareness and knowledge by healthcare professionals of the risk of TTS, the extent of changes of healthcare professionals' and patients' attitudes towards national vaccination programmes and the extent of change of national vaccination policies in six Member States. This study will support further regulatory decision-making in the context of vaccine-related safety signals (EUPAS44970).
- **Disease epidemiology studies:** Other studies were conducted to better understand the impact on health outcomes of COVID-19 infection itself, including treatment of COVID-19 disease. One example is a study of the natural history of coagulopathy and use of anti-thrombotic agents in COVID-19 patients. When the TTS signal emerged, a cohort of vaccinated subjects was added resulting in the largest analysis at the time of venous and arterial thromboembolism and TTS following vaccination as well as infection with SARS-CoV-2[18] (EUPAS40414).
- **Studies in specific populations:** The CONSIGN study (COVID-19 infectiOn aNd medicineS In preGNancy), which was still ongoing at the time of this report aims at providing data on medicines used in pregnant women with COVID-19, describing severity and clinical outcomes of COVID-19 according to treatments received during pregnancy, and assessing the rate of pregnancy and neonatal outcomes by different treatments.

  Furthermore, an ongoing 2-year safety study with access to hospital data was used to answer a PDCO request received further to proposals from developers of novel COVID-19 therapeutics to perform studies in hospitalised paediatric patients with severe or critical disease. The study was carried out in less than 4 months and confirmed low hospitalization rates, ICU admissions and death following COVID-19 disease in any paediatric age category, prior and after vaccination, consequently supporting the PDCO decision not to require full studies in children but rather to perform pharmacokinetic trials only.

All these studies contributed to the collective body of evidence around the COVID-19 pandemic, supporting regulatory decision making, in a fast-paced changing environment.

Furthermore, in May 2022, EMA and the European Centre for Disease Prevention and Control (ECDC) launched the EU Vaccine Monitoring Platform (VMP), a joint initiative for strengthening the continuous monitoring of the safety and effectiveness of vaccines in the EU. Through this platform, the two Agencies coordinate and oversee EU-funded, independent post-authorisation studies on vaccine use, safety and effectiveness in EU countries. An important achievement in 2022 was the set-up of an EU-funded study to assess the effectiveness and safety of Imvanex (EUPAS50282).

[18] Burn et al. Background rates of five thrombosis with thrombocytopenia syndromes of special interest for COVID-19 vaccine safety surveillance: Incidence between 2017 and 2019 and patient profiles from 38.6 million people in six European countries

3.4.4. Pharmacovigilance impact studies

The PRAC Impact Strategy was launched in 2016 and describes the conceptual approach, principles and stakeholders, as well as the processes for prioritisation and conduct of impact research to systematically investigate how pharmacovigilance activities and major regulatory actions translate into measurable positive health outcomes. In this context, the strategy also describes how studies conducted by regulatory authorities can complement activities performed by MAHs to assess if the risk minimisation measures work in practice and whether unintended consequences may have occurred if, for example, regulatory actions are not adequately implemented or fail to achieve their intended objectives.

As a consequence, PRAC may request EMA to perform impact research, which in view of the complexity and granularity of data required would be carried out through the FWC. In the future, impact studies may also be conducted via DARWIN EU®.

Since 2019 PRAC has established a process for prioritisation and regulatory follow-up of impact research. Between 2019 and 2022, a total of 169 PRAC-led procedures were identified as eligible for impact research. Six of these were discussed by the PRAC Interest Group on Impact, a group set up by PRAC to oversee the implementation of the strategy. As a result of these efforts, a total of 11 impact studies have been commissioned in response to PRAC needs[19]. An overview of studies commissioned under the PRAC impact strategy is available on the Agency's Big Data webpage.

During the period covered by this report, four impact studies were completed and three were ongoing. All but one of these studies were commissioned before September 2021.

Among the studies that were ongoing as of 7 February 2023, one study was initiated to explore the impact of EU label changes and communication related to the risk of TTS with SARS-CoV-2 adenovirus vector vaccines (EUPAS44970, see 3.4.3.).

The four studies completed after September 2021 include:

- A drug utilisation study (EUPAS31001), which investigated changes in utilisation and prescribing trends of **valproate** containing medicines before and after the Article 31 referral in 2018 as a result of which a new pregnancy prevention programme was put in place to avoid in-utero exposure of unborn babies, because of an increased risk of malformations and developmental problems. Despite some limitations, the study indicated that, the overall impact of the 2018 additional RMMs on valproate use and prescribing was small. Despite the declining trend in prevalence of valproate use after the 2018 intervention in most countries/regions, the number of pregnancies while using valproate is still a matter of concern. Additional studies were ongoing by the end of 2022 to complement these results and the ongoing continuous review by PRAC. This includes a study on prescriptions of valproate via DARWIN EU® (see section 3.3.).
- A drug utilisation study (EUPAS37856) to determine changes in prescription patterns of **fluoroquinolone antibiotics** over time and compliance with the warnings and precautions for use put in place after the PRAC concluded in 2018 that these medicinal products can, very rarely, cause long-lasting and disabling side effects, and consequently recommended that fluoroquinolones should no longer be prescribed for milder, non-severe or self-limiting infections. The study had heterogenous results across countries, with fluoroquinolone prescribing decreasing over time in some, but not all of the six countries included in the study.

[19] Report on pharmacovigilance tasks from EU Member States and the European Medicines Agency (EMA), 2019-2022

Overall, the extent of the decrease was limited. However, the study had several limitations including lack of prescribing data from secondary care (hospitals) and limited information on indications. As of 7 February 2023, the findings of the study were being reviewed by PRAC also taking into account the results of the DARWIN EU® study (see section 3.3.) to investigate prescription patterns of antibiotics on the WHO 'Watch' list.

- To measure the impact of an updated EU wide pregnancy prevention program for oral **retinoids** agreed by the PRAC in March 2018, a retrospective cohort study (EUPAS31095) in women of childbearing age estimated the use of isotretinoin, allitretinoin and acitretin, as well as contraceptive use and the occurrence of pregnancies during retinoid use in EHRs from four countries (NL, ES, IT, DK) before and after implementation of the measures. Monthly incidence and prevalence rates showed that retinoid prescriptions have a strong seasonal pattern, but no change was seen in user rates after implementation of the RMMs in any of the data sources. The low level of recordings of pregnancy tests and contraceptive use did not allow for a trend analysis nor a proper interpretation of the impact of the RMMs. Based on these findings the authors concluded that there was very limited measurable impact of the 2018 RMMs on oral retinoid use and of the pregnancy prevention programme (PPP) measures among women of childbearing age in the included databases. Moreover, pregnancies still seem to happen during oral retinoid treatment after the implementation which remains a matter of concern.
- A survey (EUPAS44827) to explore the risk awareness and adherence to measures put in place in 2019 further to an Article 31 referral in order to avoid dosing errors with **methotrexate** containing medicinal products, namely inadvertent overdose due to daily use instead of weekly. The survey provided some insights about the awareness, knowledge, and behaviour of prescribers, pharmacists, and patients. However, participation rate was low with a potential for self-selection of more aware and knowledgeable respondents. The PRAC critical appraisal of the study was ongoing by the end of the period covered by this report.

4. Impact of RWE for regulatory decision making and experience by Committee

4.1. Overview of study impact

To better understand the usefulness of the study results, EMA circulated a survey (Annex 6) to the requesters/Committee sponsor(s) enquiring about the impact of the results including whether the results provided were considered substantial, supportive or inadequate evidence, and consequently if the results were taken into account for the decision making. Information on whether the study was reflected in the respective assessment report was also sought.

Notably, the survey was not distributed after completion of the DARWIN EU® studies as the three completed studies were not linked to specific regulatory procedures. It was also not sent for the four observed-to-expected analyses conducted to support EMA in-house signal detection activities for COVID-19 vaccines.

Amongst the remaining 20 completed studies for which the survey was distributed, 18 responses were received. The findings are summarised below:

- The majority of the responses (12/18, 63%) confirmed that the study results were supportive and consequently considered for the assessment. These were seven studies conducted to support the PRAC review of safety signals and PSURs, three studies to support scientific advice requests at SAWP and two studies to inform PDCO decisions on PIP/waiver requests (see further details in sections 4.2.2. , 4.2.3. and 4.2.6.). For 10 of these studies, the results were included in the respective assessment reports, whereas in two cases, the results, whilst helpful, were not considered critical for the regulatory decision.
- In three cases, the results were not considered for the decision-making process. This includes two population prevalence studies conducted for the COMP. In both cases, there were questions regarding the appropriate identification of the population at risk: (i) for a study on prevalence of cytomegalovirus disease among immunocompromised patients, most of the patients were expected to be diagnosed in transplant centres, hospitals and specialist practices, and therefore likely to be missed in the predominately primary care in-house databases used for the study, and (ii) for a study on prevalence of acute liver injury, the code list used was considered too broad, consequently overestimating the prevalence rate (see section 4.2.1. for further details). In the third case, the Rapporteur agreed with the usefulness of the study (background rates of pemphigoid) but other evidence from spontaneous case reports and clinical trials data was found more relevant in the context of this procedure.
- Finally, three studies had been conducted outside any procedure including one case for which the application had been withdrawn prior to finalisation of the report. As a consequence, the impact for regulatory decision making was indicated as 'not applicable'.

Recommendation: The survey provided valuable insights into the **usefulness of the RWD studies for regulatory decision making**. It is therefore recommended to carry on with the **survey until the end of the pilots including for DARWIN EU studies**. To maximise the output of the consultation, the survey could be amended to ask **more specific feedback** on the level of satisfaction of the requester, how the results helped to address a gap/research need, how relevant the study results were compared to other available evidence or what were the main limitations/reasons for not considering the results in the assessment. Alternative routes to request feedback should be considered, e.g., via email (if preferred) or in a dedicated debriefing meeting in selected cases.

4.2. Experience by Committee

The following sections summarise the experience with RWD studies by Committee/Working Party following the order of the medicinal products lifecycle from pre-authorisation interactions to the application for a marketing authorisation and post-marketing surveillance as well as further development (Figure 18).

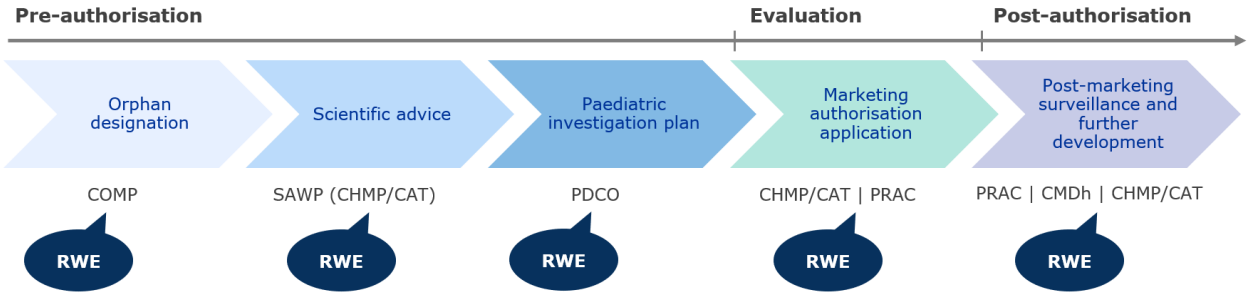


Figure 18. RWE use during the various lifecycle stage of a medicinal product

4.2.1. Committee for Orphan Medicinal Products (COMP)

Between September 2021 and 7 February 2023, a total of six RWE research topics emerged for the COMP (five requested and one offered, Figure 19).

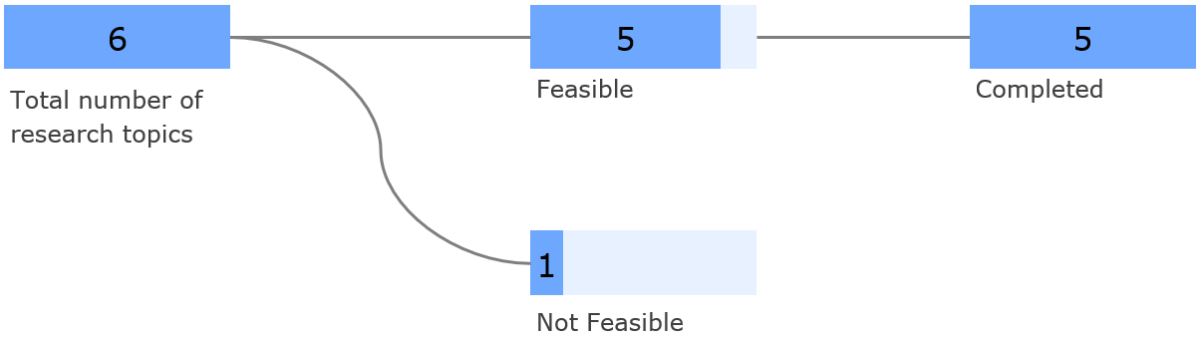


Figure 19. Number of research topics (and their statuses) for COMP

Completed RWD studies and impact on decision-making

Five out of the six requests were considered feasible, out of which four were conducted using the available in-house databases. The remaining study (prevalence of rare blood cancers in Europe) was conducted via DARWIN EU® (see section 3.3.). All studies were completed within the period of this report.

All studies intended to inform COMP opinions for (maintenance of) orphan designations, most of them being linked to a specific procedure (4/5), and one exploring the possibility to generate prevalence estimates that could be used in upcoming procedures. Although usually some data on prevalence of rare diseases are available, often the information is outdated and there is a need for up-to-date

evidence, or extending the estimates to a larger population, or simply verify estimates available in the scientific literature or claims from applicants.

An example of a typical RWD study on disease prevalence is presented below. Narcolepsy is a disease whose incidence rates were skewed by the intense mediatization of H1N1 vaccination campaign, therefore a study to estimate the actual prevalence was requested by the COMP.

COMP use case #1: COMP – Prevalence of narcolepsy (EUPAS48036)	
Problem statement	During the review of an initial orphan designation request for a medicinal product intended for the treatment of narcolepsy, an analysis of in-house RWD was requested to understand the evolution of the prevalence rate since the H1N1 vaccination campaign and the finding of an increased risk of narcolepsy in children and adolescents.
Research question	What is the yearly prevalence of narcolepsy between 2011 and 2019, stratified by sex and age group?
Findings	An analysis of the data available in IQVIA™ Disease Analyser France and Germany showed stable annual prevalence rates in France (between 0.77 and 0.98 per 10,000) during the observation period, whereas prevalence steadily increased over time in Germany (from 1.83 per 10,000 in 2011 to 3.16 per 10,000 in 2019). The observed rates in France were lower than the previously published prevalence of 2.1-2.6 per 10,000 persons in the literature and hence considered to be underestimated in the database. However, the findings in Germany were in line with estimates previously reported in the global literature (2.5-5 per 10,000 persons).
How was this useful?	The results provided up-to-date prevalence of narcolepsy in two European countries that was useful to support discussions during the review process.

For the full list of study requests and a portfolio of use cases please see Annex 1 and 2, respectively.

Other COMP requests were related to multiple myeloma, whose prevalence increased in recent years due to the availability of new treatments and resulting increased overall survival. The study was conducted in three European countries (UK, Germany and France). A possible limitation of this in-house study is that multiple myeloma may not be adequately recorded in general and in paediatric practices as this is a malignancy that will mostly be diagnosed and/or treated by oncologists. Another question arose on the representativeness of the study results for the EU since only two member state countries were included in the study.

Learning: In order to be considered for regulatory decision making, studies should aim at including as many **European countries** as possible and ideally as diverse geographically as possible (Northern, Southern, Eastern and Western Europe) to ensure that the results are **representative for the EU**.

Another request required to calculate the prevalence of cytomegalovirus disease in patients with impaired cell mediated immunity. This study was methodologically challenging, especially for the identification of the population at risk. Another limitation was that patients not visiting primary care were not included in the study (due to the nature of the in-house data sources) and this is where most of the population at risk is expected, i.e., transplant centres, hospitals and specialist practices. For example, most of the CMV infections occur in the first months after transplantation during which the patients are likely to be still monitored in the tertiary centres, and as a consequence, the information not captured in primary care data sources.

A fourth request was to calculate the prevalence of acute liver injury in the European population. The study found a high variability in the overall yearly prevalence (from 0.17-0.20% in Italy to 1.52-1.72% in Romania), and the prevalence was higher than expected. One possible explanation is that the exact definition of acute liver injury is not fixed, and different coding practices exist among different countries, making the capture of the condition difficult. The degree to which the diagnoses codes actually identified the patients with signs of acute and ongoing liver injury appropriately was not verified and it is possible, therefore, that the study may have overestimated the prevalence.

Overall, the data-related challenges experienced were expected for research into prevalence of rare diseases: first, the small numbers of patients require use of large databases and/or a network of databases; second, rare diseases are diagnosed and treated in more than one care setting, therefore linkage or access to multiple care settings is necessary. Usually, rare disease research may be best performed using disease registries, hospital databases or primary/secondary care linked databases. For very rare diseases, data may only be available in a limited number of expert centres.

Recommendation: Although most of the studies requested by COMP were considered feasible, there are some important limitations. As COMP opinions on orphan designations are based on a legally defined threshold for disease prevalence at 5 in 10,000 patients, it is important to **comprehend as much as possible any factor in a study that could lead to over- or under-estimation** of the prevalence values. To be able to better respond to COMP needs, access to **larger (networks of) databases ideally with primary/secondary care linkage as well as more specific data sources suitable for rare disease research, such as national registries**, is required. This should be taken into account with a view to onboarding of new DARWIN EU® data partners as well as research organisations as part of future framework contracts. Still some challenges are likely to remain as **data on rare diseases are often fragmented** and scattered across several database, which makes their use for observational research challenging.

Other RWE research requests/offers

One research request was considered not feasible via the in-house pathway (treatment patterns and patient outcomes for refractory or relapsed multiple myeloma) due to the disease not being recorded adequately in primary care databases. This potential study was discussed in detail with the COMP RWE liaison group, aiming to understand the strengths and limitations of the existing in-house data sources and what could be achieved. As a result of this discussion, the study (with some modification) was later proposed to be conducted via DARWIN EU®, which has access to a more diverse range of data sources and is currently ongoing (see section 3.3.).

Learnings: Close collaboration and exchange with the requester and the COMP liaison group helps to understand and address concerns regarding suitability of data sources and other limitations of a potential RWD study. **Continued close dialogue** will be important **to fully understand and leverage the potential of RWE** (as well as its limitations) to support COMP decision-making, and especially the use of the analytics and federated network of DARWIN EU® as it is growing in terms of data partners but also in other aspects of capability and capacity.

Regulatory context (use case categories) and RWE process related considerations

Three requests were received outside any specific regulatory procedure. The other three were linked to an ongoing review of either a request for an initial orphan designation or for the maintenance of an orphan designation.

Most of the requests from COMP concerned prevalence of a rare diseases in the EU population, or sometimes in a subset of that population, in order to support the evaluation of orphan designation applications.

During the pilot, methodological discussions took place with the COMP RWE liaison group during which the preferred way of calculating prevalence for the purpose of orphan designations was clarified[20] (e.g., for chronic diseases complete prevalence, as opposed to partial prevalence). This will be taken into account for future studies.

Recommendation: **Complete prevalence**, calculated as point prevalence in the entire EU population (or in a population as broad as possible), should be the preferred way to estimate prevalence rates for chronic diseases. This should be taken into account for future study protocols, leaving room for discussions on a case-by-case basis to potentially apply a different approach. For subacute disease, the period for partial prevalence should be carefully selected and agreed with relevant experts.

Learnings: It is possible to identify conditions for which knowledge gaps with regards to up-to-date prevalence estimates exist, thereby **anticipating study needs/research question in the future**. Studies, even if conducted outside a specific procedure, can be useful to inform upcoming applications for (maintenance of) orphan designations. There is also a potential for routine-repeated studies via DAWIN EU®.

A recurring methodological challenge was the risk of misclassifying patients diagnosed with the disease of interest. Although this is true for any epidemiological study, it is even more so in the rare disease research with complex disease definitions, therefore phenotyping needs attention, and might even differ from one database to another. For example, there were situations in which the dictionary of a specific database was not granular enough to capture a specific subtype of a disease or when genetic information was needed to complete the diagnosis. In some instances, it can also not be excluded that disease may be incorrectly recorded which then will results in inherent coding errors.

Recommendations: Use of a **curated and validated library of phenotypes** to identify rare conditions will help to address the risk of misclassification. In addition, **clinical experts** should be involved in the definition and validation. Notably, DARWIN EU® is building a phenotype library that will be curated by medical experts and periodically validated, which has the potential to improve rare diseases identification.

More information should be provided on data provenance, quality and completeness as well as any other **important data source characteristics and the healthcare system organisation** to understand the strengths and limitations of RWD studies conducted with these databases. Information on prior use of data sources for similar research questions would also be helpful. Study findings should be discussed in view of generally accepted prevalence values including relevant scientific publications. Obvious misalignments should be discussed in-depth for possible explanations.

All studies were requested by a COMP member or a member of the EMA Orphan Medicines Office.

An attempt was made in Q2-Q4 2022 to attend the EMA pre-COMP preparatory meetings in order to proactively identify opportunities for the generation of RWE to support the respective evaluation. However, this approach was discontinued as Committee members pointed out the need for more

[20] See also COMP Points to consider on the estimation and reporting on the prevalence of a condition for the purpose of orphan designation (EMA/COMP/436/01 Rev. 1)

specific data sources (e.g., registries) as compared to the primary care databases available at EMA to address the majority research needs on rare diseases.

Recommendation: The **interaction with RWE liaison group** was considered productive from both sides and should be continued. It is an opportunity for flexible engagement and in-depth discussions which are not possible during the scheduled plenary meetings. In order to increase the confidence in the relevance of certain types of data sources primary care databases for rare disease epidemiology studies **external validation studies** would be helpful.

4.2.2. Paediatric Committee (PDCO)

Between September 2021 and 7 February 2023, a total of 14 study requests have been received from the PDCO (Figure 20).

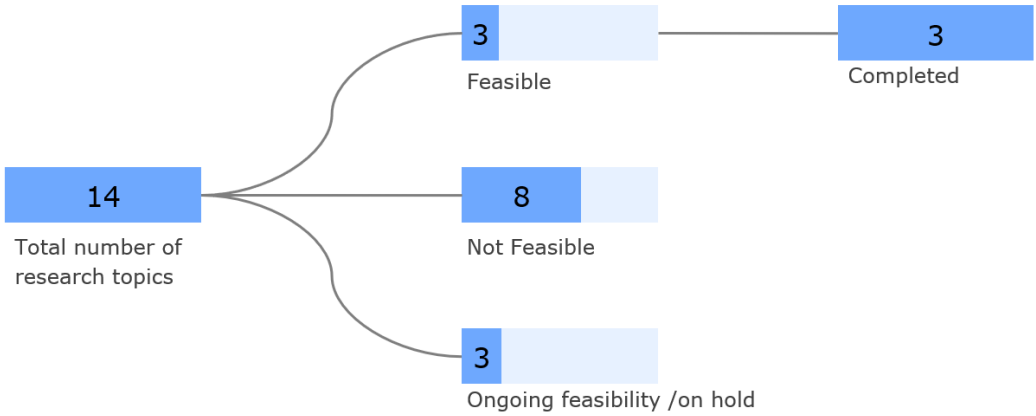


Figure 20. Number of research topics (and their statuses) to support PDCO decision-making

***Notes**: (i) 'On hold' includes research topics that need further discussion on the scope or design of the study.*

One additional request for an analysis of the burden of severe COVID-19 disease in children received during this time period was addressed via an ongoing FWC project and is further described in section 3.4.3.

Completed RWD studies and impact on decision-making

Amongst the 14 research topics, three studies were considered feasible and all three were conducted using the available in-house databases (all completed).

Amongst the three completed studies, one (prescription patterns of glucocorticoids in paediatric patients, EUPAS44839) was requested outside of a specific procedure. This question was inspired by a prior waiver request and the study was conducted as proof-of-concept study to provide an example of RWE relevant to PDCO decisions. Consequently, it was not intended to have any immediate regulatory impact.

The two remaining studies were well received and considered supportive for the PDCO decision making with results being included in the PDCO summary report:

PDCO use case #1– Prevalence of hypereosinophilia (EUPAS45202)	
Problem statement	The applicant for a medicinal product developed for the treatment of patients with eosinophilic asthma, requested a partial PIP waiver for children younger

PDCO use case #1– Prevalence of hypereosinophilia (EUPAS45202)	
	than 6 years of age. The applicant claimed that studies would not be feasible as the condition is too rare in this age group. Contrasting data was available indicating very low prevalence in a European database and higher prevalence (suggesting that the study might be feasible) in a US database. To decide on the waiver request, the PDCO requested additional European data to better inform the feasibility of clinical trials in children with hypereosinophilic syndrome (HES).
Research objective	The study aimed to describe the yearly prevalence of HES in children aged 0-5 and 6-11 years in Europe.
Findings	An analysis in IQVIA™ Disease Analyzer France and Germany showed that cases with possible HES were rare in children aged 0-5 years with an estimated yearly prevalence between 0.0 and 6.2 per million children, and no child below the age of 6 years had a confirmed HES diagnosis. Possible HES was somewhat less rare in children aged 6-11 years with an estimated yearly prevalence between 0.0 and 74.6, and a single child was identified with confirmed HES. These results were based on a paediatric population of around 30,000-60,000 children per age group per year in France and around 200,000-380,000 children per age group per year in Germany. Results of this study are consistent with the lower end of the estimates of the published literature.
How was this useful?	The results supported the applicant claims and supplemented the available scarce evidence in the scientific literature. The results supported the PDCO decision to grant a waiver for children below 6 years of age and since the analysis was performed in a short period of time, another request to the applicant could be avoided.

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

For the full list of study requests and a portfolio of use cases please see Annex 1 and 2.

Learnings: **In-house studies can generate RWE in a rapid manner** provided suitable data sources exist and support PDCO decision-making. A good understanding of the **data source characteristics** (incl data provenance, quality, content) and the **underlying healthcare system** is important. Similarly, a careful **description of the strengths and limitations** of the studies including the constraint of data sources is helpful for the interpretation of the study results and their integration into regulatory decision-making.

Other RWE research requests/offers

Amongst the remaining 11 study requests, eight were not considered feasible (with the remaining 3 requests being either on hold or feasibility assessment ongoing at the cut-off date for this report):

- In half of these cases (4/8), the outcome of interest [Vascular Ehlers-Danlos Syndrome, uveitic macular oedema, ornithine transcarbamylase deficiency and FLT3 mutation in patients with acute myeloid leukaemia (AML)] was too rare or not reported in the available in-house databases. Further, in three of these cases the related PIP/waiver assessment had already far progressed, and the timelines were too short to consider an alternative pathway for RWE generation (FWC or DARWIN EU®). In the remaining case (FLT3 mutation in ALM patients), access to data sources including genomic data would have been required. While DARWIN EU® provides access to data from a biobank in Estonia, this only includes data for adults and consequently was not further considered.
- In three cases, the data recorded in the available in-house databases were of insufficient granularity to answer the research question. In one case (autoimmune encephalitis), very few outcomes could be retrieved suggesting that potentially more generic encephalitis codes are used to document the diagnosis in clinical practice. In the remaining two cases, the level of detail of the information captured was insufficient, (i) to distinguish between bone marrow and peripheral blood haematopoietic stem cell transplantation, and (ii) to understand stages/grades of melanoma to be able to investigate unresectable or metastatic disease. Alternative RWE pathways were not pursued mostly in view of procedural time restrictions.
- Finally, in one case (use of tyrosine kinase inhibitors in ALK positive high-risk front-line neuroblastoma), data on exposure was not available in the in-house primary care databases. Once more, procedural timelines were too restrictive to consider an alternative RWE generation pathway.

Recommendation: More than half (8/14) of the research requests were related to rare diseases or specialist settings or would have required richer information as the one available, e.g., in disease-specific **registries or biobanks**. This should be taken into account with a view to contracting future in-house data sources and onboarding of new DARWIN EU® data partners.

Learnings: Currently, **research requests with short timelines can only be considered for in-house database studies**, which are not suitable for studies of conditions/medicines used in specialist settings or very rare disease. This is expected to change in the future with the DARWIN EU® network becoming more agile and with pipeline developments progressing and the range of data partners expanding.

Notably, in one of these cases, an in-house study was not considered feasible as the age category of interest was limited to children from birth to less than 6 months of age. Since the available in-house databases only include information on the birth year/month or age at registration, a sufficiently precise determination of the age at the time of diagnosis (ornithine transcarbamylase deficiency) was not

possible. However, a feasibility check showed that only very few outcome events were recorded especially for patients aged between 1 and 2 years at diagnosis, which supported the rarity of the condition in the very young.

Recommendation: For reasons of data privacy protection, some databases (including some of the existing in-house databases) do not record the exact date of birth for children younger than 1 year of age. This makes it **challenging to estimate prevalence or incidence rates in very narrow age ranges including neonates and infants**. A potential solution could be to widen access to a range of databases, including some which do not implement this restriction. Research into conditions that are specific to, e.g., neonates, would not be concerned by this limitation.

Finally, there was one research request for which feasibility assessment was ongoing by the end of the reporting period. In addition, there were two study requests put on hold pending further clarification with the requester. Amongst these was a proposal for a paediatric extrapolation framework to explore how RWE can support key areas of adult to paediatric extrapolation, including disease similarity, response to treatment, and so forth. The proposal arose from an original research request to explore off-label use of medicines prescribed for children with unresectable or metastatic melanoma. During the discussion with the requester (office of paediatric medicines at EMA), it emerged that the question was relevant to inform PDCO decisions on whether to require clinical data in children versus extrapolation approaches. The latter was identified as an important area of research need.

Learnings: Close **collaborations with requesters and the PDCO liaison group** to better understand the regulatory context and precise knowledge gap can help to identify important research needs.

Regulatory context (use case categories) and RWE process related considerations

One request was received outside a specific regulatory procedure. All other requests were linked to an ongoing review of a paediatric investigation plan (PIP) and/or waiver request.

All three completed studies were requested in order to inform PDCO decisions on the feasibility of conducting clinical trials in paediatric patients. Looking at the totality of the research questions received, in fact the vast majority (10/14) were submitted for similar reasons with the objective of generating prevalence rates for a given PIP condition to support the PDCO in assessing proposals for clinical trials in all or a subset of the paediatric age ranges or, alternatively, claims of applicants that such studies were not feasible mostly on the ground that the condition was too rare.

Recommendation: The experience to date shows a clear **need of the PDCO** for RWE that can support the review of **waiver requests** and/or the **feasibility of clinical trials in rare diseases for which there is limited information on the disease burden in children**. To be able to respond to these requests within the often-short procedural timeframes, it may be beneficial to **explore a simplified protocol**, e.g., to generate counts with denominators to provide sufficiently precise and reliable estimates representative for the EU, while at the same time being quick to execute. This could be preferably implemented via DARWIN EU®, e.g., via a dashboard.

In October and November 2022, an attempt was made to proactively identify opportunities for the generation of RWE by screening the PDCO minutes for PIP/waiver requests at an early stage of the assessment (Day 30). However, due to the limited information available in the minutes, this attempt was discontinued as no obvious research question could be identified despite a high number of Day 30 PIPs (>70) having been screened.

Recommendation: **Early identification of RWE research questions would be beneficial** as it will allow conduct of more complex/time-consuming analyses. Therefore, it should be further reflected if and how relevant research questions can be identified proactively and early during PIP/waiver reviews or even ahead of an anticipated PIP/waiver submission.

This will require expert input from the PDCO, EMA paediatric officers and potentially beyond, e.g., academic groups like Enpr-EMA and the PDCO neonatal working group. Initial discussion with the PDCO RWE liaison group highlighted a few priority research areas to be further explored:

- Drug utilisation in neonates
- Paediatric oncology as a pathfinder including RWE to support extrapolation
- Other areas: Duchenne patient characteristics/phenotypes/ages, incidence/age of onset and disease progression, specific renal diseases, novel antibiotics, off-label use in particular in children younger than 6 months of age

4.2.3. Scientific Advice Working Party (SAWP)

Overall, a total of five RWE research questions were considered for SAWP during the reporting period (Figure 21).

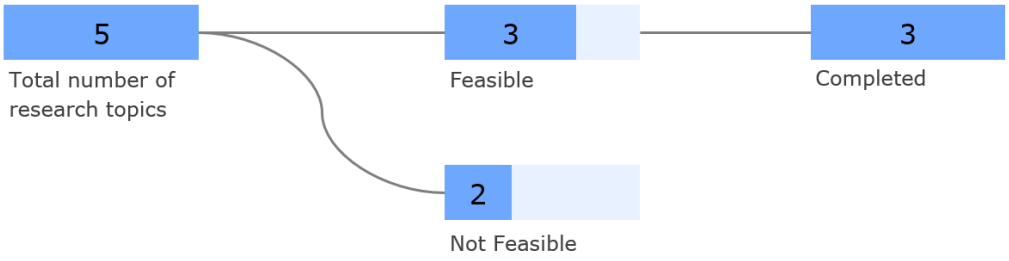


Figure 21. Number of research topics (and their statuses) to support SAWP decision-making

Completed RWD studies and impact on decision-making

Three of these studies were considered feasible and all three were conducted using the available in-house databases (all completed).

Feedback on the usefulness of the completed studies was received in two cases (see use cases below). Both were considered supportive for the SAWP advice. The study results were included in the assessment report and in one case also confirmed to have been presented during the SAWP, PRAC and CHMP plenary discussions.

One of these studies (angiotensin II receptor blocker drug utilisation) was the result of an offer by the Agency to generate RWE in relation to a recently started scientific advice procedure. This research opportunity was identified as part of a process implemented to systematically identify, screen, and track scientific advice requests involving RWD and is described below.

SAWP use case #2: Angiotensin II receptor blocker (ARB) use in paediatric population (EUPAS104305)	
Problem statement	In order to support a SAWP advice procedure, EMA suggested to provide up-to-date data on the use of angiotensin II receptor blockers (ARBs) in children with arterial hypertension, occurrence of primary versus secondary hypertension in children by age group as well as risk factors for this disease that would help to understand if secondary causes of hypertension are more common in younger children below the age of 6 years.
Research question/ objective	The study aimed to describe the population-level prevalence of arterial hypertension in the paediatric population, the main risk factors (looking at medical history of the patients) and the use of ARBs in this population.
Findings	Most children identified in the databases (IQVIA™ Disease Analyser France and Germany, and IMRD UK) with hypertension had received a diagnosis of presumed primary hypertension. Only a small proportion had a diagnosis of secondary hypertension. Large differences, up to around 20-fold, were identified between the databases in the yearly prevalence of arterial hypertension in children 2-17 years (in Germany around 6-7.8 per 1000 children, in the UK around 0.2-0.4 per 1000 children, and in France 0.5-0.8 per 1000 children). Prevalence increased with increasing age and was highest in children 13-17 years and lowest in children 2-5 years. Only few children with a history of arterial hypertension received treatment with an ARB. The highest proportion was observed in the UK (14.3%), followed by France (5.7%) and Germany (1.5%). Risk factors for hypertension varied between the three countries both in terms of history of diseases or conditions, and in terms of treatment with drugs that increase blood pressure.
How was this useful?	The study provided helpful insights in the use of ARBs and causes of hypertension across different paediatric age groups.

For the full list of study requests and a portfolio of use cases please see Annex 1 and 2.

Other RWE research requests/offers

The remaining two study requests were not considered feasible. In one case the medicinal product for which data was requested was only prescribed in hospitals and hence no data were available via the in-house databases. In the other case the outcome in question (relapsed or refractory peripheral T-cell lymphoma) was too rare for a study to be feasible.

In addition, EMA identified and screened 108 scientific advice requests including RWD. Out of these, seven were scrutinised for feasibility for an in-house study, leading to one feasible study proposed to and accepted by the SAWP Coordinators (see above). The remaining six cases were not considered feasible due to low disease prevalence counts in the databases, low treatments exposure counts, or no current access to adequate secondary care data.

Alternative RWE generation pathways (FWC and DARWIN EU®) were not feasible due to procedural time constraints.

Recommendation: Several requests and opportunities for RWD studies concerned **rare diseases and/or secondary care settings** rendering unfeasible a study using currently available in-house databases. This should be taken into account with a view to contracting future in-house data sources and onboarding of new DARWIN EU® data partners

Learnings: Currently, **research requests with short timelines can only be considered for in-house database studies**, which are not suitable for studies of conditions/medicines used in specialist settings or very rare disease. This is expected to change in the future with the DARWIN EU® network becoming more agile and with pipeline developments progressing and the range of data partners expanding.

Regulatory context (use case categories) and RWE process related considerations

All research questions emerged in the context of scientific advice procedures. Three of these questions aimed at generating evidence to inform SAWP advices on the feasibility and design of clinical trials. Furthermore, one request was obtained for a drug utilisation study and another one for a study to investigate treatment patterns (clinical management).

Recommendation: The majority of RWE research questions by SAWP concerned various aspects of **feasibility and design of clinical trials**. As these questions typically arise during the review of scientific advice requests with associated short procedural timelines, it would be desirable to have in place a **simplified protocol and/or standardised outputs** to support SAWP decision making with sufficiently precise and reliable estimates for the disease burden in the respective EU target population, while at the same time being quick to produce, leveraging the existing analytics and federated network of DARWIN EU®.

Four out of the five RWD studies were requested by a SAWP member. One (feasible) study opportunity was identified by the Agency as part of a process implemented to systematically identify, screen, and track scientific advice requests involving RWD (see above).

Recommendation: Efforts should be continued and enhanced to promote **proactive identification of RWE research questions** to support SAWP advices. Specifically, it should be further explored if and how relevant research questions can be identified early on, e.g., during pre-submission discussions or in anticipation of future scientific advice requests. This will allow conduct of more complex/time-consuming analyses and use of pathways other than in-house studies.

4.2.4. Committee for Medicinal Products for Human Use (CHMP)

Two RWD study requests have been received during the period covered by this report, one resulting in an ongoing study (background rates of severe adverse events in patients with severe asthma) via DARWIN EU® (see section 3.3.). Of note, this study was initially requested during an ongoing initial marketing authorisation application but could only be conducted after the CHMP opinion in view of complex and hence time-consuming phenotyping being required, i.e., development and validation of an algorithm to identify the relevant populations (severe asthma, MACE, severe infections, mortality).

The other research request was related to a recommendation by the CHMP to grant an initial marketing authorisation under exceptional circumstances for a new treatment for molybdenum cofactor deficiency Type A. Due to the rarity of the disease, comprehensive evidence on efficacy and safety could not be provided and further data were requested to be generated in a post-authorisation observational study.

At the time, it was not possible to generate any RWE through any of the available pathways as this would have required access to either a specific disease registry or an otherwise highly specialised data source, which was not available.

Notably, beyond the reporting period, additional research questions have been received including a proposal for a study to assess feasibility of recruitment for a post-authorisation study. Feasible studies will be pursued via the most suitable RWE generation pathway.

Recommendation: Generally, the number of RWD study topics requested and offered to support assessments conducted by the CHMP was limited during the period of this report (the same applies to CAT, CMDh and NCAs). Whether this is linked to the need or scientific value of RWD in marketing authorisation applications procedures vis-à-vis other types of evidence or due to a slow uptake remains to be seen, and should be further elucidated by exploring relevant types of research questions that could be informative for CHMP and CAT assessments. Further effort should also be undertaken to **trigger reflections on RWE needs ideally at an early stage** of the regulatory application or even ahead of a procedure start in anticipation of an upcoming application, e.g., pre-submission meetings. Whether the inclusion of a tick box to the readers' guidance template in February 2023 in order to highlight potential RWE research topics will increase the number of study requests remains to be seen. Early identification of RWE research questions will also allow conduct of more complex/time-consuming analyses (including development and validation of phenotypes) and use of pathways other than in-house studies.

Furthermore, the need to also cover **rare disease and specialist settings** should be considered when contracting future in-house data sources and onboarding new DARWIN EU® data partners, which may also include networks of registries.

4.2.5. Committee for Advanced Therapies (CAT)

To date, one disease epidemiology study has been requested (natural history of disease and treatment patterns of spinal muscular atrophy, EUPAS50476) and this study is being conducted via the FWC pathway. The study is ongoing with a total duration of 17 months so far and the study report is expected in Q3 2023 (see section 3.4.2. for details).

Recommendations: see CHMP section above

4.2.6. Pharmacovigilance Risk Assessment Committee (PRAC)

Nearly half (28/61, 46%) of all RWE research topics proposed between September 2021 and 7 February 2023 were intended to inform an assessment by the PRAC (Figure 22).

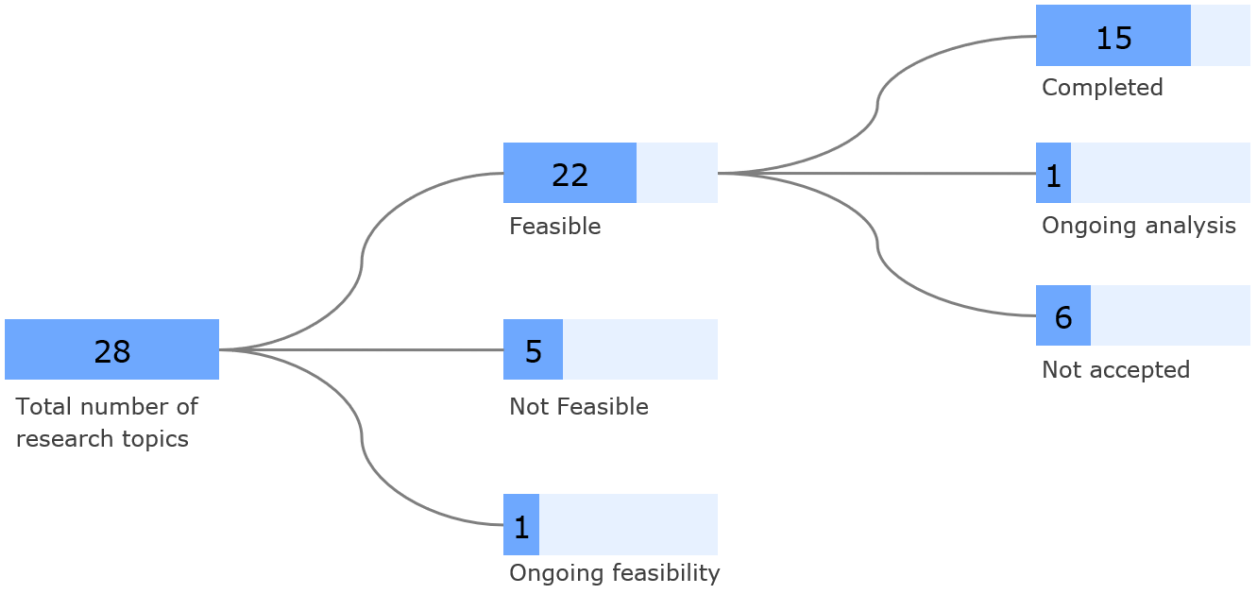


Figure 22. Number of research topics (and their statuses) to support PRAC decision-making

***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.*

Completed RWD studies and impact on decision-making

Amongst the 28 RWE research topics proposed, 22 were considered feasible of which 14 studies were offered by the EMA RWE team. Of the 14 offered studies, eight were accepted by the PRAC Rapporteur/lead member state, resulting in a total of 16 research questions that proceeded to analysis. All but one of these studies, which as of February 7th was ongoing, had been completed within the reporting period.

Thirteen of the 15 completed studies were conducted using the Agency's in-house databases and two via DARWIN EU®. While the two DARWIN EU® were conducted outside a specific procedure (see section 3.3. for a summary), all of the remaining studies were either linked to a safety signal, a PSUR or a variation application. Notably, amongst the 13 completed in-house studies, four studies were conducted to support EMA signal detection activities in the context of the COVID-19 pandemic by generating background rates of adverse events for observed-to-expected analyses.

Slightly more than half of the completed studies (8/15) were requested by a PRAC member or an EMA product team member, and the remaining seven studies were offered by EMA, mainly as a result of proactive screening of new safety signals (see summary below).

For seven studies, feedback on the usefulness of the results had been received. Four studies were considered by the respective Rapporteur/lead member state as supportive for the assessment and the results were incorporated in the respective assessment reports (immune thrombocytopenia in children following Diphtheria/tetanus/pertussis (DPT)/(acellular)/poliomyelitis (inactivated) vaccine; background rates of morphoea and scleroderma; Comirnaty and vulval ulceration; background rates of cutaneous T-cell lymphoma in patients with atopic dermatitis). Two of these studies are summarised below (see Annex 2 for additional PRAC use cases):

PRAC use case #1: Comirnaty and vulval ulceration (EUPAS50609)	
Problem statement	During routine signal detection, cases of genital ulceration (including vulval ulceration, vaginal ulceration, vulvovaginal ulceration, genital ulceration) in close temporal association to Comirnaty vaccination were identified. To support the assessment of a potential causal relationship, a RWD study was conducted using the primary care databases available to EMA.
Research question/ objective	The objectives of the study were to: (a) describe the use of the vaccine in the general population, and (b) estimate incidence rates of vulval ulceration in the general and exposed female population. In addition, a self-controlled case series (SCCS) was conducted to further explore a possible association.
Findings	The study was conducted in IMRD UK and THIN® Spain, which had sufficient exposure data. The study found no difference in post-vaccination incidence rates of vulval ulceration compared to the background incidence rates either 30 or 90 days after receiving the first dose of Comirnaty vaccine, or after receiving the second or third doses. Similar results were obtained for other COVID-19 vaccines (Spikevax and Vaxzevria). The SCCS analyses also found no increase in the incidence rate of vulval ulceration in the period after vaccination. However, confidence intervals of the incidence rates were relatively wide due to a limited number of follow-up years in each stratum analysed. This implies that the study is lacking power to provide an adequate precision in the estimates.
How was this useful?	The study results were considered helpful in absence of reliable background incidence in literature, which made an O/E analysis unfeasible. While likely underpowered (limited number of follow-up years), the study helped putting into perspective the reporting rate of vulval ulceration after vaccination and supported the PRAC conclusion that at the moment there is not sufficient evidence to conclude a causal association between vulval ulceration and Comirnaty exposure.

PRAC use case #2: Cutaneous T-cell lymphoma in patients with atopic dermatitis (EUPAS50517)	
Problem statement	During the assessment of a PSUR for dupilumab (Dupixent) the PRAC noted an increased reporting rate of cases of cutaneous T-cell lymphoma (CTCL). It is however also known that CTCL is more common in patients with atopic dermatitis (AD), which is one of the approved indications for Dupixent. While a study on the association of CTCL and use of Dupixent was not feasible with the primary care databases available to EMA (due to insufficient outcomes being recorded for exposed patients), an alternative analysis of cases occurring in the general population and patients with (severe) AD was possible.
Research question/ objective	The study aimed at describing the population incidence rates of CTCL, patient-level incidence rates of CTCL following diagnosis of AD, and patient-level incidence rates of CTCL following treatment for severe AD. Severity of AD was defined based on use of systemic immunosuppressive medicines. The study was designed to match as closely as possible a study presented by the marketing authorisation holder using OPTUM, a large claims database in the United States.
Findings	Analyses using IMRD UK and IQVIA™ Disease Analyzer Germany showed that the incidence rate of CTCL was higher in patients with AD diagnosis in comparison to the general population (four-fold in the UK and seven fold in the German database, which also includes data from specialist practices). In the UK, event rates in patients with AD who initiated treatment for severe AD were

PRAC use case #2: Cutaneous T-cell lymphoma in patients with atopic dermatitis (EUPAS50517)	
	also higher compared to all subjects with AD (around three-fold higher in UK). No difference was seen for patients with AD versus severe AD in Germany.
How was this useful?	The EMA study confirmed the findings of the OPTUM study which also indicated high incidence of CTCL in particular in patients with severe atopic dermatitis irrespective of treatments received. The results helped the PRAC reach the position that most cases of CTCL may be explained as misdiagnosis of AD, coexistence of AD and CTCL, or as a consequence of natural evolution of prior long-standing AD and that currently no causal association between dupilumab treatment and CTCL could be established based on the overall evidence.

For the full list of study requests and a portfolio of use cases please see Annex 1 and 2.

For the remaining three studies, positive feedback was received on the studies themselves. However, in one case (background rate of pemphigoid), the results of the study were not considered relevant for the decision-making as the PRAC conclusion was primarily based on spontaneous case reports and data from clinical trials. In another case (background rates of interstitial lung disease), the MAH had meanwhile submitted a type II variation to include the adverse event in the product information and the study itself was not further reflected in the assessment report. Finally, a study on macrolides use during pregnancy, while providing useful insights indicating that erythromycin is an important part of the therapeutic armamentarium in pregnancy, was not considered to impact the current recommendations of use. The study also highlighted the challenges of identifying the correct gestational age which is important for studies investigating the use of medicines during pregnancy.

Learnings: The majority of RWD studies during the reporting period (15 out of 27 completed studies) were conducted to support evaluations by the PRAC. Compared to the PRAC pilot from November 2019 to January 2021, during which 8 studies were carried out, there was an **increase in the number of studies performed** that is not entirely explained by the slightly longer duration of the present reporting period. Therefore, the comparably high number of PRAC RWD studies may not only reflect the more widely accepted use of RWE for safety surveillance of medicines, but also the **successful application of the learnings from the PRAC pilot and subsequent implementation of routine support measures**.

Recommendation**:** Generating and validating an **algorithm to identify gestational age** in different databases (in-house and/or through DARWIN EU®) will be useful for future studies in pregnant women.

Other RWE research requests/offers

Amongst the 12 study topics that did not proceed to analysis, one was undergoing feasibility assessment as of 7 February 2023, five were not feasible and the remaining six, while feasible, were study offers by EMA (based on two referrals and four signals) that were not accepted by the PRAC Rapporteur/lead member state:

- In four out of the five cases when a study was not considered feasible, this was due to the medicinal product not being prescribed in the primary care setting (terlipressin for treatment of patients with hepatorenal syndrome, regdanvimab for treatment of COVID-19 disease, amfepramone for treatment of obesity, pholcodine and risk of anaphylactic reaction with neuromuscular blocking agents). In the remaining case (Janus Kinase inhibitors), exposure

data were only available from one database, which was not considered sufficiently representative for the EU.

- Amongst the four signals for which a RWD study was offered but not pursued, the Rapporteurs or lead member state considered in three cases that there was already sufficient evidence for a comprehensive assessment and additional data would not be needed. In the remaining case (pulmonary hypertension following exposure to selective serotonin reuptake transporter inhibitors), the proposed in-house primary care databases to be used for the analysis were not considered adequate to address the research question due to limited information on confounders and the methodological challenge of constructing an adequate comparator group. For the remaining two referrals, in one case, an association study was not possible due to missing mother-child data linkage (risk of neurodevelopmental disorder after in-utero exposure) and the alternative offer for a drug utilisation study was not considered to be of substantial value. In the other case, the geographical coverage of the in-house databases was considered too limited (risk of meningioma with nomegestrol and chlormadinone).

Recommendation: Access to databases with existing **mother-child linkage** or creation of dedicated algorithms will be beneficial when investigating in utero exposure.

- The FWC and DARWIN EU® pathways were not considered in view of procedural time restrictions and since the study topics were proposed before establishment or in the very first weeks of DARWIN EU®.

Recommendation: Several research questions could have been addressed with **additional secondary care data sources** including hospital data as well as by **extending the geographical coverage** of the available data sources. This should be taken into account with a view to contracting future in-house data sources and onboarding of new DARWIN EU® data partners.

Learnings: Currently, **research requests with short timelines can only be considered for in-house database studies**, which are not suitable for studies of conditions identified/medicines used in specialist settings or very rare disease. This is expected to change in the future with the DARWIN EU® network becoming more agile and with pipeline developments progressing and the range of data partners expanding.

Regulatory context (use case categories) and RWE process related considerations

Three research topics (one request and two study offers) emerged outside any specific regulatory procedure. This includes the two DARWIN EU® studies discussed in section 3.1.3.

The vast majority of research topics (14) concerned safety signals. In addition, studies were considered in the context of safety referrals (6), PSURs (4) and type II variations (1). Consequently, the majority of RWD studies were performed either to generate background rates of the adverse event of interest or to explore the association between a safety event and the use of a medicinal product. Five of the research questions were addressed by drug utilisation studies and one (infeasible) was a request to study the impact of regulatory actions (amfepramone use for obesity).

- Systematic check of RWD study opportunities for safety referrals

The EMA process for new safety referrals systematically foresees for the referral officer to contact the EMA RWD study team in order to explore potential opportunities to generate RWE that could support the PRAC assessment.

- Proactive screening of PRAC signals

During the period covered by this report, **57 new signals** detected from EU spontaneous reporting systems or other sources have been screened by EMA. Amongst these, RWD studies were offered for 13 signals and nine of these were accepted by the PRAC Rapporteurs and/or or lead member states as potentially useful to support the respective signal assessment.

Amongst the nine signals selected, five were addressed by two studies. One study investigated the background rate of the suspected adverse event (interstitial lung disease) which was subject of two signals for different medicinal products. The other study looked at incidence rates of pemphigus and pemphigoid and the association with the use of three different COVID-19 vaccines. Consequently, a total of six safety studies were conducted (see above discussion on the usefulness of the results and reasons for study offers not being accepted).

For 44 out of the 57 signals screened, a study was not considered feasible. Across the six available primary care databases, the most frequent main reason for not conducting a study was lack of exposure data (61%): the medicinal products were either not prescribed in the care settings covered by the databases (31%) or exposure/use was too limited (30%). In one case, the product in question was not authorised in any of the countries covered by the available databases. Notably, information on recently approved and marketed medicinal products will only be available in databases after the respective data lag time has passed. Most of the data sources have a data lag of 6-12 months, with some being as fast as one month.

The second most frequent main reason for a study not being feasible was that the outcome was too rare or not recorded in the databases (19%). Other reasons included that there were no or too few exposed patients with the outcome of interest for exposed patients (13%) and the dictionary not being granular enough to capture the event of interest (2%).

Learnings: Every fourth to fifth new signal presented a feasible study opportunity. Even though not all of these studies were considered useful for the decision making, it can be concluded that the **screening of PRAC signals is a suitable tool to enable identification of RWE research opportunities** at an early stage of the assessment process.

4.2.7. Co-ordination Group for Mutual recognition and Decentralised procedures – human (CMDh)/National Competent Authorities (NCAs)

During the reporting period, three RWE research requests were received from members of the CMDh (2/3) and national competent authorities (1/3).

One of these requests was related to pholcodine and the risk of anaphylactic reaction with neuromuscular blocking agents, for which later a safety referral was initiated triggering a similar request received from the PRAC (see section 4.2.6.). The study was not considered feasible as non-prescription medicinal products are not captured in the available in-house databases, nor is the use of neuromuscular blocking agents during surgery and related cases of anaphylaxis. In another case (treatment of overdose), a survey amongst the FWC research organisations was initiated, but the study was also considered infeasible (see also section 3.4.2.).

Finally, for a request received from the Spanish national competent authority (off-label use of erythromycin as prokinetic agent), the feasibility assessment for a study to be conducted via DARWIN EU® was ongoing as of 7 February 2023.

Recommendation: The infeasible study to explore the relationship of pholcodine and the risk of anaphylactic reaction with neuromuscular blocking agents highlights the **need for full linkage of primary data to hospital care data, or, alternatively, a comprehensive claims database**. This should be taken into account with a view to onboarding of new DARWIN EU® data partners.

4.2.8. Other types of requesters/recipients of study results

Two RWE research questions arose from other sources.

One research question was linked to the EMA and Heads of Medicines Agencies (HMA) repurposing pilot which was initiated in 2021 in response to the European Commission's Expert Group on Safe and Timely Access to Medicines for Patients (STAMP) proposal for a medicines repurposing framework. The pilot targets approved products with well-established active substances intended for the treatment of a condition currently not approved and for which important public health benefits are expected. By using the available in-house data, EMA explored the feasibility of potential studies to support the pilot, by contextualizing the need for the new indication, i.e., if there is already off label use in some countries and characterizing the target population.

As part of feasibility the following checks were performed: availability of exposure to the repurposed drug candidates and availability of a population with the new indication. Especially, the already existing off-label use would be of particular interest, however, a general limitation of RWE databases is that the indication is inferred and not clearly linked to the prescribed drug. As some of the repurposed candidate drugs and new indications are well represented in the databases, further support could be provided to address RWE research questions that may arise during the upcoming scientific advice requests in 2023.

A second research topic arose from the workshop with HTA bodies and payers organisation from October 2022 and subsequent interactions. This is a study to explore the natural history of multiple myeloma including patient characterisation, treatments and survival. Multiple myeloma is a rare disease with a fast dynamic landscape regarding its evolution and standard of care, given the large number of effective medications approved recently. Therefore, updated information on clinical management was considered needed.

5. Discussion and recommendations

This analysis of the experience acquired with the conduct of RWD studies from September 2021 until the end of year 1 of DARWIN EU® in February 2023 shows both the great potential of RWD to address evidence gaps in various regulatory contexts and at the same time a number of challenges and opportunities for improvement.

Overall, during the period of this report, **27 regulator-led RWD studies** have been completed, primarily to support PRAC, COMP, SAWP and the PDCO in their regulatory assessments. Studies were performed using all three available RWE generation pathways and included safety, drug utilisation, and disease epidemiology studies, as well as studies to inform the design and feasibility of clinical trials and clinical management. Most studies were descriptive using simple analytics to describe incidence or prevalence rates of clinical outcomes or adverse events with or without prior exposure to specific medicinal products, or describing the extent and duration of exposure to medicinal products, their indications, as well as characterising the treated population. Comparative analyses were also performed, e.g., to explore the association of an adverse event with the use of (a class of) medicinal products, some of these employing more complex approaches such as self-controlled case series.

Both the number and the breadth of the types and designs of the studies performed shows the **versatility** and the **potential of the available RWE resources and pathways**, as well as the **Agency's ability** to address a range of research questions for regulatory decision making.

At the same time, in several instances, a request for a RWD study could not be addressed as the study was not feasible (19 out of 55 research topics for which a feasibility assessment had been conducted at the time of this report, 35%) or, if feasible, refused by the Rapporteur/lead member state as considered not to be of added value (6/55, 11%). Furthermore, only very few studies were requested by the CHMP, the CAT and CMDh/NCAs, and for some previously identified use case categories (notably representativeness and validity of clinical trials, as well as effectiveness) study opportunities have yet to be identified. Finally, complex analyses and phenotype development were often only possible if the study was conducted outside a specific regulatory procedure and, therefore, not subject to procedural time constraints.

This suggests that there is **room to improve in order to better leverage the full potential of the EMA RWD study framework**.

5.1. Suitability of available EMA RWD sources and pathways

In-house studies. When considering all three RWE generation pathways, data sources used in ongoing or completed RWD studies ranged across 13 European countries and included primary and secondary care settings, as well as disease registries. However, the majority of studies during the reporting period were conducted using the primary care in-house databases only, including mostly data from Germany, France and the United Kingdom. In-house studies were able to address half of the research questions identified during the reporting period (31/55, 56%). Notably, nearly all the ongoing/completed in-house studies (22/25) used IQVIA™ Disease Analyzer Germany which, in addition to primary care data also includes some information from specialist care settings and it is also the largest database available for in-house studies (representing over 15,000,000 patients).

A third of the identified RWD study topics was not feasible (19/55, 35%) mostly because the in-house databases did not adequately capture the outcome event and/or exposure of interest in combination with the fact that alternative RWE pathways (FWC and DARWIN EU®) could not be used in view of procedural time constraints. This lack of feasibility affected mainly PDCO related questions which frequently concerned (partial) waiver requests and/or the feasibility or modalities of clinical trials in

rare diseases for which there is limited information on the disease burden in children and challenges arise due to evolving nature and heterogeneity of phenotypes in the paediatric setting. Some limitations also arose from the need for more specificity (such as age), granularity (e.g. coding, information on indication, dosing, duration of use etc) and completeness of the data captured in the various sources.

DARWIN EU® studies. The capacity of DARWIN EU® to conduct studies in the first year of its establishment was limited to four studies and data partners were onboarded only towards the end of the reporting period. As a consequence, only a few studies were conducted via DARWIN EU® during the reporting period, benefiting from access to a wider range of data sources and geographical spread compared to the in-house study pathway. However, the distribution of studies by pathway is expected to change over time with DARWIN EU® analytical pipelines being developed and additional data partners being onboarded progressively. Already now, the studies conducted via DARWIN EU® showcase the potential of the large range of analyses possible per study including subgroups analyses, e.g., by age and indication, among others.

FWC studies. The FWC pathway was hardly used for the Committees pilots, primarily because the procurement process requirements are too slow to perform a study within the timelines of regulatory procedures. Nevertheless, FWC was clearly the preferred RWE generation pathway for both pharmacovigilance impact studies and studies conducted in response to the COVID-19 public health emergency.

For the latter, the FWC route provided access to research organisation and consortia with extensive experience in observational research including vaccine research and a rich range of data sources such as from Nordic countries with near real time access to vaccine exposure and outcome data. While generally time consuming to set up and conduct, a proactive approach to the FWC studies performed in relation to the COVID-19 pandemic enabled timely generation of RWE on the use and safety of the vaccines, disease epidemiology and impact of regulatory decision. All these studies contributed to the collective body of evidence around the COVID-19 pandemic, supporting regulatory decision making, in a fast-paced changing environment.

The FWC route was also frequently used for studies investigating the effectiveness of regulatory actions as part of the PRAC Impact Strategy. This was possible as the studies were not linked to a specific regulatory procedure with strict timelines. In the future, DARWIN EU® has the potential to become a principle pathway for impact studies. This would come with the advantage of systematic feasibility assessments which are routinely performed in DARWIN EU® but not for FWC studies, thereby enabling an informed decision on whether a study should be pursued. The process for impact studies is currently being updated to reflect lessons learned from past studies. This includes provisions for close collaboration with the PRAC from preparation of the study protocol to the report and a critical appraisal of the study results to inform the need for further regulatory action.

Lessons learned

- **Through the available data sources and RWE generation pathways, RWD studies can be conducted** able to address broad range of research questions and **support decision making in variety of regulatory contexts.** In 2022, this was in particular true for research questions concerning conditions and medicines used in the primary care setting, which constituted half of all queries received.

Recommendations

- The number, size, and type of **additional data sources** readily accessible to EMA should be increased in order to **expand coverage of different outcomes and exposure**, and consequently enable addressing regulatory questions into these settings. This includes:
    - electronic health records from **secondary care settings,** ideally all with **linkage to primary care data**, including ambulatory/hospital data and specialised care settings,
    - **biobanks, and large claims databases**, as well as **disease or patient registries** including those covering rare conditions,
    - data sources from additional European countries for **broader geographical representativeness**,
    - data sources that can address current **gaps in the data coverage**, e.g., information on age/birth dates especially for younger children, neonates, and mother-child linkage.

  This should be taken into account with a view to onboarding future in-house data sources, FWC research organisations and additional DARWIN EU® data partners.
- The **availability of different RWE generation pathways** (in-house, DARWIN EU® and FWC) that come with different advantages but also limitations, has proven useful to address research needs in various regulatory contexts. Once DARWIN EU® is fully established, in terms of volume of studies it is expected to become the main route for RWD studies. However, it will be important to maintain the ability of conducting RWE research in-house, especially for studies that have to be conducted within short timelines, and to have continued access to additional expertise and specialised data sources via the FWC in order to leverage the full potential of RWE research.
- This review only considered studies conducted via the RWE generation pathways available to EMA. However, in order to make full use of the EU network's capacity of conducting RWD research, **collaborations with NCAs and external stakeholders** should be explored in order to leverage **complementary pathways for RWE generation**, e.g., via national databases.

5.2. Regulatory context, timelines and usefulness of RWE for decision-making

Regulatory context and timelines. The majority of the research questions arose in the context of regulatory procedures (50/61), in particular safety signals (14), PIPs/waiver requests (13), referrals (6), PSUSAs (5), scientific advice requests (5) and (maintenance of) orphan designations (4). This highlights once more the variety of use cases for RWE to support regulatory decisions (see also portfolio of use cases in Annex 2). Notably, most studies were conducted to support PRAC decisions which suggest a successful implementation of routine support measures following the PRAC pilot in 2020.

All regulatory procedures are linked to defined timetables which also determine the timeframe for the conduct of the RWE research so that the results can be considered as part of the respective assessment. Adhering to regulatory timetables can be challenging, in particular if the research question emerges late and close to the procedure conclusion. Time constraints have affected the possibility of conducting RWD studies especially via FWC and DARWIN EU® as, at their level of maturity during the observation period (DARWIN EU® being in its first year of establishment), neither pathway allowed for the conduct of studies within less than two or three months. Even for the in-house pathway, short

timetables such as in place for scientific advice requests and or in case of late identification of research question in far advanced regulatory procedures have presented challenges, rendering some studies not being feasible.

During the reporting period, the only option in such cases was the in-house RWE generation pathway. In fact, the vast majority of in-house studies (19/24, 79%) were completed within three months and a significant subset of the studies (10/24, 42%) even within less than 30 days after receipt of the respective request, showing the agility of the in-house study pathway and ability to address RWE needs arising from regulatory procedures with demanding timelines. However, studies for conditions/treatments in secondary care settings were not or only possible to a limited extent via this pathway. This particularly affected the ability to generate RWE in order to support PDCO and COMP assessments.

Some studies were requested or proposed outside specific regulatory procedures including those conducted via DARWIN EU® and the FWC. In some of these cases, the studies addressed questions of general interest, e.g., utilisation of medicines and treatment patterns, and in other cases the studies were specifically requested in anticipation of future applications which was informed by the knowledge of dynamic development pipelines, e.g., orphan designations in rare blood cancers, PIP/waiver requests for Duchenne muscular dystrophy.

It would be beneficial to explore a more proactive approach through additional and better ways to anticipate study needs/research questions as this would allow more time for study design and conduct. Successful examples include the proactive monthly screening by EMA of new safety signals. The screening approach could potentially be expanded to other procedure types, however, the experience with the attempted review of PDCO minutes has shown that often more detailed insights into the procedure and topic expertise is needed to identify research questions of regulatory relevance. Therefore, a more active engagement of the EMA product team, Committee and Working Party members is needed.

To further improve the responsiveness of the RWD study framework, it will also be important to look into means to further accelerate the generation of RWE, especially through pathways other than in-house databases. The latter is foreseen with DARWIN EU® which aims at developing a catalogue of standard data analyses including off-the shelf and routine repeated studies that can readily be executed. Through DARWIN EU®, it is also planned to develop a phenotype library and analytical packages to support future studies as research questions emerge. Correctly identifying the patient population of interest in real-world databases is challenging and many research requests concern a very specific disease setting (e.g., only severe patients, or pre-treated patients having previously received multiple line of therapy). To this end, the DARWIN EU® Coordination Centre in collaboration with EMA is working on creating clinically accurate, validated, and reproducible algorithms for the identification of clinical phenotypes from EHR data. Finally, increased automation of repeated tasks such as report writing, graph/figure building etc. is expected to help speed up the process of RWE generation via DARWIN EU®.

Other ways of generating readily available data for regulatory purposes could include the development of simplified protocols to inform decisions on the feasibility of clinical trials and to carry out subgroup analyses, e.g., across the full range of age groups, for all DARWIN EU® studies even if not the main objective, as this could also support decisions of Committees in addition to the main RWE sponsor/requester of a study. Another option to be further explored could be to produce pre-computed, searchable data dashboards from which simple study requests can then be addressed almost instantaneously.

Usefulness of RWE for decision making. When considering all feedback received on the usefulness of the studies conducted, two out of three requesters/ Committee sponsors considered the results supportive for their assessment. In some cases, the data were either not considered critical or the study limitations hampered the interpretability of the study findings. By expanding the range of methodological approaches used, applying more advanced methods to control for confounding, developing and validating complex phenotypes, as well as facilitating the access to specialised care and mor granular data, future studies would be expected to provide even more relevant evidence to support decision making. Therefore, early identification of RWE research questions which will allow for the conduct of more complex/time-consuming studies with a broader range of data sources is likely to also increase the impact of the study results for regulatory decisions.

Furthermore, for all study requests received, the precise regulatory question/evidence gap to be addressed should be clarified as it will help understand if and how, useful evidence can be generated. A good understanding of the regulatory context may also enable those shaping the requests for RWD studies to consider alternative solutions to support the assessment, even when the original research question turns out not to be feasible. It is equally important to define the precise research question and to have a good understanding of the clinical context. Areas for which already a rich set of information is available in the scientific literature may not benefit as much from additional studies, in comparison to areas lacking previous research.

During the preparation of protocols as well as after completion of studies, the requesters/Committee sponsors frequently asked questions about limitations inherent to RWD such as accuracy, quality and completeness of the data, impact of local health systems, representativeness of the results as well as methodological issues including bias due to potential confounding factors, incorrect definition of phenotypes, etc. A thorough discussion in the study reports of both the strengths and limitations of the studies, contextualising the results vis-à-vis information already available in the scientific literature, was considered helpful to address some of these questions and consequently facilitate the interpretation of the study findings. Further efforts to make available relevant information on the data sources and methodological aspects of the studies will help achieve a better understanding and acceptance of RWE to complement other types of evidence in regulatory decision making (see also discussion in section 5.3 on capacity building).

Lessons learned

- RWE has the potential to support a variety of research questions emerging in different regulatory contexts and procedures. Currently, for studies initiated only once a procedure starts, the **in-house pathway is most suitable to generate RWE within a short time period** as needed to adhere to the demanding procedural timetables. This is expected to change in the future with the DARWIN EU® delivery model becoming more agile and with progress in the development of a catalogue of standard data analyses.
- **Early identification of RWE research questions** will allow for the conduct of more complex/time-consuming studies and more frequent use of the FWC and DARWIN EU® pathways to perform studies, thereby enabling access to a broader range of expertise and data sources.
- A good understanding of the **regulatory context and the precise knowledge gap** to be addressed is important to ensure that the study is designed in a way that it is fully suited to support regulatory decisions.
- A good understanding of **data provenance, quality and completeness** and other data source characteristics helps to understand both the strengths and the limitations of RWD studies conducted. The RWD source catalogue and data quality framework currently being prepared by EMA will help to further address these aspects.

Recommendations

- It should be **explored if and how relevant research questions can be identified proactively** and even ahead of the submission of a regulatory application, taking into account dynamic development pipelines, by expanding screening approaches for suitable procedure types and by leveraging expert input from the RWE liaison groups, the Committees and EMA product teams as well as other relevant fora.
- Additional **strategies to further accelerate the generation of RWE** should be explored:
    - As foreseen for DARWIN EU®, **pipelines** for off-the shelf and routinely repeated studies should be further developed, as well as **phenotype libraries and analytical programs** and **automation of repeated tasks**. In addition, the generation of **pre-computed, searchable dashboards** may be an option to address simple study requests almost instantaneously.
    - For questions on the feasibility of conducting clinical trials, **simple protocols** providing for **standardised outputs** could help generate evidence in a timely manner to inform SAWP and/or PDCO decisions in rare diseases including age specificities for which there is limited information on the disease burden.
    - As a standard approach for any study conducted via DARWIN EU®, a **predefined spectrum of subgroup analyses** should be conducted even if not the main objective (e.g., various paediatric age ranges), as this could help inform additional Committees other than the main RWE sponsor/requester.
- A **thorough discussion of the choice of the data sources, the study findings as well as the strengths of the study and its limitations** as well as methodological aspects, e.g., how potential confounding factors were addressed, helps the interpretation of the findings and their integration into regulatory decision-making. This should be taken into account for future study reports.

5.3. Building capacity and capability to respond to research requests

Knowledge management is critical in building capability and capacity to respond to research requests. The experience with the RWE pilots has confirmed that there is a need for educational and knowledge management tools to help decision-makers and stakeholders familiarise themselves with RWD and RWD research including associated concepts, methods, and terminologies. There are several new concepts, e.g., computational phenotyping, which is a crucial step in the development of study protocols, but despite the involvement of the study requester/Committee sponsor in all steps of the study conduct, there have been limited contributions in this area so far, potentially because of a lack of familiarity with this concept and related coding systems.

On training and onboarding, the Big Data Steering Group's Pharmacoepidemiology curriculum will start being delivered through 2023, with a wide learning offer explaining, amongst others, the role of RWE in the regulatory context, types of data sources, how to formulate a research question and how to perform RWD studies and interpret the results. In addition, the RWE training strategy provides for additional training offers specific to DARWIN EU® and in-house analytics, to help both EMA data analysts and committee requesters understand the available methods, data, and tools, such as the Instant Health Data (IHD) rapid analytics tool. Furthermore, with regard to IHD, bespoke onboarding training and advanced training materials have been developed and are provided to analysts that will use the tool. The training strategy is reviewed annually to ensure that the materials reflect the most up-to-date information. In addition, the DARWIN EU® Coordination Centre will provide a learning offer annually for coders and epidemiologists to be able to confidently use and understand both the OMOP Common Data Model and the analytical toolkits developed.

Documentation and information are ensured via the creation of SOPs, WINs and RWE companion books, the latter of which can be used as a consulting manual in the design, conduct, and interpretation of RWD studies as well as a portal to access information on SOPs, WINs and other documentation related to requesting RWD studies. The RWE companion books are revised at least annually.

Practice is the last phase of skillset creation and relates to the real-life application of the learning elements, that refreshes and consolidates knowledge. Practice is achieved through the routine application of the acquired knowledge, either through simulation, replication, or execution. For analysts, refresher sessions around the use of analytical tools are routinely provided, giving users a chance to use and hone their skillsets.

For EMA requestors, and in general, recipients of RWE at EMA, a RWE community (see also section 5.4. on collaboration) has been established providing space for simulations, from requests-to-results.

Lessons learned

- **Knowledge of RWD and RWD research concepts, methods and terminology** key to fully incorporate RWD/RWE in EU regulatory decisions alongside the gold standard of clinical trials.

Recommendations

- Execute the **Big Data Steering Group's Pharmacoepidemiology curriculum** with a wide learning offer including development of educational material and tools specifically designed for RWE sponsors in the EMRN and beyond.

5.4. Collaboration, awareness and process related aspects

Collaboration. Close collaboration between different functions and stakeholders has proven to be crucial for successful study conduct and implementation of a fit-for-purpose RWE support framework. This includes the following interactions:

- For individual RWD study requests: Close interaction between the EMA RWE team and the requester/Committee sponsors as well as relevant EMA topic/scientific leads is important throughout the RWD study process, from receipt of the study request to the feasibility assessment, preparation of the study protocol and the analysis plan, in order to ensure that the precise research question and regulatory context is fully understood and translated into a study suitable to address the respective evidence gap. Some studies also benefit from the involvement of clinical experts, e.g., to inform complex computational phenotypes, and occasionally, the audience may be expanded beyond the original requester to other relevant interested parties, e.g., PDCO in case of any research for children or COMP in case of prevalence rates for rare diseases. Finally, involvement of patient representatives should be systematically considered to ensure that the interests and the experience of patients area adequately reflected.

- To explore decision-maker/stakeholder needs and discuss the implementation of the RWE support framework: Throughout the ongoing pilots, regular interactions with the Committee RWE liaison groups have proven to be valuable to discuss both general and more specific aspects of RWD research. These forums provide an opportunity for flexible engagement to discuss in-depth Committee specific needs, experience from individual studies as well as process related matters, methodological aspects, and many other topics. Close interaction is also crucial to understand, address and potentially alleviate any concerns or doubts in relation to observational research in general or regarding a specific study.

  Furthermore, EMA is currently providing updates to relevant scientific Committees, the SAWP and CMDh on a quarterly basis to inform of any relevant developments, progress in the establishment of DARWIN EU® and to present new study results. This exchange is important to ensure awareness and continuous interaction to inform the establishment of a framework for RWE that is fit-for-purpose to support EMRN needs.

  Beyond the Agency's scientific Committees and national competent authorities, HTA bodies and payers' organisations as well as ECDC have been identified as stakeholders for RWE support. A workshop with HTA bodies and payers' organisation was held in October 2022 to identify pilot studies to be conducted via DARWIN EU®. Furthermore, in May 2022, EMA and ECDC launched the EU Vaccine Monitoring Platform (VMP), a joint initiative for strengthening the post-authorisation monitoring of the safety and effectiveness of vaccines in the EU. Through the existing communication routes at EMA as well as this platform, further interactions will be pursued.

- To maintain and expand forums for RWE knowledge sharing: EMA recently established a RWE community which is an internal forum to foster knowledge sharing and promote good practices related to RWE across various functions including the entirety of the EMA product team members, the latter being key to a smooth operation of the RWE framework and facilitating the identification of RWE research topics. A community of RWE experts from the EMRN may also be formed as part of the European Scientific Expert Communities (ESECs) pending further discussions within the Methodology Working Party. Ideally, these communities are united or work alongside each other in close collaboration.

Awareness and transparency. While the collaboration with requesters/RWE sponsors has been very productive, the present analysis has also shown that awareness of the possibility to request and obtain RWE as well as the related process remains limited.

Less than half of all requests were received via the dedicated email address and very few requesters used the email template with instructions on the information to be provided. In view of the intention to upscale DARWIN EU® aiming to deliver 140 studies per year from 2025, it would be beneficial to streamline the process for study requests by better establishing the use of and providing access to the aforementioned template. A targeted set of guidance documents should be developed and made available.

Notably, more than half of the RWD studies were conducted to support assessments by the PRAC and there was an increase in the number of studies performed compared to the PRAC pilot in 2020. While not unexpected in view of the long-standing history of use of RWE in pharmacovigilance, the high number of studies performed for PRAC also suggests a successful implementation of routine RWE support measures following the completion of the pilot. At the same time, only very few requests have been received from CHMP, the CAT and CMDh/NCAs and there has been no request for certain use case categories (notably representativeness and validity of clinical trials, as well as effectiveness). Further efforts will need to be made to help the identification of potential research topics in areas for which RWE is less established. One proposal for a more systematic approach to trigger reflections by CHMP and CAT Rapporteur teams on evidentiary gaps/research needs was implemented in February 2023 by adding a tick box in the readers' guidance template. Whether as a result more research requests will be received will be assessed in 2023 and onwards.

Furthermore, EMA intends to consult scientific Committees and Working Parties on their needs for early identification and characterisation of regulatory applications involving RWD with methodological complexities. This builds to the recommendations laid out in the EMA Final programming Document 2022-2024 and the Big Data Steering Group workplan 2022-2025 on the promotion of methodological innovation in global drug development, and on the provision of advice and interpretation of complex methodologies across (clinical) drug development and monitoring. This activity will help identify potential gaps and opportunities for methodology support and may equally present an opportunity to identify areas of need for RWE generation.

For full transparency and to facilitate sharing of information and files, EMA has put in place a folder in the Managing Meeting Document system (MMD) for RWE including all study reports completed during the pilot. Similarly, for COMP and SAWP who have already been fully migrated into IRIS, dedicated SharePoint folders in the respective Committee libraries have been created. A SharePoint solution should also be considered for other Committees, NCAs and external stakeholders as it will facilitate exchange of information, files (including draft study protocols and results) and review of documents.

Other process related aspects. To ensure a harmonised approach for the conduct of RWD studies, EMA has developed templates for in-house feasibility assessments, analysis plans and study reports. Similarly, templates are in place for DARWIN EU® studies conducted by the Coordination Centre. Further alignment of these templates and related processes may be beneficial, e.g., by implementing the HARmonized Protocol Template to Enhance Reproducibility (HARPER) used for DARWIN EU® and also for in-house studies. Similarly, the approach to feasibility assessments could be harmonised to ensure an equally well-informed decision on whether to proceed with a study irrespective of the RWE generation pathway.

For transparency and planning purposes, timetables should be developed and communicated for all RWD studies providing for sufficient time for requesters'/RWE sponsors' involvement at relevant milestones (e.g., review of draft protocol and study report). Ideally, timetables should be standardised

(e.g., 60 days for support to signal assessments) with some flexibility accounting for both the complexity of the analysis as well as time constraints arising from the related regulatory procedure.

To enable smooth integration of the study results into the assessment reports, a redacted version should be provided alongside the final report with all confidential and personal identifiable data being removed as intended for publication.

Lessons learned

- Implementation of a **harmonised approach** for the conduct of RWD studies through agreed **processes and templates**, and standard procedures aligned with regulatory procedural time have proven to be essential to generate RWE in an efficient and timely way.

Recommendations:

- **Close collaboration** between the requester/Committee sponsor of a study and the EMA RWE team is key to the successful conduct of studies. **For each study, there should always be at least one sponsor** identified from the EMRN or the wider spectrum of regulatory and decision-making bodies (e.g., HTA/payers and ECDC) as an end-user of the study findings. Involvement of additional experts, such as clinical specialists to inform the clinical context and/or identification of the study target population, as well as patients should also be systematically considered.
- Continue, and where relevant, intensify **regular interactions with relevant scientific Committees, the SAWP, and the CMDh** such as through the quarterly updates and **continue dialogue with the RWE liaison groups** to better understand Committee specific research requirements and potential research areas of interest.
- Pending further discussions within the Methodology Working Party, consider forming **a community of RWE experts from the EMRN** via the European Scientific Expert Communities (ESECs) to **facilitate knowledge sharing** and promote good practices related to RWE.
- Promote the possibility to request RWD studies via the Agency's RWD study framework and explore additional means to **systematically trigger reflections** by Rapporteurs and EMA product teams to help **identify evidentiary gaps/research needs** that could be addressed by RWE, e.g., inclusion of a tick box in the readers' guidance template for CHMP and CAT in February 2023.
- The use of the dedicated email address for requesting RWD studies and the related email template should be further promoted and access facilitated. Generally, a more easily accessible platform for sharing of files (including draft study protocols and reports for review) and access to relevant guidance should be explore, e.g., via SharePoint.
- Further **streamline and harmonise processes and templates** for an efficient conduct of RWD studies regardless of the generation pathway.

Annex 1: List of EMA RWD study requests

This Annex is available in an Excel spreadsheet here.

Annex 2: Portfolio of use cases

This portfolio summarises relevant research areas for RWE to support EU regulatory decision making and lists illustrative examples of RWD studies conducted against the various use case categories.

Use case categories

Three main areas for which RWD analyses can support committees' decision making has been identified.

- Support the planning and validity of applicant studies
- Understand the clinical context
- Investigate associations and impact

1. Support the planning and validity of applicant studies

Under the first use case objective, supporting the planning and validity of applicant studies, two main use case categories have been identified.

a. Design and feasibility of planned studies: these could include studies that inform recruitment in pre and post authorisation studies by providing number of incidence and/or prevalence patients per year (for disease and/or drugs), and geographical variation of incidence and/or prevalent patients. An example of such a use case would be in the context of waiver or paediatric investigation plan modification, investigating the feasibility of clinical studies in young children with for example a rare haematological condition. Another example where this use case could be informative, is when examining the impact of planned inclusion/exclusion criteria on either patient recruitment and its feasibility, or composition of study population vs. real world target population.

b. Representativeness and validity of completed studies: such studies would seek to evaluate the external validity, for example, by measuring the representativeness of the clinical trial (CT) population vs. real world target population, evaluating whether the standard of care use in the control arm of a CT is comparable with the current real-world standard of care, or as an external comparator.

2. Understand the clinical context

Under the second objective, understanding clinical context, three main use case categories have been identified.

a. Support the evaluation of incidence and prevalence of diseases: such studies include for example investigating the prevalence of disease for orphan designation or maintenance. Do recent data and from a broader set of databases support the maintenance of an orphan designation? Additionally, studies can also support the better understanding of the disease and its progression by investigating baseline factors at diagnosis and post-diagnosis characteristics.

b. Clinical management: these studies typically generate evidence on the actual clinical standards of care across Europe. For example, how are patients diagnosed, are medicines use according to the authorised indication and/or off-label, what are the treatment patterns?

c. Drug utilisation: studies that help characterise real world drug use. Such studies investigate the incidence & prevalence of medicine use, the indication (on and off label), amount and duration of exposure to medicine, and switching of medicine over time. For example, RWE

evidence can support the contextualisation of risk of a possible contamination of a medicinal product, by answering questions such as what is the use of the medicinal products and how has it evolved over time? What other medicinal products are available, and have they been used?

3. Investigate associations and impact

Under the third and final objective, investigating associations and impact, two main use case categories have been identified.

a. Effectiveness and safety studies: such studies investigate the association between treatment exposure and either effectiveness or safety outcomes. For example, by characterising adverse events occurring in the treated population (incidence of events, time-to-onset, stratification by subpopulations). A recent example of a safety study investigated the association between COVID-19 vaccines and the occurrence of thrombosis with thrombocytopenia syndrome (TTS). Studies were proactively initiated to calculate background incidence rates to put into context the first cases of thrombosis events received. The analysis allowed to investigate the potential signal and was central to the assessment of the EMA committees.

b. Monitor implementation of risk minimisation measures: these studies investigate the changes in drug use with time. Such impact studies also monitor effectiveness of risk minimisation measures by generating evidence on changes in incidence of harmful event with time.

Uses cases

The following use cases present examples of past RWD analyses which EMA has undertaken, and which were considered useful to support regulatory decision making:

- **Design and feasibility of planned studies:**

Use case 1: PDCO – Prevalence of hypereosinophilia (EUPAS45202)	
Problem statement	The applicant for a medicinal product developed for the treatment of patients with eosinophilic asthma, requested a partial PIP waiver for children younger than 6 years of age. The applicant claimed that studies would not be feasible as the condition is too rare in this age group. Contrasting data was available indicating very low prevalence in a European database and higher prevalence (suggesting that the study might be feasible) in a US database. To decide on the waiver request, the PDCO requested additional European data to better inform the feasibility of clinical trials in children with hypereosinophilic syndrome (HES).
Research question/ objective	The study aimed to describe the yearly prevalence of HES in children aged 0-5 and 6-11 years in Europe.

Use case 1: PDCO – Prevalence of hypereosinophilia (EUPAS45202)	
Findings	An analysis in IQVIA™ Disease Analyzer France and Germany showed that cases with possible HES were rare in children aged 0-5 years with an estimated yearly prevalence between 0.0 and 6.2 per million children, and no child below the age of 6 years had a confirmed HES diagnosis. Possible HES was somewhat less rare in children aged 6-11 years with an estimated yearly prevalence between 0.0 and 74.6, and a single child was identified with confirmed HES. These results were based on a paediatric population of around 30,000-60,000 children per age group per year in France and around 200,000-380,000 children per age group per year in Germany. Results of this study are consistent with the lower end of the estimates of the published literature.
How was this useful?	The results supported the applicant claims and supplemented the available scarce evidence in the scientific literature. The results supported the PDCO decision to grant a waiver for children below 6 years of age and since the analysis was performed in a short period of time, another request to the applicant could be avoided.

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

- **Support the evaluation of incidence and prevalence of diseases (Disease epidemiology):**

Use case 3: COMP – Prevalence of narcolepsy (EUPAS48036)	
Problem statement	During the review of an initial orphan designation request for a medicinal product intended for the treatment of narcolepsy, an analysis of in-house RWD was requested to understand the evolution of the prevalence rate since the H1N1 vaccination campaign and the finding of an increased risk of narcolepsy in children and adolescents.

Use case 3: COMP – Prevalence of narcolepsy (EUPAS48036)	
Research question	What is the yearly prevalence of narcolepsy between 2011 and 2019, stratified by sex and age group?
Findings	An analysis of the data available in IQVIA™ Disease Analyser France and Germany showed stable annual prevalence rates in France (between 0.77 and 0.98 per 10,000) during the observation period, whereas prevalence steadily increased over time in Germany (from 1.83 per 10,000 in 2011 to 3.16 per 10,000 in 2029). The observed rates in France were lower than the previously published prevalence of 2.1-2.6 per 10,000 persons in the literature and hence considered to be underestimated in the database. However, the findings in Germany were in line with estimates previously reported in the global literature (2.5-5 per 10,000 persons).
How was this useful?	The results provided up-to-date prevalence of narcolepsy in two European countries that was useful to support discussions during the review process.

Use case 4: DARWIN EU® - Prevalence of rare blood cancers in Europe (EUPAS50800)	
Problem statement	Substantial uncertainty surrounds the prevalence of rare blood cancers. Using real-world data, brought together as part of DARWIN EU®, we aimed to estimate the prevalence of rare blood cancers to assess whether they still meet the threshold to be classified as a rare disease.
Research question	What is the prevalence of rare blood cancers in Europe, specifically, of follicular lymphoma, diffuse Large B-Cell Lymphoma, multiple myeloma, chronic lymphocytic leukaemia, acute myeloid leukaemia and acute lymphocytic leukaemia?
Findings	As of the 1st January 2020, 5-year partial prevalence estimates for ALL ranged between 0.44 (0.44 to 0.44) and 0.65 (0.65 to 0.65) per 10,000. Estimates for AML ranged between 0.72 (0.72 to 0.72) and 1.03 (1.03 to 1.03). Estimates for CLL ranged between 2.83 (2.83 to 2.83) and 4.13 (4.13 to 4.13). Estimates for DLBCL ranged between 0.47 (0.47 to 0.47) and 1.73 (1.73 to 1.73). Estimates for FL ranged between 0.90 (0.90 to 0.90) and 2.83 (2.83 to 2.83). Lastly, estimates for MM ranged between 2.15 (2.15 to 2.15) and 4.27 (4.27 to 4.27). Complete prevalence was higher than partial prevalence, more than double the 5-year partial prevalence of CLL for example, while 2-year partial prevalence was substantially lower. Estimates were typically higher for older age groups except for ALL. The relationship between sex and prevalence varied depending on the study outcome. Increasing trends over calendar time were more typically seen for complete prevalence compared to partial prevalence.
How was this useful?	The study provides estimates of prevalence from five European countries to inform decision making, among others, on orphan designations for these disease areas.

Use case 5: PRAC – DARWIN EU®: Use of valproate-containing medicinal products in women of childbearing potential (EUPAS50789)	
Problem statement	Vaproic acid/valproate-containing medicines (VPA) are first-line treatment for generalised tonic - clonic seizures (epilepsy) and adjunctive therapies in other types of seizures. They are also used as second-line treatments or adjuncts for

Use case 5: PRAC – DARWIN EU®: Use of valproate-containing medicinal products in women of childbearing potential (EUPAS50789)	
	the treatment of bipolar disorder, and for migraine prevention. Valproic acid is a teratogen, with prenatal exposure carrying a substantial risk of neurodevelopmental impairment and congenital malformations in the child. Therefore, its use in women of childbearing age (WCBP) is restricted to prevent valproate exposure during conception and pregnancy.
Research question	The objectives of this study were: 1. To characterise the prevalence and incidence of use of valproate, valproate containing medicines, and alternative therapies among women aged 12 to 55 years of age, stratified by calendar year and age 2. To characterise the use of valproic acid or valproate containing medicines among women aged 12 to 55 years of age, stratified by indication, calendar year and age.
Findings	The incidence of new use of VPA amongst women 12 to 55 years decreased over the period 2010-2021 for all analysed datasets: ACI VARHA, CPRD GOLD, IPCI, SIDIAP, IQVIA Belgium LTD, and IQVIA Germany DA, from a maximum of 250 new users per 100,000 person years in 2010 to less than 89 in 2021. The median age in these cohorts of women ranged between 40 and 43 years. Healthcare utilisation was high with the median number of visits ranging between 5 in IQVIA Germany DA and 29 in CPRD. Anxiety and depressive disorders were frequent comorbidities, with 20%-39% and 16%-44% having a history of these before treatment start. The level of prescription of contraceptives was highest in CPRD GOLD, followed by IQVIA Belgium LPD, IPCI and lowest in SIDIAP and IQVIA Germany DA. Use of hormonal contraception varied greatly across age groups, with highest levels of prescriptions being observed in women between 15-39 compared to lower rates in the >50- and 12–14-year age groups. At the population level, the prevalence of use of VPA among women of childbearing age has declined since 2015 in all data sources. Incidence rates declined over the same period in all four databases. Conversely, alternative antiepileptics have increased in uptake in the same period, with gabapentinoids showing a more obvious increasing trend.
How was this useful?	The study results provide recent data on drug utilisation of valproate in WCBP, further to the implementation of risk minimisation measures by the PRAC. The study can be repeated in the future, and when necessary, with an accelerated timetable due to the re-use of the existing analytical pipeline.

Use case 6: CAT – Spinal muscular atrophy (SMA) - natural history of disease and treatment patterns (EUPAS50476)	
Problem statement	With the recent approval of disease modifying therapies, the natural course of SMA, diagnostic criteria and standard of care are expected to have evolved significantly. Recent studies have reported disease trajectories that significantly differ from the known natural history of SMA.
Research question/ Objectives	The study aims to investigate SMA patients' course of disease and standards of care delivery over time in multiple European countries including the newly

Use case 6: CAT – Spinal muscular atrophy (SMA) - natural history of disease and treatment patterns (EUPAS50476)	
	available disease-modifying therapies in real-world settings. The study uses patient registry data from seven SMA registries.
Findings	The study is ongoing. The study report is expected in Q3 2023.
How is this expected to be useful?	This study will inform future study designs and contextualise clinical data of new developments in this area. The results will also support the long-term post-authorisation efficacy and safety follow-up of advanced therapy medicinal products (ATMPs) and help to better understand the added benefit of a new therapy and its place in current practice.

- **Drug utilisation:**

Use case 7: SAWP - Angiotensin II receptor blocker (ARB) use in paediatric population (EUPAS104305)	
Problem statement	In order to support a SAWP advice procedure, EMA offered to provide up-to-date data on the use of angiotensin II receptor blockers (ARBs) in children with arterial hypertension, occurrence of primary vs. secondary hypertension in children by age group as well as risk factors for this disease that would help to understand if secondary causes of hypertension are more common in younger children below the age of 6 years.
Research question	The study aimed to describe the population level prevalence of arterial hypertension in the paediatric population, the main risk factors (looking at medical history of the patients) and the use of ARBs in this population.
Findings	Most children identified in the databases (IQVIA™ Disease Analyser France and Germany and IMRD UK) with hypertension had received a diagnosis of presumed primary hypertension. Only a small proportion had a diagnosis of secondary hypertension. Large differences, up to around 20-fold, were identified between the databases in the yearly prevalence of arterial hypertension in children 2-17 years (in Germany around 6-7.8 per 1000 children, in the UK around 0.2-0.4 per 1000 children, and in France 0.5-0.8 per 1000 children). Prevalence increased with increasing age and was highest in children 13-17 years and lowest in children 2-5 years. Only few children with a history of arterial hypertension received treatment with an ARB. The highest proportion was observed in the UK (14.3%), followed by France (5.7%) and Germany (1.5%). Risk factors for hypertension varied between the three countries, both in terms of history of diseases or conditions, and in terms of treatment with drugs that increase blood pressure.
How was this useful?	The study provided helpful insights in the use of ARBs and causes of hypertension across different paediatric age groups.

Use case 8: DARWIN EU® - Use of Antibiotics in the 'Watch' category of the WHO AWaRe classification (EUPAS103381)	
Problem statement	The inappropriate use of antibiotics can lead to the development of antimicrobial resistance (AMR). The WHO "Watch list" includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine and/or antibiotics that are at high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of stewardship programs and monitoring.
Research question/ Objectives	The objectives of this study were to investigate the incidence and prevalence of use of antibiotics (from the WHO Watch list) and to explore duration of antibiotic use as well as indication for antibiotic prescribing/dispensing.
Findings	This study included five data sources from the Netherlands, United Kingdom, Spain, Germany and France. Amongst the listed antibiotics, 78 were prescribed in at least one of the data sources during the study period. Of the prescribed antibiotics, few had an incidence rate > 100/100,000 person-years (PY). Those antibiotics with the highest incidence rates were the same within the databases with, for instance, high prescribing (amongst top 3) of ciprofloxacin in all 4 primary care databases. Other drugs frequently prescribed in primary care were clarithromycin, fosfomycin and azithromycin with some variation amongst the data sources. In secondary care, higher use of ceftriaxone, vancomycin and meropenem was observed. In some databases, an increase in incidence rate over time was observed for ceftriaxone, cefuroxime, piperacilline-tazobactam and vancomycin. For azithromycin, different patterns were observed by database with an increase in IMASIS (ES) and SIDIAP (ES) up to 2018 and 2020 respectively, a decrease in IPCI (NL) and stable use in CPRD GOLD (UK) and CHUBX (FR). A decrease or steady state in incidence rate was observed for the fluoroquinolones. Other antibiotics for which the incidence rate clearly decreased over time were pheneticillin, oxytetracycline, erythromycin and clarithromycin. The prevalence analysis was in line with the incidence rates with highest use for azithromycin, ciprofloxacin, clarithromycin, and fosfomycin. Antibiotic use was lower in children than in adults and use increased with age. For some of the antibiotics, use was also high in children or young adults such as macrolides, second generation cephalosporins and tetracyclines. In primary care databases, the median duration of treatment ranged around a week and was shorter in hospital databases. With regard to the indication of use, there was a high proportion of prescriptions/dispensing with unknown indication (i.e., presence of a disease code but not belonging to any of the infection classes that had been generated) or missing indication (no disease code around the prescription/dispensing).
How was this useful?	The study provides important data on the long-term trends in utilisation of many antibiotics at risk of AMR, spanning primary and secondary care settings in five European countries over 10 years. The analysis can be repeated with an accelerated timetable with additional antibiotics and additional data sources, as and when necessary to inform regulatory decision making. PRAC welcomed the utillity of the results as additional evidence from European countries in the monitoring of antibiotics use as part of the work on antimicrobial resistance, allowing supervision of antibiotics across healthcare settings and countries. PRAC considered these results in the context of the ongoing review

Use case 8: DARWIN EU® - Use of Antibiotics in the 'Watch' category of the WHO AWaRe classification (EUPAS103381)	
	of the EMA commissioned impact study on fluroquinoloones use after the referral (EUPAS37856) see section 3.4.4. In addition, the CMDh, the Infectious Diseases Working Party (IDWP), and members of the joint inter-agency antimicrobial consumption and resistance analysis (JIACRA) showed great interest in the study results and possible future repititions.

- **Safety studies**

Use case 9: PRAC - Immune thrombocytopenia in children receiving tetravalent vaccines (EUPAS104290)	
Problem statement	The combined vaccine diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccine (adsorbed), also referred to as DTaP-IPV, is indicated for primary vaccination in infants and for booster in children who have previously received a primary vaccination. The diphtheria / tetanus / pertussis (acellular, component) / poliomyelitis (inactivated) vaccine (adsorbed), reduced antigens content, also referred to as TdaP-IPV, is indicated for re-vaccination of children (≥4 years). Further to a signal of immune thrombocytopenia (ITP) with these combined childhood vaccines, a RWD study was conducted to support the related PRAC assessment.
Research question	The study aimed to describe: (a) the use of the vaccines in the general population and changes over time, and (b) incidence rates for ITP in the general and exposed population across three European databases: IMRD UK, IQVIA™ Disease Analyser France and Germany.
Findings	Children 0-2 years and 3-6 years had the highest population rates of immune thrombocytopenia in the main analysis in all three databases. In IMRD UK database, most children vaccinated with DTaP-IPV or TdaP-IPV were 3-6 years of age. During 90 days of follow-up a higher-than-expected incidence of immune thrombocytopenia was observed in vaccinated children in this age group, which could support the possibility that immune thrombocytopenia could be an adverse event of the vaccines. However, alternative explanations cannot be ruled out. Similar findings were not observed in this age group in Germany or France databases, but more vaccinated children in Germany and France were in the older age groups 7-11 years and 12-17 years.
How was this useful?	The study results were taken into account during the review of the signal. While the PRAC noted the higher incidence of ITP in vaccinated children 3-6 years of age, in absence of a comparative analysis of exposed versus unexposed subjects (which was not possible since a meaningful unexposed cohort could not be identified), this finding was not considered to support a causal association. This was supported by an EudraVigilance analysis (EVDA) which showed that the vast majority of ITP cases occurs within the age group 2 month to 2 years.

Use case 10: PRAC – Comirnaty and vulval ulceration (EUPAS50609)	
Problem statement	During routine signal detection, cases of genital ulceration (including vulval ulceration, vaginal ulceration, vulvovaginal ulceration, genital ulceration) in close temporal association to Comirnaty vaccination were identified. To support

Use case 10: PRAC – Comirnaty and vulval ulceration (EUPAS50609)	
	the assessment of a potential causal relationship, a RWD study was conducted using the primary care databases available to EMA.
Research question	The objectives of the study were to: (a) describe the use of the vaccine in the general population, and (b) estimate incidence rates of vulval ulceration in the general and exposed female population. In addition, a self-controlled case series (SCCS) was conducted to further explore a possible association.
Findings	The study was conducted in IMRD UK and THIN® Spain, which had sufficient exposure data. The study found no difference in post-vaccination incidence rates of vulval ulceration compared to the background incidence rates either 30 or 90 days after receiving the first dose of Comirnaty vaccine, or after receiving the second or third doses. Similar results were obtained for other COVID-19 vaccines (Spikevax and Vaxzevria). The SCCS analyses also found no increase in the incidence rate of vulval ulceration in the period after vaccination. However, confidence intervals of the incidence rates were relatively wide due to a limited number of follow-up years in each stratum analysed. This implies that the study is lacking power to provide an adequate precision in the estimates.
How was this useful?	The study results were considered helpful in absence of reliable background incidence in literature, which made an O/E analysis unfeasible. While likely underpowered (limited number of follow-up years), the study helped putting into perspective the reporting rate of vulval ulceration after vaccination and supported the PRAC conclusion that at the moment there is not sufficient evidence to conclude a causal association between vulval ulceration and Comirnaty exposure.

Use case 11: PRAC - Cutaneous T-cell lymphomas in patients with severe atopic dermatitis (EUPAS50517)	
Problem statement	During the assessment of a PSUR for dupilumab (Dupixent) the PRAC noted an increased reporting rate of cases of cutaneous T-cell lymphoma (CTCL). It is however also known that CTCL is more common in patients with atopic dermatitis (AD), which is one of the approved indications for Dupixent. While a study on the association of CTCL and use of Dupixent was not feasible with the primary care databases available to EMA (due to insufficient outcomes being recorded for exposed patients), an alternative analysis of cases occurring in the general population and patients with (severe) AD was possible.
Research question	The study aimed at describing the population incidence rates of CTCL, patient-level incidence rates of CTCL following diagnosis of AD, and patient-level incidence rates of CTCL following treatment for severe AD. Severity of AD was defined based on use of systemic immunosuppressive medicines. The study was designed to match as closely as possible a study presented by the marketing authorisation holder using OPTUM, a large claims database in the United States.
Findings	Analyses using IMRD UK and IQVIA™ Disease Analyzer Germany showed that the incidence rate of CTCL was higher in patients with AD diagnosis in comparison to the general population (four-fold in the UK and seven fold in the German database, which also includes data from specialist practices). In the UK, event rates in patients with AD who initiated treatment for severe AD were also higher compared to all subjects with AD (around three-fold higher in UK). No difference was seen for patients with AD versus severe AD in Germany.

Use case 11: PRAC - Cutaneous T-cell lymphomas in patients with severe atopic dermatitis (EUPAS50517)	
How was this useful?	The EMA study confirmed the findings of the OPTUM study which also indicated high incidence of CTCL in particular in patients with severe atopic dermatitis irrespective of treatments received. The results helped the PRAC reach the position that most cases of CTCL may be explained as misdiagnosis of AD, coexistence of AD and CTCL, or as a consequence of natural evolution of prior long-standing AD and that currently no causal association between dupilumab treatment and CTCL could be established based on the overall evidence.

Use case 12: CHMP – DARWIN EU®: Serious adverse events in patients with severe asthma (EUPAS103936)	
Problem statement	During the evaluation of the safety results of a clinical trial in patients with severe asthma, differences in rates of serious adverse events were observed in the experimental treatment arm compared to the control arm. In order to contextualise these differences, a non-interventional study was requested to generate background rates of selected health outcomes in patients with severe asthma, with a disease definition that follows recently conducted clinical trials. The results of this study may inform future drug-related safety assessments in severe asthma population.
Research question	The objectives of this study are: (i) To estimate the rate of mortality due to any cause stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2021), sex, age and country/database during the study period 2015-2021. (ii) To estimate the rate of mortality due to fatal infections stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2021), sex, age and country/database during the study period 2015-2021. (iii) To estimate the rate of mortality due to cardiovascular events stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2021), sex, age and country/database during the study period 2015-2021. (iv) To estimate the incidence rate of serious cardiovascular events (but not necessarily leading to death) stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2021), sex, age and country/database during the study period 2015-2021
Findings	The study is ongoing
How was this useful?	The study is ongoing

Annex 3: In-house databases and healthcare systems

IQVIA™ Medical Research Data (IMRD) UK (available since January 2022)

IMRD UK is a primary care database from the UK. GPs play a gatekeeper role in the healthcare system in the UK, as they are responsible for delivering primary health care and specialist referrals. Over 98% of the UK-resident population is registered with a GP, so that GP patient records are broadly representative of the UK population in general. Patients are affiliated to a practice, which centralizes the medical information from GPs, specialist referrals, hospitalizations, and tests.

IQVIA™ Disease Analyzer Germany

IQVIA™ Disease Analyzer Germany collects computerised information from specialised and general primary care practices throughout Germany since 1992. Around 3% of general practitioners (GP) practices are included, which covers all patients consulting a practice. Data from IQVIA™ Disease Analyzer Germany have been shown to be reasonably representative of German healthcare statistics for demographics and certain diseases and is considered one of the largest national medical databases worldwide. IQVIA™ Disease Analyzer Germany includes more than 2,500 practices and 3,100 physicians (13 speciality groups) representing over 15,000,000 patients. This database used to be named IMS® Germany and some use of this terminology may persist.

The quality of IQVIA™ Disease Analyzer data is ensured by a series of continuous QA controls and data refinement. These include checking incoming data for criteria such as completeness and correctness, (e.g., linkage between diagnoses and prescriptions), and standardizing certain data values such as laboratory test results in order to enable reliable analysis.

IQVIA™ Disease Analyzer France

IQVIA™ Disease Analyzer France collects anonymised patient medical records since 1997 through a representative panel of GPs. The physician sample represents approximately 2% of physicians and is weighted by age and gender of the physician, doctor region and the SNIR of the physician (National Official Indicator of the GP volume of activity in terms of visits and consultations). Some 99% of the French population is insured, but there are differences regarding level of coverage. IQVIA™ Disease Analyzer France includes around 1,000 GPs and represents more than 4,000,000 of patients and considered representative for the French population. This database used to be named IMS France and some use of this terminology may persist.

The quality of IQVIA™ Disease Analyzer data is ensured by a series of continuous QA controls and data refinement. These include checking incoming data for criteria such as completeness and correctness, (e.g., linkage between diagnoses and prescriptions), and standardizing certain data values such as laboratory test results in order to enable reliable analysis.

The Health Improvement Network (THIN®) Italy (used in analyses since June 2022)

In THIN® Italy data collection started in 2000 and this database is currently able to provide clinical monitoring data of anonymised patients managed by 500 GPs in primary care (including patients' history). The data source of THIN® Italy is electronic health care records. The entire database reaches 900,000 patients (active and non-active), from which 500,000 are currently actively followed. In order

to be representative at national and macroregional level, physicians have been recruited in accordance with their universe distribution in terms of geography, age and gender.

THIN® is an unobtrusive European medical data collection scheme that collects anonymized patient data from the Electronic Health Records of GPs and specialists, including information on patient's diagnoses, test results and medication. The databases follow a very strict anonymization process. In all countries patients are informed about the collection and anonymization of the data and are able to opt out, in which case no data are subsequently transmitted to the THIN database.

The Health Improvement Network (THIN®) Romania (used in analyses since June 2022)

THIN® Romania is a primary care healthcare database, including only General Practitioners (574 GPs). The source of data is electronic health care records. Enrolled GPs and their patients are representative of the whole Romanian population in terms of location, demographics and prevalence from the point of view of main chronic health pathologies. Data collection started in 2012.

In Romania, the insured population (background sampled population) numbered 17.1 million individuals (data from 2012). Among these, 8.5 million individuals benefited of healthcare services, in the public system. The number of GPs who worked in the public healthcare system, in 2017 was approximately 11,000 physicians. They recorded 76 million consultations and issued 71 million prescriptions (data from 2017). The number of deceased patients was of 297,000 individuals, and number of newborns in 2020 was of 179,000 individuals.

THIN® is an unobtrusive European medical data collection scheme that collects anonymized patient data from the Electronic Health Records of GPs and specialists, including information on patient's diagnoses, test results and medication. The databases follow a very strict anonymization process. In all countries patients are informed about the collection and anonymization of the data and are able to opt out, in which case no data are subsequently transmitted to the THIN database.

The Health Improvement Network (THIN®) Spain (used in analyses since June 2022)

THIN® Spain is mainly a primary care healthcare database, including practitioners (GP), specialists and pediatricians & nurses. It contains data from approximately 2,000 GPs and 2,400 specialists (cardiology, pulmonology, urology, etc.). THIN® Spain also includes partial activities related to the hospital. THIN® Spain is globally representative of the whole national demographics and prevalence on the main chronic health pathologies. THIN® Spain includes 3,000,000 individuals out of the overall population. Among these, 1,050,000 are active in the previous year and 1,800,000 are active from 2014. Number of deceased patients globally varies between 8 and 9 thousand individuals per year, and number of new-borns ranges between 10 and 12 thousand individuals. New patients are automatically included into the database, and deceased patients identified in a specific field.

THIN® is an unobtrusive European medical data collection scheme that collects anonymized patient data from the Electronic Health Records of GPs and specialists, including information on patient's diagnoses, test results and medication. The databases follow a very strict anonymization process. In all countries patients are informed about the collection and anonymization of the data and are able to opt out, in which case no data are subsequently transmitted to the THIN database.

Annex 4: DARWIN EU® data partners

By the end of year 1 of the establishment of DARWIN EU, 10 data partners from across Europe via DARWIN EU® (list of data partners) had been onboarded:

1. Auria Clinical Informatics - The wellbeing services county of Southwest Finland (Finland)
   https://www.auria.fi/tietopalvelu/en/index.html

2. Bordeaux University Hospital - Centre hospitalier universitaire de Bordeaux (France)
   https://www.chu-bordeaux.fr

3. Clinical Practice Research Datalink (CPRD) GOLD - University of Oxford (United Kingdom)
   https://cprd.com

4. Estonian Biobank - University of Tartu (Estonia)
   https://genomics.ut.ee/en/content/estonian-biobank

5. Institut Municipal Assistència Sanitària Information System - Consorci Mar Parc de Salut Barcelona (PSMar), together with Fundació Institut Hospital del Mar d'Investigacions Mèdiques (IMIM) (Spain)
   https://www.parcdesalutmar.cat/en/

6. Integrated Primary Care Information - Mieur Implementation and Exploitation B.V. (The Netherlands)
   http://www.ipci.nl

7. IQVIA Disease Analyzer Germany – IQVIA Solutions BV (Germany)
   www.iqvia.com

8. IQVIA Longitudinal Patient Database Belgium – IQVIA Solutions BV (Belgium)
   www.iqvia.com

9. Netherlands Cancer Registry - Integraal Kankercentrum Nederland (The Netherlands)
   https://iknl.nl/en

10. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària - Fundación Instituto Universitario para la Investigación en Atención Primaria de Salud Jordi Gol i Gurina (IDIAPJGol) (Spain)
    www.sidiap.org

Annex 5: List of research organisations/groups awarded a contract for Lot 5 (pharmacoepidemiological research) of the Agency's framework contract 'Quality, efficacy and safety studies on medicines' (EMA/2020/46/TDA)

1. Aetion Germany GmbH, Neuss, Germany
2. Erasmus University Medical Center Rotterdam, Netherlands
3. CEEPHE Consortium, Budapest (SYREON Kutató Intézet Kft Budapest, Hungary; Medical University of Lodz, Poland; Comenius University in Bratislava, Slovakia; RxTarget Kft., Szolnok Bacsó Nándor, Hungary; National and Kapodistrian University of Athens, Greece; Syreon Research Romania, Tg-Mures)
4. Lægemiddelstyrelsen (Danish Medicines Agency), Copenhagen, Denkmark
5. IQVIA Solutions BV, Amsterdam, Netherlands
6. EU PE & PV Research Network (Universiteit Utrecht, Netherlands; Agencia Española de Medicamentos y Productos Sanitarios, Madrid, Spain; Fundació Hospital Universitari Vall Hebron – Institut de Recerca, Barcelona, Spain; Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana, Spain; Vaccine Monitoring Collaboration for Europe, Brussels, Belgium; University of Verona – Department of Diagnostics and Public Health, Italy; University Medical Center Utrecht, Netherlands)
7. CERTEN Consortium (Quinten Health, Paris, France; CERTARA France SARL, Paris, France)
8. Pharmerit Cooperatief U.A., Rotterdam, NL

Annex 6: Survey questionnaire

Real World Evidence studies for decision-making

Fields marked with * are mandatory.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The RWE Team at EMA recently delivered a study report using Real-World Data. We would like to evaluate the impact of the study results on the decision-making process of the committee. We would be grateful if you could answer the following questions:

* Product/Disease:

* 1. Were the RWE study results included in the advice/assessment report?
- Yes
- No

* 2. Were the RWE study results taken into account during the decision making process?
- Yes
- No

* 3. Your evaluation of the usefulness of the RWE study results in the decision-making:
- Substantial evidence
- Supportive evidence
- Inadequate / not used

4. Any further comments on the usefulness of the results and the process:

Thank you!

European Medicines Agency

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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:
Report on the experience gained with regulator-led studies from September 2021 to February 2023
EMA/289699/2023