JULY/AUGUST 2026 VOL. 12, NO. 4

VALUE & OUTCOMES
SPOTLIGHT
An HEOR news magazine

REAL GROWTH:

In Health Technology Assessment, Real-World Evidence Is Thriving

ISPOR

VALUE & OUTCOMES SPOTLIGHT

JULY/AUGUST 2026
VOL. 12, NO. 4

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The mission of *Value & Outcomes Spotlight* is to foster dialogue within the global health economics and outcomes research (HEOR) community by reviewing the impact of HEOR methodologies on health policy and healthcare delivery to ultimately improve decision making for health globally.

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Improving healthcare decisions

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VALUE & OUTCOMES SPOTLIGHT
EDITORIAL OFFICE:
Value & Outcomes Spotlight
Online: ISSN 2375-8678
Published bimonthly by:
ISPOR
505 Lawrence Square Blvd, S
Lawrenceville, NJ 08648 USA

Direct photocopy permission and reprint requests to Director, Publications.

Cover photo courtesy of AdobeStock/DAndreev

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From Novelty to Necessity: Real-World Evidence Is Redefining Healthcare Decisions

Real-world evidence (RWE) has earned a permanent seat at the healthcare decision-making table. What remains unsettled is how much authority comes with it.

A clear example (as highlighted in our feature article) comes from the regulatory approvals of Kymriah, a chimeric antigen receptor (CAR) T cell therapy cleared on the strength of single-arm trials with short follow-up. Rather than delay approval by years waiting for more mature data, Italy and Spain built patient registries after launch and used the resulting real-world findings to negotiate timed-payment and risk-sharing agreements with the manufacturer. It's a clear example of RWE filling a gap that trials structurally cannot close. The question now is whether that kind of impact is becoming routine or remains the exception that proves how far the field still must go.

Regulators are aligning faster than payers are adapting. In December 2025, the US Food and Drug Administration (FDA) finalized guidance clarifying how real-world data can support medical device decisions, lowering some of the identifiability barriers that had discouraged sponsors from using large postmarket registries. In March 2026, FDA went further by adopting ICH M14, a set of principles for noninterventional studies developed jointly with the European Medicines Agency and Japan's Pharmaceuticals and Medical Devices Agency; the initiative represented the first real harmonization of RWE methodology across major regulators. The European Union's own HTA Regulation is scaling in parallel, with more than a dozen Joint Clinical Assessments underway in 2026, although researchers note that methodological guidance on how RWE should be used within those assessments is still underdeveloped.

> Regulators are writing the rules of the game; payers are still hiring the referees. Providers sit in between, generating much of the electronic health record and claims data everyone else depends on, yet rarely consulted on what would make those data more usable downstream.

Payers are the laggards in this picture. A recent survey by the Academy of Managed Care Pharmacy (AMCP) Research Institute in the United States found that only about 18% of health plans and pharmacy benefit managers currently use RWE in formulary and coverage decisions, even though roughly 80% say they want to. The barrier isn't appetite; it's that most payer organizations lack the internal expertise to interpret and apply RWE with confidence.

Regulators are writing the rules of the game; payers are still hiring the referees. Providers sit in between, generating much of the electronic health record and claims data everyone else depends on, yet rarely consulted on what would make those data more usable downstream. It's a missed opportunity, since data captured with reimbursement questions in mind from the outset tend to need far less cleanup later.

This is where HEOR can play a vital role, and the field is increasingly organizing around that need. ISPOR, the Duke-Margolis Institute for Health Policy, the International Society for Pharmacoepidemiology, and the National Pharmaceutical Council jointly run a Real-World Evidence Transparency Initiative that has produced a Harmonized Protocol Template to Enhance Reproducibility (HARPER) for hypothesis-testing studies and a public registry where researchers can preregister study designs before results are known—directly addressing the credibility problem that comes from studies designed after the fact to fit a preferred conclusion. AMCP has identified this type of standardization as an important way to address the barrier payers have described.

HEOR's value, in other words, isn't just running the analysis; it's also building the shared infrastructure of trust—preregistration, harmonized reporting, transparent handling of confounding and missing data—that allows a payer or HTA reviewer who wasn't in the room to still believe the results.

So, is RWE actually moving reimbursement and policy, or is it still supplementary? Both, depending on where you stand in the system.

For high-cost, single-arm–approved therapies like cell and gene treatments, RWE has become close to indispensable, generating the postlaunch evidence that risk-sharing and outcomes-based contracts now depend on. For routine formulary and coverage decisions, the AMCP numbers are hard to argue around: at 18% actual use against 80% interest, RWE remains aspirational for most payers, not operational. What is changing is the direction of travel. Payers are signaling that the evidence bar is rising, that retrospective analyses without real-world relevance are losing influence, and that they specifically want RWE to underwrite utilization management criteria and outcomes-based contracts rather than sit alongside them as color commentary.

HEOR's value, in other words, isn't just running the analysis; it's also building the shared infrastructure of trust.

For health economists, regulators, payers, and providers, the honest read is that RWE has graduated from novelty to necessity for the hardest cases and remains a work in progress everywhere else. The path forward runs through the standards work already underway—harmonized regulatory principles, preregistered study designs, and payer-facing education—rather than through any single breakthrough dataset or method. RWE's potential is no longer in question. Its consistency and transparency are.

As always, I welcome input from our readers.
Please feel free to email me at zeba.m.khan@hotmail.com.

Zeba M. Khan, RPh, PhD
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Value & Outcomes Spotlight

FROM THE CEO

The Shape of Current Thought on Real-World Evidence and Its Use in HEOR and Healthcare Decisions

Rob Abbott, Chief Executive Officer, ISPOR

One of the most consequential developments in the recent history of health economics and outcomes research (HEOR) is the onset—and rapid acceleration—of real-world evidence (RWE) as a key element of value assessment. RWE bridges the gap between randomized clinical trials (RCTs) and everyday clinical practice. This has important implications for HEOR and healthcare decisions because RWE can provide insights into how medical interventions perform across diverse populations. This, in turn, can guide pricing, regulatory choices, and value-based care strategies. With this in mind, I'm proud to support this issue of *Value and Outcomes Spotlight (VOS)*, which focuses squarely on the shape of current thought (and practice) in RWE. Has the hype been met by actual performance, and if not, where do we go from here?

From its origins in the late 1990s and early 2000s when studies using administrative claims and registry data first appeared, RWE has gathered considerable support. The reasons are many, but perhaps the most significant is the ability to compare (narrow) clinical trial data with actual patient outcomes across a diverse demographic range for a variety of clinical settings. This real-world context goes a long way toward proving the economic worth and comparative effectiveness of drugs and devices to health systems and payers. As a result, agencies such as the US Food and Drug Administration (FDA) use RWE to support label expansions and to monitor postmarket safety, and payers now use real-world data to determine drug reimbursement, pricing models, and formulary placement.

So far, so good. But is RWE mature enough to be—and be seen as—a central input in healthcare decisions? As the papers gathered here make clear, RWE can be a complementary input for healthcare decisions such as postmarket safety monitoring, labeling expansions, and health technology assessments (HTA), but it still faces methodological hurdles that prevent it from fully replacing RCTs as the gold standard.

These hurdles are threefold:

(1) Observational data often lack randomization, leaving analyses vulnerable to unmeasured patient confounders and missing information.

(2) Disparate electronic health records and claims data lack universal standardization and uniform quality control.

(3) Global regulatory and HTA expectations differ among nations, which can create regulatory uncertainty for cross-border submissions.

Against the backdrop I've described, it's useful to consider the current state of alignment among regulators, payers, and HTA bodies in adopting RWE. This is a question that is of particular interest to ISPOR. I would suggest that these agents show growing support for RWE, but operational and methodological fragmentation persists. While regulators like the FDA focus on safety and efficacy for market authorization, HTA bodies and payers require local comparative effectiveness and cost-value data, leading to differing evidentiary thresholds. Put another way, regulators primarily review products for binary approval, whereas HTA bodies and payers evaluate relative value, pricing, and local population generalizability. At the same time, payers and HTA bodies often demand higher standards for causal inference and comparative effectiveness than what may satisfy regulatory safety needs. Finally, global or multicountry RWE data that is acceptable to a central regulator often faces strict local scrutiny or rejection by national or regional payers requiring context-specific data.

> HEOR provides the scientific methods, data validation, and analytical frameworks needed to transform raw real-world evidence into trusted, bias-free insights for decision makers.

Our field of HEOR has played—and continues to play—a pivotal role in enhancing the credibility of RWE. We provide the scientific methods, data validation, and analytical frameworks needed to transform raw RWE into trusted, bias-free insights for decision makers. This is something that ISPOR has taken on in a very meaningful way, most recently by spearheading the Real-World Evidence Transparency Initiative alongside the International Society for Pharmacoepidemiology (ISPE) and the Duke-Margolis Center for Health Policy. This effort established ISPOR guidance and a free public protocol registry to prespecify observational study methods, which regulatory bodies like the FDA and the Centers for Medicaid and Medicare Services (CMS) now widely reference for assurances of credibility. Other important actions that bolster understanding, awareness, and use of RWE include our joint task forces with ISPE (and others) to issue methodological and procedural standards for RWE and our recommendations to improve study replicability, hypothesis evaluation, and appropriate data hierarchies for healthcare coverage decisions.

These developments, and those described in this issue of *VOS*, suggest that RWE should be seen as being in a transitional

space. It is undeniably shaping health policy frameworks and managed entry agreements, yet HTA bodies and payers still consider it complementary to RCTs rather than a standalone replacement. This isn't necessarily a bad thing; it could simply reflect the evolutionary arc of most new ideas and the need to address the pain points that inevitably arise as the "new thing" competes with the incumbent.

Moving forward, ISPOR will continue advancing into the RWE frontier and addressing the methodological concerns and infrastructure deficits that thwart wider adoption. I want payers, for example, to see that we are addressing vulnerabilities to bias, unstandardized endpoints, and confounding variables in observational data. Equally, I want to use the resources of ISPOR, particularly our global network of regional chapters, to help address the lack of internal frameworks, standardized data provenance guidelines, and analytical expertise needed at a local level across the world to appraise observational designs.

Moving RWE from novel concept to a central pillar of healthcare decision making is a journey, and we should celebrate the success and progress that has been achieved over the past 2 decades while acknowledging what is needed to move from validating or contextualizing trial outcomes to justifying an initial formulary listing in its own right. I want *VOS* readers to know I am committed to leading ISPOR's RWE work toward this future state.

HEOR NEWS

1 GLP-1 Competition in UK Intensifies as Regulators Approve Second Oral Therapy (Yahoo Finance)

The United Kingdom's Medicines and Healthcare products Regulatory Agency has approved Eli Lilly's oral weight loss therapy, Foundayo (orforglipron), 2 months after approving its rival in the weight-loss space, Novo Nordisk's Wegovy (semaglutide). Foundayo is also approved for type 2 diabetes. Read more.

2 US Restores Frozen Funding for Gavi, Provided Agency Works to Phase Out Thimerosal (Health Policy Watch)

Gavi, the Vaccine Alliance, welcomed the US government's decision to release $600 million in frozen funding for the organization. However, the US money comes with a strict caveat, demanding Gavi work toward transitioning away from vaccines that use thimerosal as a preservative. Read more.

3 Ireland Is First to Conduct National Health Technology Assessment Based on JCA Data (BlueTeq)

Ireland's National Centre for Pharmacoeconomics (NCPE) conducted the first national health technology assessment for a drug undergoing a European Union Joint Clinical Assessment. Following a rapid review, the NCPE recommended a spinal muscular atrophy drug not be reimbursed at the submitted price. Read more.

4 Surge in China-Originated Out-Licensing Deals Has Implications for HEOR in United States (Curta on Call)

China-originated out-licensing deals surged from roughly $13.9 billion in 2021 to a reported $136–138 billion in 2025, representing nearly one-third of global biopharma licensing value. This growth creates both an obligation and an opportunity for the health economics and outcomes research community. Read more.

5 Efficiency Frontier Analysis Ranks Biologic Therapies for Hidradenitis Suppurativa (JAMA Dermatology)

Researchers from Australia used efficiency frontier analysis to rank 3 monoclonal antibody therapies for hidradenitis suppurativa (adalimumab, secukinumab, and bimekizumab), based on 2 levels of clinical response and pricing data from Australia, the United States, Canada, France, and Germany. Read more.

6 Senate Passes Stopgap Bill Blocking Controversial Research Grantmaking Rule (AIP)

The US Senate passed a short-term spending bill that includes a provision to temporarily block the Office of Management and Budget from implementing its controversial proposed rule on federal grantmaking for research. The House of Representatives will vote on the bill after its August recess. Read more.

7 Low-Cost Biomarker Predicts Short-Term Function After Spontaneous Intracerebral Hemorrhage (Cureus)

C-reactive protein-to-albumin ratio could be a simple, low-cost adjunct biomarker for early risk stratification of patients with spontaneous intracerebral hemorrhage in resource-limited settings, according to research from Bangladesh indicating the ratio was associated with short-term functional outcomes. Read more.

8 Drug Spending Data Suggest US Market Has Rewarded Innovation in Last Decade (USC)

New research from the University of Southern California suggests drug spending in the last decade has become increasingly focused on highly novel drugs. This shift appears to be driven by increased prescribing of more innovative medicines rather than high prices for a small number of drugs. Read more.

9 FDA Finalizes 3 Guidance Documents to Broaden Cancer Clinical Trial Eligibility (RAPS)

The US Food and Drug Administration Oncology Center of Excellence (OCE) has finalized 3 guidance documents to improve participation and diversity in oncology clinical trials. Fewer than 5% of cancer patients currently in treatment are enrolled in clinical trials, despite more than 70% being willing, according to OCE. Read more.

10 World Health Organization Issues First Interim List of Regulatory Authorities for Medical Devices (WHO)

The World Health Organization has published its first interim list of regulatory authorities for medical devices, enabling regulators with limited resources to make use of evaluations and related work already done by others, while remaining responsible for their own decisions. Read more.

11 Real-World Prostate Cancer Outcomes Support PSA Test Threshold Used in Trials (Cancer)

An analysis of real-world data from the Veterans Health Administration supports clinical trial findings that a prostate-specific antigen nadir of <0.2 ng/ml within 9 months of initiating androgen deprivation therapy is associated with improved overall survival in men with metastatic castration-sensitive prostate cancer. Read more.

12 Survey Projects US Health Plan Costs Will Approach Highest Levels in 15 Years (Segal)

The 2027 survey report from Segal, a benefits and human resources consulting firm, suggests health plan cost trends for employer-sponsored benefits in the United States are approaching their highest levels in 15 years, with the median trend for medical plans expected to reach 9.9%. Read more.

ISPOR NEWS

Evidence by Design: Toward Coherent, Decision-Ready Data Across Europe's Regulatory, HTA, and Payer Systems

Julia Chamova, Senior Director, Global Development, ISPOR

Europe's healthcare innovation pipeline rests on a deceptively simple promise: Once a treatment is judged safe and effective, eligible patients should be able to access it. In practice, access timelines remain uneven, and evidence requirements fragment after marketing authorization. The result is not merely slower uptake—it is a structural misallocation of research effort, repeated evidence translation costs, and recurring uncertainty that delays or limits reimbursement decisions.

The central challenge for the European Economic Area (EEA) is coherence. Regulatory approval, health technology assessment (HTA), and payer pricing and reimbursement are distinct decision domains with separate mandates defined by legislation. Yet their processes remain largely sequential and inward-looking. Evidence is generated once but interpreted multiple times—through benefit–risk, comparative/relative effectiveness, and affordability lenses—without a shared upstream evidence roadmap. The system repeatedly asks stakeholders to answer new questions with incomplete information, often after pivotal trials are already complete.

> Recent reforms in Europe create genuine "windows of alignment" for facilitating a coherent, multistakeholder evidence ecosystem spanning the full technology life cycle.

The recent evolution of EEA/European Union (EU) policy—with the EU pharmaceutical legislation update, Critical Medicines Act, and Biotech Act among the most relevant examples—creates a timely opportunity. The EU HTA Regulation (EU HTAR) introduces joint clinical assessments and proactive evidence scoping, shifting Europe from reactive dossier assessment to product-specific evidence planning. Meanwhile, the European Health Data Space (EHDS) and distributed real-world evidence (RWE) networks (including the Data Analysis and Real World Interrogation Network [DARWIN] EU) offer infrastructure that can make decision-grade RWE feasible at scale, if HTA and payer needs inform data requirements early enough. These reforms create genuine "windows of alignment" for facilitating not just better bilateral communication but also a coherent, multi-stakeholder evidence ecosystem spanning the full technology life cycle.

In 2025, ISPOR launched its Strategic Dialogues Initiative, beginning with a pilot focused on the EU/EEA. The first Dialogue convened in late 2025 in Amsterdam, bringing together experts from regulatory, HTA, payer, and wider health policy fields. The primary aim of this initial pilot project has been to enhance the understanding and identification of needs, challenges, and alignment opportunities in the regulator–HTA body–payer decision-making process.

Areas of focus include evidence generation and other pertinent issues for improving the relevance and application of health economics and outcomes research (HEOR) methods and practices. In particular, because patients are the ultimate users—or "customers"—of the healthcare system, integrating patient preferences and engaging patients early, regularly, and consistently in assessment or decision-making processes is essential.

Building on that premise and momentum, ISPOR plans to continue the dialogue, while incorporating perspectives from more stakeholders (including patients), in October 2026 in Brussels.

The white paper resulting from the ISPOR Dialogue 2025, summarized below, reflects on the 2025 conversation and extends an invitation for evidence generation practitioners, decision makers, researchers, industry partners, and other relevant stakeholders to engage with the white paper's proposals.

Why Misalignment Persists: Different Mandates, Shared Consequences

More than an issue of poor communication, misalignment reflects institutional realities. Regulatory bodies assess benefit–risk and grant legal authorization. HTA organizations assess clinical value and comparative effectiveness. Payers decide coverage under constraints shaped by affordability, budget impact, and implementation feasibility.

Because these mandates are legitimate and distinct, coherence does not mean forcing identical value criteria across systems. It means designing evidence generation so that answers produced for one stage do not create avoidable new questions for the next. Three structural factors keep misalignment in place:

- **Siloed evidence planning.** Even when early dialogues exist between manufacturers and regulators or HTA bodies, payer priorities (affordability, pathway fit, budget impact) often enter too late. What looks complete from a marketing authorization standpoint may still be incomplete for comparative effectiveness or health-economic modeling.
- **Translation effort increases uncertainty.** Differences in comparators, outcome definitions, and trial populations force

stakeholders to interpret evidence through assumptions that may not match local decision frameworks. Rather than reducing uncertainty, this shifts it from the evidence-generation stage to the decision stage, causing delays.

- **RWE potential is not consistently realized.** Data may exist but are not always structured, standardized, or governed in ways that enable comparative conclusions with confidence. Without fit-for-purpose RWE, postlaunch decision making becomes slow and duplicative rather than cumulative.

From Sequential Decisions to Life Cycle Evidence Planning
Europe is now positioned to move from sequential decision making toward *life cycle evidence planning*. EU HTAR's joint clinical assessments and structured scoping processes create incentives to embed payer- and implementation-relevant questions earlier, so evidence is not only regulatory-persuasive but also decision-ready across stages.

Joint scoping should evolve beyond defining dossier requirements. It should become an exercise about *structured mapping of uncertainty*: identifying which uncertainties are critical for valuation and which directly affect affordability and access conditions. Once those uncertainties are clearly articulated, evidence generation can be designed prospectively to address the most consequential gaps.

> Joint scoping should become an exercise about structured mapping of uncertainty: identifying which uncertainties are critical for valuation and which directly affect affordability and access.

Adaptive approaches are particularly relevant in areas (oncology, orphan drugs, and transformational innovation) where a product's high uncertainty profile at launch is structurally misaligned with its premarket assessment. Adaptive pathways, conditional approaches, and living HTA models can align access decisions with evidence maturation, as long as governance is explicit about what evidence will be generated, when and how it will be appraised, and what decisions it will update.

Making RWE Truly Decision-Grade
Distributed RWE initiatives and broader European health data infrastructure can reduce the gap between data reflecting "what happened in practice" and "data decision makers can use." But RWE is valuable only when it is comparable, interpretable, and fit for scrutiny.

Fit-for-scrutiny RWE requires:

- Clarity on core data elements, endpoint definitions, and potential comparators
- Transparency on methodology, bias handling, and uncertainty quantification
- Inputs on resource use and costs that are suitable for health-economic and budget-impact reasoning

Decision makers must trust not just the statistical output, but also the inferential credibility of the methods and the governance behind data quality.

Cross-border RWE is especially valuable for smaller populations. For rare diseases with limited national sample sizes, pooled evidence generation can improve the robustness of comparative conclusions—but only when definitions and key variables are harmonized.

Payers as Strategic Buyers: Incentives Tied to Uncertainty Resolution
One of the most consequential reframes in evidence coherence is treating payers not as final arbiters in access pathways, but as strategic buyers who actively shape evidence priorities. The challenge is that evidence-generation incentives are not always aligned with what payers need most to reduce decision risk.

A coherent model would connect better evidence generation with pricing and reimbursement through:

- Prospective, uncertainty-informed evidence plans established prior to market entry
- Mechanisms for adjustments in price or access conditions when identified uncertainties are resolved—or when evidence fails to confirm expected value

This shifts the incentive landscape: It replaces ad hoc postlaunch data requests with a planned, decision-driven evidence roadmap, reducing uncertainty management costs and shortening the path from authorization to stable patient access.

Governance: The Mechanism Matters
Coherence requires more than aligned intent. It needs a *governance mechanism* for durable information exchange, scoping discipline, and life cycle evidence planning, while appropriately maintaining confidentiality and respecting institutional independence.

Stakeholders must go beyond stating general evidence needs. They should explicitly articulate context-specific uncertainties and the rationale for value judgments, priority-setting logic, and budgetary constraints. When those elements are communicated early and consistently, health technology developers can design studies and RWE strategies that directly address decision questions rather than optimizing for a single assessment stage.

> Structural heterogeneity among European nations should not be treated as a barrier but as a baseline feature that informs how evidence must be planned and packaged across stages.

To this end, the white paper calls for sustainable financing and training to enable meaningful patient engagement across the full evidence life cycle, and for patient-reported outcomes, performance outcomes, and patient experience data to be

systematically integrated—from real-world settings in addition to clinical trials—so the evidence base genuinely reflects what matters to those living with the conditions being assessed.

Coherence as a Competitiveness Strategy

Systemic coherence in evidence generation is ultimately a *competitiveness and sustainability strategy*. When evidence is misaligned across regulatory, HTA, and payer systems, delays become structural and patient access becomes uneven. When coherence is built upstream—through life cycle evidence planning, decision-grade RWE, uncertainty-resolution incentives, and durable governance—innovation becomes more predictable, reimbursement can progress more smoothly, and health systems can sustain access to therapies that deliver true value.

A critical framing point is that the EU/EEA is not a single pricing and reimbursement market. It comprises 30 member states, each with distinct pricing rules, reimbursement processes, affordability constraints, and value assessment traditions. This structural heterogeneity should not be treated as a barrier but as a baseline feature—one that informs how evidence must be planned and packaged across stages. Alignment does not mean a single shared decision outcome across nations; it means reducing avoidable duplication and translation loss while respecting national realities.

Europe's reforms (eg, EU HTAR, EHDS, and growing RWE capabilities) create favorable conditions for this shift toward systemic coherence. The remaining task is to build the mechanism that turns reforms into consistent practice.

ISPOR welcomes a wider stakeholder dialogue that will be critical to strengthen what comes next. We invite feedback on the associated white paper with its intent to contribute to realizing a patient-centered, adaptive evidence ecosystem in Europe.

ISPOR NEWS

From Evidence to Influence: How HEOR Is Redefining Value, Decisions, and Impact

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In conference rooms across healthcare, a familiar scene unfolds: a robust, carefully constructed analysis is presented to decision makers—only to land without impact. The data are sound. The methods are robust. Yet the work fails to influence decisions.

This disconnect between evidence and action was a defining theme across 3 ISPOR Partnership Group forums at ISPOR 2026 in Philadelphia featuring leading health economics and outcomes research (HEOR) experts from the biopharmaceutical industry, medical device and diagnostics industry, and consultancies. While each session addressed a different dimension—soft skills, policy, and executive engagement—they converged on a single conclusion: HEOR is being fundamentally redefined.

> Study design, statistical rigor, and analytical precision have served as the foundation of credibility. But these attributes alone no longer translate into impact.

No longer a primarily technical or reactive function, HEOR is evolving into a strategic discipline that must shape policy, influence leadership, and drive business outcomes. Achieving that shift requires more than analytical excellence. A new combination of capabilities—including communication, adaptability, business alignment, and foresight—determines whether evidence truly informs decisions.

The Limits of Technical Excellence

For decades, HEOR has been defined by its methodological strength. Study design, statistical rigor, and analytical precision have served as the foundation of credibility. But these attributes alone no longer translate into impact.

One panelist recalled, early in their career, presenting a technically sophisticated analysis to a group of executives, only to be met with silence. A commercial leader eventually asked a simple question: "Why are we doing this study?" The answer, though scientifically valid, was not meaningful to the audience in the room.

This moment captures the importance of knowing one's audience when communicating HEOR findings. Decision makers appreciate the importance of methodological rigor, but they need to understand what the evidence means, why it matters to patients, and what action it enables. As a result, communication has become central to HEOR influence.

Evidence must be translated into clear, structured narratives that connect analysis to outcomes and implications. This requires discipline and intent, focusing not on what was done but on what should be done next.

Persuasion, too, plays a critical role. By establishing credibility, logic, and emotional connection, HEOR professionals can help stakeholders not only understand the data at a high level but also recognize its relevance. Without that connection, even the strongest evidence risks being ignored.

Navigating a More Complex System

Influence also depends on context. HEOR operates within a complex ecosystem of stakeholders that includes medical affairs, commercial, clinical, research and development, regulatory, and payers, each interpreting evidence through different lenses.

Of the many factors currently reshaping how value is defined and assessed, global policy is one of the most visible. In the United States, policies such as the Inflation Reduction Act and renewed attention to international pricing benchmarks are introducing more direct links between value and cost and deepening the discussion about investment in innovation. At the same time, global frameworks such as the European Union Health Technology Assessment Regulation are driving greater alignment across markets.

These changes are raising the bar for evidence generation. Comparative effectiveness is no longer optional. Outcomes must reflect real-world impact, including quality of life and economic burden. Evidence must also be globally consistent, locally relevant, and capable of informing decisions across different healthcare systems.

Critically, this environment rewards anticipation rather than reaction. HEOR can no longer wait for policy shifts to occur. It must inform the proactive design of evidence strategies that align with evolving expectations from the outset. In doing so, HEOR

will be helping to shape policy by defining how tradeoffs among costs, outcomes, and access are measured and understood.

Speaking the Language of Decision Makers
Even as policy-driven external pressures are mounting, internal alignment remains equally important. One of HEOR's most persistent challenges is translating analytical insight into terms that resonate with executive leadership.

At the C-suite level, decisions are framed in terms of portfolio performance, financial outcomes, and risk. Executives are not evaluating individual datasets; they are determining how resources are allocated across an entire organization. For HEOR to influence these decisions, it must connect evidence directly to business outcomes.

> Too often, HEOR is engaged too late in the product life cycle. To maximize impact, HEOR professionals must be embedded earlier–during product development, trial design, and evidence planning.

For HEOR professionals, this requires a shift in focus—from methods to meaning. Rather than leading with technical detail, effective communication centers on 3 questions: Why was this evidence generated? What does it show? And what should be done as a result?

The most impactful HEOR teams embed this framing early, engaging stakeholders throughout the research process so that findings are already understood and trusted before formal presentation.

When aligned in this way, HEOR can directly influence high-stakes outcomes. Industry executives have used real-world evidence to strengthen pricing positions, inform payer negotiations, and shape reimbursement decisions in addition to advancing health outcomes. Equally important, HEOR can help those executives and organizations avoid missteps by identifying risks, understanding assumptions, and anticipating barriers before they materialize.

In both cases, its value lies in enabling better decisions.

Moving Upstream
Across all discussions, one imperative stood out: HEOR must move upstream.

Too often, HEOR is engaged too late in the product life cycle—after clinical strategies are set or challenges emerge. In these situations, its role is limited to explaining or defending decisions that have already been made.

To maximize impact, HEOR professionals must be embedded earlier: during product development, trial design, and evidence planning. At this stage, they can shape endpoints, comparators, and study questions to ensure relevance for patients, payers, and policy makers.

Early engagement extends beyond internal teams. Regulatory and HTA consultation processes (such as the European Commission's Joint Scientific Consultations) provide opportunities to align evidence expectations before they become constraints. HEOR teams within organizations that take advantage of these opportunities can help shape the decision framework itself, rather than reacting to it.

This shift, from reactive support to proactive influence, is central to HEOR's evolution.

Rethinking the Economics of Evidence
The foundational assumption that HEOR's primary role is to justify the price of therapies is being challenged by growing recognition that HEOR can also help address the cost of generating evidence.

Modern clinical development is extraordinarily expensive, driven in large part by the traditional 3-phase randomized controlled trial model. Advances in methodology, such as external control arms and sophisticated statistical adjustments, offer credible, less costly alternatives in certain contexts. For rare diseases, in particular, these approaches could dramatically reduce both development cost and time to market.

By helping redefine acceptable evidence standards, HEOR's influence has the potential to extend beyond pricing debates to impact the broader economics of innovation.

Redefining Expertise
Collectively, these ongoing shifts point to a new definition of expertise within HEOR.

Technical skills remain essential but are no longer sufficient alone. Professionals must also demonstrate strategic thinking, policy awareness, and the ability to communicate across diverse audiences. They must understand how evidence informs decisions, not just scientifically but operationally and financially. They must adapt messages to different stakeholders while maintaining analytical integrity.

They must also operate effectively under uncertainty.

As artificial intelligence begins to reshape analytical workflows, routine tasks may become more automated. But judgment, contextual understanding, and strategic insight will become even more valuable.

In this environment, adaptability is emerging as a defining skill. The most effective HEOR professionals will be those who can integrate across disciplines, navigate ambiguity, and apply evidence to drive action.

From Evidence to Action
The transformation of HEOR is already underway. Policy changes, system pressures, and organizational priorities are redefining how value is measured and how decisions are made.

Evidence is no longer an endpoint. It is a means of influence across policy, strategy, and patient outcomes. For HEOR, this shift presents both a challenge and an opportunity.

The challenge is to evolve by building new capabilities, engaging earlier, and aligning more closely with decision-making processes. The opportunity is to become indispensable—not by producing more data, but by delivering evidence that is relevant, actionable, and aligned with stakeholder needs.

In a landscape where data are abundant, but attention is limited, the ability to connect evidence to decisions will define the future of HEOR and its leaders.

Acknowledgement: *ISPOR acknowledges Russ Montgomery, GSK; Simu Thomas, Alexion AstraZeneca Rare Disease; and Joseph DiCesare, Mitch Higashi, Kelly Lenahan, Christopher Morelli, ISPOR; who helped to organize the content of these sessions for the ISPOR Partnership Group.*

For more information on the ISPOR Partnership Group, please contact sales@ispor.org.

Disclosure: *This article was created with assistance from artificial intelligence (AI). Claude Sonnet 4.5 was used to transcribe sessions, and CoPilot 2.20260527.37.0. was used to draft a summary article based on the transcripts. The article has been reviewed and edited by ISPOR staff, and it has been reviewed by all of the listed authors. For more information about ISPOR's AI policy, click here.*

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POLICY BRIEF

The ISPOR Monthly Policy Brief provides concise insights into emerging developments shaping the global health policy landscape. Each edition highlights timely issues relevant to the health economics and outcomes research (HEOR) community and beyond, examining how evolving policy decisions influence healthcare systems, evidence generation, innovation, and patient access.

Emerging Policy Signals Shaping Pharmaceutical Policy

Ana Amaris, MD, MPH, Director, Health Policy Initiatives, ISPOR, Lawrenceville, NJ, USA

Overview: This July installment delves into themes from ISPOR's recent Health Policy Leadership Exchange (HPLE), Over the past several months, pharmaceutical policy discussions have expanded well beyond traditional debates surrounding drug pricing and reimbursement. Across multiple jurisdictions, governments are increasingly linking pharmaceutical policy with broader objectives related to industrial competitiveness, trade, domestic manufacturing, innovation, and long-term health system sustainability. At the same time, questions surrounding affordability, evidence generation, and equitable access have become increasingly interconnected, challenging policy makers to evaluate policy reforms within a broader systems context.

These broader trends were also reflected during discussions at the HPLE, where experts from government, academia, industry, payer organizations, and health policy institutions examined the evolving implications of the Most Favored Nation (MFN) drug pricing initiative in the United States. While discussions centered on MFN, they consistently returned to a series of broader policy themes that increasingly extend beyond any single pricing policy.

1. Pharmaceutical pricing is increasingly becoming embedded in trade and industrial policy.
Recent developments suggest that pharmaceutical pricing is no longer being considered solely within the context of healthcare financing. In the United States, discussions surrounding MFN have increasingly intersected with trade negotiations, domestic manufacturing, supply chain resilience, and international competitiveness. Similarly, 1 year after launching an ambitious life sciences strategy, the European Commission is making progress toward positioning pharmaceutical innovation as a central component of Europe's broader competitiveness agenda—recognizing the sector's importance not only for health outcomes but also for economic growth and technological leadership.

This broader shift was echoed during the HPLE, where discussions consistently framed pharmaceutical pricing as part of a larger policy conversation involving industrial strategy, geopolitical priorities, and international competitiveness. For HEOR professionals, this evolution suggests that future policy analyses may increasingly require perspectives extending beyond traditional reimbursement and pricing frameworks.

2. The debate is shifting from drug prices toward global burden-sharing for innovation.
The policy discussion surrounding MFN has increasingly highlighted a broader question: How should countries collectively finance pharmaceutical innovation?

Recent analyses from international organizations continue to demonstrate substantial differences in pharmaceutical spending across high-income countries, while the US government has increasingly framed these differences as part of a broader conversation regarding the global distribution of innovation costs. While there is no consensus on how countries should contribute to financing pharmaceutical innovation, the question has become prominent in global policy discussions.

This broader perspective also emerged during the HPLE. Rather than focusing exclusively on whether drug prices should increase or decrease, discussions explored how innovation should be financed globally, whether the current distribution of financing responsibilities is sustainable, and what mechanisms might better align incentives for future pharmaceutical innovation.

These questions are likely to remain central as countries continue exploring approaches to balancing affordability with sustained investment in biomedical innovation.

3. Government savings and patient affordability should not be assumed to be synonymous.
Improving affordability remains a shared policy objective across healthcare systems. However, recent policy discussions have increasingly distinguished between reducing public expenditure and the need to improve affordability for individual patients.

Experience with existing rebate structures (most notably in the United States and Germany) and ongoing pricing reforms illustrates that the distribution of savings depends heavily on benefit design, cost-sharing arrangements, and implementation mechanisms. Consequently, policies generating substantial government savings do not necessarily produce proportional reductions in patient out-of-pocket costs or improvements in patient access.

The HPLE reinforced this important distinction, highlighting the need to evaluate affordability from multiple perspectives, including government budgets, payer expenditures, benefit design, and patient experience.

As pricing reforms continue to evolve, evaluating not only the magnitude of savings but also how those savings are distributed across stakeholders will remain essential for informing future policy decisions.

4. Innovation depends on a broader ecosystem than pricing alone.
Discussions regarding the implications of drug pricing policies are extending beyond affordability to include potential impacts on pharmaceutical innovation.

Recent policy initiatives in both the United States and Europe emphasize that innovation depends on multiple interconnected factors, including regulatory predictability, public investment in research, scientific infrastructure, clinical trial capacity, skilled talent, intellectual property protections, and competitive commercial environments.

The HPLE reflected this broader perspective. While participants expressed differing views regarding the potential effects of MFN on pharmaceutical research and development, there was broad recognition that innovation is shaped by an ecosystem rather than any single pricing policy.

This systems perspective reinforces the importance of evaluating pharmaceutical policy within the broader context of research, regulation, investment, and healthcare delivery.

5. International reference pricing is elevating the importance of HTA and HEOR.
As policy makers increasingly look across borders when developing pharmaceutical pricing policies, the demand for transparency is also growing. International reference pricing, confidential pricing arrangements, and managed entry agreements have become increasingly common policy tools. While these approaches may support affordability objectives, they also make it more difficult to compare prices across jurisdictions and to understand how those prices were derived.

Discussions at the HPLE reinforced that pharmaceutical prices cannot be interpreted independently of the health systems that produce them. Prices reflect national priorities, health technology assessment methodologies, reimbursement policies, budgetary frameworks, and societal preferences. As countries increasingly look at one another when informing pricing decisions, understanding these underlying contexts becomes just as important as understanding the prices themselves.

This evolution is elevating the role of health technology assessment (HTA) and HEOR in healthcare decision making. Rather than relying solely on international price comparisons, policy makers increasingly require evidence that explains the value of new technologies, evaluates comparative clinical and economic outcomes, assesses budget impact, and examines the broader system-level implications of policy reforms. HTA and HEOR provide the analytical foundation needed to interpret complex policy environments and support transparent, evidence-informed decisions.

As pharmaceutical policy becomes more interconnected globally, strengthening the generation, interpretation, and application of evidence will be essential to ensure that pricing policies continue to support innovation, affordability, and patient access.

Looking Ahead
Although recent discussions have been catalyzed by the MFN initiative in the United States, the issues raised extend well beyond any single policy. Across countries, pharmaceutical policy is increasingly intersecting with trade, industrial strategy, innovation, evidence generation, and health system sustainability.

These developments suggest that future policy discussions increasingly will require multidisciplinary perspectives capable of evaluating both intended and unintended consequences across health systems.

The conversations at the HPLE reflected this broader mindset. Rather than offering definitive answers, they highlighted the importance of continued dialogue and robust analysis to support informed decision making in an interconnected global policy environment.

As a neutral convener, ISPOR remains committed to fostering these conversations and advancing the evidence needed to inform health policy decisions around the world.

POLICY BRIEF

The Expanding, Interwoven Objectives of Pharmaceutical Policy

Ana Amaris, MD, MPH, Director, Health Policy Initiatives, ISPOR, Lawrenceville, NJ, USA

Overview: One of the signals highlighted in the July 2026 ISPOR policy brief was the growing convergence between pharmaceutical policy and broader national priorities. Rather than representing an isolated development, recent policy actions suggest this trend continues to accelerate across multiple regions. This August installment takes a closer look at how governments are expecting pharmaceutical policy to advance objectives that extend beyond healthcare, including economic competitiveness, industrial development, trade, innovation, and health security and consider what this evolution may mean for evidence generation and healthcare decision making.

Medicines as Strategic Assets

Historically, pharmaceutical policy has focused on 3 core objectives: improving patient access to medicines, ensuring affordability for health systems, and fostering continued innovation. While these priorities remain central, governments are increasingly asking pharmaceutical policy to contribute to a broader set of national goals. Across multiple regions, medicines are being viewed not only as essential healthcare interventions, but also as strategic assets that can strengthen economic competitiveness, industrial development, supply chain resilience, and health security.

Pharmaceutical Policy Beyond Healthcare

Recent developments demonstrate how pharmaceutical policy is becoming more closely integrated with broader national strategies.

In the United States, recent policy initiatives have further linked pharmaceutical pricing with domestic manufacturing, trade policy, research investment, and national security. The Administration's pharmaceutical tariff framework, for example, connects tariff treatment to commitments on domestic manufacturing, research and development, and pricing agreements, highlighting how pharmaceutical policy is progressively being used to pursue multiple policy objectives simultaneously.

A similar perspective is emerging in the United Kingdom. The government's updated *Life Sciences Sector Plan: One Year On* presents patient access, research and development, advanced manufacturing, workforce development, and investment as related components of a life sciences ecosystem rather than as independent policy priorities.

Across Europe, ongoing initiatives to strengthen biotechnology, modernize regulatory systems, and enhance the competitiveness of the life sciences sector similarly reflect a growing emphasis on aligning health innovation with long-term economic resilience and technological leadership.

Beyond Europe and North America, similar priorities are emerging in other regions. In Kenya, the recently launched *Health Products and Technologies Local Manufacturing Strategy 2026–2030* illustrates how pharmaceutical manufacturing is now viewed as both a health priority and an economic one, supporting access to medicines while strengthening local production and health security. Developed in the context of shifting global financing and geopolitical dynamics, the strategy also reflects a broader emphasis on building greater domestic resilience and long-term sustainability.

Although regional priorities differ, the underlying direction is remarkably consistent: pharmaceutical policy is increasingly expected to advance broader national objectives alongside its traditional healthcare mission.

Implications for Evidence and Decision Making

This evolution raises an important question: If pharmaceutical policy is expected to achieve multiple objectives simultaneously, how should its success be evaluated?

Measures such as patient access, affordability, health outcomes, and budget impact remain fundamental. However, they may no longer capture the full range of outcomes policy makers seek to achieve. Increasingly, governments are also interested in understanding how pharmaceutical policies influence manufacturing capacity, research investment, innovation ecosystems, workforce development, supply chain resilience, and broader economic performance.

For the health economics and outcomes research (HEOR) community, this presents an opportunity to broaden the evidence base supporting policy decisions. As pharmaceutical policy becomes more interconnected with industrial, economic, and innovation strategies, evaluating its impact may require more multidisciplinary approaches while maintaining methodological rigor, transparency, and a continued focus on improving health outcomes.

Looking Ahead

The growing connection between pharmaceutical policy and industrial strategy, trade, innovation, and health security suggests that governments are looking beyond traditional healthcare objectives when designing pharmaceutical policies.

As these expectations continue to evolve, the evidence used to inform healthcare decision making may also need to evolve.

As governments continue to broaden the objectives of pharmaceutical policy, understanding the trade-offs among access, affordability, innovation, competitiveness, and resilience will be critical. Supporting those discussions with rigorous, policy-relevant evidence will be essential to informed healthcare decision making.

FROM THE REGIONS

Real-World Data in Healthcare Technology Incorporation: A Strategic Opportunity for Latin America

Marcos Santos, MD, PhD, ISPOR Brazil Chapter; **Alfonso Gutierrez-Aguado, MD, PhD**, **Rosina Hinojosa, MSc, MPH**, ISPOR Peru Chapter; **Daniela Paredes-Fernandez, MPH**, ISPOR Chile Chapter; **Maria Gabriela Fernandez, PharmD, MBA**, **Graciela Luraschi, PharmD, MBA**, **Bruno Boietti, MD**, **María Luisa da Silva Soca, MSc**, ISPOR Argentina Chapter; **Juan Guillermo Barrientos G, MD, MSc**, ISPOR Colombia Chapter; **Rodrigo DeAntonio MD, MSc, DrPH**, ISPOR Central America and the Caribbean Chapter

From Rhetoric to Decisional Use

Real-world data (RWD) and real-world evidence (RWE) are now occupying an increasingly structured space in health technology assessment (HTA) frameworks in high-income countries. In Latin America, the discussion has imported this technical vocabulary, but without questioning the local conditions that determine what type of RWD can really underpin coverage and incorporation decisions. The pertinent question, especially for a Latin American audience, is: When does RWE really contribute to a better coverage decision, and when does it function merely as a methodological ornament accompanying a file without substantially modifying the inference that sustains the recommendation?

The consolidation of the HARPER (HARmonized Protocol Template to Enhance Reproducibility) framework published by the joint ISPE/ISPOR working group and the expansion of initiatives such as RCT DUPLICATE showed that observational studies can, under well-defined conditions, produce effect estimates comparable to those of randomized trials—but also that these conditions are demanding and often not met. Adoption of the RWE discourse without careful appropriation of its methodological standards represents a tangible risk: decisions supported by apparently empirical, but methodologically fragile, evidence.

This article proposes a shift: to stop understanding RWE as an economic substitute for randomized clinical trials and to recognize it as a complementary instrument, with its own questions and demanding methodological standards.

Answering Questions That Matter Most

What interests the payer is not that evidence is "real-world," but that the estimate of its effect is causal. Hernán and Robins put it precisely: any observational analysis that pursues a causal conclusion is, implicitly, an attempt to emulate an objective trial (or target trial). The key factor is whether this emulation is explicit—and therefore criticizable, replicable, calibratable—or whether it is implicit in the form of an opaque statistical model.

The RCT DUPLICATE program, led by Schneeweiss and Franklin, provides a concrete empirical basis for assessing the scope of RWE. In the first 10 prospectively planned emulations of cardiovascular trials of antidiabetic and antiplatelet drugs, RWE replicated the regulatory conclusion of the RCT in 6 out of 10 cases, and the hazard ratio fell within the 95% confidence interval of the corresponding RCT in 8 out of 10. Subsequent results, from a total of 32 emulations, concluded that the agreement between RWE and RCTs depends critically on the choice of active comparators, the quality of the outcome measurement, and the ability of the database to capture clinically relevant confounding variables.

> Adoption of real-world evidence discourse without careful appropriation of its methodological standards represents a tangible risk: decisions supported by apparently empirical, but methodologically fragile, evidence.

RWE does not replace the RCT; it answers questions that the RCT structurally cannot answer—or will not answer—for reasons of cost, ethical feasibility, or lack of commercial incentives. Among these questions are precisely those that matter most to the Latin American payer: effectiveness in populations with comorbidities excluded from the pivotal trials, real patterns of adherence and therapeutic persistence, use of health resources associated with incorporation, and performance of technology in subpopulations defined by access, geography, or socioeconomic level.

Minimum Requirements

Recent methodological literature—from HARPER to the NICE guidelines on RWE in HTA and the discussion of target trial emulation in the Methods Explained column of *Value & Outcomes Spotlight*—converges on 3 minimum requirements for RWE: prespecified protocol recorded before seeing the results; transparent description of the origin and quality of the data; and rigorous application of causal inference methods to control confounding, including sensitivity and unobserved bias analyses.

In the absence of these conditions, what is produced is not RWE but something less: a descriptive analysis with causal claim. This distinction is critical in the regulatory context, because the confusion between the 2 registries—analytical and causal—is what allows studies of low methodological quality to circulate as "real-world evidence" in records of HTA agencies. The problem is not the absence of data; it is the absence of quality control and analytical governance.

What is it about Latin America that makes RWE more necessary than in other contexts but also more difficult to produce? Key contributing factors include the fragmentation of Latin American health systems, the scarcity of interoperable records, and the increasing budgetary pressure on payers.

The Illusion of Abundant Data

Latin American populations are underrepresented in the pivotal clinical trials that inform regulatory approvals and, subsequently, incorporation recommendations. The differences between Latin American populations and those in the global north—related to prevalence of comorbidities, genetic profile, access to timely diagnosis, and continuity of care—make the direct extrapolation of effectiveness estimates informed approach at best. In this context, RWE is not a methodological luxury; it is a natural mechanism to bridge the gap between imported evidence and local performance.

> In our reality, where the per capita health budget is a fraction of the European one, real-world evidence emerges as the only feasible way to generate local comparative evidence in many categories.

One of the most lucid observations of the regional panorama—formulated during an RWE session of ISPOR Latin America 2021—is that the Latin American problem is not the scarcity of data, but the shortage of analytical capacity and data governance.

Brazil generates massive volumes of information through DATASUS, the information systems of the Agência Nacional de Saúde Suplementar (ANS) and the electronic registries of operators and hospitals. Mexico has Sistema Nacional de Información en Salud (SINAIS); Colombia with its insurance records; Argentina with heterogeneous national and provincial bases, highly fragmented and with limited interoperability. *[See Appendix 1 for a country-by-country overview of RWE data sources and institutionality.]*

What is missing is not information; we lack the following: a way to make this information cumulative, unique identification of the patient through the cycle of care, validated algorithms for phenotyping conditions in administrative codes, and above all, a critical mass of analysts trained in computational epidemiology.

This observation has an uncomfortable practical consequence: The mere existence of large databases does not produce useful RWE. On the contrary, it may produce descriptive studies with the appearance of comparative analysis, whose uncritical inclusion in the regulatory and coverage ecosystem can deteriorate—not improve—decision-making quality. This, in turn, will negatively impact the credibility of the RWE.

The Budget Question

Here we come to the most relevant angle for Latin American payers, public and private. Pragmatic RCTs and adaptive platforms are expensive even in high-income systems; in our reality, where the per capita health budget is a fraction of the European one and the capacity to cofinance local confirmatory studies is limited, RWE emerges as the only feasible way to generate local comparative evidence in many therapeutic categories. This is particularly true for high-cost drugs and advanced therapies, where incorporation is decided based on evidence from a single pivotal trial and where the space for risk-sharing contracts and managed entry agreements depends, crucially, on the payer's ability to monitor outcomes in its own population.

RWE makes it possible to take advantage of existing data in administrative systems, clinical records, and electronic records, significantly reducing costs and time for producing evidence compared with conventional experimental studies. This difference is not trivial from the payer's perspective: In systems where every dollar invested in evidence generation competes directly with the effective coverage of benefits, RWE is the only feasible alternative for producing local comparative information in multiple therapeutic areas.

It is important, however, to understand that while RWE is cheaper than a new RCT, it is not cheap. An interoperable, governed, auditable data infrastructure with permanent analytical capacity requires sustained investment in the medium term. Latin American health systems have historically shown difficulty in sustaining such investments because there are always more urgent problems. Ultimately, the decision to build RWE's capacity competes, at the margins, with the decision to incorporate the next technology.

> Real-world evidence in Latin America is not only a methodological complement to the clinical trial, but a structural response to simultaneous conditions of budgetary constraint, systemic fragmentation, and underutilization of data generated in insured populations.

Another important condition, which the regional debate tends to underestimate, is that the existence of data is not equivalent to the capacity to produce evidence. In most Latin American countries, a significant proportion of the relevant information is generated in insurance schemes, particularly in populations covered by social security or public insurance, where there are continuous records of use, prescription, and clinical outcomes. However, these datasets often remain underutilized due to limitations in interoperability, standardization, and analytical capability. In this sense, the greatest limitation is not the absence of information, but the absence of institutional structures that allow the transformation of administrative claims data into valid causal inferences and inputs for coverage decisions.

RWE's agenda in Latin America, therefore, cannot be reduced to database expansion, but requires a deliberate investment in analytical capabilities, epidemiology and artificial intelligence tools, causal design, and algorithm validation, to allow the

economic advantage of RWE to be effectively translated into more informed decisions (**Figure 1**).

Without this transition, beyond the risk of producing lower quality evidence, the region risks continuing to generate large volumes of data without converting it into useful knowledge for financial sustainability and health technology management.

Systemic Fragmentation

Latin American systems are pluralistic and fragmented. This creates a serious counterfactual problem for RWE: the observable population in a database rarely represents the population on which the coverage decision will be made, and adjustment algorithms designed for homogeneous databases (such as those in the United States or England) do not translate directly. They are therefore of no use here. *[See Appendix 2 for a country-by-country breakdown.]*

As a hypothetical example, a comparative effectiveness study on the use of any medication, constructed with data from a Brazilian supplementary health operator of class A/B, will produce a perfectly valid estimate—for that population. Extrapolating it to the Unified Health System (SUS) population, with a different epidemiological profile, adherence, and comorbidities, requires transportability assumptions that are rarely made explicit in the files submitted to CONITEC. Even more than RWE produced in integrated systems, RWE in Latin America needs a rigorous discussion on intracountry external validity.

A Minimum Agenda for Change

At this point, some urgent priorities can be deduced.

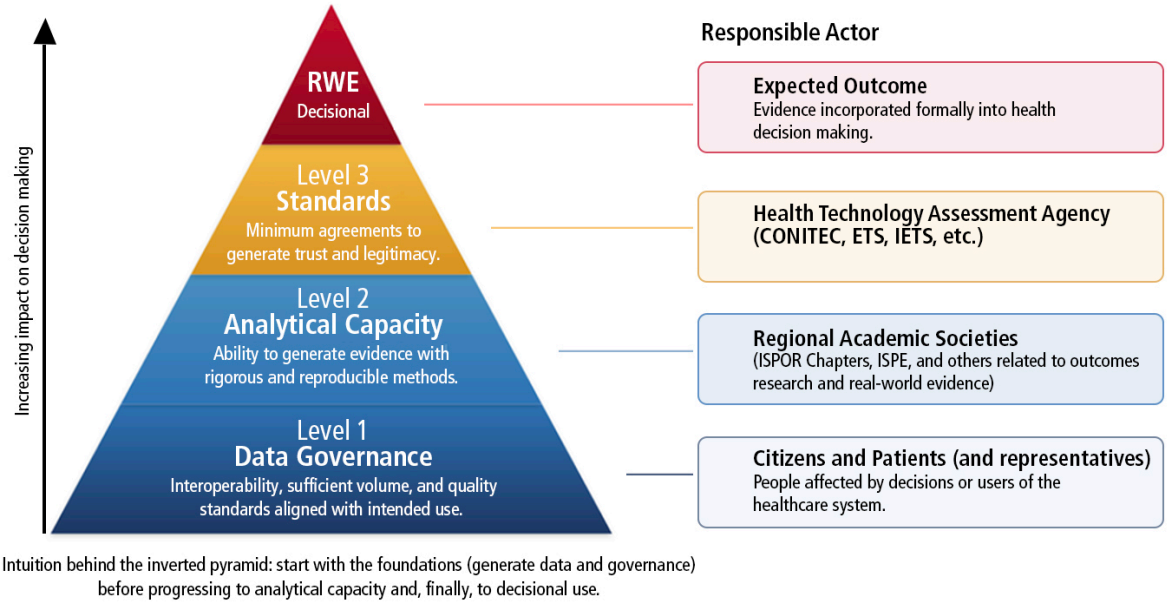
- Regional HTA agencies should formally adopt reporting standards for HARPER-aligned or equivalent RWE studies, and base conditional acceptance of this type of evidence on pre-registered protocols.
- Payers—both public and supplemental health—should invest in interoperable data infrastructure rather than ad hoc analytics. The natural succession between data governance and analytical capacity cannot be reversed.
- Regional academic societies, including the Latin American Chapter of ISPOR, have a clear role in the formation of human capital capable of producing and critiquing RWE with international standards. This is, perhaps, the most restrictive bottleneck in the medium term.

In these contexts, RWE emerges not only as a methodological complement to the clinical trial, but as a structural response to simultaneous conditions of budgetary constraint, systemic fragmentation, and underutilization of data generated in insured populations.

The central challenge is not whether the region should adopt RWE, but whether it can do so under conditions that allow the construction of valid counterfactuals, guarantee external validity, and sustain minimum standards of causal inference in systems characterized by heterogeneous care trajectories and noncomparable databases. Investment in interoperability, standardization, and analytical capacity is necessary for the economic advantage of RWE to be translated into more efficient decisions.

RWE will not, on its own, solve the prioritization dilemmas faced by Latin American systems. But it can, if taken seriously, shift part of the incorporation debate from the realm of extrapolation to that of observed local performance.

Figure 1. Minimum agenda for a decisional RWE in Latin America



RWE indicates real-world evidence; CONITEC, National Committee for Technology Incorporation; ETS, health technology assessment; IETS, Institute for Health Technology Assessment; ISPE, International Society for Pharmacoepidemiology.

FROM THE REGIONS

Experts from China, Taiwan Discuss HEOR-Driven Decisions in Student Network Webinar

Vishwanauth Persaud, MPH, PharmD Candidate, Touro College of Pharmacy, New York, NY, USA

Advancing Evidence-Based Healthcare Decisions

As healthcare systems worldwide continue to navigate rising costs, expanding therapeutic innovation, and increasing demands for value-based care, health economics and outcomes research (HEOR) has become an essential component of healthcare decision making. To explore these evolving challenges, the ISPOR Student Network hosted the webinar From Evidence to Access: Applying HEOR and Economic Evaluation in Healthcare Decision-Making, bringing together experts from China and Taiwan to discuss how HEOR informs reimbursement, pricing, and health policy across diverse healthcare systems.

The webinar highlighted how region-centric economic evidence, clinical outcomes, and real-world data are increasingly being integrated into decision making in China and Taiwan to improve patient access while ensuring the long-term sustainability of healthcare systems.

Shitong Xie, PhD, professor in the School of Pharmaceutical Science and Technology at Tianjin University in China, explained that his team has been developing population-specific instruments, like the CHROME-G and CQ-11D, because existing tools such as the EQ-5D and SF-6D don't capture the outcome dimensions that matter most locally. As he put it, the goal is that "these specific instruments can capture more precise and more related dimensions… and hopefully have a better result of the economic valuation to better inform the coverage decision making in China."

Huang-tz (Anita) Ou, PhD, professor at National Cheng Kung University in Tainan, Taiwan, shared during the webinar that Taiwan's conditional listing mechanism for new therapies requires real-world data and adverse event tracking during a temporary reimbursement period. These real-world results have shown that "these classes of drugs really work well for majority of the cancer population," although 2 indications were ultimately removed from the coverage list after the evidence showed otherwise, underscoring how real-world data directly shapes reimbursement decisions.

Key Insights From Global Perspectives

One of the most valuable aspects of the discussion was the opportunity to compare how different countries apply similar HEOR principles within their own healthcare environments. Although each healthcare system has unique priorities and reimbursement structures, the speakers demonstrated that evidence-based decision making remains central to improving access to innovative therapies.

Vishwanauth Persaud moderated the webinar.

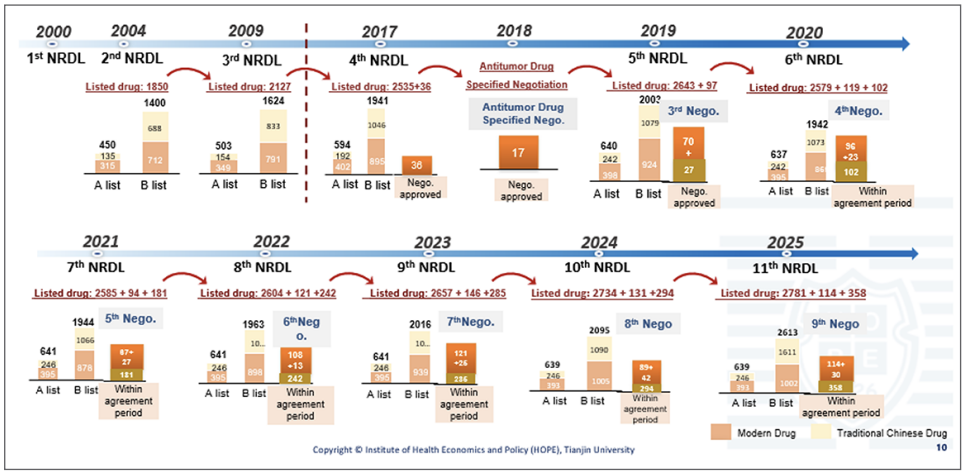
The presentations explored China's National Reimbursement Drug List process and Taiwan's established health technology assessment (HTA) framework to support universal health coverage initiatives. These examples illustrated how local policy, available resources, and healthcare infrastructure influence the implementation of HEOR while maintaining a shared commitment to delivering value-driven care.

Bridging Research and Real-World Application

One of the strongest messages from the webinar was that HEOR extends well beyond academic research. While concepts such as cost-effectiveness analysis, budget impact analysis, and real-world evidence are frequently introduced in educational settings, the speakers demonstrated how these tools directly influence reimbursement negotiations, pricing strategies, formulary development, and national healthcare policy.

For example, Xie shared how pharmacoeconomic evaluation is used in China to help set prices for innovative drugs entering the National Reimbursement Drug List (NRDL) negotiations between the government and pharmaceutical companies. He noted the goal is for population-specific outcome instruments to "capture

Fig 1. History Overview of NRDL in China



Slide presented at the Student Network webinar by Shitong Xie, PhD, of Tianjin University, illustrates how National Reimbursement Drug List negotiations in China evolved between 2000 and 2025.

more precise and more related dimensions" so they can "better inform the coverage decision making."

Ou described how, in Taiwan, real-world data drove a reassessment of a sodium-glucose cotransporter 2 (SGLT2) inhibitor originally reimbursed for diabetes. Three years after its initial listing, real-world evidence showed the drug offered better cardiovascular and kidney protection compared with a DPP4 inhibitor—evidence that, she said, "truly supports the policy changing." The findings informed the decision by Taiwan's National Health Insurance to extend reimbursement to patients with chronic heart failure and chronic kidney disease.

As the moderator, I found this particularly impactful because it reinforced the connection between evidence generation and its practical application. Understanding how research informs real-world decisions provides valuable context for students interested in market access, health policy, and value assessment, while emphasizing the multidisciplinary nature of healthcare decision making.

Inspiring Future HEOR Professionals

I hope webinar attendees gained greater appreciation for the growing role of HEOR in shaping modern healthcare systems. Students and early career professionals in pharmacy and related fields often have limited exposure to careers in market access, health technology assessment, and reimbursement strategy. Hearing directly from internationally recognized experts provided meaningful insight into these career paths while demonstrating the broad impact that HEOR professionals can have on patient care and healthcare policy.

The webinar also highlighted the importance of international collaboration. Although healthcare systems differ substantially across countries, many of the underlying challenges, including balancing affordability, innovation, and equitable access, are shared globally. Learning from these diverse perspectives encourages broader thinking and fosters a deeper understanding of how evidence can be translated into better healthcare decisions.

The Role of the ISPOR Student Network

Educational programming like this reflects the ISPOR Student Network's commitment to preparing the next generation of HEOR professionals. By connecting students with global experts and creating opportunities for meaningful discussion, these events help bridge the gap between classroom learning and professional practice.

As healthcare continues to evolve, developing the ability to translate evidence into informed policy and reimbursement decisions will become increasingly important. Webinars such as this not only strengthen students' understanding of HEOR but also inspire future leaders to contribute to evidence-based healthcare systems that improve patient outcomes worldwide.

HTA POLICY UPDATE

Section Editors: **Sandra Nestler-Parr, PhD, MPhil, MSc; Ramiro E. Gilardino, MD, MSc**

Welcome to the HTA Policy Update, which provides a brief update on notable HTA policy developments from around the globe. We welcome suggestions and guest editorials for future issues. Please contact the *Value & Outcomes Spotlight* editorial office with your ideas.

From Implementation to Evolution: Early Lessons for the Future of HTA

Recent months have brought important developments in European health technology assessment (HTA). The publication of the first Joint Clinical Assessment (JCA) reports under the European Union HTA Regulation, alongside policy discussions in the United Kingdom on the future scope of HTA, offers an early window into how assessment frameworks are evolving.

Although emerging from different policy environments, these developments raise 2 fundamental questions facing HTA systems: How do we assess increasingly complex evidence? And how do we define the value that should ultimately inform decision making?

Early Lessons from 3 Joint Clinical Assessments

The publication of JCA reports on tovorafenib in June 2026 and lurbinectedin and tarlatamab the following month marked an early milestone in the implementation of EU Regulation 2021/2282, providing the first opportunity to observe the performance of the common European assessment methodology across different evidentiary contexts in oncology.

The 3 assessments illustrate distinct evidence profiles.

Tovorafenib presented the most challenging evidence base: Of the 8 predefined PICOs for pediatric low-grade glioma, only 1 produced comparative evidence, based on an unanchored indirect comparison. After weighting, the effective sample size fell below 7 patients, confidence intervals crossed the null (no clear evidence of a positive or negative effect), and response rate analysis was excluded due to different outcome definitions across studies. As a result, the assessment is transparent about what cannot be established; 7 of the 8 clinical questions remain unanswered, and the report focused less on what can be concluded than what remains unknown.

The lurbinectedin evidentiary profile was more straightforward, with a single population, 1 PICO, and 1 randomized trial providing direct comparative evidence. Although the JCA generated interpretable comparative results, several limitations remain. The overall survival advantage was smaller at a later data readout, the open-label design introduced potential bias across multiple endpoints, and subgroup data required correction during the factual accuracy review.

Tarlatamab occupied an intermediate position. The assessment included 4 populations and 7 PICOs, with direct evidence for 3 comparisons and indirect evidence for 4 others. The indirect analyses relied on methods such as unanchored, matching-adjusted indirect comparisons and Bayesian network meta-analyses. For the 4 indirect PICOs, assessors concluded that key similarity assumptions were substantially violated, limiting confidence in the resulting estimates.

Three observations emerge from these early assessments. First, the JCA framework generates the most robust outputs when clinical development programs align closely with the assessment scope defined by the Member States. Second, indirect comparison methods continue to face substantial challenges that the current guidance does not fully resolve. Third, while the reports provide detailed documentation of uncertainty, they stop short of offering an integrated judgment regarding overall certainty. The task of translating methodological limitation into a decision-relevant conclusion therefore remains largely with each individual Member State. Whether this reflects a deliberate design feature of JCA or an area for future methodological development remains an important question for the next phase of EU HTA implementation—in 2028, when orphan medicines will enter the JCA process.

Broader Value Enters the Policy Discussion

While the European Union experience highlights challenges associated with evaluating evidence, the United Kingdom has focused its attention on a different question: What dimension of value should HTA capture?

Evidence sessions before the House of Lords Science and Technology Committee in June and July discussed whether current assessment frameworks adequately capture the wider societal impacts of healthcare interventions. Testimony from NICE, the Department of Health and Social Care, and NHS England highlighted productivity and caregiver outcomes as potential areas for inclusion into NICE's HTA methods, while also recognizing associated equity considerations.

These discussions reflect a broader international debate about whether HTA should move beyond direct health outcomes to more systematically capture societal value elements, such as productivity, caregiver burden, insurance value, and the value of hope.

Looking Ahead: Toward Better Alignment

Although these developments emerged from different policy contexts, they point toward a common observation. The first JCAs demonstrate that methodological consistency cannot fully compensate for limitations in the underlying evidence base, while the debate in the United Kingdom highlights that the very definition of value continues to evolve. Together, these experiences suggest that the next phase of HTA development may be less about refining individual assessment methods and more about better alignment of evidence generation, societal value, and healthcare system priorities.

As implementation of the EU HTA Regulation progresses and discussions about broader value continue across jurisdictions, these early experiences provide important signals for policy makers, HTA agencies, and health technology developers. Whether they lead to future methodological reforms remains to be seen, but they are likely to influence how HTA practice evolves over the coming decade.

Editors would like to acknowledge Jose Diaz, MD, MSc, for his contributions to the content for this issue.

REAL GROWTH:

In Health Technology Assessment, Real-World Evidence Is Thriving

Health technology assessment bodies are increasingly relying on real-world evidence to inform decisions that impact payment and access for medical treatments. How will health economics and outcomes research help this approach realize its potential?

By Beth Fand Incollingo

More and more, when evaluating urgently needed treatments that don't lend themselves to standard clinical trials, health technology assessment (HTA) bodies and payers are turning to real-world evidence (RWE) for answers. But while RWE's ability to inform such decisions is past its infancy, experts say it has more to offer.

"I do not believe that we have yet realized the full potential of real-world evidence," said Grace Li-Ying Huang, Senior Director of the Division of Health Technology Assessment at Taiwan's Center for Drug Evaluation. "In many ways, we are still at the beginning of this transformation. Over the past decade, much of the focus has been on building databases and developing analytical methods. Over the next 5 years, however, I expect real-world evidence to become a core component of healthcare infrastructure."

Over the past decade and a half, HTA bodies have increasingly incorporated RWE into their decisions about value, market access, and reimbursement as a supplement to data from clinical trials, and now decision makers from the United States and the European Union to Asia-Pacific and Latin America are encouraging it through a network of policies and guidelines.

> The next hurdle, experts say, will involve ensuring that the real-world evidence submitted for health technology assessments is credible, complete, relevant, and reproducible.

Consider the regulatory approvals of Kymriah (tisagenlecleucel), a one-and-done chimeric antigen receptor T-cell (CAR T) therapy that can spark long-lasting remissions in patients with certain blood cancers but has a 6-figure price tag. The US Food and Drug Administration, the European Commission, and Health Canada gave the therapy regulatory approval based on single-arm clinical trials with relatively short follow-up periods, leaving HTA bodies to decide whether or how to support it. Italy and Spain responded by building registries that generated RWE about Kymriah's effectiveness—information HTA experts in those countries needed to strike timed-payment and risk-sharing agreements with the drug's manufacturer.

RWE also helped the National Institute for Health and Care Excellence (NICE) evaluate the cost-effectiveness of pre-exposure prophylaxis (PrEP) for HIV prevention in the United Kingdom. By evaluating UK-specific RWE, NICE determined the anticipated patient need, uptake estimates, and health outcomes, ultimately finding the strategy worthwhile for citizens at high risk of contracting HIV.

Especially in the United States, private health insurers are responding to this evolution by including RWE in their assessments, and pharmaceutical companies across the world are cooperating by building RWE into their drug development life cycles in efforts that can range from creating patient registries to conducting long-term, postlaunch follow-up studies.

The next hurdle, experts say, will involve ensuring that the RWE submitted for these assessments is credible, complete, relevant, and reproducible.

Finding Real-World Value

Perhaps even more than regulators, HTA professionals appreciate real-world findings because they help determine when treatment patterns differ from clinical guidelines or controlled study environments, whether safety signals match what trials demonstrated, and how patients perceive the therapeutic experience, said Dimitra Lambrelli, MPharm, PhD, a London-based Senior Director and Senior Research Scientist on the PPD™ Evidera™, Real-World Data Scientific Solutions Team at Thermo Fisher Scientific, a life sciences and laboratory technology company.

HTA bodies can act on that information by matching costs to value through conditional reimbursement mechanisms and managed entry agreements or by imposing postlaunch restrictions on reimbursement or patient eligibility, Huang added.

Most often, experts say, HTA decision makers use RWE to assess the value of precision drugs, gene therapies, or other innovative treatments for rare diseases—for which randomized clinical trials are not always possible and approval processes may be accelerated. RWE is also frequently used to amass long-term data about safety, survival, and health outcomes in cancers or chronic conditions such as cardiovascular disease or obesity. Finally, HTA bodies may consider RWE when weighing the potential value of a label expansion for a drug.

The mission of ensuring that RWE is reliable for these purposes will fall to experts in health economics and outcomes research (HEOR), whose unique skill set includes gathering and studying data harvested from electronic health records, medical insurance claims, administrative databases, disease and product registries, and patient-generated sources such as surveys, forums, and wearable devices.

HEOR professionals also have expertise in applying advanced statistical strategies known as causal inference methods to help minimize the effect of confounding factors, such as differences between populations being studied, missing information, or inconsistencies in the way real-world data has been collected.

"To bring credibility, HEOR leaders must clearly understand the need to produce high-quality studies that meet payers' stringent demands," said Sebastian Schneeweiss, MD, ScD, a Professor of Medicine and Epidemiology at Harvard Medical School and Chief of the Division of Pharmacoepidemiology at Brigham and Women's Hospital, both in Boston in the United

States. "Real-world evidence is not a shortcut to success, and high-validity studies will get us further. Following proven guidances and principles will get us to the right place."

Shaping Robust RWE

While many of today's techniques for conducting real-world research were developed by academics, they're largely used by pharmaceutical companies seeking to inform decisions by regulators and HTA bodies, as well as by national health systems.

One key framework is target trial emulation, which enables researchers to design the randomized clinical trial they wish they could conduct and then use real-world data to create an observational study mimicking that structure. Applying causal inference methods can make it possible for researchers to meaningfully compare estimated outcomes among their emulated comparator cohorts.

A related method involves complementing a single-arm clinical trial with an external control arm. Mirroring a trial's endpoints and populations, these real-world cohorts gather patient data from electronic health records and medical charts. One notable external control arm helped provide NICE with evidence that Tecentriq (atezolizumab) could spark long-term survival in some patients with non-small cell lung cancer. That study, which supplemented the OAK trial with a real-world control cohort of patients treated with docetaxel, was created by Roche using data from the Flatiron patient database.

> Health economics and outcomes research experts working with real-world evidence must consider why data were originally collected and whether they were gathered systematically and transparently.

Causal inference frameworks are crucial in this strategy, too, to ensure that trial arms can be compared and to help prevent bias or systematically missing data, which Lambrelli said can be a challenge when using RWE. For instance, since patients typically pay for GLP-1 obesity treatments out of pocket, those transactions are missing from some key databases, such as insurance claims systems.

"A current issue in our field is the applicability of the right methodologies," she said. "While they need to become more accessible and more appropriately used, these approaches require a lot of statistical understanding, and their success depends on how knowledgeable the scientists are who apply them."

As part of that effort, HEOR experts working with RWE must consider why data were originally collected—for research, administrative oversight, commercial activities, or patient support—and whether they were gathered systematically and transparently, Lambrelli added. While data not generated for research, such as conversations in online patient forums, can be valuable, they need to be handled differently. For instance, "social media listening" studies can highlight the patient perspective as a way of setting the scene for more quantitative research.

But scientists must keep that information as pristine as possible, too.

"It's best to pick up sources that contain a lot of information and then use artificial intelligence (AI) to run sensitivity analyses that identify outliers," such as "trolls" who comment with the aim of provoking or disrupting, Lambrelli said. "The appropriate methodologies applied to harvest this information are equally important to the quality of the data itself."

Unfortunately, the credibility of real-world studies varies widely, Schneeweiss said.

Recently, a number of questionably designed studies have been published by medical students who pulled information from TriNetX, a database of anonymized electronic health records that is freely available to researchers at participating healthcare organizations. Many of these papers are misleading and can leave regulators and HTA decision makers confused, Schneeweiss said.

"With these studies poisoning the water," he said, "nobody knows what to trust anymore."

Researchers can combat that problem by prioritizing transparency about their protocols and processes—one tactic involves preregistering study designs for consideration by the scientific community—and by using established methods to quantify measurement characteristics, such as accuracy, reliability, and completeness.

HEOR professionals who rely on proven frameworks to evaluate the quality of their protocols are doing exactly what they should, Schneeweiss said, but now the field needs to seek international agreement around just a handful of these tools to bring more consistency to real-world research.

"Better reliability will come as we provide more education and training programs and harmonize and test these assessment tools with the input of regulators and HTAs," he said.

Leading the Effort

HTA bodies in the United Kingdom, Scotland, Canada, France, and Germany are among those that incorporate RWE into their decisions, using it to better understand patients and their medical needs and to assess the cost-effectiveness of treatments after they've hit the market.

Beyond simply evaluating that evidence, though, some countries and regions are leading efforts to shape how RWE is collected and applied.

These initiatives include the public-private GREG project in the European Union, which aims to help stakeholders generate

consistently reliable RWE for use in HTA decisions; Canadian Real-World Evidence for Value of Cancer Drugs (CanREValue), which is producing a framework for the use of RWE in funding decisions about oncology drugs; and a proposal by academics from ISPOR's Taiwan chapter to establish a framework that would help HTA experts define and assess the value of expensive new oncology, orphan, and other drugs whose treatment efficacy remains uncertain.

Focusing on RWE is not unusual in Taiwan, where HEOR experts have developed several efforts that are changing the way the country makes value decisions about medical treatments, with more under consideration, Huang said. Those initiatives include:

- A Cancer Drugs Fund. Informed in part by Taiwan's exchanges and collaboration with NICE International, this mechanism allows promising cancer drugs that address important unmet medical needs to receive temporary reimbursement despite remaining clinical uncertainty. During the temporary reimbursement period, additional postlaunch evidence, including RWE, may be collected or submitted to assess clinical effectiveness, safety, utilization, and budget impact. This evidence can then inform health technology reassessment and subsequent reimbursement decisions.
- A national registry of patients who take immune checkpoint inhibitors, which supports reimbursement decisions and label expansions for those drugs.
- The international Fast Healthcare Interoperability Resources standard, which Taiwan is applying across 5 oncology areas with the goal of making it easier for the country's healthcare organizations to exchange real-world data.
- Consent forms that are now routinely requested from patients to allow the collection and analysis of their health information. This effort aims to ease concerns about privacy that can sometimes stand in the way of data exchange.
- Proposed guidance for drug developers about the RWE components they are expected to include in HTA review packages. Taiwan hopes to publish a final version by the end of 2026.

Taiwan is particularly well positioned to conduct real-world research, Huang said, because its National Health Insurance program covers more than 99% of the population and provides access to nationwide healthcare databases that may be linked for research under appropriate data-governance arrangements. Nevertheless, researchers must apply rigorous causal inference methods to address confounding, selection bias, and other methodological challenges. They must also carefully assess and manage data-quality issues, such as potential misdiagnosis or overdiagnosis, coding inconsistencies, incomplete documentation, and fragmented patient records across different healthcare institutions, Huang said.

Some low- and middle-income countries, such as India and Brazil, have found it much more challenging to incorporate RWE into HTA decisions, largely because they lack access to high-quality real-world data. That can occur due to immature digital infrastructures or disconnected systems for sharing health information.

"We like to say that your real-world evidence is as good as your real-world data, so if you don't have those data or appropriate methodologies for assessment, there's not much you can do," Lambrelli said.

She added that while privacy policies can sometimes restrict the sharing of real-world information, the application of data governance techniques, patient de-identification approaches, and AI strategies "should allow all the players to work together to ensure the privacy of individuals while at the same time granting wider access to good-quality data."

Maximizing RWE's Potential With AI

Not surprisingly, AI is transforming the generation of RWE used in HTA decisions by enabling better data extraction, quality, and anonymization, along with predictable analytics and nearly real-time health outcomes surveillance, experts said.

"Through natural language processing and machine learning, we're able to use data that we could not have analyzed before—notes in patients' medical charts, pathology reports, imaging narratives, laboratory findings, insurance claims, patient registries, and information reported by wearable devices," Lambrelli said. "AI can also help us assess the quality of that data and whether it's fit for purpose by identifying missingness, coding inconsistencies, duplicate records, and outliers."

> Artificial intelligence is transforming the generation of real-world evidence for health technology assessment by enabling better data extraction, quality, and anonymization, along with predictable analytics and nearly real-time health outcomes surveillance.

That can benefit HTA bodies by clarifying therapy sequencing patterns and the incidence of medicine switching in the real world, as well as by predicting the likelihood of disease progression, hospitalization, treatment response, therapeutic adherence, reasons for drug discontinuation, relapse, and adverse events.

AI can also save money, preserve privacy, and reduce the need for vast real-world collection of information by providing synthetic data, sometimes even creating "digital twins" that can stand in for patients in certain research settings, Lambrelli said. Limiting the involvement of real patients can be especially useful in rare-disease research, she said, where trial populations are typically small and easily identifiable through context clues.

Despite the gains these functions can bring, experts caution that HEOR professionals must remain in the loop to supervise

AI's activities, checking in at various points to make sure they can see and understand the processes it's using to gather information. Otherwise, they can end up with a black-box model, which may produce statistically accurate data but offers no transparency about how outputs are connected to inputs.

"AI is already very helpful in extracting unstructured information and turning it into structured information, which then can feed into the analytic causal inference pipeline," Schneeweiss said. "There are published agentic AI tools to write and evaluate protocols, turn them into analyses, and interpret data. The key things that consumers of this information need to consider are how much they want to remain in control and how much transparency they need from AI agents and tools to make decisions about big populations and big budgets."

Moving Toward Maturity

Moving forward, Huang expects HEOR professionals across the drug development process to not only continue generating traditional cost-effectiveness analyses, but to increasingly integrate RWE into evaluations of healthcare utilization, long-term value, patient quality of life, health equity, caregiver burden, and broader societal outcomes.

For RWE to become a core component of healthcare evaluations, Huang said, stakeholders will need to tackle complex projects designed to improve methodology, data interoperability, ethical guidelines, and AI applications—all of which will require international cooperation.

In Taiwan, we are eager to collaborate with partners from different countries," Huang said. "We value opportunities both to share our experiences and to learn from others. This kind of collaboration can help all of us use real-world evidence more effectively as part of robust and transparent HTA and reimbursement decisions."

***Beth Fand Incollingo** is a freelance writer who reports on scientific, medical, and university issues.*

By the Numbers: Has RWE Reached Its Potential?

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Is Real-World Evidence Mature Enough to Be a Central Input in Healthcare Decisions?

20%

The proportion of regulatory assessments where real-world evidence (RWE) played a primary role in decision making, compared with **9%** of health technology assessments (HTAs).

- RWE was used as supportive evidence in **46%** of regulatory assessments and **57%** of HTAs.
- RWE was discussed but not used in **22%** of regulatory assessments and **34%** of HTAs.

TAKEAWAY **RWE is now part of healthcare decision making, but most often in a supportive role.**

Citation: Candore G, Martin C, Mills MJ, et al. FRAME: framework for real-world evidence assessment to mitigate evidence uncertainties for efficacy/effectiveness—an evaluation of regulatory and health technology assessment decision making. *Clin Pharmacol Ther.* 2025;118:649-661. doi.org/10.1002/cpt.3713

How Aligned Are Regulators and HTA Bodies in Their Views of Real-World Evidence?

9

The number of RWE studies that were assigned similar roles by both the European Medicines Agency and the US Food and Drug Administration, out of **13** studies assessed by both authorities.

- Authorities were aligned on how RWE influenced their decision making for **5 of 9** studies assessed by at least 2 regulatory agencies and 2 HTA bodies.
- The 2 studies submitted for atidarsagene autotemcel were considered primary or supportive by all **6 of 6** authorities that evaluated both of them.

TAKEAWAY **Despite increasing adoption, the extent to which RWE influences decision making varies across regulators and HTA bodies.**

Citation: Candore G, Martin C, Mills MJ, et al. FRAME: framework for real-world evidence assessment to mitigate evidence uncertainties for efficacy/effectiveness—an evaluation of regulatory and health technology assessment decision making. *Clin Pharmacol Ther.* 2025;118:649-661. doi.org/10.1002/cpt.3713

What Is Limiting Payers' Use of Real-World Evidence for Coverage Decisions?

18%

The proportion of US-based payers who said in a survey that they regularly use RWE in coverage decisions, versus **80%** who said they want to.

- The findings came from an Academy of Managed Care Pharmacy (AMCP) Research Institute survey of representatives from **17** health plans and **19** pharmacy benefit managers.
- Respondents said the largest barrier to using RWE was their lack of understanding and experience interpreting and applying RWE.

TAKEAWAY **The survey findings led AMCP to develop a framework to standardize how payers evaluate RWE for decision making.**

Citation: Lockhart CM, Powers E, Sweet B, Gleason PP, Brixner D. AMCP real-world evidence standards: overcoming barriers to using real-world evidence in US payer decision-making. *J Manag Care Spec Pharm*. 2025;31(12):1230-1236. doi:10.18553/jmcp.2025.25108

Real-World Evidence in Europe: Closing the Gap Between Ambition and Execution

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KEY TAKEAWAYS

Europe's evolving regulatory framework is accelerating drug reviews and introducing Joint Clinical Assessments for regulatory and health technology assessments (HTA), raising expectations for real-world evidence (RWE) in decision making.

In practice, RWE remains underused and often not fit-for-purpose: In an analysis of recent European Medicines Agency oncology approvals, only 15% included RWE and two-thirds were deemed inadequate to inform decisions.

Closing the gap between regulatory expectations and practice requires early planning, fit-for-purpose data, and alignment among sponsors, regulators, and HTA bodies.

Elevated Expectations in Europe

Real-world evidence (RWE) shows how treatments perform beyond controlled clinical trials and is increasingly expected to play a role in how drugs are evaluated in Europe. This shift is being reinforced through concrete policy changes.

The European Union Health Technology Assessment Regulation (EU HTAR) introduced Joint Clinical Assessments (JCA), in which HTA bodies from participating European countries jointly evaluate how a new treatment compares to existing options before making country-level decisions on access and reimbursement. Initially scoped for oncology and advanced therapy medicinal products, JCA will expand to cover most new medicines. While sponsors have traditionally adapted evidence for individual countries, JCA reduces the ability to tailor evidence post hoc and instead requires a single evidence base that is relevant across multiple healthcare systems at the time of assessment. In parallel, new EU pharmaceutical legislation aims to shorten regulatory assessment timelines, requiring decision-ready evidence at the time of submission and leaving less opportunity for postsubmission evidence generation.

> Expectations for real-world evidence in Europe are increasing faster than the availability of clear, operational frameworks to support sponsors in meeting those expectations.

To support evidence generation at scale, the Data Analysis and Real-World Interrogation Network (DARWIN EU), a federated network of data sources coordinated by the European Medicines Agency (EMA), connects hospitals, registries, and other real-world data sources across Europe. Through this network, regulators can request analyses of real-world data to contextualize sponsor-provided evidence. As a result, RWE submitted by sponsors is subject to greater scrutiny, increasing expectations that it will be robust, transparent, and decision relevant.

> Real-world evidence is frequently planned late in product development, limiting the ability to define appropriate comparators, prespecify analyses, and align with regulatory expectations.

Yet despite these advances, no internationally harmonized framework for RWE currently exists. Regulators, including the EMA, have issued guidance on the use of RWE; however, these recommendations remain fragmented and are not always sufficiently detailed to ensure consistent implementation across countries. As a result, expectations for RWE are increasing faster than the availability of clear, operational frameworks to support sponsors in meeting those expectations. Recognizing the need for international harmonization beyond Europe, the International Council for Harmonisation (ICH), which brings together regulators and industry from Europe, the United States, Japan, and other regions, has initiated efforts to align terminology, data standards, and methodological expectations for RWE across regions, but these efforts are still evolving.

These developments mark a shift in how RWE is expected to support decision making in Europe. In practice, however, RWE often falls short of these expectations due to limitations in data quality, study design, and analytical approaches, raising questions about its fitness for purpose in regulatory and HTA decision making.

Reality Check and a Silver Lining

Despite growing expectations, RWE is still not consistently used and often lacks the quality needed to inform decisions. In our review of oncology drugs receiving initial

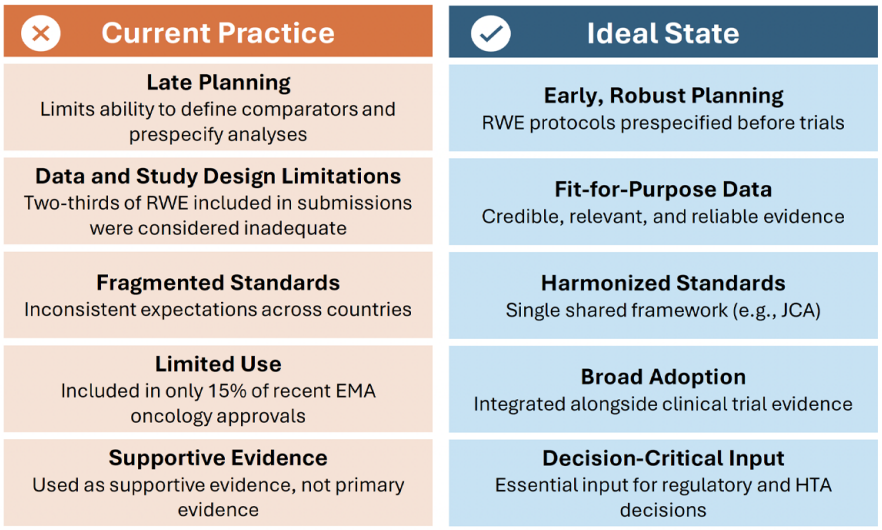
marketing authorization by the EMA between January 2023 and August 2025, only 6 of 40 (15%) included RWE. In all 6 cases, RWE was submitted as supportive rather than primary efficacy evidence. Use of RWE varied across submissions, from descriptive benchmarking analyses to formal external control arms (ie, using real-world patients as a comparison group). However, in two-thirds of the submissions, the RWE was considered inadequate due to limitations related to data or study design. In contrast, 2 case examples illustrate successful applications of RWE: benchmarking in rare diseases (Welireg [belzutifan]) and contextualizing trial outcomes in later-line refractory multiple myeloma (Elrexfio [elranatamab]).

This pattern of infrequent RWE inclusion is consistent with the broader literature. A study of EMA approvals across all therapeutic areas from 2020 to 2023 found that fewer than 1 in 10 incorporated RWE in regulatory submissions. Where RWE was included, assessment reports often lacked key details on data sources or study design or used terminology inconsistently. In addition, assessment reports rarely clarified whether or how these data influenced the final decision, limiting interpretability.

> With expectations now embedded in regulatory and health technology assessment processes, the key question is no longer whether real-world evidence should be used, but whether it is being generated in a way that meets decision-making standards.

Similar findings have been reported outside Europe, where a systematic review of US Food and Drug Administration (FDA) approvals for orphan-designated, non-oncology rare disease therapies (2017-2022) found that only 20 of 151 applications (13%) included RWE to support efficacy outcomes. In more than half of these submissions (11/20; 55%), the FDA raised concerns regarding the use of RWE, citing issues related to study design, population comparability, and missing information. Together, these findings help explain why RWE continues to fall short of decision-making expectations.

Figure 1. Gap Between Ideal State and Current Practice of RWE in Europe



EMA indicates European Medicines Agency; HTA, health technology assessment; JCA, Joint Clinical Assessments; RWE, real-world evidence.

Why Hasn't RWE Reached Its Potential?

Figure 1 illustrates the gap between what regulators expect from RWE and current practice.

Many real-world data sources are not inherently fit-for-purpose. Key variables may be missing, recorded inconsistently, or measured differently across healthcare settings. In our review, two-thirds of the RWE used in submissions were considered inadequate. Tepkinly (epcoritamab) illustrates this challenge: A retrospective observational study using electronic health records was submitted as supportive evidence to characterize treatment outcomes, but regulators noted several limitations—including inconsistent response assessment, incomplete records, and variability across sites—that affected the interpretation of these data.

Study design and analytical approaches are often insufficiently robust. RWE is frequently planned late in development, limiting the ability to define appropriate comparators, prespecify analyses, and align with regulatory expectations. In our review, historical benchmarks and indirect comparisons were frequently associated with methodological limitations. For Ezmekly (mirdametinib), the external control analyses were defined in a statistical analysis plan addendum after the data cut-off date, meaning key analytic choices may have been influenced by observed data rather than prespecified statistical and clinical rationale (eg, endpoint definition, covariate selection, and weighting or matching approaches), potentially introducing bias.

Expectations for RWE remain inconsistent across countries. Although the JCA process under HTAR is designed to minimize these inconsistencies by providing a single, shared clinical evaluation across Member States, the same evidence may be interpreted differently by decision makers, creating uncertainty for sponsors and limiting the influence of RWE in joint and national assessments. Together, these challenges reinforce the gap between rising expectations for RWE and its current ability to inform decision making.

RWE's Greatest Promise

Yet there are settings where RWE is delivering meaningful value. For rare diseases with small populations, RWE can provide essential context for interpreting trial outcomes. For Welireg (belzutifan), natural history data in von Hippel–Lindau disease provided context for interpreting response rates in a small, single-arm trial,

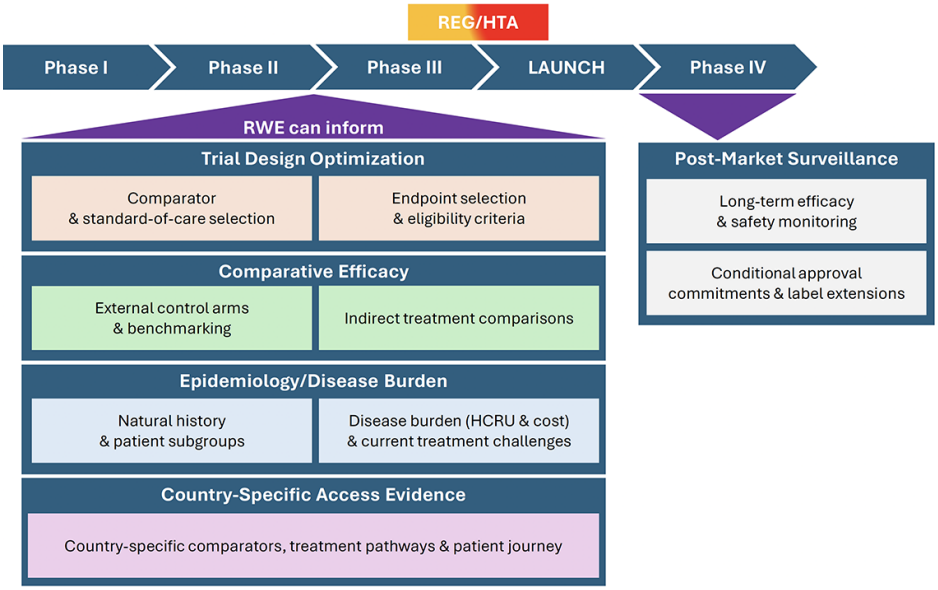
supporting the primary endpoint in the absence of a randomized comparator. More broadly, in our review, therapies with an orphan designation were more likely to include RWE than the overall cohort, suggesting that both sponsors and regulators are turning to RWE when trial-based evidence is most limited.

In single-arm trials without a comparator, RWE can help contextualize effectiveness and safety, particularly in underrepresented or clinically complex patient populations where randomized evidence is difficult to generate. For Elrexfio (elranatamab), external real-world cohorts were used alongside trial data to contextualize effectiveness in heavily pretreated multiple myeloma patients. This highlights where RWE is most impactful: addressing evidence gaps that randomized trials cannot. In practice, this helps ensure that treatment decisions reflect how therapies perform in real-world clinical settings, not just in trials.

From Data Availability to Decision-Grade Evidence

With expectations now embedded in European regulatory and HTA processes, the key question is no longer whether RWE should be used, but whether it is being generated in a way that meets decision-making standards. As summarized in **Figure 2**, RWE contributes across the product life cycle, from informing trial design and establishing disease context, through generating comparative evidence and supporting regulatory and HTA submissions, to post-market surveillance and post-approval commitments. Beyond regulatory decisions, decision-grade RWE is increasingly informing health economic evaluations, helping HTA bodies assess the comparative value of treatments in local healthcare contexts where trial-based evidence alone may be insufficient.

Figure 2. Examples of How RWE Can Contribute Across the Product Life Cycle



Examples are for illustrative purposes, not comprehensive.
HCRU indicates healthcare resource utilization; REG, regulatory; RWE, real-world evidence.

Closing the gap between expectations and practice requires action on 3 fronts.

1. Evidence planning must shift earlier. Evidence generation strategies must be defined at the outset of development, with RWE considered alongside clinical trials rather than retrospectively. Early alignment with regulators and HTA bodies is critical to ensure that data sources, comparators, and analytical approaches are appropriate and decision relevant. The JCA process further underscores that RWE strategies for a single evidence base across multiple Member States must be defined well before submission.

2. Data quality and methodological rigor must be treated as non-negotiable. Limitations in data completeness, consistency, and variable capture must be addressed proactively. The examples of Welireg and Elrexfio highlight that even when RWE adds useful context, it is typically positioned as supportive unless study designs, comparators, and analytical methods are clearly prespecified and transparent.

3. European decision makers must work toward more consistent expectations for what constitutes fit-for-purpose RWE. Without this, sponsors will continue to face uncertainty, and RWE will remain underutilized in joint and national assessments. Initiatives such as HTAR, JCA, and ICH provide an important foundation, while our findings underscore the need for clearer guidance on generating and evaluating RWE across countries.

Has Real-World Evidence Reached Its Potential?

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KEY TAKEAWAYS

Randomized controlled trials and real-world evidence (RWE) answer fundamentally different questions, but both contribute to a holistic view of disease, health, and medicines.

As technology has evolved, the use of RWE methodologies and real-world data (RWD) in health economics and outcomes research (HEOR) has grown.

Key opportunities at present include increasing connectivity, standardization, and formalization of RWE and RWD use across HEOR.

Formation and Formalization of RWE

Observational studies and evidence in the real world are established pillars of research that are fundamental in epidemiology and public health. Within medical research, the gold standard for research has long been randomized controlled trials (RCTs), and unfavorable comparisons have frequently been made regarding the relative strength, value, or relevance of observational evidence. Recently, however, observational research, including real-world evidence (RWE), has received increased recognition within research and from regulatory and payer bodies. This growing acceptance reflects the reality that RCTs and RWE are addressing fundamentally different questions, while both are contributing to a holistic view of disease, health, and medicines.

> Randomized controlled trials and real-world evidence are addressing fundamentally different questions, while both are contributing to a holistic view of disease, health, and medicines.

To support this development, RWE frameworks setting out approaches and standards for the use of RWE in product evidence submissions have been published by several payer and approval bodies, including the US Food and Drug Administration (FDA), European Medicines Association (EMA), National Institute for Health and Care Excellence (NICE), Haute Autorité de Santé (HAS), and Canadian Drug Administration (CDA). Accordingly, the use of RWE in health technology assessment (HTA) submissions has increased over time; the FDA recently detailed more than 70 device submissions that used RWE between 2020-2025. Importantly, RWE also has featured in successful drug submissions, including several submissions to NICE for oncology therapies.

As acceptance and recognition of RWE has increased, so has its methodological formalization and development. While the principal aim of observational research—to describe health and disease as experienced by people every day, often at scale—has remained consistent, wider growth in computing power, speed, and efficiency has improved our ability to store and analyze ever larger amounts of data and to operate increasingly complex statistical methods for handling uncertainty, expanding the capabilities of observational research.

Even with the strictest data collection, validation, and analytics processes, the "messiness" of human life and experiences brings a particular and unavoidable humanity to real-world data (RWD) and RWE. Many in the field have been drawn to the "messiness" of RWD as a scientific challenge. The methods developed to account for and harness this character have been key to the evolution of RWE. For example, propensity scores and weighting methods allow for estimates from unbalanced populations to be brought into closer balance; causal frameworks allow for explicit handling of confounding relationships (including those involving genetic variants); and target trial emulation (TTE) allows for the exploration of a specific "what if?".

Current Developments in RWE

With RWE now accepted as part of regulatory grade evidence, it seems an opportune time to ask: Is there further to go? If so, where next?

While RWE is past its infancy, it has yet to reach its potential. As with any data-driven field, advancements in RWE methodologies will continue to develop along with the continual change of computing technology, associated data storage, and processing power. Increasingly complex methods being developed and adopted today will likely be standard practice within a decade. For example, machine learning model-based approaches have a wide range of potential applications, including feature

identification and analysis, but arguably are yet to be an established "core" method in RWE.

The ability to store and handle larger datasets allows for summarizing of patients' healthcare experiences across a range of settings and providers in a single analysis. Challenges arise when RWE for secondary data studies is drawn from data systems that were not designed for use in research, but rather to support the delivery of informed, quality patient care (such as electronic health record [EHR] or administrative data). Such data are often care-context specific and may not be connected across the full range of care settings with which a patient interacts. In these circumstances, data tokenization and record linkage can provide insight into each patient's whole healthcare journey, joining these segmented datasets into a more complete picture. Studies conducted using this type of linked data are better informed about patients' general health state and ongoing care needs. Unfortunately, at the moment, linked datasets are sporadic in coverage and quality across contexts and countries.

> Data tokenization and record linkage can provide insight into each patient's whole healthcare journey.

Another developing change in research practice involves the interaction between RWE and RCT evidence. In an explicit deviation from any perceived competition as evidence, RWE/D can be leveraged to augment and strengthen RCTs. Within a trial, RWD can be used in 2 key ways: to augment RCT data, such as through passive follow-up of participants via EHR systems, and as an external control arm (ECA). At a recent ISPOR Europe issue panel, the use of RWD sources for ECAs was explored, with a particular focus on the acceptance of such evidence by regulatory authorities. The discussion from this panel concluded that, for the moment at least, ECA studies have to reach a high bar to be acceptable, and that prospective primary data collection (ideally planned alongside the associated trial) represents the best opportunity for successful use of this approach.

Machine learning and natural language processing (NLP) have been used to enhance and curate RWD sources, including the extraction of data from EHR documents to improve dataset completeness, and for hypothesis generation and predictive analysis using advanced methods. In the future, artificial intelligence, large language models, and other technologies offer the potential to collect, store, and analyze data in new ways that help maximize the potential value of RWE/D.

Opportunities for RWE

The clear theme for the development of RWE is opportunities for increased connectivity: in prespecified development of RWE with onward use for other health economics and outcomes research (HEOR) methodologies, and within RWE itself through increasing connection of RWD sources.

Preplanned connection of RWE to other HEOR methodologies enables robust and well-informed evidence. Particularly in the postlaunch environment, many modes of health economic modeling now frame estimates and assessments in terms of real-world care. This requires real-world estimates.

A collaborative cross-functional approach, connecting efforts and expertise from RWE and economic modeling specialists, can be employed to efficiently generate cohesive bodies of real-world and economic evidence that are fit for each specific purpose from design. An RWE study can be designed with model parameterization in mind, generating evidence on the target population and outcomes while simultaneously providing designed-for-use parameter estimates for a parallel model. In evidence generation that is cross-functional from first principles, RWE can make an exclusive but vital contribution and bring a new viewpoint or contextualization that adds value to evidence across HEOR.

Within RWE, increasing connectivity between RWD sources could help overcome issues of sample size (especially affecting rare diseases) and increase the generalizability of results.

The European Health Data Space (EHDS) regulation came into force in 2025, setting the framework for pan-European Union health data sharing and a timeline for the first datasets (patient summaries and prescribing) to be included by 2029. This marked a major step forward for data interoperability and introduced the potential for true cross-border working across Europe in RWE. In addition, following the establishment of the EU Health Technology Assessment Regulation framework in 2021, the first Joint Clinical Assessments (JCAs) were submitted. This international alignment in assessments provides clear motivation for internationally aligned evidence.

> In evidence generation that is cross-functional from first principles, real-world evidence can bring a new viewpoint or contextualization that adds value across health economics and outcomes research.

Data standards such as the Observational Medical Outcomes Partnership (OMOP) Common Data Model, Fast Healthcare Interoperability Resources (FHIR), and openEHR are intended to address the challenges of interoperability. However, despite the great potential offered by tools such as OMOP, FHIR, and openEHR, challenges remain—including complete and clinically appropriate data mapping and broad agreement on extract-transform-load approaches—for their integration at scale.

The JCA and EHDS regulations set the stage for a drive toward increasing data standardization and connected working over the next few years. What remains to be seen is how fast changes will happen and exactly what this alignment will look like. The potential for innovation in RWE methods and research is substantial and could include a landscape shift toward a future in which cross-country studies with built-in alignment and standardization are the norm.

Conclusion

RWE contributes a unique and unreplicable view into the day-to-day reality of people's health, experience of living with disease, treatment patterns, and associated outcomes. There are groups of patients who likely will never contribute to RCT evidence, due to lack of access, health-related issues, or demographic-based exclusions. The power of RWE lies in its potential to capture and quantify this reality—with all its heterogeneity, missingness, and that's-an-unusual-treatment-pathways—and, specifically, to include patients who will not ever contribute to RCT evidence.

The growth and change in RWE over the last decade have been expansive. From its beginnings in observational research, RWE has developed into a completely new field. The formalization and standardization of newer methods (such as TTE and ECA), and the increasing acceptance of these methods for use with RWE, illustrate the potential for further change and growth. The opportunities for RWE in data standardization and connection, and by-design integration with other HEOR methodologies, could be revolutionary.

RWE has certainly not reached its ultimate potential. A coalescence of technology-enabled data handling and analysis ability, buy-in from regulators and HTA bodies, and motivation in the form of policy change is set to drive RWE toward widespread innovation and optimization.

Real-World Evidence in Canadian Health Technology Assessment: Is it Worth It?

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KEY TAKEAWAYS

Real-world evidence is included in many health technology assessment submissions in Canada to address clinical trial evidence gaps, but we found that this evidence was heavily criticized by assessors and its usefulness was unclear.

Rather than real-world evidence, we suggest the idea of *real-world* ***payer evidence*** that is real, robust, and relevant to the decision problem faced by health technology assessment agencies.

We call upon those agencies to help define "good quality" payer evidence and demonstrate how it will be used in review.

RWE in HTA: What's the Issue?
In Canada, to have new medicines reimbursed by the public healthcare system, drug manufacturers are required to submit evidence packages to health technology assessment (HTA) agencies, such as Canada's Drug Agency (CDA-AMC) and Institut national d'excellence en santé et en services sociaux (INESSS).

In addition to randomized controlled trials (RCTs), manufacturers may include real-world evidence (RWE) as part of their submission package to address evidence gaps. RCTs, while the gold standard of clinical evidence, do not always have all the answers needed for HTA agencies to make funding recommendations. For instance, multinational RCTs might not reflect Canadian practice. Furthermore, RCTs often follow strict protocols designed for regulatory purposes and not fully reflect real-world situations such as discrepancies in access to care, demographics, and socioeconomics. Well-conducted RWE can illuminate evidence gaps that RCTs miss.

There are many types of RWE, ranging from provincial and hospital health record data to privately held patient support program data. It is challenging to know specifically how to balance what is considered "best," practically feasible, and most useful for HTA given the circumstances.

Why Include RWE in HTA Submissions?
In many cases, drug manufacturers conduct RWE to answer questions RCTs would not be able to answer such as:

- How many patients are currently using Drug X?
- How long are patients adhering to Drug Y?
- How do patients on Drug Z perform in the long-term?
- How many times do patients end up at the emergency room?
- What costs does the healthcare system incur?

In some cases, RWE can also be used to construct a "synthetic" control arm to help demonstrate comparative effectiveness when the clinical trial only has a single intervention arm.

> There are many types of real-world evidence, ranging from provincial and hospital health record data to privately held patient support program data. It is challenging to know which type is "best," most feasible, and most useful for health technology assessment.

So why not always perform RWE studies? A single RWE study potentially takes several months and hundreds of thousands of dollars to complete, a significant investment of time, money, and human resources. Before initiating a study, we must ask: **Is it worth it?**

How Did We Investigate This Issue?
With the help of researchers from the University of Toronto and University of Calgary, we commissioned a comprehensive environmental scan to better understand the RWE included in HTA submissions to CDA-AMC. Reviewers assessed HTA review reports published between January 2020 and June 2024 and thematically summarized the findings; the results were presented at the ISPOR 2025 conference in Montreal.

We found that between January 2020 and June 2024, drug manufacturers submitted a total of 274 HTA submissions to CDA-AMC, with 70 (25.5%) including RWE and 27 (9.9%) including more than one source of RWE. Table 1 summarizes the most common purposes of RWE beyond describing treatment patterns and patient characteristics:

(1) Inform comparative clinical effectiveness (54%),

(2) Address evidence gaps from pivotal trials or systematic reviews (52.2%), and

(3) Support pharmacoeconomic models (54.9%).

Retrospective cohort design (57.5%) represented most studies, especially for oncology indications. Prospective cohort studies (20.4%) were more common for nononcology indications (30.4% vs. 4.5% for oncology indications). RWE were predominantly from the United States (39%) or Europe (38%); studies from Canada (11%) were in the minority (**Table 1**). The majority of submissions (82.9%) received a "Reimburse with Conditions" recommendation.

Reviewer criticism of RWE is presented narratively in their review reports in an unstructured format. A summary of the criticisms of RWE is presented in **Table 2**; 70% of studies had data quality issues, such as collection protocols, data provenance, and analytical validity.

Methodological concerns about bias and residual confounding were noted in 50% of studies, stemming from the reliance on retrospective cohort designs (57.5%) which lack a priori protocol-driven data collection. Short follow-up duration (52.9%) and sample size limitations (48.6%) further constrained the ability of RWE to address long-term effectiveness questions. Generalizability concerns (61%) encompassed patient populations, clinical practice patterns, and treatment sequencing.

> We propose a set of complementary principles to help build real-world payer evidence that is real, robust, and relevant to the decision problem faced by health technology assessment agencies.

In summary, these findings demonstrate that RWE might support HTA submissions by addressing certain clinical, comparative, and economic evidence gaps. However, there were many criticisms, and it is not clear whether those RWE studies even played a role in the expert committee's deliberations.

Table 1. Summary of Real-World Evidence Studies Included in Health Technology Assessment Submissions

Study Characteristic	Percentage of RWE Studies
Purpose of the RWE Study	
Inform comparative clinical effectiveness	54.0%
Address evidence gaps	52.2%
Support pharmacoeconomic models	54.9%
Study Type	
Retrospective cohort	57.5%
Prospective cohort study	20.4%
Other	22.1%
Origin of RWE Study	
United States	38.9%
Europe	38.1%
Canada	10.6%

RWE indicates real-world evidence.

Table 2. Summary of Health Technology Assessment Agency Criticisms of Real-World Evidence Studies

Reviewer Criticism	Percentage of RWE Studies
Data quality	70.0%
Bias and residual confounding	50.0%
Short follow up	52.9%
Sample size	48.6%
Generalizability	61.0%
Lack of Canadian data	50.0%
Generalizability (Canadian RWE subset)	40.0%

CDA-AMC indicates Canada's Drug Agency; RWE, real-world evidence.

Because RWE are considered supplementary in a HTA submission, it is difficult to assess the counterfactual: ***What would the outcome of an HTA have been if RWE had not been submitted?***

RWE as Payer Evidence: the 3R's

At AstraZeneca Canada, our approach is to support HTA agencies in their assessments so that medicines are made available to Canadian patients. In many cases we have generated and submitted RWE; however, it was not clear whether these RWE studies made a difference in the HTA. In fact, our findings suggest that RWE studies across the board had varying degrees of quality, and as such, were often heavily criticized and even diminished in the review.

Despite this, we are not discouraged by these results but suggest a shift in how RWE should be generated and used. We encourage the development of meaningful real-world **payer evidence** and believe that it is a shared responsibility of the evidence generator and reviewing agencies to distinguish what "good quality" payer evidence is so it can be used in a review.

In May 2023, CDA-AMC issued guidance on the reporting of RWE, but there is still an opportunity to better define what "good quality" RWE is and how it could be used in HTA. Therefore, we propose a set of complementary foundational principles—the 3R's quality framework—to help build real-world payer evidence that is real, robust, and relevant to the decision problem faced by HTA agencies:

- **Real:** The findings from the RWE are reflective of and generalizable to the payer's decision setting.
- **Robust:** The methods for generating the RWE minimize biases and are transparently reported. Sample sizes and duration of study are reasonable and sufficient.
- **Relevant:** The study parameters of the RWE are applicable and purposefully designed to support payer decision making.

It is important that evidence generation leads to "good quality" RWE so that it then can be appropriately used by HTA agencies. But without explicit processes for how that RWE will be used in HTA, manufacturers (as we uncovered in our research) may submit RWE that is not considered real enough, robust enough, or relevant enough, resulting in these studies being perceived as unhelpful for the review. This further undermines HTA reviewers' trust in RWE in a submission, increasing the risk that it could be categorically disregarded without the opportunity to show its true potential. While there is hesitancy to overprescribe how evidence should be generated, foundational principles, such as the 3R's above, may help facilitate the inclusion of better quality, real-world payer evidence.

Refocusing for the Future

With the world of clinical trials becoming more complex, RWE will undoubtedly play a role in answering pertinent clinical questions. When considering what is needed for HTA, RWE needs to be reclassified as real-world "payer evidence" so that evidence generators, such as drug manufacturers, can better design the "what", "how", and "why" of studies. Evidence generated for the purpose of supporting reviews can be very helpful; however, our research findings suggest that RWE currently does not have a clear role in HTA and may be less readily accepted for review in the future.

> Real-world evidence that is intentionally designed as real-world payer evidence could be very useful for health technology assessment purposes.

Aside from our research findings, it is also important to consider the logistics of developing RWE in Canada. Canada's health databases are fragmented across different provinces and disparate agencies. An integrated pan-Canadian database could support future studies with larger, more reflective study sizes. The time required for large-scale provincial database studies hampers the creation of RWE locally, so in some cases, nonlocal RWE may be adapted through transportability analysis for use in local HTA submissions.

It is up to drug manufacturers to decide whether the development of RWE is worth the time and cost. But without clear agency processes for differentiating what is good (and useful) from what is not (and of poor quality), generating future evidence for HTA may prove to be a fruitless endeavor.

RWE that is intentionally designed as real-world payer evidence could be very useful for HTA purposes. While our research findings did not find any definitive association between the inclusion of RWE and favorable funding recommendations, we still believe that good quality payer evidence plays an important role in HTA decision making and Canadian health research. With improvements such as clearer use-case guidance, definitions of quality, and a coordinated data infrastructure, Canadian real-world payer evidence may be worth it in the future.

Bridging Evidence Gaps for Rare Disease Decision Making: The Role of Real-World Evidence

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KEY TAKEAWAYS

Real-world evidence is increasingly central to rare disease health technology assessments (HTAs) related to clinical effectiveness, long-term outcomes, safety, and economic value, particularly when randomized trials are infeasible.

Natural history cohorts and patient registries represent key sources of real-world evidence for HTA submissions, but their methodological acceptance and evidentiary weight vary across agencies in Europe and the United Kingdom.

The impact of real-world evidence depends on methodological rigor and contextual fit, with biases, confounding, outcome relevance, and data maturity influencing reimbursement decisions.

Rare diseases present distinct challenges for health technology assessment (HTA). Small patient populations, heterogeneous clinical presentations, and limited treatment options constrain the generation of robust evidence to support benefit-risk and value assessment for new therapies. In many rare disease settings, randomized controlled trials (RCTs), the traditional gold standard for evaluating clinical benefit, are impractical due to feasibility and ethical constraints, limitations in endpoint development, and logistical barriers. As a result, HTA bodies often face considerable uncertainty when assessing benefit-risk and economic value of novel rare disease treatments.

In this context, real-world evidence (RWE) is increasingly gaining prominence as a complementary source of information for rare-disease HTA decision making. Derived from sources such as patient registries, electronic health records, insurance claims, and observational studies, RWE provides insights beyond those captured in clinical trials. In rare disease settings, RWE is commonly used to characterize disease natural history, establish benchmark trajectories for outcomes without treatment, and provide external comparator data to supplement single-arm clinical trials. Collectively, these uses help contextualize observed treatment effects and may reduce uncertainty by addressing knowledge gaps where conventional clinical evidence may come up short.

Recent implementation of the European Union Health Technology Assessment Regulation (EU HTAR) has further increased attention on evidence requirements for rare disease therapies. A coordination group of delegates from all Member States now oversees Joint Clinical Assessments (JCAs) of new pharmaceutical products, each of which is tasked with generating a single evidence-based report to inform pricing and reimbursement decisions across those Member States—a mandate that creates pressure to address evidence gaps consistently across jurisdictions. The JCA rollout began in 2025 with submissions for oncology and advanced therapy medicinal products; the call for orphan medicine submissions is scheduled for 2028. Although the role of RWE within JCAs is still evolving, real-world data (RWD) are increasingly recognized as a potential source of evidence for addressing uncertainties related to comparative effectiveness, treatment patterns, and external control generation in rare diseases.

Beyond evidence scarcity, HTA is shaped by the unique parameters of precision medicine, with therapies targeting molecularly or genetically defined subgroups. This is most evident in rare oncology and genetic disorders, where populations are highly stratified and pathways evolve rapidly. Surrogate endpoints and shifting comparators complicate oncology assessments, while durability and long-term safety challenge genetic therapies, increasing the need for flexible approaches in which RWE informs reimbursement under uncertainty.

> Real-world evidence is increasingly gaining prominence as a complementary source of information for decision making during rare disease health technology assessment.

Against this backdrop, we examined the role of RWE in HTA evaluations for rare disease therapies across the EU4 (France, Germany, Italy, and Spain) and the United Kingdom. A targeted literature review of HTA appraisals and peer-reviewed publications from 2014 to 2025 was conducted involving therapies with European Medicines Agency (EMA) orphan drug designation that incorporated RWE in submissions.

Information on sources and types of real-world data (RWD) such as patient registries, observational studies, and electronic health records was extracted and qualitatively assessed. Cross-country comparisons examined how RWE informed benefit-risk assessments, cost-effectiveness, and budget impact, and identified patterns related to the influence on price and reimbursement decisions.

RWE and HTA for Rare Diseases

Across the EU4 and the United Kingdom, the review identified 16 rare disease therapies that incorporated RWE within HTA submissions to support pricing and reimbursement decisions. Thirty-two submissions for these therapies were evaluated by 5 major HTA agencies: National Institute for Health and Care Excellence (NICE) in the United Kingdom (n=8), Haute Autorité de santé (HAS) in France (n=6), Federal Joint Committee (G-BA)/ Institute for Quality and Efficiency in Health Care (IQWiG) in Germany (n=6), Agenzia Italiana del Farmaco (AIFA) in Italy (n=5), and Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) in Spain (n=7) (**Table 1**).

Neurological disorders represented the most common therapeutic area, followed by oncology, immunology and metabolic disorders (**Figure 1A**). Gene therapies comprised the largest treatment category, followed by enzyme replacement therapies and antisense oligonucleotides (**Figure 1B**).

Variation in RWE use across therapeutic areas may reflect the maturity of existing data infrastructures rather than HTA preferences. Neurological, genetic, and metabolic disorders often benefit from long-standing international registries that provide established data sources for generating RWE, whereas other therapeutic areas have less developed ecosystems. This distinction is important when interpreting why certain rare disease therapies appear more heavily supported by RWE.

While this review focused on the EU4 and United Kingdom, the findings may have broader relevance across Europe. Although reimbursement processes for rare disease therapies differ across countries, many smaller European and Nordic markets face similar challenges related to limited clinical evidence, small patient populations, and uncertainty regarding long-term outcomes.

How RWE Is Being Used for Rare Diseases

Across the 16 therapies identified in this review, different RWE sources were used to address distinct evidentiary objectives (**Table 1**). Data from patient registries, the most common source (n=10), were used to characterize disease progression and long-term outcomes. Natural history or historical comparator studies (n=6) primarily supported untreated benchmarks and external controls for single-arm trials, while observational/ postmarketing studies (n=5) assessed real-world safety, durability, and effectiveness.

RWE contributed to HTA evaluations in 4 main ways, each addressing a specific evidence gap commonly seen in rare-disease drug development:

1. External comparators for single-arm trials. The most prevalent application of RWE was the creation of external comparator arms, particularly where pivotal evidence came from single-arm trials, a frequent scenario in ultra-rare conditions. For 9 of 16 analyzed therapies, RWE provided comparator data to contextualize treatment benefits when randomized trials were infeasible, drawing on natural-history datasets, and disease registries. Examples included onasemnogene abeparvovec for spinal muscular atrophy (SMA), atidarsagene autotemcel for metachromatic leukodystrophy, cerliponase alfa for CLN2 disease, eculizumab for atypical hemolytic uremic syndrome, and strimvelis for adenosine deaminase severe combined immunodeficiency.

2. Safety and postmarketing outcomes. In several submissions (lutetium [Lu 177] oxodotreotide, voretigene neparvovec, tabelecleucel, and elosulfase alfa), observational and registry data characterized safety, tolerability, and treatment durability under real-world conditions, complementing small or short-duration clinical programs and informing the net clinical benefit at decision time.

3. Evidence of long-term effectiveness. RWE extended the evidence horizon beyond trial follow-up in several cases, demonstrating sustained clinical benefit, especially for enzyme-replacement therapies and gene therapies, where durability is central to value assessment. These data included real-world functional trajectories, progression rates, and survival observed in routine practice. Examples included elosulfase alfa for mucopolysaccharidosis type IVA, nusinersen for SMA, alglucosidase alfa for Pompe disease, tegsedi for hereditary transthyretin amyloidosis, and atidarsagene autotemcel for metachromatic leukodystrophy.

4. Economic and utility inputs. In 2 cases (givosiran and volanesorsen), RWE fed directly into economic models, providing measures of health-related quality of life (HRQoL), utilities, resource-use patterns, or other model parameters

Figure 1. Clinical (A) and therapeutic (B) categories seen across included rare disease HTA submissions

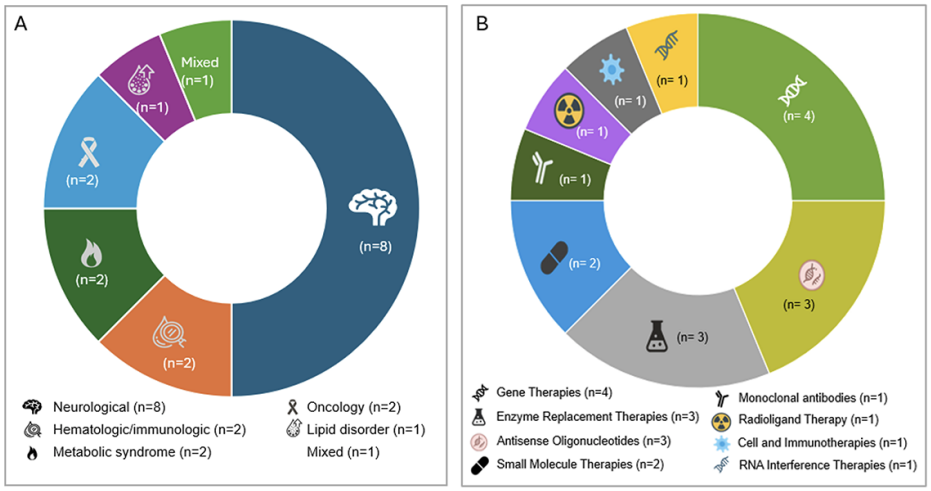

Table 1. Overview of drug therapies approved for reimbursement utilizing RWE across EU4 + UK

Drug	HTA (year of approval)	Indication	RWE Source	Outcome	HTA decision
Alglucosidase alfa	HAS (2020), GBA (2006 & 2020)	Pompe disease	French Pompe registry, disease registries, natural history cohorts	Long-term outcome and disease progression vs. untreated populations	Reimbursed/added benefit acknowledged (with limitations)
Ataluren	GBA (2014, reassessed 2018)	Duchenne Muscular Dystrophy	Longitudinal registry data	Support delay in functional decline vs. natural history	No added benefit of drug recognized
Atidarsagene autotemcel	NICE (2022)	Metachromatic Leukodystrophy	Natural history studies	Comparator for survival and cognitive decline	Conditionally reimbursed (Managed Access Agreement)
Cerliponase alfa	NICE (2019), AIFA (2019), AEMPS (2019)	CLN2 Batten disease	DEM-CHILD, CLN2 registries (EU/US)	Natural history comparators for progression	Reimbursed with restrictions/conditional agreements
Eculizumab	GBA (2014), HAS (2015), AEMPS (2016)	aHUS	Global/International aHUS registry, historical controls	Comparator for renal outcomes, dialysis use, TMA events	Added benefit recognized; reimbursed
Elosulfase alfa	GBA (2015), HAS (2015), AEMPS (2015), AIFA (2016), NICE (2020)	Mucopoly-saccharidosis IVA	International/registry cohorts, observational studies, post-marketing data	Demonstrate long-term effectiveness and functional improvements	Fully reimbursed (GBA); conditional (NICE, AIFA); restricted (HAS, AEMPS)
Givosiran	NICE (2020)	Acute Hepatic Porphyria	Global Porphyria Registry	Baseline attack rates, utility values	Recommended for routine use
Lutetium (Lu 177) oxodotreotide	AEMPS (2017+)	Neuroendocrine Tumors (GEP-NETs)	Erasmus cohort (1,200+ patients)	RW safety and effectiveness post-launch	Reimbursed, supported by RWE
Nusinersen	GBA (2018), HAS (2018), AEMPS (2018), NICE (2019)	Spinal Muscular Atrophy (SMA Types 1–3)	Global SMA registry (TREAT-NMD), expanded access, national cohorts	Reinforce survival and motor function benefits; supplement limited trial data	Fully reimbursed (GBA, AIFA); conditional (NICE); with restrictions (AEMPS)
Onasemnogene abeparvovec	GBA (2020), HAS (2020), AIFA (2021), AEMPS (2021)	Spinal Muscular Atrophy (SMA Type 1)	SMA registries (PNCR, TREAT-NMD)	External comparators for survival/milestones due to lack of RCTs	Fully reimbursed (GBA); conditional (NICE, AEMPS); restricted (AIFA, HAS)
Strimvelis	AIFA (2017)	ADA-SCID	Historical registry cohort	Comparator due to single-arm trial	Reimbursed with pricing discount
Tabelecleucel	AEMPS (2023–24)	EBV+ PTLD	EAP RWD; retrospective/ natural history	Effectiveness and safety in RW setting	Conditional approval based on RWE
Tegsedi	HAS (2019)	Hereditary Transthyretin Amyloidosis	RW follow-up, TTR-FAP registry	Supplement long-term and indirect comparisons	Conditional reimbursement (ASMR IV, SMR important)
Viltolarsen	NICE (2022)	Duchenne Muscular Dystrophy (exon 53 skipping)	CINRG & natural history registries	External control for motor outcomes	Not recommended
Volanesorsen	NICE (2021)	Familial Chylomicronaemia Syndrome	UK EAP, case series	Frequency of pancreatitis, QoL impact	Not recommended
Voretigene neparvovec	AIFA (2020)	RPE65-mediated inherited retinal dystrophy	AIFA Monitoring Registries + clinical cohort	Post-marketing follow-up	Reimbursed with follow-up obligation

ADA-SCID indicates adenosine deaminase severe combined immunodeficiency; AHP, acute hepatic porphyria; aHUS, atypical hemolytic uremic syndrome; CINRG, Cooperative International Neuromuscular Research group; DEM-CHILD, patient database for the study of dementia in childhood; EAP, Early Access Program; EBV, Epstein-Barr Virus; FCS, familial chylomicronemia syndrome; GEP-NETs, gastroentero-pancreatic neuroendocrine tumors; HTA, hereditary transthyretin amyloidosis; MLD, metachromatic leukodystrophy; PNCR, Pediatric Neuromuscular Clinical Research Network; PTLD, post-transplant lymphoproliferative disorder; SMA, spinal muscular atrophy; QOL, quality of life; RCTs, randomized controlled trials; RD, retinal dystrophy; RW, real-world; RWE, real-world evidence; TMA, thrombotic microangiopathy; TREAT-NMD, Translational Research in Europe for the Assessment and Treatment for Neuromuscular Disorders; UK, United Kingdom; US, United States.

to reduce uncertainty in cost-effectiveness estimates where trial-based HRQoL or utilization data were sparse or nongeneralizable.

Differences in Agency Acceptance

Our findings suggest that acceptance of RWE in HTA submissions varies by agency. Within the therapeutic assessments included in this review, NICE (United Kingdom) and AEMPS (Spain) demonstrated relatively greater openness to RWE, particularly when natural history data or external comparator analyses were used to contextualize outcomes from single-arm clinical trials. AIFA (Italy) frequently considered RWE from registry-based monitoring systems and, in some cases, outcomes-based agreements, reflecting the agency's strong reliance on structured RWD collection. HAS (France) tends to consider RWE primarily during postlaunch reassessments or as supplementary evidence in broader reimbursement decisions. In contrast, G-BA/IQWiG (Germany) applies more stringent evidentiary standards, generally accepting RWE only in ultra-rare disease settings or when no alternative evidence sources are available. This finding aligns with previous research reporting considerable variation in the acceptance, weighting, and interpretation of RWE across European HTA agencies, even when assessing the same therapy.

In many markets, RWE is not a one-off submission element but part of a life-cycle evidence plan: Coverage is granted alongside managed access and registry-linked obligations, with time-bound reassessments to resolve residual uncertainty (eg, NICE Managed Access Agreements and AIFA monitoring registries for advanced therapies). This embeds ongoing effectiveness, durability, and safety tracking into routine care and links evidence delivery to continued reimbursement.

Influence on Reimbursement Outcomes

Overall, 6 of 16 therapies that incorporated RWE in their HTA appraisals received full/positive reimbursement outcomes. For another 4 of 16 therapies, conditional reimbursement or restricted access was granted to manage residual uncertainty. Additionally, 3 of 16 therapies had mixed reimbursements across different HTA agencies.

> The most prevalent application of real-world evidence was the creation of external comparator arms, particularly where pivotal evidence came from single-arm trials.

The remaining 3 of 16 therapies did not achieve positive or conditional outcomes, underscoring that RWE complements but does not replace robust clinical evidence. Notably, onasemnogene abeparvovec and elosulfase alfa achieved reimbursement across all 5 markets, with RWE included in evidence packages. While RWE was included in all assessed submissions, its specific contribution to the final reimbursement decision could not be consistently determined from the available HTA documentation.

Looking Ahead: Toward Greater Harmonization

The increasing reliance on RWE across European HTA submissions aligns with broader policy developments, most notably the implementation of the EU-JCA process. That process is still evolving, but JCA has the potential to align the expectations of Member States around evidence generation, including how and when RWD may be used to address uncertainty in rare-disease evaluations.

For manufacturers, the implications are clear. As advanced rare-disease therapies increasingly undergo assessment by HTA bodies with limited clinical data, successful reimbursement strategies require a proactive approach to evidence generation throughout the product life cycle. Manufacturers should develop an integrated strategy with patient registries, natural-history studies, and postlaunch evidence generation infrastructure to ensure that the right data are available to meet diverse HTA requirements, ultimately supporting timely and sustainable patient access.

For HTA bodies and policy makers, the challenge lies in maintaining methodological rigor while recognizing the practical realities of rare disease research, where randomized evidence is often infeasible and natural history may be the only viable comparator. Differences in national processes will persist, but ongoing collaboration through JCA dialogue and national initiatives to define good-practice RWE methods may improve alignment over time.

As innovation accelerates, particularly in gene and cell therapies and precision-medicine oncology, where treatments target biomarker-defined subgroups that make randomized trials challenging, RWE is poised to play an even more central role in demonstrating clinical value, supporting economic evaluations, and reducing decision uncertainty. While RWD rarely replace traditional clinical evidence, they have the potential to add value for HTA committees navigating the complex, evolving landscape of rare disease treatment assessment.

Beyond Posters and Publications: Defining the Value of Real-World Evidence Scientific Content

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KEY TAKEAWAYS

Real-world evidence (RWE) scientific content is purpose-built, truthful, balanced, non-promotional scientific material for use in scientific exchange with healthcare professionals and key decision makers.

Although RWE is frequently produced by health economics and outcomes research (HEOR) professionals, many may be unfamiliar with RWE scientific content development.

HEOR professionals' expertise can substantially strengthen RWE scientific content development and disseminate the evidence beyond posters and publications.

Introduction

The US Food and Drug Administration (FDA) defines real-world evidence (RWE) as the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of real-world data routinely collected from sources such as electronic health records (EHRs), medical claims, registries, and digital health technologies.

RWE adds important value by showing how treatments perform in routine practice, capturing effectiveness, safety, patient experience, and economic impact across broader and more diverse populations than randomized clinical trials (RCTs) alone, although careful attention to data quality and bias is essential when analyzing RWE.

> Scientific content has long been created to support the nonpromotional scientific exchange and engagement activities of medical affairs teams in pharmaceutical and biotechnology companies.

Pharmaceutical and biotechnology companies have increasingly generated RWE to complement RCTs in communicating with healthcare professionals (HCPs) and key decision makers (KDMs) to inform decision making. This type of exchange and engagement often is facilitated by RWE scientific content.

Scientific content has long been created to support the nonpromotional scientific exchange activities of medical affairs teams in pharmaceutical and biotechnology companies, yet no formal definition exists. In general, it may be understood as nonpromotional material containing scientific information derived from congress presentations and publications. Historically, such content has focused on clinical trial findings, sometimes supplemented with epidemiological and disease information for context. More recently, scientific content focused on RWE and other health economics and outcomes research (HEOR) has become increasingly prominent.

As with scientific content in general, there is currently no official definition of RWE scientific content, nor are there dedicated guidelines governing its development. In practice, its development often relies on guidance for scientific exchange in defined scenarios, such as FDA guidance on scientific information for HCPs about unapproved uses of approved medical products and FDA draft guidance on responding to unsolicited requests for off-label information, while also following relevant principles from guidance on promotional materials, such as FDA guidance and recently updated draft guidance on communications with payers and formulary committees and the PhRMA Code on Interactions With Health Care Professionals.

Although RWE is frequently generated by HEOR professionals, scientific content development has historically centered on clinical trials and has therefore been led by individuals with pharmacy or clinical backgrounds. HEOR-trained professionals have not yet established a strong presence in this field, and many, including those working as researchers in pharmaceutical and biotechnology companies, may still be unfamiliar with the subject.

This article introduces RWE scientific content and discusses its importance, best practices, and relevance to HEOR practice. It aims to provide HEOR researchers with a basic understanding of RWE scientific content to facilitate more effective collaboration with scientific content experts and introducing scientific content development as a potential career path.

What Is RWE Scientific Content?

For the purposes of this article, RWE scientific content is defined as purpose-built, truthful, balanced, nonmisleading, and nonpromotional scientific materials based on 1 or more RWE sources,

intended for use by pharmaceutical or biotechnology medical affairs teams in scientific exchange with HCPs and KDMs. Like broader scientific content, RWE scientific content can be either reactive (addressing stakeholders' questions) or proactive (anticipating and discussing questions before they are raised). Scientific content can come in multiple formats, such as slide decks, question-and-answer documents, evidence summaries, and interactive or dynamic content.

The importance of RWE scientific content includes its practical value alongside existing RWE posters and publications and its role in scientific exchange.

Practical Value Beyond Posters and Publications

Posters and publications serve to help preserve the complete scientific record. They present comprehensive methods and full results, enabling other scientists to critically evaluate and reproduce the work. They are suited to conference settings and journal audiences seeking a detailed review of a study. By contrast, scientific content is developed to facilitate meaningful, nonpromotional exchange. It distills essential methods and highlights key findings that clinicians and payers need to inform practical decision making. It can also bring together findings from multiple related posters or publications as a single, coherent narrative, enabling the audience to rapidly understand the broader evidence base.

Posters and publications may include exploratory language appropriate for research discourse; however, scientific content must remain strictly truthful, balanced, and non-misleading. Any content referencing off-label use must be clearly labeled. Proactive content, as well as content related to comparisons with competitor products often requires legal review before dissemination.

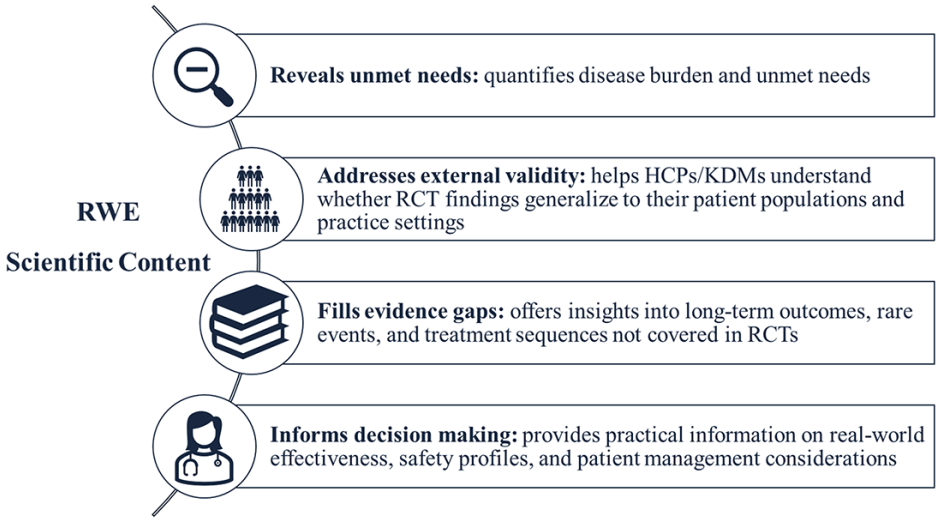
These differences are summarized in **Table 1**.

Table 1. Comparing RWE Scientific Content with Posters and Publications

	POSTERS & PUBLICATIONS	SCIENTIFIC CONTENT
Purpose	Preserve complete record of research	Facilitate meaningful, nonpromotional exchange
Audience Fit	Target broad scientific community at conferences or journals	Tailored to highly trained HCPs/KDMs for 2-way scientific dialogue
Story Breadth	Focus on limited objectives	Summarize a single study or integrate multiple studies into a coherent narrative
Content Depth	Provide exhaustive methodological detail and full results	Distill essential methods and key findings
Tone and Compliance	Formal academic tone; may include exploratory or hypothesis-driven statements	Must be truthful, balanced, non-misleading and free of promotional claims or recommendations
Practicality	Too detailed for HCP/KDM interactions; time-consuming to review during exchanges	Streamlined, focused, and designed for effective scientific conversation
Risk and Management	May include off-label data without audience-specific labeling	Clearly identify off-label content; consult legal when unsure

HCP indicates healthcare; KDM, key decision maker; RWE, real-world evidence.

Figure 1. The Role of RWE Scientific Content in Scientific Exchange



HCP indicates healthcare; KDM, key decision maker; RCT, randomized controlled trial; RWE, real-world evidence; SOC, standard of care.

Enabling Scientific Exchange and Engagement

RWE scientific content plays a critical role in bridging the gap between clinical trial evidence and routine clinical practice. It reveals unmet needs by assessing disease burden using measures like event rates and healthcare utilization, while demonstrating the limitations of standard of care, such as its real-world effectiveness, safety, and tolerability profile. It addresses the external validity of RCTs by helping HCPs and KDMs consider how medical products perform in their own patient populations and practice settings. It fills important evidence gaps by providing insights on long-term outcomes, rare events, and treatment sequences that RCTs may not capture. Finally, it informs decision making by delivering practical, actionable information on real-world effectiveness, safety profiles, and patient management considerations. Together, these aspects of RWE scientific content support more informed, pragmatic decisions by HCPs and KDMs (**Figure 1**).

Best Practices and an Example

As mentioned above, best practices for RWE scientific content should align with the principles set forth in FDA guidance

and the PhRMA Code regarding communications by pharmaceutical or biotechnology companies with HCPs and KDMs. Such content should be based on high-quality RWE, address relevant data gaps in scientific exchange, clearly cite the original publication or poster, and be presented in a truthful, nonmisleading, balanced, and nonpromotional manner. It should also be tailored for knowledgeable HCPs and KDMs, while remaining easy to understand and practical for medical affairs teams to use in time-limited communications.

These principles may sound straightforward, but in practice, they require vigilance by scientific content experts to keep them in mind and apply them to every decision, big or small. The following hypothetical example illustrates how this works in practice.

Rosie is a scientific content expert at a pharmaceutical company. Her US medical affairs counterpart, Jimmy, told her HCPs had been asking questions about the RWE for effectiveness of the company's Product A that was launched 2 years earlier.

Rosie searched for RWE posters and publications and found a conference poster based on a small sample of patients from 1 hospital. The reported real-world survival results were much better than the RCT results, but the methodology was not described in sufficient detail for her to assess study quality. She also found a publication based on a nationally representative EHR dataset with a large sample size and detailed, standard methodology reporting. Its survival results were similar to the RCT results. Rosie chose the larger, nationally representative publication because it provided stronger and more reliable evidence, even though the results were less favorable.

Jimmy shared the HCPs' preferences for a study to be summarized in a 3-page fact sheet. Rosie began by including only the essential background points needed to support the study rationale, given that HCPs were likely already familiar with the disease. She took the same approach to the methodology section, including only the information needed to support HCPs' understanding of the study design, reserving space to present the results in detail.

Rosie used accurate and clear tables and visuals to present the results, ensuring that medical affairs experts could easily demonstrate and explain the findings to HCPs and that HCPs could quickly comprehend them. Jimmy suggested listing the real-world survival results line by line alongside the RCT results and overlaying the real-world and clinical trial survival curve for easier comparison; Rosie explained that she could not do this because the real-world study population differed from the clinical trial population, and presenting the data this way could mislead HCPs into thinking the results were directly comparable.

Jimmy also suggested adding the authors' interpretations of the findings, such as that Product A may work better in the real world because real-world patients were sicker but had similar survival to clinical trial results. Rosie explained that the authors' claims were based on their interpretation of available data, rather than on research designed to test the validity of that interpretation. While such claims may be acceptable in a publication, including them in scientific content is not advisable because it could be viewed as nonfactual, misleading, and promotional.

Rosie also noticed that only a small amount of space remained to present the study's limitations. She considered using a smaller font size for the limitations section to make it fit, but then remembered that the need to present balanced information extends to visual presentation. By reducing the size of the figures in the summary without affecting their readability, she made room to include the limitations section in the same font size as the rest of the content. Rosie added the citation to finalize the content and submitted it for review.

This example is simplified; in real-world content development, more issues will likely arise, and at times these high-level guiding principles will be insufficient to guide sound judgment. In such cases, it may be necessary to consult other experts, management, or the company's legal department for further guidance.

Discussion

While posters and publications remain important mechanisms for disseminating RWE, scientific content offers greater flexibility and can be tailored more deliberately to specific audiences, objectives, and communication channels. At the same time, it must remain truthful, balanced, nonmisleading, and nonpromotional.

However, there are currently no specific guidelines providing detailed instructions for scientific content development. Scientific content experts should therefore develop strong RWE knowledge to support sound decisions regarding source material selection and content creation, while adhering to existing high-level principles. When in doubt, they should seek guidance from colleagues, management, or legal.

> Real-world evidence scientific content informs decision making by delivering practical, actionable information on real-world effectiveness, safety profiles, and patient management considerations.

In the long-term, more detailed guidance and best practices should be developed to ensure that scientific content development is consistent, scientifically rigorous, and standardized, while also helping to mitigate risk and improve efficiency and productivity. Government agencies may continue to provide high-level guiding principles, while professional societies like ISPOR may play an important role in convening task forces composed of stakeholders with relevant expertise to establish more detailed guidance and best practices.

For HEOR researchers, particularly those working within pharmaceutical and biotechnology companies, it is essential to recognize that the dissemination of their research extends beyond posters and publications. Close collaboration with scientific content experts and proactive sharing of updates on recent presentations and publications, can

accelerate scientific content development and better support the decision-making needs of HCPs and KDMs.

As RWE and other HEOR scientific content assume an increasingly prominent role in the scientific exchange activities of pharmaceutical and biotechnology companies, scientific content development is likely to evolve from a discipline led primarily by professionals with pharmacy or clinical training to one that incorporates more experts with HEOR backgrounds.

The participation of HEOR researchers in this space are welcome, as their subject matter expertise can substantially strengthen content development.

However, success in this role also requires adaptability to the distinct demands of scientific content creation, including the ability to integrate scientific rigor with effective storytelling and data visualization, as well as collaboration across a broad range of internal and external stakeholders. This work requires ongoing learning from diverse expertise and continuous refinement of scientific content development capabilities. However, optimizing the impact of RWE can facilitate decision making and advance patient access to quality care.

Disclosures: *Nan Qiao is an employee of Merck Sharp & Dohme (MSD). The views expressed in this article are her own and do not necessarily reflect the views of MSD.*

Value & Outcomes Spotlight has partnered with PharmaBoardroom to share content that is relevant to the global HEOR community. This interview was originally published on the PharmaBoardroom website in June 2026. For more information and other stories like this, visit PharmaBoardroom.

Not Just Operating Within Our Own Lane: European Medicines Agency's Role Expands Across Drug Development Life Cycle

Interview with **Emer Cooke, MBA**, Executive Director, European Medicines Agency

Q&A

As the European Medicines Agency (EMA) navigates the most significant expansion of its mandate in a generation, Executive Director Emer Cooke highlights how the regulator is further strengthening its role across the full life cycle of medicines. Cooke sets out how EMA is enhancing its engagement—from early developer support and clinical trial reform to artificial intelligence governance and the emerging health technology assessment interface—and why she believes the conditions for a step-change in European competitiveness have rarely been better aligned.

"I often say that you can be the best regulator in the world, but if the products don't reach the patient, they have no value."

– Emer Cooke

PharmaBoardroom: With the European Union (EU) pharmaceutical legislation now agreed and the EMA's extended mandate fully operational, Europe is asking far more of its regulator than it did a decade ago. Has the EMA's DNA changed to reflect that broader role?

Emer Cooke: I started as executive director in November 2020, right in the middle of the COVID-19 pandemic, which was a real wake-up call in terms of the importance of working collaboratively. That lesson is still shaping our work and outlook today, especially in the context of the new EU pharma legislation, health technology assessment (HTA) regulation, and the EMA's extended mandate.

Even if our core mission as a medicines regulator remains unchanged, we are increasingly focused on making that work matter more for European patients. I often say that you can be the best regulator in the world, but if the products don't reach the patient, they have no value. We have to think not only about what we do, but about how our scientific work is perceived, how it is translated into the work of other bodies, and what it ultimately takes to get to the patients.

PB: The new EU pharmaceutical framework gives much greater weight to unmet medical need in determining incentives for innovation. How are you working to standardize that definition and ensure sufficient predictability for developers?

EC: It is important to realize that the concept of unmet medical need already exists across various pieces of legislation—in our conditional marketing authorizations, in the orphan regulation—and we already use it to determine regulatory pathways.

But it is a difficult concept, because one person's unmet need is not necessarily another's.

The new legislation requires us to produce a guideline on the application of the criteria for unmet medical need, and, critically, we are required to consult with payers and HTA bodies on this guidance development. That has not been the case before. It gives us the opportunity to look at unmet medical need from a wider perspective but also places a responsibility on EMA to ensure that our understanding better aligns with that of other stakeholders—including patients, whose conception of unmet need can be very different from that of health systems.

The challenge, in the context of the new legislation, is to find the right balance: one that provides sufficient certainty for developers, while giving downstream decision makers a voice in the criteria for identifying an unmet medical need.

PB: In 2024, your colleague Peter Arlett told us that while European clinical trial numbers were stable at around 300 per month, they were not growing at the same pace as in the United States or China. He described ACT EU as a potential game changer. Two years on, where do things stand?

EC: ACT [Accelerating Clinical Trials] EU is a broad initiative, established in 2022, that aims to accelerate and streamline clinical trials across the EU. It is a joint effort between the EMA, the European Commission, and the Heads of Medicines Agencies and was born out of a recognition that concerted action on clinical trials in Europe was needed. The Clinical Trials Regulation had not yet come into full operation, fragmentation was increasing, and Europe was losing ground as a destination for trials.

> The challenge is to find the right balance: one that provides sufficient certainty for developers, while giving downstream decision makers a voice in the criteria for identifying an unmet medical need.

ACT EU addresses this by focusing on several priority areas. We have established a multistakeholder platform to help set those priorities and are working across 8 different workstreams. One covers clinical trials in public health emergencies and the acceleration of the clinical trial approval process, which could include having a standard protocol ready to deploy by sponsors—rather than starting from scratch each time a crisis emerges. Another looks at the landscape of scientific advice offerings across Europe: how they can work better together and where there is a case for streamlining. We also have a dedicated workstream on methodological innovation in clinical trial design and conduct.

Two other developments are worth highlighting. First, ethics committees have been brought into the ACT EU framework, recognizing the essential link between ethics approval and clinical trial authorization. Second, we collaborate closely with the COMBINE initiative, which brings together efforts on clinical trials for medicines and medical devices—an area that has historically operated in silos.

PB: With so much already underway, what are the key remaining objectives for the EMA, particularly around speed and simplicity for developers?

EC: There are a few things I would add. One is transparency. We now have an interactive clinical trial map where you can click on any part of Europe and see which trials are running, in which therapeutic areas and diseases, which are recruiting, and which are in progress. That is available across all EU languages, and it is a genuinely useful tool for patients and doctors to navigate the clinical trial landscape and, importantly, to find suitable trials.

> One of the more significant shifts in the last 2 years has been an initiative whereby we reach out to developers rather than waiting for them to come to us.

Perhaps the most concrete initiative to highlight here is FAST-EU [Facilitating and Accelerating Strategic Clinical Trials in the EU], a pilot project run with EU member states that aims to bring the current average assessment time down from 106 days to 70 days. The results so far are encouraging: 83 expressions of interest and 17 clinical trials accepted for accelerated assessment across 15 different member states and with 18 different sponsors. Three have already been completed—all within the FAST-EU timeline.

What makes this particularly meaningful is that participation was voluntary. Member states that signed up had to commit to delivering on that timeline and had to bring their ethics committees along with them. That kind of institutional buy-in is not easy to secure, and the fact that it is working is impressive.

PB: Life sciences venture capital in Europe now represents just 7% of the global market, and many biotechs continue to look outside Europe for funding and IPOs. Is there a role for the EMA in making Europe more attractive in that regard?

EC: This is something we are very much aware of, and it connects directly to the question of whether we are more than a medicines regulator and can also be an active contributor to innovation and competitiveness.

We already offer scientific advice to academic sponsors and small and medium-sized enterprises (SMEs), and there are specific regulatory incentives in place for SMEs. Companies can come to our Innovation Task Force to discuss regulatory challenges early, which also helps us build the expertise we may need at a European level.

But one of the more significant shifts in the last 2 years has been an initiative whereby we reach out to developers rather than waiting for them to come to us. What we were finding was that many early stage developers simply were not aware of

the regulatory requirements, which meant they risked failing in delivery of medicinal products not because of the science, but because they had not addressed the regulatory dimension.

But it is not only about awareness. It is also about connectivity—helping developers understand where European funding is available and making the right introductions. Increasingly we see our role is about bringing partners together across the life cycle, not just operating within our own lane.

We also have an innovation network spanning all member states, with innovation offices in each country that know the national funding landscape. The support structure already exists at both the European and member state levels; the challenge now is making sure developers know how to access it.

PB: At the same time as faster approval pathways are being pursued, HTA bodies are now demanding more robust comparative evidence. How do you manage those potentially competing pressures?

EC: I would push back slightly on the idea that what HTA bodies are asking for today is inherently more robust than what we look at during marketing authorization evaluations. I would say it is different.

That said, the real challenge is achieving a shared understanding of what evidence is needed for regulatory purposes versus what is needed for HTA. This is work we have been doing since 2010, even before the HTA Regulation was adopted.

But the regulation is still in early rollout. We currently have 5 products that have received a positive opinion from our human medicines committee and are in scope of the Joint Clinical Assessment process, with the first one completed in April *[editor's note: 2 more products completed the process in July]*. It is a fantastic achievement seeing these parallel, European-level reviews of clinical data progressing. This work is certainly a catalyst for supporting the introduction of innovative medicines into healthcare systems. And at the same time, the transparency of these assessments provides the insights that show there is still significant work to do on aligning approaches to evidence between the regulatory and HTA sides and for developers to generate a holistic evidence plan.

One encouraging sign from this collaboration is that HTA bodies have developed a much greater appreciation of just how rigorous the regulatory process is. That shared understanding matters. But we cannot require a full comparative assessment for every innovative product. For medicines in situations where there are few available treatments, or where the standard of care differs across member states, that simply is not feasible—and we have a responsibility to patients that means we cannot always wait. The answer lies in greater use of the tools available to us: real-world evidence, additional follow-up studies, registries. These are some of the means by which we can build confidence in new products over time.

PB: You have spoken recently about artificial intelligence (AI) and data being the backbone of trustworthy medicines regulation. What progress is the EMA making, and where do you see AI having the greatest impact?

EC: AI is part of everyone's work these days, whether they know it or not. For us at the EMA, this technology's impact falls into 3 broad areas.

The first is understanding how AI is being used in medicines development itself: screening for new medicines, accelerating clinical trials, preparing regulatory dossiers. The industry is already using these tools extensively, and we need to understand how, in order to regulate them properly.

The second is using AI to make ourselves more efficient: managing pharmacovigilance data, handling large datasets, embracing digitalization more broadly. There is significant work underway in this space.

> It is a fantastic achievement seeing these parallel, European-level reviews of clinical data progressing. This work is certainly a catalyst for supporting the introduction of innovative medicines into healthcare systems.

The third covers our operational processes: social media monitoring, literature surveillance, managing invented names (where AI can flag similarities with existing names and help prevent medication errors), and more generally freeing our staff from routine procedural tasks so they can focus on critical thinking.

Across all 3 areas, trustworthiness is the central concern. We have rolled out an AI literacy program for all staff, we are developing common approaches across the European network of regulatory agencies, and we are fully compliant with the AI Act. We have a risk assessment process that every new tool must go through before it is deployed, and keeping the human in the loop is something we are very deliberate about.

On the international side, we have published good AI principles for medicines regulation jointly with the US Food and Drug Administration, with the aim of extending these to the broader international community.

PB: Finally, what gives you cause for optimism about Europe's future in medicines regulation?

EC: Honestly, I think the future is now, and the stars are aligned for a brighter future. There is a huge opportunity to enable innovation and improve competitiveness in Europe. We have done the thinking. Now is the time to put it into practice.

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