

# Expert Perspectives on Next Generation Health Guidelines: How to Integrate RWE in EBM

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**Abstract:** Integrating real-world evidence (RWE) into evidence-based medicine (EBM) enhances healthcare decision-making. RWE provides insights into the real-world effectiveness and safety of therapies and health technologies, filling gaps that clinical trials may



leave. EBM, which concentrates on therapeutic issues, depends on rigorous evaluation of evidence, including data from randomized controlled trials (RCTs) and RWE. Combining evidence from RCTs and RWE when forming recommendations offers a comprehensive understanding of benefits and risks by considering their strengths, limitations, and standardized methods. The 2nd European Academy of Allergy & Clinical Immunology/Respiratory Effectiveness Group (EAACI/REG) Workshop, held in Rome, Italy, on October 4th, 2023, discussed integrating RWE and EBM. The goals were to develop recommendations for high-quality RWE and its inclusion in evidence syntheses, with a particular focus on airway diseases. During the discussion, key topics emerged. An “action plan” is needed to share these topics in various formats. RCTs are currently seen as providing the strongest evidence, so how to incorporate Non-Randomized Studies of Interventions (NRSI) requires careful consideration. An educational plan and collaboration with patients’ organizations are also very important. A collaborative approach involving patients, clinicians, and regulators is essential for achieving meaningful results and can be adapted as needed for cultural differences. A “glossary” of terms used in this context will be created to improve understanding. Setting benchmarks for data quality and reliability, such as quality thresholds, in disease-specific studies requires collaboration with research method experts. Managing and recording registries according to standardized protocols and quality standards from well-designed registries will ensure the data is valid and accurate.

**Keywords:** real world evidence, evidence-based medicine, real world data, registries

## Introduction

While randomized controlled trials (RCTs) are considered the gold standard for establishing efficacy because of their internal validity and ability to reduce bias through randomization and controlled conditions, they also have well-known limitations. These include highly selective inclusion criteria, limited sample sizes, short follow-up periods, and artificial treatment environments—all of which decrease their external validity and generalizability to broader patient populations. Consequently, RCTs might not fully reflect the effectiveness, safety, and adherence patterns of interventions in everyday clinical practice. Real-world data (RWD), when collected and analyzed properly, can complement RCTs by offering evidence on how interventions perform across diverse populations, care settings, and over longer periods. This complementary role is especially important for informing clinical guidelines, health technology assessments, and regulatory decisions.

Real-world evidence (RWE) can be obtained from RWD using various study designs, each with unique methodological features and regulatory considerations. These include prospective pragmatic clinical trials, which evaluate interventions under routine care conditions while maintaining randomization; non-randomized interventional studies, which follow prospective protocols without random assignment; randomized controlled trials (RCTs) that utilize external control arms built from real-world data sources such as disease registries or electronic health records (EHRs); and retrospective observational studies, which analyze pre-existing data from structured sources (eg, registries, administrative claims databases, EHRs) to assess treatment effects or disease patterns. The suitable approach depends on the research question, data availability, feasibility, and regulatory environment. Importantly, methodological standards—such as pre-defining hypotheses and protocols, validating RWD sources for their intended purpose, and maintaining transparency in reporting—are critical to ensure the credibility of the evidence produced. These issues have increasingly been addressed in guidance documents issued by the FDA and EMA, as well as in academic literature exploring the strengths, limitations, and appropriate uses of different RWE-generation methods.<sup>1–4</sup>

The integration of RWE into evidence-based medicine (EBM) improves healthcare decision-making. RWE, derived from RWD, offers valuable insights into the real-world effectiveness and safety of therapies and health technologies outside of clinical trial settings,<sup>5</sup> filling knowledge gaps that may exist because of the limitations of randomized controlled trials (RCTs) that use an explanatory study design.<sup>6,7</sup> Guidelines systematically evaluate a relevant evidence base and then utilize the best available evidence.<sup>8</sup> By combining RWE and EBM, decision-makers can gain a more comprehensive understanding of the benefits and risks of health interventions (Table 1).<sup>9,10</sup> RWE provides real-world context and long-term outcomes data, while high-quality RCTs establish a solid evidence foundation for initial efficacy evaluations. This integration demands careful consideration of the strengths and limitations of both methods and the development of standardized approaches for data collection, analysis, and interpretation.<sup>11,12</sup> Drawing from the existing

**Table 1** Defining the Pillars of Modern Clinical Practice: A Concise Overview of Real-World Evidence (RWE) and Evidence-Based Medicine (EBM)

	Definition
Real-World Evidence (RWE)	RWE pertains to health care information derived from multiple sources outside of typical clinical research settings, including electronic health records, insurance claims, and product and disease registries.[A]
Evidence-Based Medicine (EBM)	EBM is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. EBM means integrating individual clinical expertise with the best available external clinical evidence from systematic research. [B,C]

**Notes:** [A]: Milone V et al. *Int J Environ Res Public Health*. 2024 Jan 15;21(1):95. [B]: Chen S et al. *J Manag Care Spec Pharm*. 2021 Jan;27(1):95–104; [C] Roche et al *Eur Respir J*. 2019 Sep 19;54(3):1901511.

knowledge repository for RWE, along with the perspectives and guidance from experts and scholarly organizations, in 2021 Paoletti et al proposed a hierarchy of RWE (Box 1).<sup>13</sup>

To understand and discuss how to integrate RWE into guidelines, the 2nd European Academy of Allergy & Clinical Immunology/Respiratory Effectiveness Group (EAACI/REG) Workshop was organized.

## Materials and Methods

The meeting was held as a hybrid event on October 4<sup>th</sup>, 2023, in Rome, Italy, and online. The main goals of the meeting were to develop recommendations for producing high-quality RWE, understanding how to report and evaluate it, and integrating RWE with other sources of EBM.

## Results

### Meeting Objectives and Context

This was the second of two meetings in a series focused on standardizing the integration of Real-World Evidence (RWE) into clinical guidelines. The primary objective of the Rome meeting was to create a framework for producing, evaluating, and incorporating high-quality RWE into evidence-based recommendations.

Participants identified ongoing confusion about the definition and use of RWE and called for better education on RWE methodologies. This includes training for investigators and guideline developers on how to collect, analyze, and apply real-world data.

### Regulatory Frameworks and Initiatives

The EAACI-ROC (Research and Outreach Committee) METHODOLOGY PROJECT has increasingly been used to develop clinical practice guidelines, addressing the need to include real-world data like data from registries, electronic health records, or patient-generated information. However, there is still a lack of clarity about what RWE means, how it can be produced, and how it can be integrated into the evidence-to-decision processes.

#### Box 1 The Definition of the Type of Real World Studies (Paoletti G et al. *Allergy*. 2021 Sep;76(9):2663–2672)

**Pragmatic randomized controlled trial:** trials designed to evaluate the effectiveness of interventions in real-life routine practice conditions, opposite to explanatory trials that aim to test whether an intervention works under optimal situations.

**Registry real-world evidence:** an organized system that uses observational methods to collect uniform data relative to real-world setting on specified outcomes in a population defined by a particular disease, condition, or exposure

**Prospective database real-world evidence:** is a type of cohort study, where participants are enrolled into the study before they develop the disease or outcome in question in a real-world context.

**Retrospective multicentre database real-world evidence:** is based on the use of an existing database to respond retrospectively to clinical questions

**Retrospective multicentre real-world evidence:** is a clinical trial conducted at more than one medical centre or clinic where, in contrast to a prospective study, the outcome of interest has already occurred at the time the study is initiated

**Expert experience/evidence:** is somebody who has a broad and deep competence in terms of knowledge, skill, and experience through practice and education in a particular field

Another important point emphasized is the need for education on the methodologies used for generating, collecting, and analyzing high-quality Real-World Evidence. This educational component aims to equip investigators and guideline developers with a clear understanding of the complex processes involved, ultimately promoting expertise and ensuring the development of reliable and robust guidelines.<sup>14</sup>

Since the inaugural meeting, several documents and manuscripts have been published by different groups to support the use of real-world data and real-world evidence in regulatory decisions. The European Medicines Agency (EMA) and the Food and Drug Administration (FDA) are actively working to develop a sustainable framework that promotes the value and use of real-world evidence.

In EMA, the main focus is determining the evidentiary value of real-world evidence (RWE). In 2019, the OPTIMAL framework was introduced, covering three main pillars: operational, technical, and methodological. More recently, the European Union (EU) approach has placed RWE within the larger context of big data, in line with the key recommendations of the Big Data Task Force, which are carried out through the Big Data Steering Group. A framework to ensure the quality of real-world data (RWD) has also been published.<sup>11</sup>

Measures are also being taken to improve the discoverability of RWD through standardized metadata and the creation of a public catalog of RWD sources, building on the initial work of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). The ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which was extensively updated in 2021, along with recently issued guidance on conducting studies based on patient registries, serve as the foundational documents for updating RWE study method standards. Additionally, the Data Analytics and Real World Interrogation Network (DARWIN EU), a distributed RWD network across the EU, was launched in early 2022.

Additionally, the FDA finalized guidance on using real-world evidence in the drug approval process. According to this release, real-world evidence may be used to expand a product's indication.<sup>15</sup>

It is encouraging that sponsors increasingly prioritize transparency by making their study protocols publicly available on platforms such as ClinicalTrials.gov or ENCePP's webpage, or by encouraging independent peer review, such as the Anonymised Data Ethics & Protocol Transparency (ADEPT) Committee of REG and the Independent Scientific Advisory Committee (ISAC) for the Clinical Practice Research Datalink (CPRD). Additionally, sponsors should provide detailed descriptions of patient characteristics and study populations in their final reports, highlighting any differences that may influence the study findings. Each study should have a statistical analysis protocol, to which analyses conducted on the final dataset should adhere, and any additional analyses should be clearly labeled as post hoc or exploratory, as appropriate. Study monitoring aims to ensure protocol adherence, improve data submission reliability to regulatory agencies, and ensure proper data protection. For non-randomized studies, even early in the registry process, it is helpful to verify that permissions have been obtained for using copyrighted questionnaires and to ensure sites obtain consent and record data correctly. This involves verifying the accuracy and consistency of real-world data, ensuring compliance with prespecified plans and protocols,<sup>16</sup> and documenting and evaluating any deviations. The minimum monitoring requirements for non-randomized studies include obtaining appropriate consent, ensuring data accuracy and consistency, adhering to study protocols and statistical analysis plans, and identifying and documenting deviations from prespecified plans and protocols, with necessary interventions.

## Monitoring and Quality Standards for RWE

The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach is the primary framework for evaluating evidence that informs recommendations and guidelines. Used by over 100 organizations, the GRADE approach employs a transparent and structured process to assess factors that reduce the certainty of evidence (also known as quality of evidence). These factors include limitations in the design and execution of studies (ie, risk of bias), consistency of results, precision of results, potential publication bias, and the relevance of evidence to the target population, setting, interventions, and outcomes (ie, directness).<sup>17,18</sup>

Factors that increase confidence in the results are also considered, such as a large magnitude of effects, a dose-response gradient, and reciprocal confounding. In addition to providing a framework to rate the certainty of evidence, the GRADE approach also offers a framework for developing recommendations. The following factors are systematically

assessed when forming recommendations: the balance of desirable and undesirable health outcomes (ie, benefits and harms or burden), certainty of evidence, equity, feasibility, acceptability, and resources.

Non-randomized studies of interventions (NRSI) can be used sequentially, as complements, or as substitutes for randomized controlled trials (RCTs) within the GRADE framework. When RCTs do not provide evidence for outcomes considered critical or important by a guideline committee, NRSI can inform the committee about those outcomes. If RCTs offer moderate or lower certainty evidence due to issues like inconsistency, imprecision, or indirectness, then NRSI can serve as complements to the RCTs. Ultimately, when RCTs are unavailable or provide low or very-low certainty evidence, NRSI can replace RCTs, provided they offer higher certainty. Therefore, both NRSI and RCTs contribute to the evidence base guiding guideline recommendations, with non-randomized studies—often classified as “real-world evidence (RWE)” —sometimes being more applicable.<sup>19</sup>

When combining NRSI and RCTs, a practical approach is essential. It is important to assess the certainty of evidence from both NRSI and RCTs, as well as how well they agree. Agreement can be evaluated through visual comparison, statistical significance, or interaction tests.

Defining thresholds<sup>20–27</sup> of benefits and harms will help determine congruency. The integration of NRSI with experts from diverse fields is the most effective way to combine NRSI and RCTs. One group of individuals may include clinicians who work in the real world, another group may include individuals with research expertise, and a final group may include individuals with expertise in evidence synthesis. It is important to emphasize that when evaluating an intervention, it is crucial to consider aspects of the evidence beyond study design alone.

Guideline methodology requires that recommendations be based on the best available evidence; therefore, rigorous methodology should be used to conduct and register NRSI, such as registry-based studies, to enhance the certainty of evidence and increase the likelihood that NRSI will inform guideline recommendations. The purpose of a rigorous research methodology is to reduce bias, as biases lead to systematic deviations from the truth. Common research biases include confounding, selection bias, information bias, time-related bias, and prevalent-user bias. Despite efforts to improve inclusion and applicability, bias can still occur in research design and implementation. For example, registries may be subject to selection bias if the main pathway to enrollment is through specialist care; additionally, low- and middle-income countries are often underrepresented. Two common scenarios that may contribute to biased research are design and execution issues or applicability challenges. Efforts to prevent these issues can increase the chances that research results will inform guideline recommendations and patient care.

All decisions are made based on challenging thresholds, and clinical data can be helpful in their determination, especially if more evidence about thresholds becomes available.

## Glossary and Terminology Harmonization

Another critical point concerns the terminology used in RWE/NRSI. Many patient associations, clinicians, and researchers need to become more familiar with the acronyms used in studies and their definitions. Moreover, the term “RWE” is used with different meanings among health professionals and researchers, causing confusion within the global clinical research framework and its related terminology. Therefore, developing a comprehensive glossary to address these issues is essential. This glossary would serve as a vital foundation for widespread dissemination. It can be expanded gradually by implementing an algorithm that allows for the addition of new terms over time. Collaboration among different groups and organizations in the field is crucial; therefore, the glossary should be written in plain language to be accessible to patients and clinicians unfamiliar with research terminology. It is also important to align these efforts with the recommendations issued by regulatory and funding agencies, including the Data Quality Framework for EU medicines regulation, the EU-funded REALM project, the EMA-HMA catalogs of data sources and non-interventional studies, and the BDSG report on RWE framework to support regulatory decision-making.<sup>3</sup>

## Role and Governance of Registries

Another important aspect involves registries, emphasizing their role, which can vary in terms of data collection type and quality.<sup>4</sup> The use of registries in the drug approval process depends on their compliance with specific quality standards.

When setting up a registry, several factors are considered, including identifying the target population, defining the registry's purpose, and establishing criteria for patient inclusion and exclusion.

The procedural framework needs to be established; however, specifying every characteristic to be recorded in advance might hinder adding new patients over time as our understanding of the disease and its treatment options evolves. Other factors worth considering include the follow-up process (focusing on addressing low follow-up rates in some registries; it's important to develop a system that minimizes the risk of losing patients to follow-up) and data analysis (which involves creating methods for monitoring, reporting, and conducting sensitivity checks when the data are used for regulatory purposes).

All the above information must be shared with scientific societies, regulatory agencies, and individuals creating new registries.

According to the EMA Guideline on registry-based studies, a registry's characteristics should include certain essential elements. First, administrative information should be easily accessible, such as a website that provides detailed information about the registry's main features. Additionally, there should be a designated contact point for questions, a publicly available collaboration policy, a governance structure for decision-making, and support functions for scientific, technical, ethical, and legal issues. Furthermore, a template for research agreements between the registry and external organizations should be available.<sup>4</sup>

Secondly, the registry should adhere to the requirements of informed consent and data protection. This includes complying with the General Data Protection Regulation (GDPR) and relevant local data protection laws, providing detailed information about consent in the Informed Consent Form, obtaining permissions for data use in research, patient re-contact, and quality management.<sup>4</sup>

Thirdly, the registry should identify its funding sources, assess their impact on financial sustainability, and address any potential conflicts of interest that may arise.<sup>4</sup>

Moving on to the methods used by a registry, it is important to clarify the purpose of the data collection system, as it influences the inclusion criteria for the registry population and the data collected. Additionally, detailed information about data providers, such as patients, caregivers, and healthcare professionals, should include their geographic area, selection criteria, and characteristics of the local health system.<sup>4</sup>

A record of permission to use any copyrighted questionnaires and compliance with their format for electronic data collection should be maintained.

The patient population covered by the registry should be defined based on the disease, condition, time period, and procedure. Information about the setting and geographic coverage should be provided, along with the inclusion and exclusion criteria for patient eligibility. Methods to reduce selection bias and loss to follow-up should be implemented, and statistics such as the number of patients, new entries, and exits per year should be recorded.<sup>4</sup>

The registry should also specify the core and optional data sets collected, including their definitions, dictionaries, formats, and plans for updates to these data elements. Applied standards and terminologies should be explicitly stated.<sup>4</sup>

Regarding the infrastructure, the registry should detail its data collection, recording, and reporting systems, along with the timelines for these processes. It should also have the capability for expedited and periodic reporting, data cleaning, transfer, and record linkage. Additionally, safety reporting procedures should be established.<sup>4</sup>

Quality requirements are vital for maintaining the integrity of the registry. This includes plans for planning, control, assurance, and improvement processes, as well as data verification methods and their frequency. The approach to managing missing data should be specified, and details of auditing procedures should be included.<sup>4</sup>

A multi-center registry can enhance transparency and compliance with standards in its governance and data collection methods by following these detailed guidelines.

The issue involves integrating evidence from registries and other sources of real-world evidence (RWE) with randomized controlled trials (RCTs), while also developing new tools for collecting patient-reported outcomes, which are currently often gathered by clinicians rather than patients themselves. As a result, collaboration with patients becomes essential. It's important to recognize that registries are not always the final solution.

## Discussion

The workshop's findings are highly relevant to the broader goal of improving how real-world evidence (RWE) is integrated into evidence-based medicine. However, their practical impact depends on following key methodological standards. Participants recognized that credible RWE requires more than just access to real-world data (RWD); it needs a strict and transparent approach to study planning and execution. This includes clearly defining study hypotheses, protocols, and data analysis plans (DAPs), all of which should be registered and publicly available before starting the study. Additionally, RWD sources must be assessed for their suitability—ensuring they are relevant, complete, consistent, and reliable for the research question. Transparent reporting of the study process, including protocol deviations, population details, and outcome definitions, is equally vital for allowing reproducibility and regulatory review. These principles are increasingly included in guidance documents such as the FDA's Real-World Evidence Program Framework and the EMA's Guideline on Registry-Based Studies,<sup>3,4</sup> both of which offer detailed recommendations on planning, conducting, and evaluating RWE studies. Applying these standards in everyday practice will be essential to ensure that initiatives like this workshop lead to meaningful improvements in how real-world evidence is generated.

## Expert Opinion and Future Directions

The integration of Real-World Evidence (RWE) into evidence-based decision-making has become a practical necessity rather than just a theoretical concept. The workshop consensus highlights that high-quality RWE, when generated and interpreted with rigorous methods, can effectively supplement or sometimes replace data from randomized controlled trials (RCTs).

One clear outcome of the meeting was recognizing the necessity for structured educational programs targeted at clinicians, patients, and decision-makers. Without a fundamental understanding of RWE principles—such as bias reduction, transparency in protocols, and relevance—its usefulness will be limited. Similarly, the support for a straightforward, easy-to-understand glossary underscores the urgent need to standardize terminology to enhance communication among different stakeholder groups.

From a methodological perspective, the push for standardization in registry governance and study oversight aligns with evolving regulatory standards. Ensuring RWE studies meet the quality benchmarks established by the EMA and FDA will be crucial for their inclusion in guidelines and regulatory decisions.

Looking ahead, the next key step is to put these principles into practice through collaborative pilot projects, joint initiatives between academia and regulators, and cross-disciplinary working groups. Enhancing the representativeness of RWE—both geographically and across various health systems—will be essential for global relevance. Additional guidance from the GRADE Working Group and research focused on implementation will help establish best practices for integrating evidence.

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