Perspective

For reprint orders, please contact: info@becaris.com

Journal of **Comparative Effectiveness Research**

Advancing real-world evidence harmonization: lessons from the UK, EMA and global policy frameworks

Alexandros Sagkriotis*,[1]

[1]Independent Consultant in Real-World Evidence & Health Data Science, London, UK

*Author for correspondence: asagkriotis@gmail.com

Aim: Real-world evidence (RWE) – defined here as clinical evidence derived from the analysis of real-world data (RWD) on patient health status and healthcare delivery – has become a cornerstone of regulatory and health technology assessment (HTA) decision making. However, despite broad consensus on its value, policy frameworks governing RWE generation and evaluation remain heterogeneous across jurisdictions. Importantly, this heterogeneity partly reflects the distinct purposes for which RWE is used, including regulatory safety assessment, effectiveness evaluation, health-economic modeling and natural-history research. These functional differences are not inherently problematic; however, fragmented operational requirements can create duplication, inefficiency and delays in patient access. **Materials & methods:** This study employed a narrative comparative policy review of RWE guidance issued by twelve major regulatory and HTA agencies, including the Medicines and Healthcare products Regulatory Agency (MHRA), the EMA, the US FDA and the Canadian Agency for Drugs and Technologies in Health (CADTH). Frameworks were compared across four domains: data quality, statistical methods, registry governance and transparency. Harmonization is defined as alignment across these domains sufficient to enable consistent planning, analysis and interpretation of RWE across jurisdictions, rather than uniformity of decision making. **Results:** The analysis identified convergence in high-level principles but persistent divergence in operational expectations. The MHRA emphasizes flexibility and scientific dialogue; the EMA prioritizes consistency and structured governance; and the FDA provides comprehensive but resource-intensive guidance, reflecting detailed documentation requirements, prespecified analytic expectations and extensive methodological review. HTA bodies apply additional evidentiary criteria related to comparative effectiveness and value, sustaining functional fragmentation even within the same healthcare systems. **Conclusion:** RWE fragmentation reflects both legitimate functional differences and avoidable operational misalignment. Progress toward harmonization therefore requires shared minimum standards and transparency mechanisms rather than additional guidance documents. The UK's post-Brexit autonomy positions it as a test environment for collaborative pilots with the European Medicines Agency, the International Council for Harmonization (ICH) and the International Coalition of Medicines Regulatory Authorities (ICMRA). Six strategic actions are proposed to support pragmatic alignment while preserving contextual flexibility.

First draft submitted: 6 November 2025; Accepted for publication: 9 February 2026; Published online: 27 February 2026

Keywords: global alignment • health technology assessment • HTA • policy harmonization • real-world data • real-world evidence • RWD • RWE • regulatory science

In 2012, real-world evidence (RWE) generation was still an agile and relatively unregulated field. Observational studies using routinely collected healthcare data often required minimal formal documentation that acted simultaneously as protocol, statistical analysis plan and contractual proposal. Approval was secured after a short internal health economics and outcomes research (HEOR) meeting, and initiation followed within weeks. This period is highlighted because it preceded the widespread formalization of regulatory and HTA guidance on RWE, reflecting an era when exploratory use of routine data was largely governed by internal scientific norms rather than external scrutiny.

For the purposes of this review, RWE is defined as clinical or policy-relevant evidence generated through the analysis of real-world data (RWD), including electronic health records, administrative claims, registries and patient-reported data. Importantly, RWE serves multiple functions across the healthcare system: regulators may prioritize safety, validity and causal inference; HTA bodies emphasize comparative effectiveness, generalizability and value; and researchers may use RWE for natural-history characterization or health-economic modeling. These functional differences are not inherently problematic but complicate alignment when operational expectations diverge.

Today, the landscape has changed significantly. Regulatory agencies and health technology assessment (HTA) bodies worldwide now issue detailed RWE guidance. An environmental scan in 2024 identified 46 such documents [1], and by early 2025 at least 58 separate guidance documents had been released across fourteen agencies [2]. Similarly, Burns and colleagues have highlighted that regulators increasingly formalize the role of RWE in decision-making, illustrating simultaneous methodological maturation and increasing operational divergence [3]. This shift represents the evolution of RWE policy frameworks rather than a change in the underlying concept of RWE.

For this review, 'harmonization' refers to the alignment of definitions, quality standards, data models and methodological expectations that enable RWE to be generated and interpreted consistently across jurisdictions. These criteria were selected because they directly influence study planning, analytical reproducibility and cross-jurisdictional interpretability; they are not intended to represent an exhaustive list of all dimensions of evidence assessment.

While these frameworks share broad principles – robust planning, fit-for-purpose data, transparent reporting – they diverge in operational details. A key distinction is that regulatory agencies, such as the EMA, the Medicines and Healthcare products Regulatory Agency (MHRA), and the US FDA, concentrate on study design, validity and safety, whereas HTA bodies, including the National Institute for Health and Care Excellence (NICE) in the UK, the Canadian Agency for Drugs and Technologies in Health (CADTH now operating as the Canadian Drug Agency–Agence des médicaments du Canada [CDA-AMC]), the Haute Autorité de Santé (HAS) in France and the Federal Joint Committee (G-BA) in Germany, emphasize comparative effectiveness, economic value and transferability to local contexts. These distinctions reflect differing decision mandates rather than conflicting scientific standards and help explain why complete uniformity in RWE assessment may be neither feasible nor desirable. Recognizing this duality between regulatory science and HTA evaluation is essential for understanding the roots of fragmentation.

For example, sample-size representativeness is treated as part of 'relevance' by some agencies but as a marker of 'quality' by others. The FDA emphasizes adequacy under quality, whereas the EMA defines relevance by whether a dataset contains the necessary elements to answer the research question [2,4]. Beyond definitions, divergent data models and infrastructures further limit interoperability; the OMOP Common Data Model (OMOP-CDM), for instance, has enabled standardized analytical pipelines across European and global RWE initiatives, although its use is primarily driven by collaborative research networks rather than formal regulatory requirements, which often continue to rely on CDISC-formatted submissions. Even where principles converge, definitional inconsistencies create inefficiencies for sponsors, regulators, HTA bodies, clinicians and ultimately patients, forcing them to repeat or reframe analyses.

These inconsistencies have practical consequences. Studies that once commenced within weeks now require 3 months when using secondary data and nine or more months for primary data collection. The resulting delays increase operational costs and postpone the evidence required for patient access. As Sarri and Hernandez described, the field evolved from a 'desert' of limited guidance into a 'jungle' of overlapping frameworks [1]. Large-scale infrastructures such as the FDA Sentinel Initiative, the Observational Health Data Sciences and Informatics (OHDSI) community and the European Health Data and Evidence Network (EHDEN) illustrate that regulatory science and technical enablers are advancing – yet global harmonization remains aspirational and uneven.

Within this environment, the UK exemplifies both innovation and challenge. NICE incorporated real-world data into its appraisals as early as the 2000s, and MHRA created pathways that welcomed hybrid evidence [5]. While NICE has historically been the main UK driver of methodological innovation in data gathering and appraisal, MHRA's contribution has been more regulatory, focusing on flexible scientific advice and exploratory pilots following Brexit. The EMA and Heads of Medicines Agencies (HMA) similarly defined RWE as "*clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real-world data*", signaling its role alongside randomized control trials [4]. Since Brexit, MHRA autonomy has fostered flexibility but also duplication and operational complexity. The UK's contribution is therefore best viewed as complementary to – rather than leading – global harmonization efforts.

Despite these complexities, the UK remains one of eight global priority markets shaping RWE strategy, alongside the US, China, Japan, Canada, Germany, France, Italy and Spain. Increasingly, countries such as Canada, South Korea and Saudi Arabia have formalized RWE frameworks, signaling worldwide momentum [6–8]. Parallel initiatives such as the European Health Data Space (EHDS) and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) strengthen secondary-data governance and transparency, while global fora – including the International Coalition of Medicines Regulatory Authorities (ICMRA) and the draft International Council for Harmonization (ICH) M14 guideline – represent emerging platforms for methodological convergence [2].

Together, these developments raise a central policy question: do existing RWE frameworks support consistent, efficient and decision-ready evidence across the product life cycle? This review builds upon prior peer-review feedback to enhance methodological clarity and coherence, and it is guided by three interrelated questions:

Key questions

- How does the proliferation of RWE guidance – 58 documents across regulators and HTA bodies – affect study timelines, resource allocation and the consistency of decision-making?
- What are the implications of the UK's evolving role in this landscape, particularly the effects of post-Brexit divergence between the MHRA and EMA?
- Do current guidance documents cover the entire drug life cycle? How can we support that evidence generated from RWD is sufficiently robust to inform decision-making?

Aim

The aim of this work is to examine the operational, methodological and policy implications of fragmented RWE guidance and to identify opportunities for harmonization. Specifically, the paper highlights the inefficiencies and duplication resulting from divergent frameworks, while positioning the UK as a collaborative rather than dominant actor in shaping a coherent global RWE ecosystem. It also explores whether current guidance sufficiently addresses the full product life cycle and how and how current guidance addresses the full product life cycle and supports the generation of RWE that is methodologically sound, transparent and decision-ready. For the purposes of this manuscript, harmonization refers to the alignment of policy, methodological standards and data models to enable consistent planning, analysis and interpretation across jurisdictions.

Materials & methods

Study design & scope

This study employed a narrative comparative policy review approach, which is appropriate when analyzing heterogeneous policy documents that differ in scope, terminology and legal status. Unlike systematic reviews, this approach prioritizes conceptual comparison and policy interpretation rather than exhaustive evidence synthesis. The objective was not to produce a quantitative meta-analysis but to systematically compare definitions, methodological standards and governance principles across major agencies. Frameworks were compared across four domains: data quality, statistical methods, registry governance and transparency, drawing on European transparency initiatives such as ENCePP.

Data sources & selection criteria

Official guidance documents were retrieved between January and October 2025 from the websites of twelve key regulatory and HTA bodies: EMA, MHRA, FDA, CADTH, Therapeutic Goods Administration (TGA), HAS, G-BA, Pharmaceuticals and Medical Devices Agency (PMDA), Ministry of Food and Drug Safety (MFDS), National Medical Products Administration (NMPA), Saudi Food and Drug Authority (SFDA) and Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency; ANVISA). Secondary literature peer-reviewed policy analyses, conference presentations and agency white papers was – used to provide contextual triangulation. Documents were included if they:

- Presented formal guidance or frameworks on RWE/RWD use in regulatory or HTA decision-making.
- Addressed at least one of four domains: data quality, statistical methods, registry governance or transparency.
- Draft consultations, internal or nonpublic reports and purely technical data-model papers were excluded.

10.57264/cer-2025-0183

Table 1. Gap analysis of real-world evidence frameworks across regulators.

Domain	MHRA	EMA/EU States	CADTH†	FDA	Australia	Gap/implication
Data quality definition	Broad	Detailed	High	Specific	Moderate	UK less prescriptive than others
Statistical methods	General	Detailed	Justification	Prescriptive	Flexible	UK lacks methodological clarity
Registry Governance	Encouraged	Often mandated	Encouraged	Required	Flexible	UK guidance less formalized
Timelines for advice	Fast	Variable	Moderate	Moderate	Variable	UK speed advantage fragile
Global alignment	Low	High (within EU)	Moderate	High	Moderate	Risk of UK isolation

Source: Author analysis of publicly available guidance (2025).
†CADTH is included as a health technology assessment (HTA) organization rather than a regulatory authority.
AU: Australia; CA: Canada; EU: European Union.

Analytical framework

Each document was reviewed for scope, definitions, quality dimensions, statistical guidance, registry governance and transparency mechanisms. Information was manually extracted by the author using a structured comparison framework and cross-checked against multiple independent sources, including peer-reviewed policy analyses and agency publications. The synthesis represents a qualitative, interpretive comparison rather than a quantitative scoring exercise. Illustrative case examples – some hypothetical and others drawn from published literature – were used to contextualize the practical implications of these differences across therapeutic areas such as ophthalmology, oncology and dermatology.

Quality assurance & verification

All information was extracted from publicly accessible sources and cross-checked against multiple independent references where possible. The analytical synthesis was structured to ensure traceability of each interpretation to its originating document.

Limitations

Because this analysis relied on publicly available documents rather than primary data, findings reflect the author's synthesis and interpretation. However, the narrative comparative approach is appropriate for identifying conceptual and methodological gaps across jurisdictions, and it aligns with established practices for policy analysis.

Summaries presented in Table 1 reflect a qualitative synthesis of recurring themes within each agency's published guidance and should be interpreted as indicative policy orientations rather than formal ratings or sentiment analyses.

Results/findings & policy implications

Findings & policy implications

The UK provides one of the clearest illustrations of both the potential and the risks created by fragmented RWE governance. NICE, incorporated RWE into technology appraisals as early as the 2000s [5], and MHRA advanced pilots exploring hybrid designs, registries and external comparators [1,3]. Post-Brexit autonomy created space for innovation but also forced sponsors to prepare separate evidence packages for MHRA and EMA, increasing workload and the likelihood of divergent outcomes. The UK's role is therefore best understood as that of a policy innovator and early adopter, with lessons potentially transferable through multilateral fora such as ICMRA and ICH [2]. Going forward, MHRA's flexibility could enable it to serve as a convening hub for alignment across regulatory and HTA communities – provided these efforts remain coordinated with EMA, ENCePP and other partners.

Across Europe, the EMA has attempted to foster consistency through infrastructure and governance. DARWIN EU coordinates access to pan-European data sources and, by 2024, had scoped more than 60 research topics and initiated 27 regulator-led RWD studies [9]. This move from principle to practice accelerated during COVID-19, when RWE supported vaccine-safety monitoring and informed EMA strategy [4,9]. Yet national HTA bodies such as HAS (France) and G-BA (Germany) continue to apply distinct registry and design criteria, slowing harmonization. Divergence is therefore not only geographical but also functional: regulators prioritize evidentiary validity and safety, whereas HTAs emphasize comparative effectiveness, budget impact and societal value. A shared appreciation of these complementary roles is essential for progress.

The adoption of common data models such as OMOP-CDM within EHDEN and OHDSI, together with emerging EHDS legislation, has begun to reduce inconsistencies by improving interoperability and transparency.

ENCePP strengthens quality and reproducibility through its registry of noninterventional studies and methodological guidance – providing a model of transparency that could be scaled globally via ICMRA and ICH collaboration.

In the United States (US), the FDA developed one of the most comprehensive frameworks through the 21st Century Cures Act (2016). Its RWE Program emphasizes data reliability, relevance and transparency, supported by detailed guidance on electronic health records (EHRs), claims data, registries and pragmatic trials [10,11]. Using a 'learning-by-doing' model, the FDA employs demonstration projects to clarify expectations for external control arms (ECAs), registries and digital-health data. The Sentinel Initiative remains the cornerstone of this approach, illustrating how structured, regulator-led infrastructures can accelerate learning and standardization across large populations.

Canada positioned itself as a leader in transparency. In 2023, CADTH and Health Canada issued joint guidance codifying expectations for RWE submissions and reproducibility [6]. This collaboration between regulator and HTA body demonstrates how parallel scientific advice can reduce duplication and promote coherence – a model worth scaling through international networks.

Across the Asia–Pacific region, regulators moved quickly but unevenly. South Korea's MFDS enabled use of insurance claims and EHRs for post-marketing studies in 2021 [7]; Japan's PMDA issued 'points to consider' for registry-based RWE [12]; and China's NMPA released interim guidance for pediatric, oncology and post-marketing applications [13]. Australia's TGA contributed 2021 guidance emphasizing patient-reported outcomes [14]. These initiatives share a commitment to RWE integration but vary in methodological rigor, highlighting the need for international convergence on data quality and governance.

The Middle East and Latin America are also advancing. In 2025, Saudi Arabia's SFDA published draft guidance on integrating RWD and RWE into regulatory submissions [8]. Brazil's Anvisa Guide 64/23 (2023) established best practices for RWD studies, marking the region's first formal step toward regulatory integration [15]. Both illustrate expanding global engagement with RWE policy.

Taken together, the global picture is one of convergence in principle but divergence in practice. Regulators universally endorse RWE's value, yet operational definitions of quality, relevance and reliability differ. For sponsors, this translates into inefficiency: evidence packages must be adapted or duplicated across jurisdictions, extending timelines and raising costs. Fragmentation delays access, increases workload and sustains inequities in evidence interpretation. Conversely, alignment promises efficiency, faster innovation and greater trust in RWE. The UK's autonomy therefore remains a valuable policy test bed but not a global convenor; its flexibility can instead support pilot alignment initiatives in collaboration with EMA, ENCePP, ICMRA and ICH.

Comparative analyses confirm these patterns. Zong *et al.* reviewed EMA and national HTA oncology assessments and found that although RWE appeared in about a third of submissions, its role varied widely: the EMA often treated RWE as supportive, while the G-BA and HAS frequently judged it insufficient [16]. This illustrates that divergence occurs not only across regions but also between regulatory and HTA perspectives within the same system, highlighting the operational challenges created by divergent interpretations of data quality and evaluation criteria across agencies and the resulting need for greater transparency around minimum expectations.

For example, minimum data-quality expectations may include documented data provenance, completeness assessments for key variables, validation of outcome definitions and prespecified handling of missing data. These thresholds are intended to support methodological rigor rather than replace context-specific analytical judgment.

Importantly, most frameworks focus on regulatory submissions and HTA decisions but rarely address the vast volume of observational research used for burden-of-disease estimation, safety profiling or value demonstration. Such studies influence clinical practice and stakeholder perception but often escape methodological scrutiny. ENCePP's registry and methodological guidance could serve as a template for improving transparency and reproducibility in this 'nonsubmission' RWE space.

Case examples

To illustrate the operational consequences of fragmented RWE governance, this section presents a combination of documented and illustrative examples from major therapeutic areas. Together, they highlight how heterogeneity in regulatory and HTA requirements contributes to duplication of effort, delayed access and inefficiencies in evidence generation.

The following case examples combine documented evidence from the literature with illustrative scenarios intended to demonstrate how differences in regulatory and HTA requirements can translate into operational

inefficiencies. Where examples are drawn from published studies, references are provided; where illustrative, they are presented to reflect commonly reported regulatory interactions rather than specific agency decisions.

Ophthalmology

A registry-based study of wet age-related macular degeneration provides a clear example of how divergent governance requirements can shape timelines. One regulator may accept an EHR-linked registry within months, while another may require additional validation of coding accuracy and linkage procedures before approval. Each additional review cycle extends timelines and raises operational costs, delaying access to new treatments.

These discrepancies reveal that although regulators broadly endorse the use of RWE, they differ in their operational definitions of quality and relevance. As noted earlier, agencies differ in how they classify core quality dimensions, for example, whether sample-size representativeness is treated as an element of 'relevance' or 'data quality'. This variation contributes to inconsistent assessment criteria across frameworks. The resulting variability directly influences the speed of evidence generation and, by extension, the timeliness of patient access to innovative therapies.

Oncology

In oncology, a real-world comparative-effectiveness study examining epidermal growth factor receptor-mutated non-small-cell lung cancer can face similar obstacles. In one jurisdiction, a robust study using ECAs could support a conditional listing, while another authority may require additional statistical adjustments or sensitivity analyses before acceptance.

The FDA has increasingly accepted ECAs in regulatory submissions where randomized control trials are infeasible, such as in rare cancers or single-arm studies. This practice demonstrates how methodologically rigorous RWE can accelerate regulatory decisions and improve access when aligned with agency expectations [17–19]. However, inconsistent acceptance criteria among regulators mean that ECA methodologies often need to be redesigned or recalibrated for each jurisdiction [3,16–19]. This duplication increases the analytical burden and lengthens timelines, undermining RWE's promise of efficiency.

Dermatology

A long-term registry-based study of chronic hand eczema (CHE) highlights similar inconsistencies. Some agencies welcome registry data as valid evidence of effectiveness, while others require additional assurances regarding data governance, patient-reported outcomes and privacy protection.

These differing expectations prolong review timelines and can result in heterogeneous outcomes across jurisdictions, even for identical datasets. For sponsors, this variability translates into additional analysis cycles and delayed time to market. For patients, it means unequal access to treatment advances depending on geography. This case underscores the need for more consistent outcome measures and harmonized requirements for patient-reported data across regulators and HTA bodies.

COVID-19 as a proof of concept

The COVID-19 pandemic provided an unprecedented, real-world test of how coordinated infrastructures can generate rapid, decision-ready evidence. The Data Analysis and Real-World Interrogation Network (DARWIN EU), initiated by EMA, enabled multicountry observational studies that supported vaccine safety monitoring at speed and scale [9,20,21].

This experience demonstrated that when data models, governance frameworks and analytic pipelines are harmonized – as in DARWIN EU – cross-border RWE generation can be both rapid and reproducible. However, similar federated models are still not operational in many non European Union (EU) regions, underscoring the need for wider adoption of interoperable data frameworks [9,20,21].

Synthesis of operational themes

Across these therapeutic areas, the pattern is consistent: while agencies universally recognize RWE's potential, they diverge on operational requirements such as registry validation, analytical methods and governance safeguards [9,18,21]. These discrepancies multiply administrative workload, extend study timelines and ultimately delay equitable patient access to innovation.

At the same time, successful examples such as DARWIN EU and FDA accepted ECAs illustrate that when standards and analytical frameworks are aligned, RWE can deliver rapid, reproducible and decision-ready evidence that complements traditional trials [9,18,21,22].

The broader landscape of nonregulatory RWE

Beyond formal submissions, a much larger volume of observational research is generated for scientific communication, burden-of-disease estimation or demonstration of product value [23,24]. These studies often inform policy debates and clinical practice yet remain outside formal regulatory or HTA oversight.

The challenge is not that nonregulatory RWE fails to meet regulatory standards, nor that all observational research should be regulated as part of approval pathways. Rather, when such studies influence clinical practice, reimbursement debate, or policy discourse, the absence of basic transparency and methodological safeguards increases the risk of misinterpretation and over-reach [23,25]. This unregulated evidence base risks reinforcing bias, misinterpretation and duplication. To close this gap, transparent study registration, use of validated outcomes and adoption of minimum methodological standards should be encouraged across all RWE projects – regardless of sponsorship or intent [24–26].

A detailed example from dermatology

A recent dermatology study illustrates this challenge vividly. Andersen *et al.* analyzed patients with CHE using registry linkage and patient interviews to identify risk factors relevant to Janus kinase (JAK) inhibitor safety. The investigators reported the prevalence of regulatory risk factors – diabetes, hypertension, obesity, cancer, venous thromboembolism, major adverse cardiovascular events and age ≥65 years [27].

While the analysis aligned with lists of recognized comorbidities from EMA, it stopped at descriptive prevalence rather than measuring clinical outcomes such as myocardial infarction, venous thromboembolism, or cancer incidence under treatment exposure. Moreover, primary end points commonly used in eczema – patient-reported outcomes such as itch or sleep Numeric Rating Scale scores – were not captured.

Without adjustment for confounding, time-to-event modeling, or sensitivity analyses, the conclusions risked stretching descriptive data toward causal inference. This example reflects a broader trend across therapeutic areas: unrestricted access to registries has increased the volume of descriptive RWE publications, yet many lack analytical depth, appropriate comparators or transparency in design.

Policy implications of nonregulatory RWE

These findings underscore the importance of extending harmonization principles to the entire spectrum of RWE – not only regulatory submissions but also the broader academic and industry-sponsored studies that shape perception and practice.

Frameworks such as the ENCePP already provide models for methodological consistency and transparency. Adapting such frameworks globally – through organizations like the ICMRA or inclusion in ICH guidelines – would help ensure that all real-world studies meet minimum expectations for pre-specification, validated end points and reproducibility.

By raising standards across the entire evidence ecosystem, agencies can mitigate bias, improve comparability and enhance the overall credibility of RWE as a foundation for decision-making.

Summary of lessons from the case examples

- Alignment works: harmonized frameworks, such as DARWIN EU and FDA accepted ECAs, enable rapid, robust and decision-ready evidence.
- Fragmentation costs time and trust: divergent registry and governance requirements delay access and reduce confidence in outcomes.
- Transparency is nonnegotiable: study registration, protocol availability and methodological clarity should be universal norms.
- Quality must extend beyond regulatory RWE: academic and descriptive studies influence practice and policy and must meet minimum methodological thresholds.
- Global coordination is achievable: agencies such as EMA, FDA, MHRA and CADTH already share best practices that can underpin an interoperable, transparent RWE ecosystem.

10.57264/cer-2025-0183

Gap analysis

A comparative review of RWE frameworks highlights consistent strengths and persistent misalignment across agencies. The MHRA offers speed and flexibility in accepting RWE but is less prescriptive on statistical methods and registry governance [5]. The EMA and EU Member States provide more detailed requirements – especially for registry validation and statistical adjustment – yet slower timelines can delay decisions [9]. The FDA is comprehensive and prescriptive [18]; CADTH and Health Canada emphasize transparency and reproducibility [6] and TGA is flexible but less detailed [14]. Differences in data models and infrastructures (e.g., OMOP-CDM, EHDS, Sentinel and DARWIN EU) further contribute to inconsistent analytical expectations [2,9,18,20].

The gap descriptors used in this section (e.g., 'flexible', 'prescriptive' and 'moderate') represent relative positioning derived from recurring themes across publicly available guidance documents – such as the level of methodological detail, degree of mandatory requirements and formality of registry governance – rather than a quantitative scoring or ranking exercise.

Table 1 summarizes these differences across key regulatory and HTA domains.

Regulator–HTA interface

Regulatory frameworks define study-level parameters (end points, comparators, design), whereas HTA frameworks apply broader evaluative constructs (real-world effectiveness, transferability, cost impact). Without early alignment, the same RWE package can be interpreted differently. Joint scientific advice between regulators and HTAs remains the most effective mechanism to close this structural gap and should be institutionalized [2,6].

Operational implications

- The UK's agility advantage risks inconsistency in sponsor submissions without clearer methodological expectations.
- EMA's infrastructure (e.g., DARWIN EU) strengthens credibility but may slow innovation [9,20].
- FDA's prescriptiveness reduces ambiguity but raises analytical burden [18].
- Absent alignment, systems incur duplication, inefficient evidence generation and delayed patient access – affecting regulators, HTA bodies, clinicians and patients [1–3].

Table 1 provides a qualitative synthesis of these recurring patterns rather than a formal scoring or ranking exercise.

In Europe, the ENCePP sustains baseline transparency and methodological quality through its study register, guidance and code of conduct [26] – offering a template for nonregulatory RWE worldwide. Global convergence efforts – ICMRA joint work and the draft ICH M14 guideline – are now essential to translate regional lessons into common international standards for data quality, governance and reporting [2].

A core dilemma remains: agencies share goals yet diverge in operational detail, producing a fragmented system that increases timelines, costs and administrative complexity while patients wait longer for evidence-informed access. Although ICMRA, HMA and ICH M14 signal movement toward shared expectations, practical harmonization is still limited [2,9]. Coordinated international action is required – hence the targeted, jointly implemented recommendations presented in the next section.

Blind spot: nonregulatory RWE

Most frameworks focus on RWE for regulatory/HTA submissions and do not extend to the growing body of observational research used for scientific communication, burden-of-disease, unmet-need awareness or value demonstration [23,26]. These studies rarely undergo protocol pre-registration, analytic transparency, or validated outcomes checks. The result is variable reliability, reproducibility and integrity. Extending ENCePP-like transparency requirements and embedding them into ICH M14 deliverables offers a practical next step to close this gap [2,26] – an opportunity directly addressed in the recommendations that follow.

Recommendations

The gap analysis demonstrates that while regulatory agencies share a commitment to harnessing RWE, their frameworks diverge in ways that increase inefficiency and delay patient access [1–3]. The UK now faces a strategic choice: whether to use its post-Brexit autonomy to act as a convener for harmonization or risk reinforcing fragmentation. Rather than leading unilaterally, the UK could serve as an early adopter and test environment for

multi-agency pilots under the coordination of the ICMRA and the ICH [2,9]. Addressing these systemic issues requires not only recognition but sustained, coordinated action.

To maximize the benefits of RWE globally, six complementary strategies are proposed. Together, they aim to harmonize frameworks, raise quality standards for nonregulatory research, and ensure that patient-relevant evidence is generated and applied responsibly – through greater transparency, competence and international collaboration.

Establish a living international roadmap for RWE

The priority is to move beyond static, siloed guidance documents toward a 'living' international roadmap for RWE that is continuously updated [2]. The MHRA, working with EMA, FDA, CADTH, TGA and NICE, could initiate a joint task force to define shared minimum standards on data quality, statistical methods and registry governance [5,6,9,20]. Such a roadmap would provide a dynamic reference point for sponsors and regulators, reducing duplication and supporting consistent interpretation of evidence across markets. To ensure neutrality, it should be developed under the auspices of ICMRA and ICH rather than through national leadership [2]. By adopting an open, collaborative model, the UK could position itself as a convener of international dialogue rather than an isolated outlier.

Embed transparency as the default

Credibility in RWE rests on trust. Agencies should require disclosure of study protocols, dataset provenance and completeness, analytic code and risk-of-bias assessments as part of every submission [26]. This move toward transparency would enable independent scrutiny and replication, strengthening confidence in both regulatory and HTA decisions. Far from slowing innovation, open reporting accelerates adoption by reducing repeated negotiation on data standards.

The UK has a strong tradition in open science; extending this ethos to RWE would reinforce its global credibility. The ENCePP already provides a tested model through its methodological guidance and public study register, which could be scaled globally via ICMRA collaboration [2,26]. Professional societies and HTA bodies could jointly develop a minimum RWE transparency checklist to support consistent implementation.

Scale up joint scientific advice

One of the most practical mechanisms for harmonization is coordinated early dialogue. Joint review pilots – where MHRA, EMA and CADTH provide parallel advice on the same study protocol – would allow sponsors to align expectations before data collection begins [6,9,20]. By front-loading consensus, agencies could avoid later methodological disputes, shorten timelines and reduce operational burden.

These pilots should systematically include HTA bodies alongside regulators to ensure coherence across the development-to-access continuum. Expanding such pilots specifically to RWE would generate tangible efficiency gains and foster a culture of convergence. ICMRA working groups could maintain an international registry of multi-agency advice sessions to document best practices and lessons learned [2].

Invest in analytical capacity & expertise

Fragmentation in RWE policy is not only about governance but also about capability. Many agencies – and some sponsors – lack sufficient in-house expertise in pharmacoepidemiology, advanced statistics and causal inference. Requiring that RWE studies be designed or supervised by qualified professionals would raise methodological standards and reduce bias.

In parallel, regulators should invest in capacity-building programmes to ensure consistent expertise across regions [9,20,23]. Without such investments, even harmonized guidance risks uneven application. This effort could include joint training programmes delivered through academic–regulatory partnerships and funded via existing capacity-building schemes. A globally coordinated training initiative under ICH or ICMRA would help standardize competencies, ensuring comparable analytical quality worldwide. Sustained funding for shared infrastructures such as OHDSI/EHDEN would further strengthen harmonization and reproducibility [9,20].

Share & celebrate success stories

Demonstrating the practical value of RWE is essential for cultural change. Publishing anonymized case summaries of successful RWE submissions across therapeutic areas would illustrate best practice, while sharing examples of

10.57264/cer-2025-0183

studies that fell short – due to data, methodological, or governance limitations – would encourage learning from failure rather than repetition [2].

Together, such precedents can guide sponsors in study design and reassure stakeholders that RWE is not experimental but an integral component of modern evidence generation. To facilitate this learning, ICMRA could convene an annual cross-agency RWE forum to exchange case experiences and strengthen alignment between regulatory and HTA perspectives [2,9].

Integrate RWE into life-cycle HTA & reimbursement decisions

RWE should not be confined to pre-approval submissions but embedded throughout the product life cycle. Static, one-off assessments miss opportunities to incorporate evolving data on safety, effectiveness and value. Integrating RWE into HTA and reimbursement enables earlier patient access through managed-entry agreements while ensuring that evidence is continually updated [5,6].

NICE has already piloted such models through managed access agreements linked to registry data collection [5]. Scaling this approach systematically would align reimbursement with real-world performance. Canada and several European agencies have advanced life-cycle frameworks, proving feasibility and value [6,9]. The long-term vision is a joint regulatory HTA life-cycle model, coordinated under ICH and ICMRA guidance, enabling global interoperability while preserving regional flexibility [2,9,20].

By implementing these six strategies, regulators, HTA bodies and industry partners can move beyond fragmented guidance toward a coherent, trusted ecosystem for RWE generation. This transition will also prepare the field for its next frontier – artificial intelligence (AI)-driven analytics, personalized medicine and patient-centered evidence – ensuring that RWE remains rigorous, transparent and relevant in the era of data-intensive healthcare [1–3,9,20,23].

Discussion

This discussion integrates lessons from multiple regulatory and HTA frameworks to explore the operational and methodological implications of RWE harmonization. Effective convergence requires both regulatory alignment and HTA engagement, ensuring that methodological innovation – such as that seen in the UK and the EU – is pursued collaboratively rather than unilaterally.

A key counter-argument to harmonization is that excessive standardization may constrain innovation, particularly in rapidly evolving areas such as digital health, AI and rare-disease research. Continuous updates to methodological expectations may also create uncertainty for developers navigating long development timelines. These concerns highlight the need for harmonization to focus on baseline principles and transparency rather than rigid methodological uniformity.

This review highlights both the progress and the persistent challenges in integrating RWE into regulatory and reimbursement frameworks worldwide. Regulators and HTA bodies increasingly accept RWE in principle, yet divergence in operational requirements continues to create duplication, inefficiency and inequity in patient access. Such inconsistencies manifest in several ways: registry validation disputes that delay approval [9,16,17], methodological disagreements that prolong analysis [3,17,18] and data governance requirements that slow access to innovation [1,4]. These challenges affect not only industry but also regulators, HTA bodies, clinicians and – most importantly – patients, who experience delays in accessing evidence that could inform timely decision-making.

At a systemic level, the proliferation of RWE guidance – 58 documents across 14 major regulatory and HTA agencies [2] – signals maturity but also fragmentation. The UK experience since Brexit illustrates this paradox. Freed from EMA oversight, the MHRA has demonstrated agility in piloting flexible RWE pathways [1]. Yet this same autonomy has compelled sponsors to prepare parallel evidence packages for UK and EU submissions, increasing duplication, cost and the risk of divergent outcomes [3,10,28]. The contrast between flexibility and fragmentation underscores the need for structured alignment through common data models and interoperable analytical frameworks such as OMOP-CDM, OHDSI/EHDEN and DARWIN EU.

International convergence efforts – such as the draft ICH M14, the ICMRA joint statement and the EMA's DARWIN EU initiative – represent meaningful steps toward harmonization [2,20,21]. However, without clear minimum global standards for data quality, statistical methodology and registry governance, RWE remains vulnerable to duplication and delays [1,3]. These inefficiencies are not theoretical; they directly affect patients, particularly those with rare or urgent conditions where timely access to real-world data could accelerate care [16,17]. Greater alignment on methodological expectations and minimum quality criteria would substantially reduce variability in how RWE contributes to both regulatory and HTA decision-making.

A further gap concerns the balance between regulatory and nonregulatory observational research. Evidence points to a structural imbalance: the EU Post-Authorization Studies (EU PAS) Register listed over 1090 completed studies by early 2023 [24,26], while the FDA reported that among 116 approvals between 2019 and mid-2021 referencing RWE, only 88 included a formal RWE study, 65 influenced decisions and 38 affected product labeling [11,22]. In oncology, roughly a third of European submissions incorporated RWE, typically as supportive rather than pivotal evidence [16,19,29]. By contrast, the majority of observational publications aim for scientific visibility or disease awareness, not regulatory impact [23,30]. As a result, much of the evidence shaping clinical perception lies outside formal frameworks, exposing decision-makers to variable analytical quality and interpretation. Closing this gap would ensure that all RWE shaping scientific and clinical dialogue meets minimum analytical and transparency standards, thereby reducing the risk of misleading or nonactionable findings.

The Danish Skin Cohort study on CHE exemplifies this blind spot. While aligned to EMA's Janus kinase inhibitor safety risk-factor list, the analysis focused on proxy variables rather than outcomes, lacked statistical adjustment and sensitivity checks and overstated causal interpretation [27]. This demonstrates how privileged registry access can yield descriptive papers that overreach in interpretation without sufficient analytical depth.

The solution is not to regulate all observational research as though it were part of a label-expansion dossier – an approach that would stifle scientific exploration – but rather to extend minimal governance expectations across the continuum of RWE. Three pragmatic measures are proposed:

- Encourage public registration of noninterventional study protocols (e.g., via EU PAS or ENCePP [24,26]), even when intended primarily for scientific communication.
- Promote transparency in phenotype algorithms, variable definitions and prespecified analysis plans, where feasible [5,18].
- Link privileged data access to demonstrable analytical competence and governance standards, ensuring responsible and methodologically sound interpretation [1,4,22,31].

Adopting these measures would elevate the credibility of nonregulatory RWE, prevent over-interpretation of proxy-based studies and strengthen public trust. Further research should explore mechanisms for global alignment on these practices, including the potential roles of the HMA, ICH and ICMRA in defining minimum standards for nonregulatory RWE.

This work has limitations. The analysis draws primarily on published policy documents, regulatory frameworks and illustrative case examples rather than primary empirical data. As such, the scenarios presented may reflect selective illustrations rather than comprehensive evidence across all therapeutic areas. Future research should systematically evaluate the operational and patient-level consequences of fragmented RWE guidance through empirical case studies and comparative analyses.

Addressing these systemic issues requires not only recognition but sustained and coordinated international action. The six recommendations outlined above combine study-level improvements with broader policy reforms, aiming to harmonize frameworks, raise quality standards for nonregulatory research and ensure that patient-relevant evidence is generated and applied responsibly – anchored in transparency, competence and cross-agency collaboration.

Looking forward

Taken together, these findings and recommendations call for a model of pragmatic and inclusive harmonization. The goal is not to erase local or contextual differences but to establish a baseline of shared principles that reduce duplication, accelerate innovation and improve patient access.

- Addressing Question 1 (comparability of frameworks): A global baseline would mitigate fragmentation while respecting national priorities.
- Addressing Question 2 (implications of divergence): Stronger international alignment would reduce inefficiencies, shorten timelines and improve equity in access.
- Addressing Question 3 (nonregulatory RWE): Extending methodological guardrails to scientific communication ensures that registry access produces robust, outcome-focused evidence rather than descriptive or proxy-based studies.

The UK – with its legacy of regulatory innovation and post-Brexit flexibility – can play a catalytic and convening role in this agenda. By fostering dialogue, championing transparency, investing in analytical capacity and sharing

10.57264/cer-2025-0183

practical success stories, the UK can demonstrate that RWE is not merely a methodological tool but a cornerstone of equitable and efficient healthcare decision-making.

Looking ahead, the challenge is to ensure that RWE evolves in step with personalized medicine, AI-enabled analytics and integrated patient-reported outcomes. Only by embedding these dimensions into future frameworks can RWE truly fulfill its promise: bridging science and practice, accelerating innovation and placing patients at the center of evidence generation.

Conclusion

RWE has evolved from a peripheral support tool to a central pillar of modern regulatory and reimbursement decision-making. Yet its full potential remains constrained by fragmented global governance. Despite broad endorsement, definitional inconsistencies and operational divergences continue to generate avoidable costs, inefficiencies and inequities in patient access. Greater alignment on minimum expectations for data quality, methodological standards and data governance is therefore essential to unlock the full value of RWE.

The UK, positioned at the intersection of agility and fragmentation, illustrates both the opportunities and the risks inherent in this evolving landscape. Rather than acting as a solitary convenor, the UK can serve as a collaborative test bed for multi-agency innovation – working alongside the EMA, FDA, HMA, NICE and global platforms such as the ICMRA and the ICH. Together, these entities can co-develop shared standards, strengthen transparency mechanisms such as ENCePP and expand analytical capacity across jurisdictions.

Meaningful harmonization will depend on aligning regulatory and HTA perspectives at the level of minimum expectations, transparency and analytical competence, while preserving the flexibility required for context-specific decision-making. If these steps are taken, RWE can finally fulfil its promise – not only complementing clinical trials but accelerating equitable global access to safe and effective healthcare innovation. Achieving this vision will require sustained collaboration, transparent evidence generation and continuous capability building to ensure that RWE remains robust, reproducible and trusted worldwide.

Summary points

- Real-world evidence (RWE) plays an increasingly central role in regulatory and health technology assessment (HTA) decision-making, yet governance frameworks remain heterogeneous across jurisdictions.
- Differences in RWE requirements partly reflect legitimate functional divergence between regulators and HTA bodies, rather than conflicting scientific principles.
- Fragmentation becomes problematic primarily at the operational level, where inconsistent expectations generate duplication, inefficiency and delays in patient access.
- A comparative review of twelve major regulatory and HTA agencies reveals convergence in high-level principles but persistent divergence in data-quality standards, methodological requirements and registry governance.
- The UK, European Union and United States exemplify contrasting approaches, balancing flexibility, consistency and prescriptive oversight in distinct ways.
- Nonregulatory uses of RWE contribute to scientific and clinical insight but raise credibility risks when transparency and governance standards are insufficient.
- Harmonization should focus on shared minimum standards and transparency mechanisms rather than uniform decision rules or rigid methodological prescriptions.
- The UK's post-Brexit regulatory autonomy provides a test environment for piloting pragmatic alignment with international partners.
- Strategic coordination across regulators, HTA bodies and global initiatives could reduce administrative burden while preserving contextual flexibility and innovation.

Acknowledgments

The author acknowledges his daughter for her encouragement and inspiration, which have been a constant reminder of the importance of striving for a better, evidence-informed future in healthcare. He also thanks colleagues and peers in the RWE community whose public discussions and published work have indirectly informed this analysis. Furthermore, the author extends his sincere gratitude to the peer reviewers for their thoughtful, constructive and rigorous feedback. Their comments improved the clarity, balance and scientific integrity of this manuscript and helped ensure that the work meets the expectations of the scientific community. The author is genuinely grateful for the time and expertise invested in reviewing this work. Portions of this manuscript, including drafting, language refinement and structural suggestions, were supported using OpenAI's ChatGPT-5 model for language enhancement and idea framing. All AI-assisted outputs were critically reviewed, validated and edited by the author

to ensure accuracy, originality, scientific integrity and alignment with journal standards. The author has held senior leadership roles across several global pharmaceutical companies over a 30-year career, with a focus on clinical development, RWE and medical affairs. This manuscript reflects an effort to share accumulated knowledge and insider industry perspectives to support future generations of researchers, healthcare leaders and policymakers.

Financial disclosure

The authors have no financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Writing disclosure

No funded writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Sarri G, Hernandez LG. The maze of real-world evidence frameworks: from a desert to a jungle! An environmental scan and comparison across regulatory and health technology assessment agencies. *J. Comp. Eff. Res.* 13(9), e240061 (2024).
2. Nafie M, Parker VJ, McClellan M, Hendricks-Sturrup RM. A brief report on proposed areas of international harmonization of real-world evidence relevance, reliability and quality standards among medical product regulators. *Pharmacoepidemiol. Drug Saf.* 34, e70127 (2025).
3. Burns L, Le Roux N, Kalesnik-Orszulak R *et al.* Real-world evidence for regulatory decision-making: updated guidance from around the world. *Front. Med.* 10, 1236462 (2023).
4. Maison P, Zureik M, Hivert V *et al.* Real-world evidence (RWE): a challenge for regulatory agencies. Discussion of the RWE conference with the network of the European medicine agencies, patients, and experts. *Front. Pharmacol.* 13, 969091 (2022).
5. National Institute for Health and Care Excellence (NICE). Real-world evidence framework: framework for use in health technology assessments and decision-making. (2022). Available from: https://www.nice.org.uk/corporate/ecd9/resources/nice-realworld-evidence-framework-pdf-1124020816837

•• **This framework provides a leading health technology assessment (HTA) perspective on how real-world evidence (RWE) is evaluated for reimbursement and coverage decisions, illustrating evidentiary expectations beyond regulatory approval.**

6. Health Canada; Canadian Agency for Drugs and Technologies in Health (CADTH). Guidance for reporting real-world evidence to support decision-making. (2023). Available from: https://www.cda-amc.ca/guidance-reporting-real-world-evidence

• **This joint guidance highlights HTA-focused transparency and reporting requirements for RWE, supporting the manuscripts discussion of functional divergence between regulators and HTA bodies.**

7. Ministry of Food and Drug Safety (South Korea – MFDS). Guideline for Medical Information Database Research. Guideline for Citizens-1128-01. Published 29 June 2021. Available from: https://www.mfds.go.kr/brd/m_1060/view.do?seq=14861
8. Saudi Food and Drug Authority (SFDA). Draft guideline on the use of real-world data and real-world evidence for regulatory use. (2025). Available from: https://istitlaa.ncc.gov.sa/en/health/sfda/dmdsfdagov/Documents/RWDRWE.pdf
9. Prilla S, Kurz X, Mol PGM *et al.* Real-world evidence to support EU regulatory decision-making: results from a pilot. *Clin. Pharmacol. Ther.* 116(5), 1188–1197 (2024).
10. Food and Drug Administration (FDA, USA). Considerations for the use of real-world data and real-world evidence to support regulatory decision-making for drug and biological products. (2023). Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-real-world-data-and-real-world-evidence-support-regulatory-decision-making-drug

•• **This guidance exemplifies a comprehensive and prescriptive regulatory approach to RWE, informing the manuscript's discussion of resource-intensive regulatory expectations.**

11. Purpura CA, Garry EM, Honig N, Case A, Rassen JA. The role of real-world evidence in FDA-approved new drug and biologics license applications. *Clin. Pharmacol. Ther.* 111(1), 135–144 (2022).

12. Pharmaceuticals and Medical Devices Agency (PMDA, Japan). Points to consider for ensuring the reliability in utilization of registry data for applications. (2021). Available from: https://www.pmda.go.jp/files/000240807.pdf

13. National Medical Products Administration (NMPA, China). Guidelines for real-world evidence to support drug development and review (Interim). (2020). Available from: http://english.nmpa.gov.cn/2020-01/07/c_456245.htm

14. Therapeutic Goods Administration (TGA, Australia). Real-world evidence and patient-reported outcomes in the regulatory context. (2021). Available from: https://www.tga.gov.au/sites/default/files/real-world-evidence-and-patient-reported-outcomes-in-the-regulatory-context.pdf

• **Illustrates a flexible regulatory model that integrates RWE and patient-reported outcomes, contributing to cross-jurisdictional comparison of regulatory practices.**

15. Brazilian Health Regulatory Agency (ANVISA). Best Practices Guide for Real-World Data Studies (Guide No. 64/23). Published September 2023. Available from: https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2023/anvisa-publica-guia-de-evidencias-de-mundo-real-e-anuncia-grupo-de-trabalho-para-outubro/Guian64_2023_versao1.pdf openknowledge.worldbank.org+3gov.br+3DCVMN+3

• **Provides an example of emerging regulatory frameworks in middle-income settings, broadening the global perspective on RWE governance.**

16. Zong J, Rojubally A, Pan X, Wolf B, Greenfeder S, Upton A *et al.* A review and comparative case study analysis of real-world evidence in European regulatory and health technology assessment decision making for oncology medicines. *Value Health* 28(1), 31–41 (2025).

17. Burcu M, Dreyer NA, Franklin JM *et al.* Real-world evidence to support regulatory decision-making for medicines: considerations for external control arms. *Clin. Pharmacol. Ther.* 108(4), 653–665 (2020).

18. U.S. Food and Drug Administration. *Considerations for the design and conduct of externally controlled trials for drug and biological products*. MD, USA (2023).Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-and-conduct-externally-controlled-trials-drug-and-biological-products

19. Wang X, Chen Y, Li Y, Yang J, Zhang W, Wang Z. Current perspectives for external control arms in oncology clinical trials: analysis of EMA approvals 2016–2021. *J. Cancer Res. Clin. Oncol.* 149(12), 10689–10705 (2023).

20. European Medicines Agency (EMA). Data Analysis and Real-World Interrogation Network (DARWIN EU) overview. (2021). Available from: https://www.ema.europa.eu/en/about-us/how-we-work/data-regulation-big-data-other-sources/real-world-evidence/data-analysis-real-world-interrogation-network-darwin-eu

•• **DARWIN EU represents a structured, network-based approach to RWE generation in Europe and underpins several governance and interoperability themes discussed in the manuscript.**

21. Arlett P, Kjaer J, Broich K, Cooke E. Real-world evidence in EU medicines regulation: enabling use and establishing value. *Clin. Pharmacol. Ther.* 111(1), 21–23 (2022).

22. Jarow JP, LaVange L, Woodcock J. Multidimensional evidence generation and FDA regulatory decision making: defining and using "real-world" data. *JAMA* 318(8), 703–704 (2017).

23. Khosla S, White R, Medina J *et al.* Real-world evidence (RWE): a disruptive innovation or the quiet evolution of medical evidence generation? *F1000 Res.* 7, 111 (2018).

24. Chioureas D, Bjornfors R, O'Connell S, Smith JY, Mourskaia A. Real-world evidence in post-authorisation studies: review of European databases in the ENCePP EU PAS Register 2010–2023 [poster]. Presented at: *ISPOR Europe 2023*, Copenhagen, Denmark (12–15 November 2023). Poster RWD178.

25. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on methodological standards in pharmacoepidemiology (Revision 11). EMA/95098/2010. (2023). Available from: https://encepp.europa.eu/encepp-toolkit/methodological-guide_en

•• **ENCePP provides influential methodological and transparency standards for European RWE studies, supporting the manuscript's emphasis on minimum quality and governance principles.**

26. Andersen YMF, Sieborg J, Nymand L *et al.* Risk factors that limit use of oral JAK inhibitors in chronic hand eczema: findings from the Danish Skin Cohort. *JAAD Int.* 17, 61–66 (2024).

27. Arondekar B, Noseworthy P, Arlett P *et al.* External control arms in regulatory decision-making: current status, methodological considerations, and global perspectives. *Drug Discov. Today* 29(6), 103648 (2024).

28. National Medical Products Administration (NMPA, China). Guidance for real-world data used to generate real-world evidence (Interim). (2021). Available from: https://english.nmpa.gov.cn/2021-04/13/c_644136.htm

• **Illustrates how large regulatory systems outside Europe and North America are formalizing RWE use, reinforcing the manuscript's global harmonization perspective.**

29. U.S. Food and Drug Administration (FDA). *Use of External Controls in Clinical Trials. Guidance for Industry (Draft)*. FDA, MD, USA (2023). Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-external-controls-clinical-trials

30. Mohetaer M, Tuersun A, Li P, Wang S, Zhang X, Chen Y. Drug review and approval policies based on real-world evidence in China and the United States: a comparative study. *Clin. Therapeut.* 46(12), 1059–1068 (2024).

31. Falcão MG, Soares RL, Costa PL, Santos GM. RWD and RWE in Brazil: perspective of the Brazilian Health Regulatory Agency (Anvisa). DIA Global Forum, November 2020. Available from: https://cdn.diaglobal.org/dia-now/articles/global-forum/2020/11/gf-rwd-and-rwe-in-brazil-perspective-of-the-brazilian-health-regulatory-agency-anvisa.pdf

10.57264/cer-2025-0183