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Editorial

Real-world evidence for regulatory purposes: The example of DARWIN EU®

Evidencias de la Vida real Para uso regulatorio: el ejemplo de DARWIN EU®

Randomised controlled trials have been recognised as the gold standard method for the demonstration of efficacy when a medicinal product is first approved.[1] While this remains as the best available standard design, the regulatory landscape is increasingly integrating Real World Evidence (RWE) as a complementary approach to improve the evidence base and inform decision-making.

RWE is derived from the analysis of Real-World Data (RWD) which is defined as data that describe patient characteristics (including treatment utilisation and outcomes) in routine clinical practice.[2] RWD may originate from primary data collection (i.e. data collected specifically for the study in question), or secondary use of existing data sources. Data sources for secondary use include electronic health records, medical claims, prescribing and dispensing records of medicinal products, or patient registers, among others. The key strengths of RWD typically lie in its representativeness, large sample size, and its ability to reflect routine clinical practice. These characteristics make RWD a valuable resource for complementing evidence from clinical trials, as their conduction is not always ethical or feasible, and can be limited by high cost, long timelines, and -in some cases- constraints in generalisability.[3,4]

RWE is already used in the regulation to support the development, authorisation, and monitoring of medicines in the European Union (EU),[1] and examples of cases where RWE has been pivotal for regulatory decisions have been described elsewhere.[5,6] While the role of RWE is well-established for post-approval safety monitoring and disease epidemiology, use cases in the early stages of medicine development or effectiveness are less established. However, the vision of EU regulators is to enable the use of RWE and establish its value across the full spectrum of regulatory use cases by 2025.[1]

With this vision in place, the European Medicines Regulatory Network (EMRN) launched in 2021 the creation of an EU-wide distributed network of RWD named the Data Analytics and Real World Interrogation Network (DARWIN EU®; https://www.darwin-eu.org/). This network of data, services, and expertise, delivers RWE from across Europe on diseases, populations and the uses and performance of medicines. The aim of this network is to support scientific committees from the European Medicines Agency (EMA) and regulators in the EU in their decision-making and has become one of the main RWE generation pathways for studies to support regulatory decisions.[6] DARWIN EU® involves multiple actors, with EMA and the DARWIN EU® Co-ordination centre playing a central role. Erasmus University Medical Center Rotterdam was appointed as the DARWIN EU® Co-ordination centre following a public tendering procedure and is responsible for providing structure for developing and managing the network of data partners, for implementing and operating study execution processes, and for methodological developments for DARWIN EU® under the guidance and directives of EMA.

Since its establishment in February 2022, the network has expanded to more than 30 data partners, enabling access to information from approximately 160 million patients from 16 European countries. Additional data partners will be onboarded to reach approximately 40 data partners by early 2026. The DARWIN EU® network is also diverse in terms of healthcare settings. It contains data from primary and secondary care (both inpatient and outpatient) settings, claims databases, biobanks, and disease registries. All databases onboarded in DARWIN EU® have previously mapped their information to the Observational Medical Outcomes Partnership (OMOP) Common Data Model. This enables the development of studies across federated data networks, in which standardised analytical code is distributed across data partners and executed locally without sharing patient-level data.[7] The advantages of this approach are substantial, especially in terms of governance, reproducibility and timeliness of evidence generation. OMOP is supported and maintained by the Observational Health Data Sciences and Informatics (OHDSI) open science community. In addition to the OMOP common data model and vocabularies, OHDSI has also created multiple analytical tools to facilitate the generation of RWE at scale, as demonstrated during the COVID-19 pandemic.[8]

Over 20 studies were initiated in the two first years of DARWIN EU®, with an increasing number of studies planned for the coming years.[6] Most of them are designed to be executed within weeks and often in less than six months, depending on their complexity. The capability to perform studies is increasing over the years and is possible through the standardisation of many of the steps involved in conducting studies, from administrative processes that expedite ethical and scientific approvals to standardised analytical pipelines that enhance the speed of the generation of results without compromising quality or data protection. The full protocol and reports for all DARWIN EU® studies are published in the HMA-EMA catalogue of RWD studies: https://catalogues.ema.europa.eu/.

The research questions that EU regulators ask to DARWIN EU® are diverse in nature and methods. Study types and standard data analyses supported by DARWIN EU® have been specified in a catalogue of standard analytics co-created between EMA and the DARWIN EU® Co-ordination centre, which is regularly reviewed and available on the DARWIN EU® website: https://darwin-eu.org/index.php/methods/standardised-analytics. Depending on their anticipated level of complexity, studies can be grouped into several categories,

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including off-the-shelf (OTS), complex, or very complex studies. OTS studies include studies for which a generic protocol is adapted to a research question and typically involve descriptive research questions. They typically are characterisation studies on disease epidemiology or drug utilisation, both at patient- or population-level. Examples include studies assessing incidence and prevalence of health outcomes and of drug use, studies describing patient characteristics or drug utilisation, typically in terms of dose and duration of drug exposures, and its indications. Complex studies involve the development or customisation of specific study designs, protocols, analytics and/or phenotyping algorithms to identify populations or outcomes of interest. Examples of complex studies conducted to date or currently ongoing include:

- Studies assessing the effectiveness of human papillomavirus (https://catalogues.ema.europa.eu/node/3981/) and COVID-19 vaccines (https://catalogues.ema.europa.eu/node/3850/).
- Studies on the safety of existing medicines, e.g. on the risk of suicidality associated with the use of doxycycline (https://catalogues.ema.europa.eu/node/4181/).
- Analyses of the background rates of complex safety outcomes, e.g. to contextualise safety assessments in clinical trials of severe asthma treatments (https://catalogues.ema.europa.eu/node/3688/), or for the monitoring of vaccine safety (https://catalogues.ema.europa.eu/node/4155/).

Finally, routine repeated analyses represent an additional study category and are either OTS or complex studies that can be repeated on a regular basis, following the same protocol and study code with updated data and/or different data partners. Very complex studies involve studies which cannot rely on readily available data, and might require the collection of data prospectively or the mapping of additional information or the inclusion of not previously onboarded data sources, or which would require complex methodological work.

Studies using RWD for non-randomised comparisons require important methodological considerations to minimise potential sources of bias and confounding, which need to be addressed through appropriate study designs and analytical methods.[9] As an example, the DARWIN EU® catalogue includes the use of active comparator designs, which compare treatment alternatives commonly used for the same indication. This design mitigates confounding by indication and is restricted to new users whenever possible to minimise the potential for other biases.[10] Self-controlled designs including self-controlled case series and self-controlled risk interval are also included for drug safety assessments. In such designs, comparisons are made by looking at different treatment periods within the same person, eliminating all time-invariant confounding by design.[11] Analytical strategies to assess potential bias due to measured or unmeasured confounding are also considered. Examples include the use of large-scale propensity scores as an adjustment approach to balance all measured covariates between treatments compared,[12] and the use of negative control outcomes to inform the risk of systematic error and to enable the empirical calibration of estimates and *p*-values.[13,14]

Over its first three years, DARWIN EU® has played a pivotal role in advancing the EU regulators' vision to enable the use of RWE and establish its value for regulatory decision-making in Europe. Achieving this vision will improve the timeliness, accuracy and relevance of regulatory decisions, with the ultimate goal to better support the development and evaluation of medicines for patients.[1,15]

CRediT authorship contribution statement

Berta Raventós: Writing – original draft, Methodology, Conceptualization. **Daniel Prieto-Alhambra:** Writing – review & editing, Project administration, Conceptualization.

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