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European Medicines Agency

Real-world evidence provided by EMA

Support for regulatory decision-making

The use of Real-World Data[1] (RWD) is increasingly embedded in the scientific evaluation of human medicines. At the European Medicines Agency, the Real-World Evidence Team (TDA-RWE) of the Data Analytics and Methods Task Force has direct and indirect access to RWD in the form of patient electronic medical records which can be used to facilitate regulatory evaluations and inform decision-making. On this basis, EMA provides a service to generate and deliver Real-World Evidence[2] (RWE) to EMA's scientific committees, national competent authorities (NCAs), EMA functions and other EU decision-makers and partner organisations[3].

This document briefly describes how RWE, derived from the analysis of RWD, can be useful in the context of regulatory decision-making, the types of studies that can be performed and how EMA can help identify the best resources to address a research question. The process for requesting RWD studies is also explained.

All work on RWD is conducted in full compliance with data protection legislation.

Why can studies using RWD be useful?

RWD can be used to achieve better informed and more efficient regulatory decision-making as a complement to existing evidence. Analyses of RWD provided by EMA could have the following additional benefits:

- **Filling knowledge gaps**, for example by validating evidence submitted by companies or providing additional information such as more recent data, data from different geographic regions, additional sensitivity analyses, or access to different and more data sources (e.g., those established and maintained by public health authorities);
- Providing **independent and transparent** sources of RWE;

[1] Real-World Data are routinely collected data relating to patient health status or the delivery of health care from a variety of sources other than traditional clinical trials (e.g. claims databases, hospital data, electronic health records, registries, M-health data, etc.)
[2] Real-World Evidence is evidence derived from the analysis of RWD
[3] **IMPORTANT NOTE**: Requests from organisations other than the aforementioned bodies and institutions will not be considered. This includes academia, contract research organisations and pharmaceutical companies. In case of queries regarding RWD/RWE or DARWIN EU, you may consult the Agency's website or send a question via the Agency's online request form.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

- Providing **tailored** analyses to the Committee's questions, with involvement of the Committee/requester at relevant steps;
- Potentially **faster evidence** generation, reacting immediately to RWE generation needs and avoiding the procedural steps needed for marketing authorisation holder (MAH) sponsored studies;
- Studying multiple products of the same class avoiding unnecessary duplication and inefficiency that might be features of studies done by industry.

What data and RWE generation pathways are available?

Currently three different pathways are available to answer research questions:

- ***The Data Analysis and Real World Interrogation Network*** (***DARWIN EU®***): In 2022, DARWIN EU® was established as a pan-European federated network to deliver RWE from across Europe. At the end of 2023, 20 data partners were active or being onboarded into the network including data from sources such as hospitals, primary care, health insurance, registries and biobanks and a total of 18 studies were completed or were on-going. Additional databases are foreseen to be added to the network each year up to and including 2025. Similarly, the capability to perform studies will increase with around 60-70 studies in 2024 and then up to 150 planned in 2025. More up-to-date information is available at https://www.darwin-eu.org/.
- ***Studies using in-house electronic health databases***: EMA has currently access to several databases consisting of primary care health records from different countries in Europe, including primary care with specialist health records. To increase access to data obtained from specialised settings, EMA is currently working on accessing also specific hospital prescribing data (date to be confirmed). These datasets can be interrogated to provide quick turnaround answers to simple questions or support more complex studies.
- ***Studies procured through the EMA framework contracts***: through a framework contract, EMA has access to eight research organisations and academic institutions that can be asked to perform studies on behalf of EMA. Via this pathway, EMA has (indirectly) access to a wide network of data sources (59 from 21 EU countries) and the ability to leverage the scientific expertise of the organisations involved.

What type of question can be addressed?

Committee Members/Rapporteurs, assessors and other NCA representatives as well as EMA staff and other EU decision-makers with whom EMA has agreed to provide support, are welcome to submit research questions that might help them in the evaluation of medicinal products all along their development and lifecycle. The figure below provides an overview of the three main areas in which RWE can support regulatory decision-making.

Figure 1: Use case objectives and categories in which RWE can support regulatory decision-making

Use case objective	Support the planning and validity of applicant studies	Understand the clinical context	Investigate associations and impact
Use case category	Design and feasibility of planned studies	Disease epidemiology	Safety studies
		Clinical management	Effectiveness studies
	Representativeness and validity of completed studies	Drug utilisation	Impact of regulatory actions

Simple studies which can be done to address the areas listed in the figure above would estimate, amongst others:

- The prevalence of diagnosed conditions;
- The incidence or background rates of specific conditions in the general or a specific population;
- Drug utilisation or treatment patterns, typically stratified by age, sex and indication (including changes over time);
- Rates of events following exposure to specific medicines.
- In DARWIN EU, these studies are expected to be carried out with a generic protocol and are referred to as **off-the-shelf studies**.

We can also address more **complex issues**, for example:

- Causal inference studies establishing if there is an association between an exposure and the occurrence of a health outcome, adjusting for baseline factors;
- Complex coding or phenotyping[4], e.g., using events that cannot be defined by existing diagnosis codes, but require combining diagnosis codes with other data such as results of laboratory tests;
- Complex analytical approaches that might include, amongst others, clinical prediction models and testing for heterogeneity of treatment effects.

Regardless of the level of complexity, a study conducted via DARWIN EU can be repeated with a pre-specified regularity, e.g. yearly (**routine repeated**) to obtain up-to-date information or information on trends over time.

Examples of RWD studies realised by TDA-RWE in the past are provided in a report covering the experience with conducting RWD studies for the period from September 2021 to February 2023 (see portfolio of use cases in Annex 2).

As of February 2024, DARWIN EU has entered full operation mode and has become EMA's primary RWE generation pathway. This means that for any research question, DARWIN EU will be considered first when exploring if a study is feasible. While data reliability is already considered at the time of onboarding of data partners, when performing a feasibility assessment, the DARWIN EU Coordination Centre will explore via the network of data partners if relevant data are available, e.g. sufficient patient numbers and follow-up time, geographical regions and all key data elements required for answering

[4] A phenotyping algorithm (or phenotype) is the collection of observable and measurable patient characteristics in electronic health databases that defines a population of interest, e.g., any codes used to record diabetes mellitus or age > 65 years.

the research question in a methodologically sound and robust manner. Based on the proposal from the Coordination Centre, EMA, together with the requester, will decide if it is fit-for-purpose, i.e. expected to generate evidence suitable to support the regulatory or public health decision. Timelines to generate the desired evidence will also be considered in the decision whether or not to pursue a study.

If not feasible via DARWIN EU, alternative pathways will be considered: in-house and framework contract.

When to request a study?

Research questions could be submitted in two different scenarios:

- **Linked to a procedure**: research questions may be identified while preparing and commenting on assessment reports, or during a discussion by a scientific Committee. In these cases, RWE will need to be generated and delivered within the procedure timelines. It is therefore important to highlight the research question to be addressed at the earliest opportunity and specify the timelines (latest due date for the study report);
- **Outside a specific regulatory procedure**: these requests could arise either for a specific product, when the need for additional evidence is anticipated (for example background rates for Covid19 vaccination related adverse events, or an upcoming regulatory submission, e.g. at the time of pre-submission meetings for an initial marketing authorisation application), or for non-product specific questions (for example where information is required relating to a disease of interest, e.g. natural history of a disease before after approval of disease modifying therapies or patient characteristics for a condition with several product developments in the pipeline).

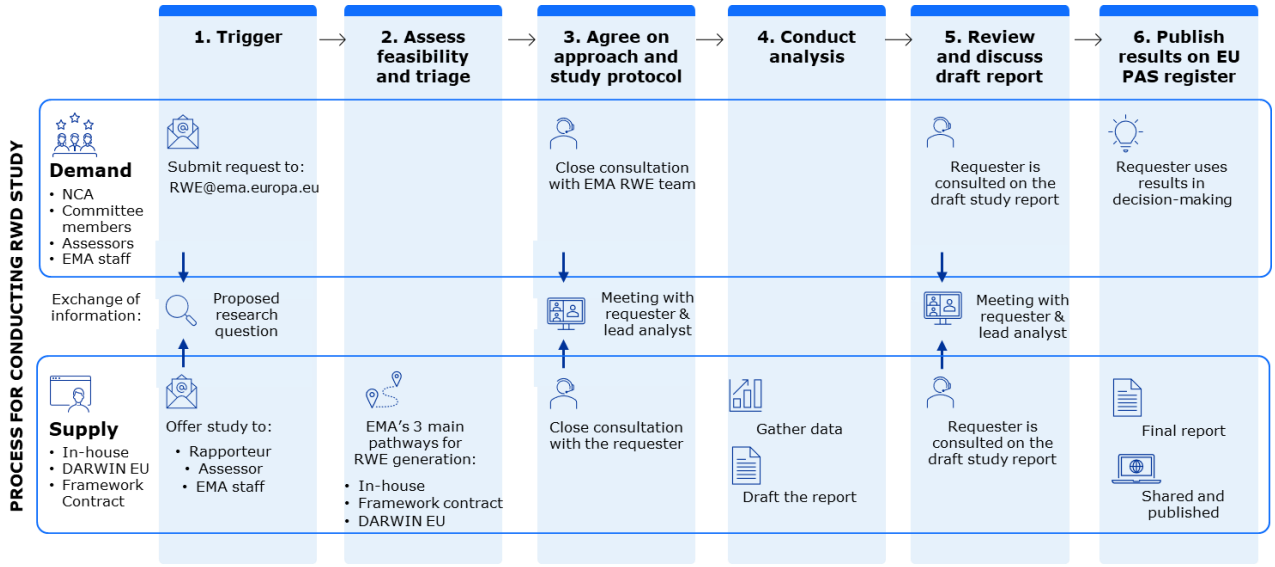
What is the process for requesting and performing a study?

Once you have identified a situation in which you consider that a RWD study could be helpful, the following steps are (to be) followed (also see the figure below):

1. Please contact RWE@ema.europa.eu including relevant information on the research question (see template e-mail below);
2. Within seven days from the initial request, EMA RWE team replies to the request and refines the research question in close contact with the requester, and advises about the pathway to be used to address the question;
3. EMA RWE team initiates the feasibility assessment (except for studies conducted via the framework contract which does not foresee formal feasibility assessments), informs the requester of the outcome and together with the requester decides on whether or not to pursue a study, including the final research question and details of the study design and timelines;
4. If agreed to pursue a study, the EMA RWE team will inform of the next steps to generate the study protocol and report;
5. Once a draft protocol is available, EMA consults the requester and if agreed, the EMA RWE team asks the DARWIN EU Coordination Centres or the contract research organisation to proceed with the data analysis, or runs the analysis in case of an in-house study.
6. Once a draft study report is available, EMA consults the requester and if agreed, proceeds with the sign-off for the study (DARWIN EU or framework contract);
7. If needed, a meeting is arranged to discuss outstanding issues in the context of the protocol and/or the study report;

8. The report is finalised and sent to the Rapporteur and other relevant stakeholders. The protocol and the report are also published on the HMA-EMA catalogue of studies and made available to Agency's scientific Committee members through the RWE MMD folder.

Figure 2: Overview of the process to request, conduct and receive the results from a RWD study



Who is the contact point?

The RWE generation service is offered by TDA-RWE, which is part of the Agency's Data Analytics and Methods Task Force. The EMA RWE team at TDA-RWE includes epidemiologists, statisticians and data analysts with broad expertise and experience in analysing RWD to address medicines-related research questions.

This support is provided to the members of the European Medicines Regulatory Network (EMRN) and other EU decision-makers and partner organisations with whom EMA has agreed to provide support.

If you are a member of the EMRN or one of the other aforementioned bodies and institutions, you can request a study or contact the Agency to discuss a potential research question by sending an email to RWE@ema.europa.eu. To ensure that relevant information is provided to enable the EMA RWE team to consider the request without delay, you may find the following template email useful.

TEMPLATE TO REQUEST RWE

IMPORTANT NOTE: Requests from organisations other than the aforementioned bodies and institutions will not be considered. This includes academia, contract research organisations and pharmaceutical companies. In case of queries regarding RWD/RWE or DARWIN EU, you may consult the Agency's website or send a question via the Agency's online request form.

What if a study cannot be done?

We aim to embed regulator-led generation of RWE into the assessment process and to do this in a learning, evidence-based way. Past years have increased our understanding of the EMRN's requirements, what studies can and cannot be done, and within which timescales. While the Agency is

in a phase of scaling up the capacity to generate RWE, we are gathering further experience which will be shared with the public in form of regular reports. If certain studies are not feasible because of a lack of adequate data, this will inform the choice of additional data sources to be onboarded via DARWIN EU or made available via one of the other two RWE generation pathways in the future. If certain studies are not feasible within the required timelines, we will aim to adapt our processes, for example by anticipating future needs and by creating greater awareness of the need to raise requests at the earliest opportunity, as well as by increasing our agility to respond to research questions.

How long will a study take?

A feasibility assessment can be produced within a few days/weeks. The time required for the preparation of the study protocol, performing the analysis and finalising the report will vary depending on the complexity of the study. It is anticipated that very simple studies can be carried out within 6-8 weeks, whereas more complex studies will normally take longer, in certain cases up to several months. An orientation of the time required to perform studies via the different pathways can be derived from the report covering the experience with conducting RWD studies during the period from September 2021 to February 2023. However, we expect to be able to further accelerate the generation of RWE, especially via DARWIN EU which is developing a catalogue of standard data analyses including off-the shelf and routine repeated studies that can readily be executed.

How will the generated evidence be useful?

Examples of RWD studies realised by TDA-RWE in the past are available via the report covering the experience with conducting RWD studies for the period from September 2021 to February 2023 (see portfolio of use cases in Annex 2). These use case examples showcase how RWD studies can or have been useful in aiding the regulatory decision-making process.

How valid will the results be?

EMA has taken great care to assemble datasets and analytical pipelines and software that are of the highest standards. Data reliability is checked at the time of onboarding of the data partners (DARWIN EU and in-house) or during the procurement procedure (framework contract).

Standard analytical packages based on R and the OMOP common data model are used in DARWIN EU, increasing the consistency and validity of the results. These packages undergo validation and are published in CRAN. Further information is available at https://www.darwin-eu.org/. Selection of data partners for each study is guided by the research question and the necessary variables to be included, and this is formalised in a fitness-for-purpose assessment in the protocol. The most suitable sources are included, although not all sources may be able to answer all objectives. A future routinely repeated study can be considered with additional data partners, if multi-country relevant information is paramount for the research question (e.g. adherence to risk minimisation measures, anti-microbial resistance, etc.).

Analytical software used for in-house studies consist of rapid analysis software (IHD) capable of rapid turnaround times and standard statistical analysis software (SAS, R) capable of producing bespoke analyses. The framework contracts include rigorously selected centres of academic excellence in epidemiology, pharmacoepidemiology and data science from across Europe. Any studies that are done will be subject to rigorously reviewed protocols and analysis plans.

The weight placed on individual study results will depend on the use case, the data available and the methods applied. The team aims to work closely with study requesters to support that the appropriate conclusions are reached.

How will standards be maintained?

EMA will continuously review processes and test methodologies to ensure we can consistently deliver high-quality results, and then subsequently valid and reliable evidence, within the required timelines. The landscape is ever changing with new data sources and new options for analyses becoming ever more available. This document will be kept updated to reflect such changes.