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POINT OF VIEW

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From data to evidence: the evolving role of observational studies and target trial emulation in regulatory decision-making

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ABSTRACT

Introduction: The European Medicines Agency (EMA) has updated its Reflection Paper on the use of Real-World Data (RWD) in Observational Studies (OS), emphasizing the regulatory importance of Real-World Evidence (RWE).
Objectives: Summarize the main methodological recommendations of the EMA's 2025 guidance, highlight challenges and opportunities for the use of RWD in regulatory contexts, and discuss implications for clinical researchers, with particular attention to the role of pharmacists.
Discussion: The new guidance distinguishes descriptive from causal OS and endorses Target Trial Emulation (TTE) to improve causal inference in observational research. It stresses transparency, reproducibility, and rigorous data governance, while calling for robust strategies to manage bias and confounding. Pharmacists are recognized as key contributors to drug utilization research and post-marketing surveillance, ensuring data quality and interoperability and supporting the integration of RWE into regulatory decision-making.
Conclusions: EMA's roadmap affirms the value of RWE in strengthening regulatory science. Its implementation will require cultural change, technical expertise, and resource allocation, offering both challenges and opportunities for healthcare researchers, particularly pharmacists, to transform RWD into trusted evidence.

Keywords: Clinical pharmacy, Drug utilization, Observational studies, Real-world evidence, Target trial emulation

Introduction

In recent years, Real-World Evidence (RWE) has gained significant traction as a complementary source of information to traditional randomized controlled trials (RCTs) in the evaluation of medical interventions. The European Medicines Agency (EMA), through its updated 2025 Reflection Paper, offers a detailed regulatory perspective on how Real-World Data (RWD) should be leveraged in Non-Interventional Studies (NIS) to inform healthcare decision-making. In line with regulatory frameworks, RWE can also be generated from randomized designs such as pragmatic or large simple trials when conducted under real-world conditions. This article aims to explore the conceptual and methodological shifts introduced by the EMA and highlight their implications for clinical researchers, with a focus on the evolving role of pharmacists.

The Regulatory Weight of Observational Evidence

RCTs remain the gold standard for demonstrating efficacy and safety. However, their rigid structure and exclusion criteria limit their external validity. In contrast, OS allow for the observation of treatment effects in real-world settings, capturing clinical complexity, comorbidities, and variations in adherence. Recognizing this, EMA now provides clearer recommendations for when and how RWD can be used to generate RWE for regulatory purposes (1).

Accordingly, EMA underscores the importance of adhering to established methodological standards - such as those provided in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)

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Guide (2)—and of using structured tools, like checklists and visual design aids, to enhance the rigor, clarity, and transparency of observational studies (OS).

Descriptive vs. Causal OS*: a Conceptual Framework*

The updated Reflection Paper draws a critical distinction between descriptive and causal OS. Descriptive studies focus on patterns of drug utilization, prevalence, incidence, and user characteristics. Causal OS, on the other hand, aims to infer treatment effects. Descriptive studies also demand rigorous upfront work: transparent a priori outcome definitions; validation of coding algorithms; assessment of data quality (completeness, timeliness, accuracy); and explicit sampling rules to prevent selection artifacts. Importantly, neither observational nor randomized studies necessarily mirror routine practice: external validity depends on protocol choices (e.g., inclusion/exclusion criteria, follow-up intensity, outcome definitions) and on the study's position along the 'pragmatism' continuum.

Target Trial *Emulation: A Methodological Evolution*

Among the most significant contributions of the new EMA guidance is the endorsement of Target Trial Emulation (TTE) as a methodological standard for causal inference in OS (3).

Traditional OS, while essential, have often been limited in their ability to infer causal relationships.

Target Trial Emulation (TTE) tackles the inherent limitations of OS by first imagining the RCT that would provide the best possible answer to the research question, if conducting it were feasible. This "target trial" is defined in detail as eligibility criteria, treatment strategies, assignment procedures, follow-up, and outcomes, and then these elements are systematically reproduced using RWD. In doing so, TTE may allow researchers to bring the methodological rigor of RCTs into observational settings, narrowing the gap between the practical constraints of RWD and the reliability of evidence generated by randomized trials. This approach aligns the definition of time zero for eligibility, treatment assignment, and follow-up, to avoid immortal time bias and other common pitfalls. Statistical methods may be used to adjust for baseline differences, approximating the balance achieved through randomization. Consequently, TTE enhances causal inference from RWD, improving the validity and applicability of findings on drug effectiveness and safety in routine clinical practice. TTE may offer a powerful framework to generate timely, robust evidence, supporting more informed decisions by clinicians, regulators and payers, particularly in contexts where RCTs are unethical, impractical, or prohibitively expensive. Alongside observational approaches, pragmatic randomized trials remain an important pathway to generate RWE.

Managing Bias and Confounding in OS

Because of their observational design, OS are inherently exposed to biases that may threaten the validity of their findings. Selection processes, misclassification of exposures or outcomes, and uncontrolled confounding can all distort the estimated associations and hinder causal interpretation. To mitigate these risks, careful study planning, appropriate analytical strategies, and transparent reporting are required. In addition, attention must be paid to potential effect modification to identify population characteristics that shape treatment outcomes and determine the extent to which results can be generalized to the intended target population.

Also, within the TTE framework, rigorous control of bias and confounding is essential to preserve internal validity. While the approach is designed to reduce distortions common in OS, it remains susceptible to systematic errors, particularly those arising from incorrect specification of time zero, exposure misclassification, and residual confounding.

Immortal time bias can be minimized by clearly defining the eligibility window and ensuring precise temporal alignment between cohort entry and exposure assignment. To address confounding, investigators should pre-specify a set of baseline covariates measured prior to exposure initiation, ideally informed by a Directed Acyclic Graph (DAG) representing the hypothesized causal structure.

Recommended strategies include:

i) Restriction and matching on key covariates to enhance comparability across exposure groups.
ii) Inverse probability of treatment weighting (IPTW) based on propensity score models to balance baseline characteristics.
iii) Multivariable outcome modeling to further adjust for residual confounding.
iv) Doubly robust estimators, combining treatment and outcome models, to reduce susceptibility to model misspecification.

Sensitivity analyses, such as the E-value or quantitative bias analysis (4,5), should be used to evaluate the potential impact of unmeasured confounding and to test robustness under alternative definitions of exposure and outcome.

Transparent reporting of all methodological decisions, including underlying assumptions and exclusion criteria, is essential to facilitate replication and critical appraisal.

Operationalizing RWE: Data Quality and Transparency

Generating credible RWE depends on the quality and traceability of the underlying RWD. The EMA highlights the importance of robust data governance, including pre-specification of outcomes and minimum quality thresholds for analytic datasets, ensuring that information is collected and processed in compliance with data protection regulations and ethical standards. It also calls for prospective study registration and the availability of raw datasets to guarantee reproducibility. Equally crucial is transparency, with full disclosure of protocols, analysis plans, and sensitivity analyses in line with the principles of ICH E6(R3) and E9(R1) (6,7). These requirements, though demanding, elevate the scientific credibility of OS and reinforce the accountability of researchers.

Linkage and Completeness: The Italian Challenge

In Italy, the regionalized structure of the NHS presents a unique and persistent challenge to the integration of RWD. Despite several attempts at harmonization, the lack of a national interoperable data infrastructure and the absence of common standards for data storage and exchange continue to hinder access to complete and unified datasets (8). Electronic

health records, administrative claims, disease registries, and pharmacy dispensing data are often 'siloed' within individual regions or institutions, making linkage difficult and analysis fragmentary.

This fragmented landscape not only limits the generalizability of OS but also undermines the reliability of RWE for national regulatory or HTA decision-making. While some regions have developed advanced local data systems, e.g., "Edotto" system in Apulia, the national picture remains heterogeneous, and no central repository or federated model has yet been fully implemented. The resulting lack of interoperability and the variable quality of data across territories prevent a consistent, country-wide approach to evidence generation.

A partial but promising response to these challenges is represented by the ongoing development of the Electronic Health Record (EHR), or Fascicolo Sanitario Elettronico (FSE). Initially introduced by Legislative Decree No. 179/2012 (9) and strengthened by subsequent reforms [notably Budget Law 2020 and the Ministerial Decree of May 20, 2022 (10)], the FSE is intended to be a unified digital platform for collecting, storing, and sharing patient data across all Italian regions. Its full implementation, now backed by investments from the National Recovery and Resilience Plan (PNRR - Mission 6) (11), aims to ensure nationwide interoperability and accessibility to healthcare data for both care and research purposes.

However, progress has been uneven. As of 2024, many regions have not yet achieved full compliance with the FSE integration standards, and concerns remain about governance, data quality, and patient privacy. The success of the FSE will depend on effective coordination among national and regional authorities, robust IT infrastructure, and active engagement from healthcare professionals (12).

In line with the PNRR milestones, FSE 2.0 is expected to reach: (i) ≥85% of general practitioners feeding the FSE by Q4-2025 (M6C2-11); (ii) full operation of the Electronic Health Card system and the national FSE interoperability infrastructure by mid-2026 (T2-2026; M6C2-12); and (iii) nationwide adoption and use across all 21 Regions/Autonomous Provinces by mid-2026 (T2-2026; M6C2-13). Progressive targets also include stepped increases in GP participation (≈5% mid-2023; ≈30% mid-2024; 85% H2-2025) and document indexation towards ≈90% by mid-2026 (13). In this context, pharmacists and local health professionals are often the only actors with continuous access to patient-level data in real time, and their engagement in data capture and validation becomes even more critical. They can serve as data stewards, ensuring that what is collected at the point of care can be leveraged for high-quality RWE studies with national relevance.

Pharmacists at the Forefront: From Drug Utilization to Risk Minimization

Pharmacists are uniquely positioned to play a central role in the generation of RWE, and among the six regulatory case studies referenced by the EMA reflection paper, two directly concern everyday pharmacy practice, namely the description of drug utilization patterns, including indications, dose, duration, and adherence, as well as the conduct of post-marketing surveillance and the evaluation of the effectiveness of risk minimization measures. Beyond the traditional functions of dispensing and procurement, pharmacists also contribute to data quality and interoperability, ensuring that prescribing and dispensing information captured at the point of care is reliable and usable for regulatory-grade evidence.

Moreover, their participation in the HTA process and regional governance processes places them at the intersection of clinical practice and policymaking, where RWE plays an increasingly decisive role. Their proximity to the patient and involvement in therapy management further strengthen this role, positioning pharmacists as essential actors in observational research.

In a healthcare system increasingly oriented toward value and safety, pharmacists' contributions to RWE generation can support regulatory evaluations, improve therapeutic appropriateness, and inform evidence-based decision-making at both regional and national levels. This evolving role extends beyond traditional dispensing and procurement and requires strengthened competencies in pharmacoepidemiology, data governance, interoperability, and applied analytics (including causal inference and statistical programming), enabling pharmacists to act as methodological stewards of RWE generation.

In line with these considerations, the third report "Real-World Evidence Framework to Support EU Regulatory Decision Making" on the advancements of RWE to promote EU regulatory decisions, published by EMA (14), reported that, in the previous year, among 59 real-world studies coordinated by EMA, 42% focused on drug utilization, 24% on drug safety and 24% on disease epidemiology. This means that two-thirds of studies concerned activities inextricably linked to drugs and pharmacists, highlighting their key role in the management of RWD, generating RWE.

For instance, drug utilization research, aiming to understand how patients take their medications, whether they adhere to their prescribed treatments or how long they take their therapy (persistence), represents an area of research in which pharmacists play an important role. First, they can systematically track each drug dispensing; in addition, thanks to computerized systems, pharmacists can access patients' entire drug history, allowing them to derive drug utilization indicators.

Various international working groups are interested in this field, and in Italy, as part of the FORIERO group (hospital pharmacists for independent research in the economic field, rational use of technology, and outcome evaluation), we are involved in conducting several drug utilization studies in RW covering different therapeutic areas (e.g., oncohematology) (15). One of these, "The Multi-Bio drugs" study, aims to evaluate how biological drugs are used in different therapeutic indications concerning rheumatology, dermatology, and gastroenterology (i.e., Inflammatory Bowel Disease). To date, out of 12 Italian regions involved in the project, 21 hospitals and community pharmacies were recruited to share their RWD on biological drug use, to generate and analyze RWE concerning treatment adherence and persistence, therapy switching, and treatment-related costs.

Challenges Ahead: Culture, Capacity, and Change

Although enthusiasm for RWE is growing, its broader adoption is still hindered by the tendency of clinicians and policymakers to privilege RCTs and perceive RWD as anecdotal, by the limited technical expertise available in non-academic institutions to design and analyze causal OS, and by the considerable investments in IT, personnel, and education required to meet EMA standards; overcoming these challenges will depend on coordinated efforts among academic institutions, healthcare providers, professional associations, and regulators, with a crucial role for pharmacists, whose up-skilled training in data science, epidemiology, and regulatory methods (e.g., TTE and pragmatic designs) will be pivotal to deliver regulatory-grade evidence.

Conclusions

The updated EMA Reflection Paper outlines an ambitious roadmap for integrating RWE into regulatory science, endorsing TTE as a structured method to improve causal inference and generate reliable evidence on drug effectiveness and safety when RCTs are not feasible. To realize this potential, investment in methodological training and cultural change is essential, offering clinical researchers, particularly in pharmacy and health services, both a challenge and an opportunity to transform RWD into trusted evidence for better patient outcomes.

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