JULY/AUGUST 2025 VOL. 11, NO. 4

VALUE & OUTCOMES SPOTLIGHT

An HEOR news magazine

SETTING A NEW PACE:

REAL-WORLD EVIDENCE IS FINDING ITS FOOTING IN HEOR

ISPOR
Improving healthcare decisions

VALUE & OUTCOMES SPOTLIGHT

JULY/AUGUST 2025
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An HEOR News Magazine

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.

ISPOR
Improving healthcare decisions

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FROM THE EDITOR

Leveraging Real-World Evidence for Better Health Outcomes

In recent years, real-world evidence (RWE) has gained substantial traction in the realm of health economics and outcomes research (HEOR). This paradigm shift is largely driven by the growing abundance of real-world data (RWD), which offers a practical and comprehensive insight into healthcare interventions and patient outcomes. RWE provides a means to complement traditional randomized controlled trials (RCTs) by bridging the gap between controlled clinical environments and the realities of everyday healthcare. Despite its promising contributions, the utilization of RWE does not come without challenges and scrutiny.

One of the most significant advantages of RWE is its ability to represent a diverse population in healthcare studies. Unlike RCTs, which often have narrowly defined inclusion and exclusion criteria, RWE encompasses data from real-world settings, enhancing inclusivity and generalizability. This inclusivity extends to ethnic, socioeconomic, and demographic diversities that are often underrepresented in RCTs. By analyzing outcomes within these broader populations, healthcare providers can tailor treatments more effectively, ensuring that the needs of all patients are met.

Additionally, RWE can be generated quickly and at a lower cost compared to RCTs. This expedited process is crucial in the swift evolution of healthcare, where timely evidence can directly influence practices and policies. For instance, during the COVID-19 pandemic, RWE was vital in assessing the effectiveness of interventions such as masks, social distancing, and treatments. Without the constraints of the lengthy timelines and high costs of RCTs, RWE offers a pragmatic avenue for immediate application, potentially reducing trial costs by 5% to 50%, as estimated by researchers.

> RWE provides a means to complement traditional RCTs by bridging the gap between controlled clinical environments and the realities of everyday healthcare.

RWE also shines in areas where conducting traditional trials is difficult or impractical. In conditions with limited patient populations, such as rare diseases, RWE facilitates single-arm trials that leverage external comparative groups, providing essential evidence without the need for randomization. This approach has proven successful in regulatory scenarios, as seen with the US Food and Drug Administration's approval of treatments based solely on RWD, such as the case with Vijoice (alpelisib) in 2022 for PIK3CA-Related Overgrowth Spectrum.

However, the utilization of RWE is not without challenges. One primary concern is the quality and reliability of RWD. Because RWE relies on data collected from diverse sources like electronic health records, patient registries, and wearable devices, there can be inconsistencies in data collection and recording. These discrepancies may raise questions regarding the internal validity of the studies, leading to potential biases or inaccuracies in results.

The ability to discern causality in RWD presents another challenge. RWE often uses observational data, which makes establishing cause-effect relationships more complex compared to RCTs, where randomization controls bias. Critics argue that RWE could be susceptible to "data dredging," where researchers may run multiple analyses to achieve desired outcomes, compromising the objectivity and credibility of the evidence produced.

Moreover, concerns about patient privacy linger as healthcare providers and researchers navigate the ethical complexities of data sharing. Protecting patient privacy while maintaining transparency is paramount, yet challenging, given the diverse regulations governing data usage across regions and countries.

Efforts to overcome these challenges are underway. Organizations such as ISPOR and the Duke-Margolis Center for Health Policy have emphasized the importance of transparency and reproducibility in RWE studies. Initiatives like the Real-World Evidence Transparency Initiative are striving to create guidelines that ensure the robustness and credibility of RWE, promoting routine registration and reporting practices and deploying tools such as the HARmonized Protocol template to clarify study designs.

Ultimately, while RWE offers significant opportunities to enhance HEOR and healthcare decision making, its challenges highlight the need for rigorous standards and practices. By striving for transparency, reliability, and inclusiveness, the research community can leverage RWE's full potential to deliver actionable insights for healthcare decisions.

> RWE can be generated quickly and at a lower cost compared to RCTs. This expedited process is crucial in the swift evolution of healthcare, where timely evidence can directly influence practices and policies.

As the landscape of data-driven healthcare continues to evolve, balancing the pros and cons of RWE will be instrumental in achieving HEOR's ultimate goal—improving healthcare decision making and broadening patient access to effective treatments. A concerted effort by researchers, policy makers, and key stakeholders to address these challenges will ensure that RWE emerges as a credible and reliable component of health outcomes research and ultimately benefits the global patient population through greater access to more effective treatments.

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
Editor-in-Chief,
Value & Outcomes Spotlight

FROM THE CEO

Using Real-World Evidence to Improve Healthcare Decision Making

Rob Abbott, CEO & Executive Director, ISPOR

The randomized controlled trial (RCT) has long been viewed as the "gold standard" for evaluating the efficacy of new drugs or medical products. That said, as good as the RCT might be, it is still just a trial with a sample population and there is something to be said for supplementing the evidence generated through the RCT with what is now popularly known as "real-world evidence" or RWE.

RWE is evidence about a drug or medical product's safety and efficacy that is generated outside of the RCT using real-world data (RWD) from patient experience with the product. In this way, RWD and RWE complement clinical trial data by providing insights from broader, more diverse populations in real-world settings, offering a more complete picture of a product's effectiveness and safety. Among the questions that RWD and RWE can help to answer are the following:

- Did the drug or product perform as expected?
- Were there side effects, and if so, what was the nature of those effects?
- Based on real-world experience, does the drug or product still merit reimbursement?

To be sure, clinical trials are crucial for controlled evaluation—and they often have limitations in generalizability due to strict inclusion/exclusion criteria and specific study populations. This is where RWD and RWE become important. RWD, whether from patient-reported outcomes, electronic health records claims data, or other sources such as wearables can include a wider range of both patients and outcomes, helping to bridge the gap between controlled research settings and the complexities of real-world clinical practice.

In light of the above, I'm gratified that this issue of *Value and Outcomes Spotlight* is focusing on the ways in which RWD and RWE are being used by health economics and outcomes researchers around the world to strengthen the evidence base that we collectively use to improve healthcare decision making. As the papers gathered together here make clear, RWD and RWE complement RCTs in many ways:

1. Expanding Generalizability:
- Clinical trials often involve specific patient populations, potentially excluding individuals with comorbidities or those who are not representative of the broader patient population.
- RWD captures data from diverse patient populations and real-world settings, allowing researchers to understand how a treatment performs across a wider spectrum of individuals.

2. Addressing Knowledge Gaps:
- RWD can help fill gaps in knowledge about a drug's effectiveness or safety in specific patient subgroups or clinical settings not adequately covered in clinical trials.

3. Enhancing Trial Design and Execution:
- RWD can be used to identify potential participants for clinical trials, optimize eligibility criteria, and improve recruitment strategies.
- By analyzing RWD, researchers can better understand the feasibility of a clinical trial, refine study protocols, and potentially accelerate the trial process.

4. Supporting Regulatory Decisions:
- Regulatory bodies like the US Food and Drug Administration in the United States and European Medicines Agency in the European Union are increasingly recognizing the value of RWE in supporting regulatory decisions.
- RWE can provide additional evidence to support drug approvals, postmarket surveillance, and other regulatory actions.

Ultimately, the greatest value of RWD and RWE is in improving healthcare decision making. I passionately believe that if we understand the "real-world" performance of a drug or product, we can better assess its value and make smarter resource allocation decisions—and this applies just as much to healthcare providers as it does payers, patients, and other stakeholders in the healthcare ecosystem. What unites us is our desire to bring the best that medical science has to offer to the greatest number of patients at reasonable cost. RWD and RWE can help all of us to make that dream a reality.

> As good as the RCT might be, there is something to be said for supplementing the evidence generated through the RCT with what is now popularly known as "real-world evidence."

As the CEO of ISPOR, I am so proud of the work our Society has done in the RWD and RWE space. This is especially true with respect to improving standards and practice for the collection and analysis of RWD. ISPOR and the International Society for Pharmacoepidemiology (ISPE) created a task force to make recommendations regarding good procedural practices that would enhance decision makers' confidence in evidence derived from RWD studies. Peer review by ISPOR/ISPE members and task force participants provided a consensus-building iterative process for the topics and framing of

recommendations that address topics such as study registration, replicability, and stakeholder involvement in RWE studies. These recommendations provide a trustworthy foundation for the expanded use of RWE in healthcare decision making.[i]

In addition to the collaboration with ISPE cited above, I also want to call out the Real-World Evidence Transparency Initiative Partnership, a joint collaboration and ongoing effort between ISPOR, ISPE, the Duke-Margolis Center for Health Policy, and the National Pharmaceutical Council. The objective of this initiative is to establish a culture of transparency for study analysis and reporting of hypotheses evaluating RWE studies on treatment effects.[ii] An important output of the Transparency Initiative is the Real-World Evidence Registry, a fit-for-purpose platform that enables researchers to register their study designs *before* they begin work to facilitate the transparency needed to elevate the trust in the study results.

As the volume and diversity of RWD continues to grow exponentially—aided by technology and integrated electronic medical records—I pledge to work with our members and other collaborators to keep expanding our understanding of how RWD can be converted into RWE that, in turn, can be used to improve healthcare decision making and make healthcare more accessible, effective, efficient, and affordable for more people globally.

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[i] See Berger ML, Sox H, Willke RJ, et al. Good practices for real-world data studies of treatment and/or comparative effectiveness: recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making. *Value Health*. 2017;20(8):1003-1008.

[ii] The Real-World Evidence Transparency Initiative published a plan to encourage routine registration of noninterventional real-world evidence studies used to evaluate treatment effects. The report, "Improving Transparency to Build Trust in Real-World Secondary Data Studies for Hypothesis Testing—Why, What, and How: Recommendations and a Road Map from the Real-World Evidence Transparency Initiative," was published in the September 2020 issue of *Value in Health*.

HEOR NEWS

1 Development of Machine Learning Prediction Models for Systemic Inflammatory Response Following Controlled Exposure to a Live Attenuated Influenza Vaccine in Healthy Adults Using Multimodal Wearable Biosensors in Canada: A Single-Center, Prospective Controlled Trial

(The Lancet Digital Health)

A Canada study used multimodal wearable sensors, host-response biomarkers, and machine learning to predict systemic inflammation following controlled exposure to a live attenuated influenza vaccine, without relying on symptoms. Researchers say the use of sensors and biomarkers provided "rich and objective data" to train machine learning algorithms, and the approach outperformed symptom-based detection. Read more

2 Trump Signs "Big Beautiful Bill": Here's What It Means for Healthcare (Healio)

Over the next decade, federal support for Medicaid will be cut by $930 billion, with certain able-bodied adults aged 19 to 64 years required to work, participate in job training, volunteer, or enroll in school at least 80 hours a month to maintain their benefits. Additionally, there are also new changes to the Affordable Care Act that are expected to reduce enrollment. Read more

3 Harnessing Digital Innovation for Children's Mental Health (NICE)

In implementing NICE's recommendation for Lumi Nova, a digital therapy app for children aged 7 to 12 years with symptoms of anxiety, East London NHS Foundation Trust was able to address a gap in mental health services support for primary school children. Read more

4 Prescription Use and Spending After the Introduction of a Real-Time Prescription Benefit Tool

(JAMA Network Open)

A study that looked at real-time prescription benefit tools that provide prescription cost estimates to clinicians at the time of prescribing found although these tools have many anticipated benefits, further research is needed on how to design and deploy them to maximize potential benefits. Read more

5 Immune Checkpoint Inhibitors and Survival Disparities by Health Insurance Coverage Among Patients With Metastatic Cancer (JAMA Open Network)

Although the use of expensive immune checkpoint inhibitors can substantially improve median survival among individuals with cancer, researchers found widening survival disparity between people without health insurance and those with private insurance. The findings suggest that programs aimed at improving health insurance coverage and providing comprehensive financial assistance to people without coverage may help to mitigate these disparities. Read more

6 Workplace Mental Health at Risk as Key Federal Agency Faces Cuts (KFF News)

A little-known federal agency, the National Institute for Occupational Safety and Health, has had a majority of its staffers fired and is facing severe budget cuts. Experts predict the lack of funding will cause the collapse of workplace mental health programs such as those for suicide prevention and assistance with drug addiction. Read more

7 Measles Cases Rise in the Americas in 2025 (PAHO)

A total of 7132 confirmed cases of measles and 13 deaths have been reported in the Region of the Americas as of mid-June 2025, representing a 29-fold increase compared to the 244 cases reported during the same period in 2024. Canada, Mexico, and the United States account for the majority of cases and deaths, and experts say the rise in cases underscores the need to address gaps in routine immunization. Read more

8 Leading Medical Groups Sue Kennedy Over Changed COVID-19 Vaccine Recommendations (STAT)

Six major medical groups and a pregnant physician are suing health secretary Robert F. Kennedy Jr, arguing that the May 19 directive, under which the COVID-19 vaccine is no longer recommended for healthy children and pregnant people, violates decades of policy governing how vaccines are reviewed, approved, and recommended in the United States. Read more

9 Findings Reveal Gaps in Care for Pregnant Minority Women With Cancer (AJMC Evidence-Based Oncology)

In an interview with AJMC, Duke Appiah, PhD, MPH, associate professor at Texas Tech University Health Sciences Center, highlighted the findings of his abstract "Higher Risk of Adverse Pregnancy Outcomes Among Racial and Ethnic Minority Women With Cancer in the United States," which he presented at the American Association for Cancer Research Annual Meeting 2025. Appiah found in women with breast cancer, as well as thyroid cancer, there was a 30% elevated risk in these groups for conditions including hypertensive disorders of pregnancy, gestational diabetes, fetal growth restriction, intrauterine fetal death, preterm birth, and maternal mortality. Read more

10 Efficacy and Safety of Varenicline and Bupropion, in Combination and Alone, for Alcohol Use Disorder: A Randomized, Double-Blind, Placebo-Controlled Multicenter Trial (The Lancet Regional Health Europe)

In looking at the administration of bupropion and varenicline for alcohol use disorder, a study funded by the Swedish Research Council determined that the drugs reduced alcohol consumption more than placebo alone, with the greatest effect shown when both drugs were administered together and compliance was high. Read more

Advancing Acceptability of Real-World Evidence for Healthcare Decision Making: A Summary of the ISPOR Real-World Evidence Summit 2024

Madeline Shipley, MPH, ISPOR, Lawrenceville, NJ, USA; **Shirley Wang, PhD**, Brigham & Women's Hospital, Harvard Medical School, Boston, MA, USA; **Massoud Toussi, PhD**, Toussilver, Paris, France; **Laura T. Pizzi, PharmD, MPH, Kelly Lenahan, MPH**, ISPOR, Lawrenceville, NJ, USA

Key Takeaways:

1. There is a growing role for real-world evidence (RWE) in healthcare decision making
2. Improving the reliability of RWE will require the use of advanced causal inference methods such as target trial emulation and thoughtfully constructed external control arms
3. Maximizing the impact of RWE will rely on coordinated efforts across stakeholders and the harmonization of methods and standards

Since 2017, there have been more than 50 guidance documents published globally on the use of real-world evidence (RWE) in regulatory and health technology assessment (HTA) decision making. The increasing number of guidance documents highlights the importance of RWE to the field of health economics and outcomes research (HEOR). On Sunday, 17 November 2024, ISPOR hosted a Real-World Evidence Summit 2024, a co-located event at the ISPOR Europe 2024 conference in Barcelona, Spain. The Summit covered the latest developments in the use of RWE across the regulatory-HTA-payer decision-making continuum. Four sessions covered methods-related topics, including causal inference and external control arms for comparative effectiveness analyses, the hierarchy of RWE studies, and the role of patient registries. View the full program here.

Unleashing the Latent Power of RWE in Decision Making

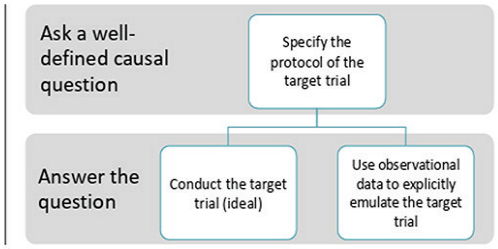
Real-world data (RWD) is defined as "data used for decision making that are not collected in conventional randomized control trials (RCTs)."[1] These data relate to areas such as patient health status and/or healthcare delivery and can come from a variety of sources such as electronic health records, medical claims, surveys, and registries, which can go on to generate RWE. To look more closely at the role of RWE to inform regulatory, payer, and HTA decisions, it is important to showcase success stories where RWE has been pivotal in assessing value and exploring challenges. One such success story example comes from the European Union (EU), where coordinating centers like DARWIN-EU offer a better exchange of and access to healthcare data. Speakers emphasized its usefulness for conducting RWE studies, as it provides cross-national information about prevalence, incidence, treatment patterns, adverse events, and effectiveness, which can be used by national authorities such as the European Medicines Agency and other regulatory bodies conducting HTAs using RWD and RWE. Similarly, agencies like the National Institute for Health and Care Excellence (NICE) have developed their own RWE Framework and routinely use RWE to inform their decisions. NICE has used RWE to inform their reimbursement policies in many ways, including informing the design, parameters, and validation of economic models; understanding the safety of medical technologies; assessing the impact of interventions on service delivery and decisions about care; and assessing the applicability of clinical trials to patients in the National Health Service.

Regulatory and HTA decision makers agree that data quality is an essential component for RWE studies and that a fit-for-purpose RWD source is equally dependent on the question being asked as well as data relevancy and quality. However, there is currently not a clear consensus on how researchers should demonstrate data quality to decision makers. Additionally, as they become more comfortable with RWE to address causal questions, it will become increasingly important to develop guidance and standards for methods that assess the generalizability and transportability of evidence generated from one database to other data and populations. Such analyses will help stakeholders answer the question, "how do these results apply to my patient population?"

Methods for Causal Inference Using RWD

To use RWE in HTA and health policy decision making, it is crucial to use valid estimates of the benefits, harms, and costs of interventions of interest. This requires a closer look at methodological approaches and frameworks for causal inference and their applicability, such as target trial emulation, calibration, and hybrid designs. The target trial in target trial emulation approaches is the ideal hypothetical randomized trial that would answer the causal question of interest. For comparative effectiveness or safety research, this requires the researcher to: (1) ask a well-defined question, and (2) answer the question using observational data (**Figure 1**).[2] The target trial emulation estimand is defined by eligibility criteria, treatment strategies, treatment assignment, follow-up, outcome(s), causal contrast(s), and an analysis plan. Emulating these key study design parameters in an observational study may help investigators to clarify the causal study question of interest and avoid design flaws. HEOR professionals should become more familiar with these methods for using RWD to support HTA.

Figure 1. Components of the target trial in target trial emulation



External control arms (ECAs) are an alternative study design when RCTs are not feasible or ethical. Like other causal inference methods, it comes with challenges that must be acknowledged, such as selection, measurement, and confounding biases. One example of how measurement challenges can be overcome is by enhancing ECA analyses using calibration and hybrid designs,[3] which take primary data from a single-arm trial to identify a larger set of secondary data that is highly similar in baseline characteristics via exact- and or score-matching. Hybrid designs combine underpowered internal control arms, which are arms drawn from the same clinical trial, with external control arms.

Methods like target trial emulation, ECAs, hybrid, and calibrated designs have the potential to support more informed and effective healthcare decision making when used appropriately. Expert use of high-quality RWD for causal inference can help support HTA and policy decision making. However, as with any method, there must still be careful consideration of their strengths, limitations, and applicability to the causal question.

Embracing Diversity and Tackling Heterogeneity in Data, Methods, and Jurisdictions

As decision-maker demand for evidence on the effects of drugs as they are used in clinical practice increases, the need for robust healthcare data infrastructure grows as well. To enhance the value of RWD for decision making, diverse data and methods may be used across various jurisdictions. Multi-database studies are studies that use at least 2 healthcare databases that are not linked to each other at an individual level. Possible sources of heterogeneity in a multi-database study can include variation in study protocols, variation in study quality, differences in interventions, differences in measurement or data capture, differences in follow-up length, and treatment-covariate interaction. But heterogeneity is not inherently negative. Possible sources of heterogeneity that are inherent to the data, such as measurement differences, are unwanted, but clinical heterogeneity, such as differences in prescription patterns between geographical regions, can be informative (**Figure 2**).[4] Unwanted heterogeneity can be mitigated through harmonization of protocols or data. One way that DARWIN-EU manages the inevitable heterogeneity of routinely collected data is by converting disparate source data into the Observational Medical Outcomes Partnership Common Data Model, which uses a common structured format and ontologies.

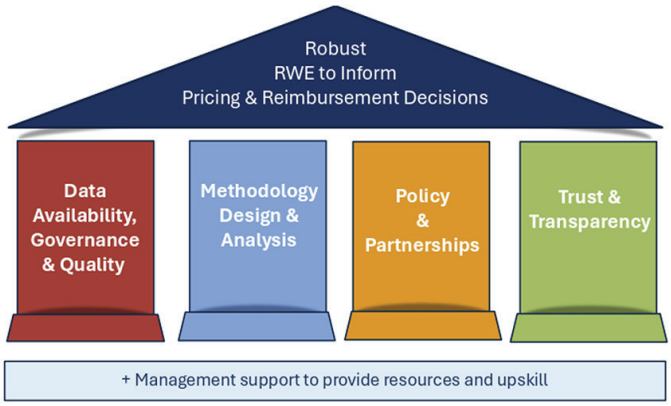
Figure 2. Visual representation of homogeneity versus heterogeneity

Overcoming Obstacles: Charting the Path Ahead

Multistakeholder learning networks such as RWE4Decisions have focused on identifying the gaps in RWE that need to be filled to inform HTA/payer decisions. By promoting collaboration across 7 different stakeholder groups, which consists of national HTA/payer collaborations, pharmaceutical industry, clinical teams, patient groups, disease registry holders, and RWD analytics experts, learning networks like RWE4Decisions helps those stakeholders generate and utilize better RWE to inform HTA, joint clinical assessments, and payers. The 58 actions for stakeholders fall under 1 of 4 pillars supporting development of robust RWE: (1) data availability, governance, and quality; (2) methodology design and analysis; (3) policy and partnerships; and (4) trust and transparency (**Figure 3**).[5]

The ALIGN Matrix—aligning investigational designs and data sources with evidence needs in healthcare research—has been proposed as a tool to address the complexity of matching evidence needs with appropriate study designs and data sources. Ensuring that data sources are aligned with evidence needs when collecting RWD is beneficial to a researcher as it will allow the collection of quality data that matches their needs.

Figure 3. RWE4Decisions 4 pillars to support development of RWE



Abbreviation: RWE, real-world evidence

In conclusion, the Real-World Evidence Summit underscored the growing impact of RWE in shaping healthcare decision making. Advancements in methods like hybrid designs and target trial emulation, as well as collaborative initiatives such as DARWIN-EU and RWE4Decisions, are helping to address challenges in areas like data quality and reliability, transportability, and applicability. Continued collaboration to meet decision-making needs will be key to unlocking the full power and potential of RWE. ISPOR is actively working to improve standards and practices for improving the quality of RWD to increase the generation of rigorous RWE and to promote transparency in conduct and reporting of RWE studies. Additional details about RWE initiatives at ISPOR are available here. ISPOR will host its next Real-World Evidence Summit—*Through the Lens of Asia Pacific*—28-30 September 2025 in Tokyo, Japan. More information is available here.

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ISPOR Conferences and Events

ISPOR Real-World Evidence Summit 2025:
Through the Lens of Asia Pacific | 28-30 September

Tokyo Prince Hotel | Tokyo, Japan

Gain exclusive access to the latest advancements in real-world evidence (RWE) methodologies, data analysis, and applications designed specifically for the Asia Pacific healthcare landscape! Connect with leading experts, including researchers, healthcare professionals, policy makers, and industry leaders at the ISPOR Real-World Evidence Summit 2025: Through the Lens of Asia Pacific. Spotlighting the latest breakthroughs, cutting-edge research, and innovative solutions to the region's most pressing healthcare challenges, this is a must-attend event for all seeking to stay at the forefront of RWE and health economics and outcomes research (HEOR) in Asia Pacific. Explore the program and register!

More at www.ispor.org/Summit2025-RWE

Join the conversation on social media using #ISPORSummit.

ISPOR Europe 2025 | 9-12 November
Scottish Event Campus | Glasgow, Scotland, UK

Through cutting-edge research, dynamic discussions, and real-world case studies, ISPOR Europe 2025 is set to highlight the latest advancements in HEOR that enhance patient-centered innovation, advance healthcare access, and drive better outcomes for all. Engage with leading experts, strengthen patient-centered collaborations, and shape the future of value-based healthcare—join us in Glasgow, Scotland for the premier European conference for HEOR. The program has been announced, and registration is open!

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28-30 September | Tokyo, Japan

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ISPOR Europe 2025

9-12 November | Glasgow, Scotland, UK

11 courses to choose from on 9 November

Explore short courses at www.ispor.org/shortcourses.

ISPOR Education

ISPOR Webinars

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HTA in Pluralistic Healthcare Systems: A Global Perspective

Uncover the challenges of health technology assessment in pluralistic healthcare systems and gain recommendations to overcome these challenges.

Brought to you by the ISPOR HTA Council and ISPOR HTA Roundtable – Middle East and Africa.

September 3 | 8:00AM – 9:00AM EDT

Evolving RWE Standards Under IRA & JCA: Implications for Asia's HTA

Explore how transatlantic shifts in evidence standards—driven by the US Inflation Reduction Act (IRA) and Joint Clinical Assessment (JCA) being implemented in the European Union—may reshape health technology assessment (HTA) practices, pricing negotiations, and reimbursement policies in Asia.

Brought to you by the ISPOR Asia Consortium.

September 9 | 11:00AM – 12:00PM EDT

Fit-for-Purpose RWD: An Integral Part of Evidence Planning

Gain an understanding of the evolving real-world evidence (RWE) landscape and key data sources; assess "fit-for-purpose" real-world data (RWD); and examine common limitations of using RWD and ways to solve them.

Brought to you by ISPOR Corporate Partner, Cencora.

September 16 | 11:00AM – 12:00PM EDT

Why Serve on the ISPOR Board? Hear From ISPOR Leaders

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Brought to you by the ISPOR Executive Office.

October 8 | 11:00AM – 12:00PM EDT

Defining Patient-Centered Access to Improve Health Outcomes

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ISPOR Education

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HEOR ACROSS THE GLOBE

ASIA PACIFIC

Section Editor: **Paula Lorgelly, PhD**, Auckland, New Zealand

ISPOR Philippines Reactivation: Highlights and Strategic Directions

Jason Alacapa, MD, MBA, MPH, MHM; Bernadette Joy Almirol, RMT; Richard Simon Binos, BS; John Paul Caesar delos Trinos, PhD, MPH, MHM; Madeleine de Rosas-Valera, MD, MSc; Mac Ardy Gloria, PhD, MPH; Carlo Irwin Panelo, MD, MA; Pura Angela Wee-Co, MD, MSc, MAHPS, ISPOR Philippines, Metro Manila, Philippines

The ISPOR Philippines hosted a 2-day conference in early October 2024 that brought together a wide range of stakeholders, reflecting the growing momentum and multisectoral support for institutionalizing health technology assessment (HTA) in the country. There were more than 100 participants from the government (eg, HTA Philippines, Department of Health, Philippine Health Insurance Corporation), academia, industry, patient organizations, professional medical societies, and development partners (ie, World Health Organization and Vital Strategies). The conference aimed to (1) discuss the progress, challenges, and opportunities for HTA in the Philippines; (2) present the updated HTA administrative order, methods guide, process guide, and stakeholder engagement framework; and (3) highlight the roles and responsibilities of various stakeholders in HTA.

The key recommendations for improving HTA in the Philippines included leveraging existing recommendations, providing additional resources for HTA Philippines, institutionalizing nominator-led assessments, clarifying and streamlining the prioritization of health technologies to undergo HTA, and improving interagency coordination. During the 2-day conference, members of ISPOR Philippines also elected its new set of board members for 2025-2026. The election marks a significant step in the reactivation of the ISPOR Philippines Chapter with its renewed commitment to advancing health economics and outcomes research in support of evidence-informed healthcare decision making in the country. Following the elections, the new Board convened for a strategic planning session to identify the Chapter's priorities and activities for the coming years. Three priorities were identified and discussed to further explore the Chapter's role in driving country-level policies on HTA, universal healthcare, and patient access to medicines in the Philippines.

The full version of the conference proceedings and strategic plan summary can be found here. For more information about ISPOR global group activities and engagement opportunities, please contact globalgroups@ispor.org.

Participants at the ISPOR Philippines conference held on October 8–9, 2024.

Section Editor: **Diego Rosselli, MD**, Bogotá, Colombia

New Chilean Law on Rare Diseases Aligns With HEOR Principles

Carla Campaña, PhD, Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Facultad de Psicología Universidad del Desarrollo, Santiago, Chile

Recently, the law on rare, orphan, and low-prevalence diseases was enacted in Chile. This law establishes a national registry and a multisectoral technical advisory commission with representation from civil society, academia, and public institutions. This law, developed through years of advocacy by patient organizations, represents a significant shift toward inclusive and participatory health governance. The active involvement of patient communities strengthens the law's legitimacy and exemplifies how collaborative policy making can align with the broader principles of health economics and outcomes research. This alignment emphasizes the importance of real-world impact, data transparency, and stakeholder engagement. These inputs are essential for making health decisions that are both scientifically rigorous and socially responsive. Moreover, incorporating civil society into health technology assessment (HTA) and policy advisory roles has enhanced transparency, accountability, and public trust. Patient and public involvement can improve the relevance and applicability of HTA outcomes, leading to policies that better reflect the lived experiences of affected individuals. Chile's recent law sets a valuable precedent for other countries in the region by demonstrating how participatory models of governance can contribute to more equitable and evidence-based healthcare systems.

Healthcare Challenges in the Dominican Republic: A Call for Systemic Improvements

Diego Rosselli, MD, EdM, MSc, Pontificia Universidad Javeriana, Bogotá, Colombia

The Dominican Republic, home to nearly 11 million people, faces significant healthcare challenges despite its economic growth in sectors such as tourism, construction, and mining. The country operates a multitiered healthcare system common in Latin America, combining universal public services with private care. While the system aims to provide broad access, including free basic coverage for the most vulnerable through the Seguro Nacional de Salud, substantial gaps remain.

The public healthcare sector, managed by the Ministry of Public Health, struggles with chronic underfunding, resource shortages, and wide regional disparities affecting quality and access. Public facilities, although nominally free, often suffer from understaffing, poor equipment, and supply shortages. Patients frequently must provide basic items such as bedding, and some essential medical treatments incur high out-of-pocket costs.

With only 5% of the gross domestic product allocated to healthcare, the distribution of resources is uneven. Private hospitals, primarily situated in major cities, provide high-quality, technologically advanced care to those who can afford it, while rural and poorer populations rely on lower-quality public services. Emergency services tend to be slow, and waiting times are often extremely long.

Health experts emphasize the need for significant investments to strengthen primary care and improve the availability and equitable distribution of medical personnel and supplies. Attempts to implement health technology assessment-driven decision making have been hindered by concerns about rising healthcare costs and a shortage of adequately trained human resources. This shortage is exacerbated by high turnover rates in key positions within the responsible public institutions.

Recent media attention on the healthcare system may serve as a catalyst for change. Health economists and researchers suggest that broad discussions involving all stakeholders could help address the current challenges effectively. They propose focusing on improving resource allocation, enhancing primary care networks, and developing strategies to retain healthcare professionals.

Despite the challenges, there's cautious optimism among healthcare experts. They believe that by embracing evidence-based practices and innovative approaches, the Dominican Republic can make significant strides in improving its healthcare system. Key areas for improvement include strengthening primary care, implementing targeted interventions to address regional disparities, and leveraging technology to enhance efficiency and access.

As the country moves forward, the role of health economists and outcomes researchers will be crucial in providing the analytical framework and evidence base to support these transformations. Their goal is to help create a healthcare system that effectively serves all residents of the Dominican Republic, regardless of their socioeconomic status or geographic location.

Note: This article was refined with assistance from artificial intelligence (AI) and has been reviewed and edited by ISPOR staff. For more information or for inquiries on ISPOR's AI policy, click here or contact us at info@ispor.org.

HEOR ACROSS THE GLOBE

EASTERN EUROPE, MIDDLE EAST, AND AFRICA

Section Editor: **Bertalan Németh, PhD**, Budapest, Hungary

Recent HTA Developments in the Middle East

Ahmad Nader Fasseeh, BSc, MBA, Syeron Research Institute, Alexandria, Egypt; **Ahmed Yehia Khalifa, MSc**, World Health Organization, Cairo, Egypt; **Anas Hamad, MSc, PhD**, Qatar University, Doha, Qatar; **Hana Al-Abdulkarim, MSc, PhD**, National Guard Health Affairs, Riydah, Saudi Arabia; **Jenan Shaaban, MSc**, Ministry of Health, Hawally, Kuwait; **Mouna Jameleddine, MSc, PharmD**, National Authority for Assessment and Accreditation in Healthcare, Tunis, Tunisia; **Sara Al Dallal, MD, MSc**, Emirates Health Economics Society, Dubai, United Arab Emirates; **Said Wani, PhD**, Ministry of Health, Muscat, Oman

Health technology assessment (HTA) in the Middle East is experiencing considerable momentum, driven by strategic commitments and structured implementation efforts across multiple countries. Notably, Oman and Abu Dhabi's Department of Health have recently published comprehensive methodological guidelines, providing detailed guidance on conducting HTA research and establishing official cost-effectiveness thresholds with differential considerations for orphan drugs. Oman further introduced an advanced critical appraisal checklist comprising more than 100 detailed evaluation questions, significantly enhancing the rigor of HTA submissions.

The United Arab Emirates continues to advance HTA within a broader regional shift towards value-based healthcare, leveraging formal frameworks to inform healthcare coverage and optimize resource allocation. Kuwait demonstrates a strong political commitment to implementing HTA through a meticulously structured 3-year strategic plan aimed at developing both human capacities and essential tools to realize their HTA objectives.

In Egypt, the HTA landscape has evolved significantly following the establishment of key authorities (UPA, EDA, UHIA) and the Ministry of Health's stewardship role, with current efforts aimed at unifying HTA processes nationally and in collaboration with international partners. Saudi Arabia further strengthens the regional landscape by establishing a dedicated national HTA entity under the Center for National Health Insurance, reflecting substantial progress towards system-wide value-based healthcare integration.

In Qatar, HTA institutionalization efforts are gaining momentum through a national HTA project led by the Ministry of Public Health as part of the National Health Strategy 2024-2030. Tunisia's INEAS continues to set a regional benchmark, consistently delivering robust HTA evaluations across healthcare technologies. These assessments inform national-level decision making and are underpinned by comprehensive methodological guidelines and active international collaboration. Tunisia is currently prioritizing capacity transfer efforts, both at the national level and regional level, to support broader collaboration. Collectively, these developments highlight the region's growing dedication to structured, evidence-based, and transparent healthcare decision making.

*If you have ideas for a story or want to contribute an update, please email **voseditor@ispor.org**.*

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.

Latest Data Demonstrate Significant Disparity Across Countries in Europe in Time to Availability and Total Availability of New Medicines

Guest Editor: **Mark Orchard, BSc**, Senior Consultant, Cogentia, Cambridge, United Kingdom.

As the first few technologies undergo Joint Clinical Assessment (JCA) as part of the European Union Regulation (EU-HTAR; Regulation 2021/2282) on health technology assessment (HTA), there is an aim to harmonize the approach to clinical assessment across EU Member States, with the objective to reduce duplication of effort, and ultimately achieve faster, broader, and more equitable access to medicines.

The latest report from the European Federation of Pharmaceutical Industries and Associations (EFPIA), Patients' Waiting to Access Innovative Therapies (W.A.I.T.) Indicator, illustrates the importance of this objective, painting a stark picture of the disparity across countries in Europe in time to access and availability of medicines. Based on an analysis of 173 medicines approved by the European Medicines Agency (EMA) between 2020-2023, average time to availability across 36 countries was 578 days in the 2024 analysis, an increase of over a month relative to the 531-day average observed in the 2023 report. There was a greater than 700-day difference between the countries with the fastest and slowest availability: 128 days in Germany and 840 days in Portugal.[1]

Total availability ranged from 156 of 173 medicines in Germany to 6 of 173 medicines in Türkiye. Of the 36 markets scoped, 20 had a rate of availability below 50%. Even where access in a market is achieved, this is often on a named patient basis only, with access on an individual patient basis accounting for >30% of the available medicines in Austria, Denmark, Greece, Cyprus, Iceland, Lithuania, Serbia, and Bosnia.

Comparing data between the EFPIA W.A.I.T. Indicators for 2022, 2023, and 2024, permits an assessment of trends for specific markets. Total availability of medicines increased year-on-year in Spain, Bulgaria, Portugal, and Slovakia. Meanwhile, total availability decreased year-on-year in France, Denmark, Sweden, Greece, and Hungary. Looking at time to availability, Bosnia, Scotland, and Poland improved each year, while 9 countries, including England, The Netherlands, and France saw increased delays to availability year-on-year.

Notably for data collection for the 2024 W.A.I.T. Indicator, there was some pushback from national payers at the summary data presented by EFPIA. Most prominently, Spain's health ministry published a separate report that provides an alternative picture to that in the EFPIA report.[2] While there is detail provided in the accompanying reports, headlines and discourse around the EFPIA W.A.I.T. Indicator tends to frame time to access around time from central EMA marketing authorization to availability. National payers may reasonably argue that this unfairly biases the data against them, given that they can only begin their national HTA procedure once a dossier has been submitted.

The topic of time from central approval versus time from filing of a pricing and reimbursement submission by marketing authorization holders was explored in the accompanying access hurdles portal report.[3] This analysis found that 31% of the total time between marketing authorization and availability can be attributed to time between EU marketing authorization and national pricing and reimbursement filing, with the remaining 69% attributed to national decision making.

Further analysis found that, on average, 59% of products were either reimbursed or filed for reimbursement in individual European countries, with this being as high as 91% in Germany, and as low as 9% in Malta. The most common reason for not filing for national reimbursement was economic viability (37%), followed by value assessment process (28%), health system infrastructure (20%), and pricing and reimbursement process (15%).

As well as data for Europe, a similar W.A.I.T. indicator was recently published for 2025 by FIFARMA,[4] analyzing access of all medicines globally approved (defined as the US Food and Drug Administration [FDA] or EMA approval) between 2014-2024 in 10 Latin American countries. Compared to an average of 19 months from marketing authorization to availability in Europe, in Latin America the total time to availability is on average 67 months from FDA or EMA approval, equating to over 5 and a half years of delay. Notably, these 67 months comprised 38 months from EMA or FDA approval to national regulatory approval in Latin American countries, and a further 29 months from national regulatory approval to local availability. Perhaps most notably, of FDA/EMA approved medicines, only 33% are available publicly in at least one of the 10 Latin American countries included in this analysis.

In summary, time from marketing authorization to patient access to novel medicinal products continues to increase in Europe, with products assessed in the 2024 EFPIA W.A.I.T. report taking 47 days longer than observed in 2023, although this does not capture the extent to which delays were due to HTA, price negotiation, or companies not submitting an HTA application. There is a wide disparity in time to availability, with a range of over 700 days between the fastest and slowest countries to achieve access. Furthermore, of the markets assessed in 2024, over half (20 of 36) had a rate of availability below 50%. These data support the need for a more harmonized HTA process across Europe to drive efficiency, breadth, and speed of availability of new medicines. The new JCA procedure may provide a solution, although this is entirely contingent on it delivering against its stated aims, as well as on Member States adapting their local methods to incorporate the JCA report, thereby streamlining assessment.

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Fitting nicely with the theme of this issue of *Value & Outcomes Spotlight*, we are covering target trial emulation (TTE) in this edition of Methods Explained based on a conversation with Miguel Hernan and Seamus Kent. Miguel Hernan, MD, is the Director of CAUSALab and Professor of Biostatistics and Epidemiology at the Harvard T.H. Chan School of Public Health, and a driving force in the adoption of TTE within the field of health economics and outcomes research. Seamus Kent, PhD, is Assistant Professor at the Erasmus School of Health Policy & Management and a well-known expert on the use of real-world evidence for health technology assessment, as demonstrated by his leadership on the real-world evidence framework that was published by the National Institute of Health and Care Excellence (NICE) in 2022.

Target Trial Emulation

Section Editor: **Koen Degeling, PhD**

What is target trial emulation (TTE)?
Although the title of this section may suggest otherwise, TTE should be considered a framework rather than a method. It is a general approach to articulate causal questions and guide the use of observational data to answer them.

Estimating causal effects, such as the effectiveness of healthcare interventions, can be done through randomized controlled trials. If such trials are performed properly, unbiased estimates of the intention-to-treat effect can be obtained. In cases where there is no randomized study, observational data can be used. This could be data from a nonrandomized study or from real-world data. When estimating causal effects using data from an observational study, researchers are emulating (whether implicitly or explicitly) a randomized trial that they would ideally have performed (ie, the target trial). The TTE framework provides a structured approach towards defining the causal question, target trial and data analysis, helping to eliminate biases that can arise from decisions made in the design of the research.

Causal effect estimates from observational data are prone to biases and controlling aspects that may bias the estimate is essential to analyzing such data. The TTE framework makes this bias control explicit through connecting the target trial and the analysis performed. This transparency helps to focus the discussion regarding the interpretation of results from observational studies on the quality of the data rather than the use of the data.

The TTE framework is useful for causal inference from observational data if the interventions are well-defined and it is feasible to map the components of the target trial protocol to the data that are available or will be collected.

Conceptually, how does it work?
Emulating a trial comes down to transparently writing down the research question and how it will be answered. The target trial is made explicit by articulating the randomized trial that would answer the research question according to a structured framework.

As with most research, the starting point is a research question that is relevant to decision makers and can be answered with the available data or data that can be gathered. Subsequently, the target trial is specified by defining the ***causal estimand***, identifying assumptions, and estimator. Defining the causal estimand concerns the design of the target trial, including the eligibility criteria, interventions, outcomes, and follow-up period. The ***identifying assumptions*** concern the assumptions underlying the study, such as those regarding the loss to follow-up. The ***estimator*** covers the data analysis and any modeling assumptions. Once the design of the target trial has been established, the data analysis methodology often follows naturally, based on the boundaries of the data.

> The TTE framework provides a structured approach towards defining the causal question, target trial and data analysis, helping to eliminate biases that can arise from decisions made in the design of the research.

Once the target trial has been defined, the emulation is performed by describing and performing the mapping of the trial elements to the observational data, and capturing any additional assumptions made in doing so.

Are there alternatives to the TTE framework?
One may expect that data analysis methods commonly applied to observational data are alternatives to TTE. These may include techniques like propensity score matching, instrumental variable estimation, etc. However, the TTE framework is not a method to analyze data, the data analysis methods are subsumed as a component of the emulation.

Therefore, there are no alternative approaches to TTE, per se. Any attempt to answer a causal question using observational

data is an attempt to emulate a target trial. The question is whether the target trial is made explicit or kept implicit. When things are kept ***implicit***, reviewers of the study have to reverse-engineer the target trial, which often is challenging and can lead to misinterpretation. When making things ***explicit*** through the TTE framework, researchers not only can avoid fundamental mistakes that may result in erroneous conclusions but also facilitate reviewers in effectively and efficiently appraising their work.

To what extent is it currently being used?
The TTE framework has been incorporated as best practice in several health technology assessment (HTA) guidelines, including in those of the European HTA, NICE in England, Haute Autorité de santé in France, Agency of Health Quality and Assessment in Catalonia, Spain, and the Canadian Drug Agency. The Cochrane Collaboration uses the target trial framework for its Risk of Bias in Non-randomised studies (ROBINS) tool. The FDA's Sentinel group has incorporated the target trial framework into its PRINCIPLED approach for causal inference from observational data.

> Any attempt to answer a causal question using observational data is an attempt to emulate a target trial. The question is whether the target trial is made explicit or kept implicit.

Even though it is recommended by guidelines, TTE is not yet common practice. The HTA and regulatory agencies themselves will have to build their internal capacity and expertise to be able to review the information provided. Furthermore, the acceptance of observational data is still often hampered by issues regarding confounding and data quality, such as missing data or alternative definitions of outcomes. The TTE framework does not change this—it makes these challenges (even more) explicit.

The number of applications may increase in the years to come as HTA bodies such as NICE increasingly request information is provided according to the TTE framework. Positive experiences through better informed conversations on confounding based on transparent reporting of study design and results may contribute further to its uptake. These benefits will become more evident once there are more reevaluations of reimbursement based on real-world data.

What are remaining challenges for the adoption of TTE?
TTE helps researchers and reviewers to understand what risks and trade-offs are in designing observational studies. However, many researchers and decision makers may be looking for additional guidance on how to make such trade-offs based on their impact or importance. Although the intent of the TTE framework has never been to provide this guidance, a potential mismatch regarding expectations of the scope of the framework may hamper its adoption.

Although the use of the term ***target trial emulation*** is increasing, practice is not necessarily changing at the same pace. This suggests there may be some misuse of the term, whereas the framework should not just be a reporting checklist, but practice changing. People need to learn to ask the right questions early in the study design phase. It will be a gradual process from understanding what needs to be reported to using the framework to inform the design of studies. Our field, which is generally experienced in setting up and reporting clinical trials, is still learning and further training will be important. Aligning TTE with the setup and reporting of clinical trials could therefore help in bringing the framework to a broader audience. There are ongoing efforts to establish reporting guidelines for TTE.

Further reading
Professor Hernan and colleagues have written several papers that informed this Methods Explained article and provide a great starting point for further reading on the TTE framework.[1,2] These include references to applied examples. Another impactful study for which the TTE framework was utilized concerns the estimation of the effectiveness of a third dose of a COVID-19 vaccine, findings of which were later confirmed by prospective randomized trials.[3]

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We welcome your feedback on this article and any suggestions for methods to be covered in future editions. Send your comments and suggestions to the *Value & Outcomes Spotlight* Editorial Office.

SETTING A NEW PACE:

REAL-WORLD EVIDENCE IS **FINDING ITS FOOTING** IN HEOR

By Beth Fand Incollingo

In 2021, something unprecedented occurred in the pharmaceutical arena—the US Food and Drug Administration (FDA) approved a medication based exclusively on retrospective real-world data (RWD), without any evidence from clinical trials.

Vijoice (alpelisib) had been administered on a compassionate-use basis to patients with severe symptoms of PIK3CA-related overgrowth spectrum, and a study of data from their charts led to the FDA's accelerated approval.[1]

That protocol will be less likely to raise eyebrows in the future, as stakeholders are increasingly basing their healthcare decisions on real-world evidence (RWE), which is generated from routinely collected clinical data, including treatments, prescription patterns, patient behaviors, and healthcare outcomes.

Collected from medical claims databases, electronic health records, wearable health monitors, patient-reported outcomes, and product, patient, and disease registries, RWD and the RWE it generates comprise a growing component of health economics and outcomes research (HEOR) worldwide. RWE is being used to help boost prevention efforts, identify patients who are at risk for illness or eligible for clinical trials, shape clinical guidelines, determine the value of medical interventions, establish reimbursement strategies, expand drug safety testing, create public health policy, and support regulatory reviews.

Compared with the data used in clinical trials, RWD can be collected and studied more quickly and affordably, can more realistically demonstrate usage patterns and health outcomes, and can represent larger and more diverse populations. To help pave the way, regulatory authorities in many countries have created RWE guidelines, and ISPOR is also pursuing initiatives—from hosting summits to promoting transparent study design—with the goal of effectively applying RWE to healthcare decision making.[2] Still, some experts are skeptical about the quality of RWE because nonrandomized studies can leave room for bias or erroneously interpret chance patterns as causal relationships.[2] Stakeholders also grapple with how best to protect patients' privacy when using or sharing their health data. To help pave the way, regulatory authorities in many countries have created RWE guidelines, and ISPOR is also pursuing initiatives—from hosting summits to promoting transparent study design—to effectively apply RWE to healthcare decision making.[2]

"As data become richer and richer, the potential for informing healthcare decisions using real-world evidence will continue to grow," said Mark McClellan, MD, PhD, director of Duke University's private, nonprofit Margolis Institute for Health Policy in Washington, DC, which takes a multidisciplinary approach to developing healthcare-related policy solutions. "What's it's really enabling is more precise, relevant, timely information on questions that matter to patients but are hard to address using traditional clinical trials."

Who's Compiling RWE?
Internationally, databases that track patients' health journeys and fuel retrospective and prospective studies are being hosted by a variety of sponsors, including:

- **Public entities.** The United Kingdom's Clinical Practice Research Datalink has collected data on about 60 million patients from general practitioners and supported more than 3500 peer-reviewed publications, and the *All of Us* program run by America's National Institutes of Health (NIH)—which tracks genomics and health-record information for nearly 850,000 people—has led to 15,000 studies. Meanwhile, the FDA's Sentinel Initiative, sourced from payer records, is collecting data about millions of patients as a means of monitoring medical product safety.
- **Nonprofit efforts.** One example is the Margolis Institute's PCORnet Common Data Model, which is compiling data from US health encounters with more than 47 million people.
- **Public/private collaborations**, such as Canada's effort by GEMINI and ICES, focused on gathering information about patients' health journeys from 35 Ontario hospitals.[3]
- **Private initiatives.** Numerous private organizations, including health insurance companies and consulting firms, are actively engaged in RWD collection and research initiatives. A notable example is IQVIA's real-world database, which encompasses healthcare information on approximately 1.2 billion patients across more than 60 countries. Another prominent example is the Premier Healthcare Database, owned by Premier, a technology-driven healthcare improvement company that collaborates with over two-thirds of US healthcare providers.

"What RWD is really enabling is more precise, relevant, timely information on questions that matter to patients but are hard to address using traditional clinical trials."

– Mark McClellan, MD, PhD

Premier's database is a key example of the kinds of practice-changing breakthroughs that can be generated using RWE from deidentified patients, whose health information can legally be studied if they have consented to care under HIPAA, and without approval from institutional review boards.

The Premier Healthcare Database contains electronic medical records and chargemaster billing data from over 1400 US

hospitals and 300 healthcare systems. Dating back to 2000, it includes time-stamped service records encompassing diagnoses, treatments, medications, devices, demographics, and provider information from approximately 25% of all US inpatient visits and over 40% of all US hospital-based outpatient visits—more than 1.5 billion encounters in all. To enable the longitudinal tracking of individual health journeys, each patient is assigned a unique identifier.[4]

About one-third of participating hospitals contribute laboratory data, helping to define clinical outcomes, and the database also tracks costs and charges, making it possible to estimate the economic burden of specific diseases and procedures, said Ning Rosenthal, MD, PhD, MPH, assistant vice president of applied research at Premier. To get a broader picture of patients' treatment journeys across care settings, she added, information from the Premier Healthcare Database can be tokenized and linked to external sources such as medical and pharmacy claim repositories.

What Can RWE Accomplish?

For providers and payers, Rosenthal said, this database is "a gold mine." Information from Premier's database has fueled more than 1200 peer-reviewed publications, including studies on the cost, effectiveness, safety, and outcomes of interventions across a host of medical specialties.[5]

Stakeholders licensing the Premier Healthcare Database have included US regulatory agencies such as the FDA, Centers for Disease Control and Prevention, and Department of Health and Human Services, as well as private healthcare, pharmaceutical, and medical device companies. And, of course, Premier's experts conduct their own studies.

> "After the 21st Century Cures Act was passed, the FDA was asked by Congress to speed up the drug-approval process by leveraging real-world evidence."
>
> – Ning Rosenthal, MD, PhD, MPH

"Because our database is both large and nationally representative," Rosenthal said, "it can be leveraged to develop predictive models that support earlier diagnosis and treatment decisions by clinicians—ultimately improving patient outcomes."

Rosenthal described a recent real-world study in which investigators developed an algorithm using laboratory data from the database to find over 400,000 patients who had presented to participating health systems with symptoms of chronic kidney disease but never received a diagnosis. Now, Premier is collaborating with hospitals to improve chronic kidney disease diagnosis and follow-up care—a move expected to save not only lives but dollars, as preventable dialysis and hospitalizations tend to be costly in this population.[6]

With its healthcare database, Premier is also boosting clinical study efficiency by enabling the selection of trial sites based on their access to eligible patients, Rosenthal said. Another key use for the healthcare database is in studies supporting drug approval or label expansion.

> Real-world studies have proven to be more streamlined, reducing the path to drug approval from as long as 5 years to just 1 year.
>
> – Xin Sun, PhD

"After the 21st Century Cures Act[7] was passed in the United States in 2016, the FDA was asked by Congress to speed up the drug-approval process by leveraging real-world evidence," Rosenthal said. "Since then, the FDA has released guidelines for conducting studies using real-world data to support regulatory submissions."

That trend made headlines in 2021, due not only to Vijoice's approval but to the use of RWE as primary evidence to support an indication expansion for the drug tacrolimus. In that case, data from an observational study arm—compared against historical controls—supported the drug's indication for the prevention of organ rejection in lung transplants.[8]

Wearable health monitors are another way to collect RWD—a practice common in China, where information about sleep quality, glucose levels, heart rate, and blood pressure can be gathered by the public health system and sometimes used in studies.

But in America, wearable monitor tracking and research are lagging—as is the collection and application of health information pulled from social media. While *All of Us*[9] has fueled studies[10] by collecting Fitbit data from 60,000 patients, Premier has not gathered much information from wearables because a lot of it is proprietary to device vendors, Rosenthal said.

To help the United States catch up, Margolis convened a working group that made protocol recommendations, including creating a research community to publish standards and employing wearables to enroll patients in real-world studies and secure their consent,[11] said Rachele Hendricks-Sturrup, DHSc, MSc, MA, who leads the Institute's RWE Collaborative.

Leading the Way in China

Another key test of RWE is happening in the Boao Lecheng International Medical Tourism Pilot Zone, where initiatives include treating seriously ill patients with interventions that have been approved in other countries, but not yet in China. This enables researchers to track the real-world safety and health outcomes associated with novel products as an alternative path to Chinese regulatory approval.

"For most of these products, no trials will be conducted in China," said Xin Sun, PhD, a professor and director of clinical epidemiology at West China Hospital's Evidence-Based Medicine Center. "This process will be like a bridge, enabling our regulatory authorities to consider trial evidence from other countries along with real-world evidence from the Chinese population."

Compared with clinical trials, Sun said, real-world studies have proven to be more streamlined, reducing the path to drug approval from as long as 5 years to just 1 year.

As of December 2024, 40 products approved in other countries had undergone real-world study in Boao Lecheng, with 17 receiving regulatory approval.[12] However, many of those have not yet been deemed reimbursable, Sun said, as they'll need to accrue more cost-effectiveness data first. Involved in much of that research, Sun's team is also using RWE both inside and outside the pilot zone to conduct post-market studies of treatments already approved in China. The team is also generating RWE to support regulatory applications for herbal medicines, which are heavily used in Chinese clinical practice.

"For investigational herbal treatments," Sun said, "real-world research could eventually take the place of phase II clinical trials."

Overcoming Barriers

In a 5-year plan, Margolis's Collaborative has outlined 4 goals for real-world study: to incorporate reliable and relevant RWE into regulatory decisions, payer evaluations, and routine care while helping to make it transferable across regions and countries.[13]

Yet, accomplishing that will mean overcoming significant barriers, Sun said, including the varying comprehensiveness of RWD across medical specialties and the inability for researchers to follow up with patients when working with deidentified data.

Real-world study design can also raise concerns, Rosenthal said. "In head-to-head studies, the populations treated with drug A and those with drug B can be quite different, since patient characteristics may affect doctors' prescribing patterns," she said. "The good news is that we can use a propensity score method to create a matched sample, along with multivariable regression methods to control known confounders, making real-world studies robust and, in some cases, not inferior to clinical trials."

Margolis aims to support the practice of leveraging observational RWD in causal inference studies in their published white paper,[14] and has conveyed tools that can be used in practice to vet the relevance, reliability, and quality of real-world data,[15] Hendricks-Sturrup said.

Still, other obstacles remain. "Fragmented healthcare and fee-for-service payments, common in the United States, don't lend themselves to reliable longitudinal tracking," McClellan said. "Fortunately, that is changing because of healthcare reforms that focus payments more on patient outcomes."

> "Given that we're dealing with data and technology that can range from being highly regulated to not regulated at all, we have to identify best practices, frameworks, tools, and principles that can guide our decision making."
>
> – Rachele Hendricks-Sturrup, DHSc, MSc, MA

Yet another challenge is that healthcare providers—from hospitals to national healthcare systems—don't often work together to gather RWD, and they typically don't share it with each other. Usually, that's due to differing rules governing ethics and privacy.

To guide the playing field, regulatory authorities including those in the United States, Europe, the United Kingdom, Canada, and China have published guidelines on data quality and relevance, registries, and external control arms. Margolis's Collaborative compiles those guidelines online so it's easier for stakeholders to compare them,[16] Hendricks-Sturrup said.

ISPOR has been supporting such efforts by publishing best-practices documents and hosting summits designed to help standardize RWE methodologies, including one planned for September 2025 that will highlight the Asia-Pacific region and feature Sun as a panelist. ISPOR has also created a tool that helps decision makers evaluate RWE-driven comparative-effectiveness research.

In a combined effort, ISPOR, Margolis, and other partners have created a Real-World Transparency Initiative and a related registry through which scientists can share their study designs to ensure that their tests will follow a prespecified analytic protocol.

"Given that we're dealing with data and technology that can range from being highly regulated to not regulated at all, we have to identify best practices, frameworks, tools, and

principles that can guide our decision making on a case-by-case basis," Hendricks-Sturrup said.

Preparing for Success

Despite challenges to its implementation, RWE is bringing expediency and affordability to healthcare decisions, and that could be especially helpful as new challenges arise—for example, slashed funding for scientific research and healthcare regulation in the United States.[17]

McClellan, who served as former commissioner of both the FDA and the Centers for Medicare & Medicaid Services (CMS), noted that "there's a lot going on at CMS around advancing real-world data interoperability to support better patient-care decisions, such as protocols to slow the progression of diabetes or coronary artery disease."

He added that the FDA can turn to RWE[18] to resolve critical epidemiology questions, such as which subpopulations should be eligible to receive specific vaccines.

For the research community to fully embrace RWE, education about the process will be needed, Sun said.

"In China, we have polarized opinions about real-world evidence, with some people treating it very seriously while others do not," he said. "It all depends on how the evidence is interpreted, and that means that training efforts will be really important."

Sun added that RWE can only have a global impact if communication improves between researchers in high-income countries, who are using the strategy, and those in the developing world, where its applications remain limited. That's my dream," Sun said. "It will be difficult, but filling those gaps is worth doing."

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By the Numbers: Real-World Evidence in Healthcare Decisions

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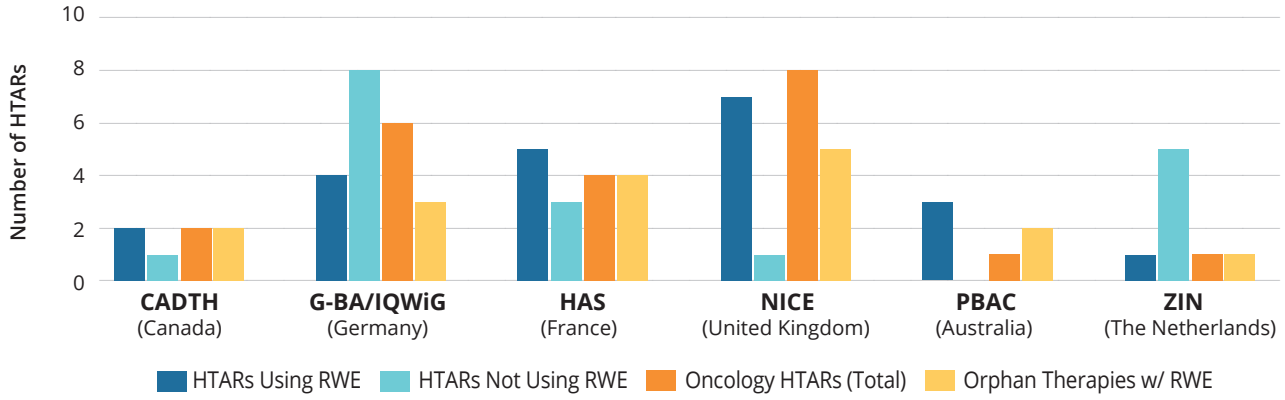
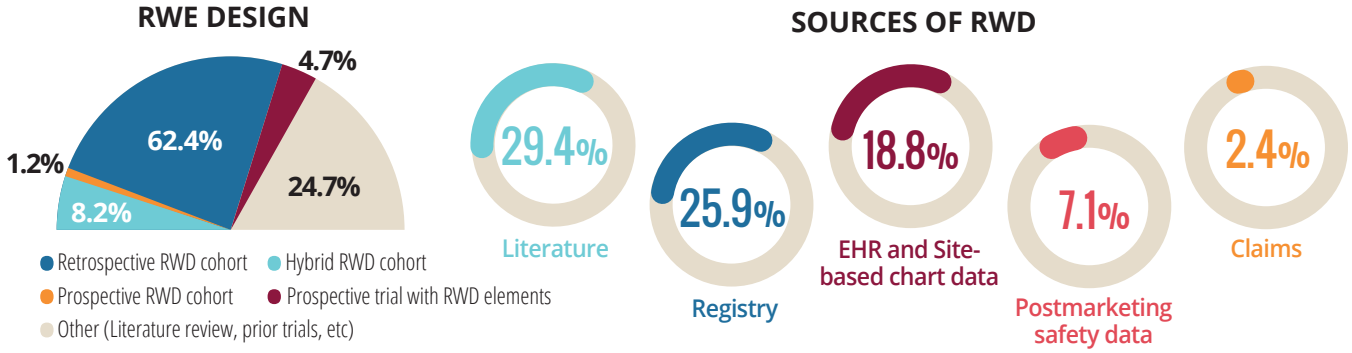
Use of Real-World Evidence in Health Technology Reassessments Across 6 Agencies

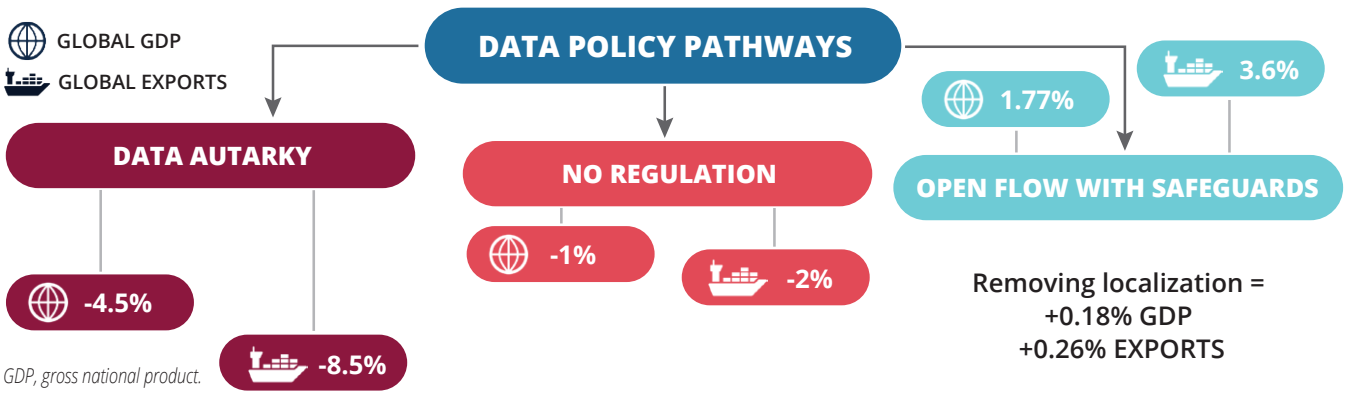


Use of Real-World Evidence in Regulatory Approvals



EHR, electronic health record; RWD, real-world data; RWE, real-world evidence.

Quantifying Economic Impacts of Data Fragmentation and Safeguards



GDP, gross national product.

Dear Health Economics and Outcomes Researcher: It's Time We Had the Transparency Talk

Shirley V. Wang, PhD, MSc, Brigham and Women's Hospital, Harvard Medical School, Boston MA, USA

KEY TAKEAWAYS

One of the most pressing challenges facing both public health and science in general is the growing spread of misinformation.

To combat misinformation and protect the public's trust, we must show our work clearly, honestly, and consistently.

We must make transparency an expectation, applying practices that make our methods understandable, our reasoning clear, and our decisions traceable.

One of the most pressing challenges facing both public health and science in general is the growing spread of misinformation. In an environment where public trust in research is being eroded, simply doing rigorous work is no longer enough. We also need to make that rigor *visible*.

To combat misinformation and protect the public's trust, we must show our work clearly, honestly, and consistently. We must make transparency an expectation.

Transparency isn't just about reproducibility. It's about credibility. But we need to be thoughtful in how we pursue and promote openness. Language around "transparency" and "open science" can be misused or repurposed to question legitimate findings or to apply pressure that undermines—rather than strengthens—scientific integrity. Our goal should not be performative openness, but purposeful transparency: practices that make our methods understandable, our reasoning clear, and our decisions traceable.

Other disciplines such as psychology,[1] economics,[2] and cancer biology[3] research had to stumble very publicly before meaningful changes could begin. Clinical trials had to undergo massive pressure[4] by legislation and journal editors before embracing preregistration and open reporting. But our field remains at the starting line—aware enough to know that we should do better, but still hesitant to make transparency a default.

Transparency doesn't require perfection. It requires intention. We have a rapidly growing set of resources designed to support transparency in our field:

- Protocol registration platforms that are built for real-world evidence (RWE).
- Templates like the HARmonized Protocol template to Enhance Reproducibility[5,6] (HARPER) that bring structure and clarity to our studies.
- Transparency statements[7] that help to tell the full story behind a study. What was planned, what was amended, and what was done.
- Infrastructure for sharing code,[8,9] tools,[10-13] and logic[14] even when data must stay private.

I would argue that in our field, the challenge isn't a lack of tools. It is integrating them into our everyday work. But culture change doesn't come from toolkits or templates. It starts with people.

> In an environment where public trust in research is being eroded, simply doing rigorous work is no longer enough. We also need to make that rigor *visible*.

Change can begin with small, deliberate choices made by you and me. And when each of us commits to clarity and openness, the whole research community moves forward together. But if we wait for the perfect conditions to get started, we never will. The time to start building better habits is now.

What counts as "doing transparency right" today?

1. Preregistering protocols. Whether it's the Open Science Frameworl-hosted Real-World Evidence (RWE) Registry (https://osf.io/registries/rwe/), the Heads of Medicines Agencies-European Medicines Agency Catalogue (https://catalogues.ema.europa.eu/), or ClinicalTrials.gov, the point isn't which platform, it's that you're using one. Preregistration doesn't mean your study is locked in stone. It simply creates a transparent, traceable starting point. We all know that data can lead us in new directions. Amendments are not only acceptable—they are expected. The key is to document those changes so that others can follow your reasoning as clearly as your results.

2. Using templates that make rigor visible. HARPER[5,6] is a deliverable of a joint task force between ISPE and ISPOR that is now endorsed by global organizations such as International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use,[15] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance,[16] Council for International Organizations of Medical Sciences,[17] National Institute for Health and Care Excellence,[18] and Centers for Medicaid & Medicare Services.[19] Protocol templates such as HARPER aren't just templates, they are thinking tools. They encourage clear articulation of study decisions, estimands, potential biases, and assessment of data quality.
3. Making analyses reproducible even without sharing data. We know patient privacy and data use agreements make sharing raw data tricky. But you can still share clearly annotated and documented analytic code, synthetic data, diagnostics, and workflow logic. Transparency isn't all-or-nothing. Just be sure to avoid dumping disorganized spaghetti scripts and cryptic outputs. Usability is what makes sharing valuable.
4. Proudly declaring your transparency efforts. The new transparency statement framework[7] makes this easier: What did you register? What's open? Where can people find it? Even if parts of your study can't be open, you can still make your process visible.

What stands in the way?
It's not a lack of awareness. Most of us know that transparency is important. The real barriers are inertia and hesitation. The feeling that this is yet another step in a process that already takes considerable time and effort, the fear of being scooped, losing a competitive edge, or the discomfort of committing too early.

Yes, it can feel like more work up front. But that investment pays off. When you start with a clear, transparent protocol, you reduce confusion later. You streamline analysis, facilitate cleaner documentation, and make peer review smoother by minimizing ambiguity and making it easier to retrace your own steps weeks or months later.

Transparency isn't just good science; it's good project management. It also makes life easier for your team. Clear protocols and documented decisions mean fewer misunderstandings, less rework, and easier onboarding for collaborators.

> Our field remains at the starting line—aware enough to know that we should do better, but still hesitant to make transparency a default. Transparency doesn't require perfection. It requires intention.

And for your future self? It's a gift. When you revisit a study 6 months later (or have to explain it to a reviewer or regulator), you'll be glad that everything was clearly laid out from the start.

What if we flipped the perspective?
What if preregistration and transparency weren't extra burdens—instead they were protective measures? What if sharing your study protocol upfront actually strengthened your credibility? What if transparency stopped being viewed as an added burden and started being valued as evidence of a rigorous and well-planned process?

Concrete steps, collective momentum
If you're an early career researcher? Start here.

- Preregister your next protocol. The platform matters less than the act itself.
- Use the HARPER[5,6] template. Even if your funder doesn't require it, your future self will thank you.
- Include a transparency statement in your next manuscript. Even partial openness is valuable.

If you're a supervisor, journal editor, or policy maker?

Your example speaks louder than any checklist. Model transparency. Be the first to register. Reward transparency in peer review. Ask about reproducibility at the next team meeting. Help normalize the behavior that we all say we value.

Institutional support is growing
The good news is that momentum is building. ISPOR—The Professional Society for Health Economics and Outcomes Research—and the International Society for Pharmacoepidemiology have established joint task forces focused on transparency and reproducibility in RWE. The society journals *Value in Health* and *Pharmacoepidemiology and Drug Safety* have revised author submission guidance to strongly encourage transparency statements.

These badges are more than symbolic. They send a clear message that open, reproducible research is not only encouraged but celebrated. And as more institutions and communities begin to recognize and celebrate open science practices, that recognition will become a powerful driver of change—helping to shift transparency from an individual choice to a shared expectation.

Building a culture of transparency is a team effort.
I encourage you to join the movement and proudly display the open science practices you have used in your next study. Let's do this together. One study, one protocol, one statement at a time.

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Assessing the Impact of the National Institute for Health and Care Excellence's Real-World Evidence Framework on Health Technology Assessments

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KEY TAKEAWAYS

This research aimed to assess the impact of the National Institute for Health and Care Excellence's real-world evidence (RWE) framework on the use of RWE to inform the clinical effectiveness of interventions assessed in the technology appraisal (TA) program within the first 18 months of implementation.

RWE is included in oncology TAs more frequently than TAs in any other disease area, particularly through use of the Cancer Drugs Fund (CDF). Following introduction of the RWE framework, the use of RWE from non-CDF sources increased from 40% to 78% of the reviewed oncology TAs.

Overall, the implementation of the framework had minimal impact on the inclusion of RWE in HTAs; however, a longer time frame may be required.

Introduction

Real-world evidence (RWE) is generated from healthcare data collected outside the context of randomized controlled trials (RCTs).[1] Sources of RWE can include electronic health records, registries, claims/billing data, digital wearables, and even social media.[2] RWE can optimize and complement the design of RCTs by extending data collection and reducing financial burden and risk and by providing more generalizable insights into the safety, usage, and effectiveness of medicinal interventions in real-world settings. RWE can be particularly useful in instances where there is insufficient clinical trial data to demonstrate the value of an intervention at the time of reimbursement decision.[3,4] However, there are several concerns regarding the use of RWE in Health Technology Assessment (HTA), including potential increased bias and poorer methodological quality.[2]

> There are several concerns regarding the use of RWE in HTA, including potential increased bias and poorer methodological quality.

To combat this, payers worldwide have implemented frameworks to improve understanding and enhance the quality of RWE, including England's National Institute for Health and Care Excellence (NICE), who introduced their RWE framework on June 23, 2022.[1] This framework aimed to improve the quality of RWE used in decision making and help identify where RWE can reduce uncertainties.[1]

This article reviewed the use of RWE in NICE technology appraisals (TAs) in the 18 months pre- and postimplementation of the NICE RWE framework. TAs published on the NICE website between January 1, 2021 and January 1, 2024 were identified and categorized as being pre- (01.01.2021–23.06.2022) or postframework (24.06.2022–01.01.2024). If the clinical section of the TA included RWE, details of the NICE recommendation, disease area, study type (observational, retrospective, etc), study location, and reasons for inclusion were recorded. TAs were excluded if they had been terminated or if they were treatment guideline updates from TAs originally published more than 5 years ago. The outcomes of TAs include the following possibilities: the drug may be recommended for use, not recommended for use, or, in the case of oncology products, NICE may opt for an additional decision pathway by recommending the drug for use within the Cancer Drugs Fund (CDF; a managed access agreement requiring further RWE collection to address clinical uncertainty).[5] It was also noted whether the RWE included in the TA was used as the main source of evidence or as supporting evidence. RWE was defined as main evidence if it was mentioned in the final NICE guidance as a key evidence source for decision making and as supporting evidence when it was either mentioned elsewhere in the NICE guidance or only included in the committee paper(s). In cases where multiple sources of RWE were used, these parameters were recorded for each source of RWE within the TA.

Use of RWE within NICE TAs pre- and postimplementation of the RWE framework

In the 18 months preimplementation of the RWE framework, 103 TAs were published, and 108 TAs were published postimplementation. RWE was used to inform clinical effectiveness in 27% (28/103) of TAs preframework, and in 31% (33/108) postframework, representing a slight increase in RWE use postframework.

RWE use in TAs by disease category

TAs for oncology products utilized RWE more frequently than TAs for nononcology products preframework

(oncology versus nononcology; 20 [71%] versus 8 [29%]) and postframework (oncology versus nononcology; 18 [55%] versus 15 [45%]). Oncology TAs were further categorized based on whether they used RWE from the CDF, such as the Systemic Anti-Cancer Therapy (SACT; a database of all disease-modifying cancer treatments delivered by National Health Service [NHS] England providers[6]) dataset (**Figure 1**). The proportion of oncology TAs using the CDF SACT dataset substantially decreased pre- to post-framework, from 60% (12/20) to 22% (6/18). However, there was also a slight decrease in the number of oncology TAs using RWE overall. Key nononcology disease areas utilizing RWE included cardiovascular, autoimmune, respiratory, and kidney diseases (**Figure 1**).

RWE study types utilized in TA submissions

Across all disease categories, the types of RWE used in TA submissions pre- and postintroduction of the framework included the CDF SACT (43% [12/28] versus 18% [6/33]), retrospective studies (14% [4/28] versus 30% [10/33]), other registries (11% [3/28] versus 15% [5/33]) and other observational studies (32% [9/28] versus 36% [12/33]); eg, non-interventional and prospective studies; **Figure 2**). The use of the CDF dataset decreased postframework, while the use of RWE from other sources all appeared to increase, particularly retrospective studies. This may indicate a shift in the types of real-world studies used following publication of the NICE RWE framework.

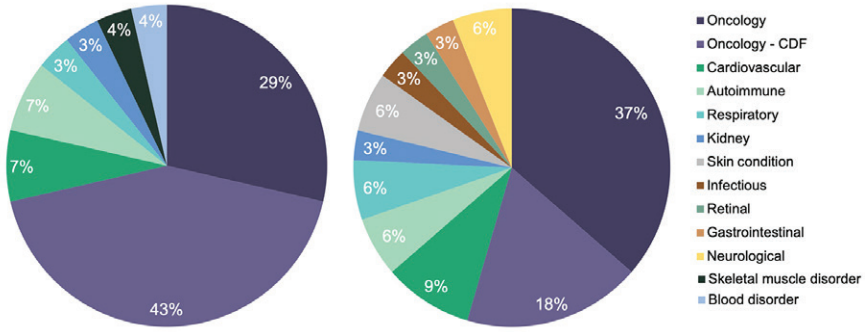
How prominently is RWE used to support TA evidence submission

Of the 61 TAs that included RWE, approximately two-thirds (64% [39/61]) used RWE as a main source of evidence. While RWE was utilized as a main source of evidence both pre- and post-framework, the proportion decreased postframework (pre-framework 71% [20/28] versus postframework 58% [19/33]; **Figure 3**).

Reasons for inclusion of RWE in TAs

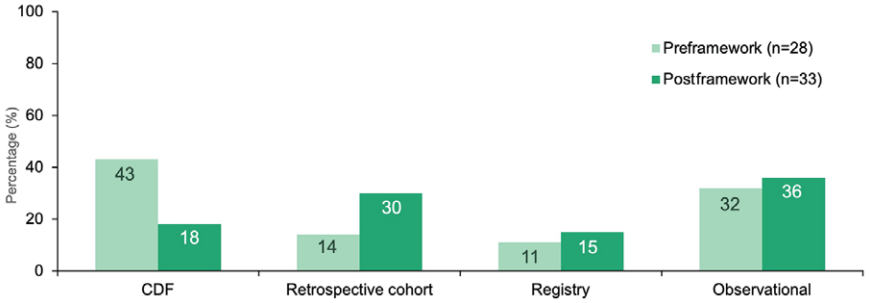
In this analysis, the most common reasons for RWE inclusion both pre- and postframework were to inform indirect treatment comparisons (ITCs; 39% versus 46%) and to demonstrate generalizability of the evidence to NHS clinical practice (29% versus 31%; **Figure 4**). Often the

Figure 1. NICE TAs including RWE published pre- and postimplementation of the NICE RWE framework, by TA disease category



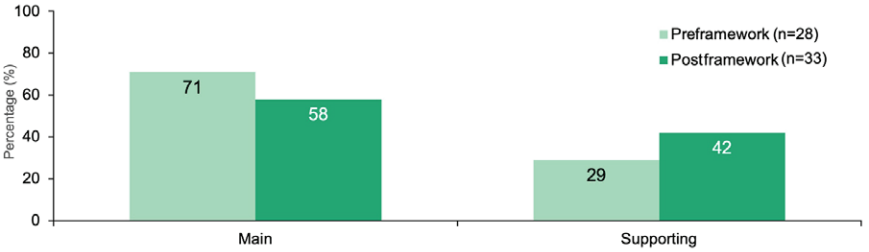
CDF, Cancer Drugs Fund; NICE, National Institute for Health and Care Excellence; RWE, real-world evidence; TA, technology appraisal.

Figure 2. Proportion of NICE TAs including RWE published pre- and post-implementation of the NICE RWE framework, by study type



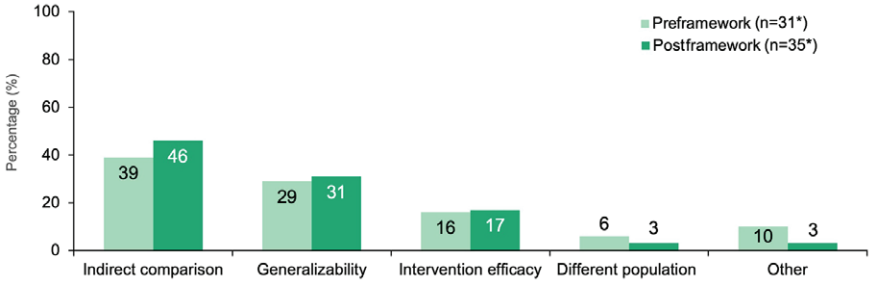
CDF, Cancer Drugs Fund; NICE, National Institute for Health and Care Excellence; RWE, real-world evidence; TAs technology appraisals.

Figure 3. NICE TAs including RWE published pre- and postimplementation of the NICE RWE framework, by whether the RWE comprised the main or supporting evidence



CDF, Cancer Drugs Fund; NICE, National Institute for Health and Care Excellence; RWE, real-world evidence; TAs technology appraisals. RWE was defined as main evidence when it was mentioned in the final NICE guidance as a key evidence source for decision making and supporting evidence when it was either mentioned elsewhere in the NICE guidance or only included in the committee paper(s).

Figure 4. NICE TAs including RWE published pre- and post-implementation of the NICE RWE framework, by reason for inclusion



NICE, National Institute for Health and Care Excellence; RWE, real-world evidence; TA, technology appraisal.
**Some TAs used more than one source of RWE.*

SACT database was used to demonstrate generalizability to clinical practice in oncology drugs. Lack of generalizability on the use of a health technology in the NHS is often a key limitation in TAs.

Other reasons for the inclusion of RWE were to provide further evidence for intervention efficacy (16% versus 17%) and to address differences in populations (6% versus 3%; ie, where there are differences in characteristics between the main trial population and the target population of the TA submission). Examples include the use of phenylketonuria registries to provide evidence for the sustained and durable efficacy of a drug to treat hyperphenylalaninemia beyond the length of the RCTs (TA729),[7] and the use of RWE studies to demonstrate the efficacy of an asthma intervention in a subpopulation for which the RCTs did not provide sufficient evidence (TA751).[8]

> While the NICE framework provides a structured approach to incorporating RWE into technology appraisals, challenges remain surrounding the lack of clear thresholds for evidence acceptability or suitability.

The formation of ITCs remained the most common use of RWE both pre- and post-framework. This likely reflects the use of ITCs to create comparisons where trial comparators did not reflect the current NHS standard of care and in cases of single-arm trials.

Conclusions

Overall, TAs for oncology products included RWE more frequently than any other disease area (62% compared with 8% for cardiovascular, 7% autoimmune, etc). Challenges associated with conducting RCTs in rarer tumor types, regional discrepancies in the standard of care, and the availability of RWE sources, including the CDF SACT dataset, may be drivers for this.[9,10] A contractual requirement of CDF funding includes the submission of treatment activity to the SACT dataset, so RWE data is available and included in the resubmission.[11]

In the future, the proportion of non-oncology TAs using RWE may increase due to the introduction of the Innovative Medicines Fund (IMF), a second NICE-managed access option. Building on the success of the CDF, the IMF aims to support access to nononcology drugs through collecting data needed to address uncertainty in their evidence base.[12] One of the key principles of the IMF is to ensure there is equal access to the latest medicines for both patients who have cancer and those who do not have cancer.[13]

While the NICE RWE framework provides a structured approach to incorporating RWE into TAs, including offering guidance on study design, data quality, and methodological rigor, challenges remain surrounding the lack of clear thresholds for evidence acceptability or suitability. To increase the use of acceptable RWE in future, NICE could develop more robust standards for RWE use; ensure alignment of the framework with regulatory agencies, including the Medicines and Healthcare Products Regulatory Agency; and offer early engagement opportunities with developers. Consequently, developers could proactively integrate RWE studies into their evidence generation plans.

In conclusion, while there were variations in the type of study and the disease areas using RWE for TA submissions, the overall use of RWE has remained consistent since the implementation of the RWE framework. A longer timeframe is likely needed to assess the true impact of the framework on the use of RWE. It is possible that many of the TAs in this review were designed prior to the introduction of the framework and in the future, and we may see more RWE specifically designed to meet framework requirements.

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Fit-for-Purpose Real-World Data: An Integral Component of Evidence Planning

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KEY TAKEAWAYS

The evidence generation landscape has been rapidly evolving with the emergence of diverse and novel real-world data sources in recent years.

Insurance claims continue to be a cornerstone of real-world evidence generation. However, differences between closed and open claims must be thoroughly evaluated when selecting fit-for-purpose real-world data.

Electronic health records, registries, genomic/biomarker data, patient-generated data (including wearables, mobile apps, surveys, and patient-reported outcomes [PRO] measures), and social determinants of health data could be used independently or merged with other available data sources to provide a more holistic view of patients and/or the healthcare system.

Introduction

Integrated evidence planning in pharmaceutical/biotechnology companies is a holistic plan developed and implemented to ensure that evidence generation is aligned with regulatory, clinical, and commercial objectives throughout the product lifecycle.[1] In recent years, real-world evidence (RWE) has emerged as a crucial element in integrated evidence planning. Regulatory bodies are increasingly accepting findings from RWE studies to support the safety, efficacy, and value of pharmaceutical/biotech products beyond traditional clinical trials.[2-4] And evidence required by downstream stakeholders such as payers, policy makers, healthcare providers, and patients is being planned and sometimes even generated at early development stages.

> Regulatory bodies are increasingly accepting findings from RWE studies to support the safety, efficacy, and value of pharmaceutical/biotech products beyond traditional clinical trials.

At the same time, evolution of the healthcare and technology landscape has expanded the diverse and novel real-world data (RWD) sources, from claims (open and closed), electronic health records (EHRs) (structured and unstructured), registries to linked data from wearable devices, mobile health apps, genomic data, social determinants of health, and patient-reported outcomes collected via digital platforms. An example of evolution with respect to EHRs is increased digitization of patient records as well as global adoption of Fast Healthcare Interoperability Resources standards allowing healthcare data to be shared across health systems to enable automated decision support and other machine-based processing.[2] While emerging data sources offer richer, more granular insights into patient health and treatment effects, they also introduce significant complexity in assessing fit-for-purpose RWD that are reliable, relevant, and robust enough to answer specific research or regulatory questions. This paper evaluates key RWD sources and explores critical factors involved in identifying the appropriate RWD source to generate RWE.

Sources of RWD

Health insurance claims

Insurance claims data have long been a cornerstone of RWE generation in the pharmaceutical and biotech industry. There are 2 types of claims data: closed and open.

Closed Claims

Closed claims are sourced directly from payers or health plans. Open claims are sourced from practice management systems, clearinghouses, or other information systems. Closed claims capture all healthcare interactions for a patient reimbursed by a specific payer. Claims derived from a closed source are fully adjudicated; they contain limited to no duplicate claims and costs represent the final approved amount. However, the adjudication process results in a lag of approximately 3 to 6 months from submission to data acquisition. These data allow patients to be followed longitudinally for as long as they remain eligible for insurance. If a patient changes insurers, they will be lost to follow-up. This is common in the US healthcare system, where insurance is often provided by employers. The average duration of follow-up for patients in the United States is approximately 3 years.

Closed claims are beneficial when the research objective requires a patient to be evaluated over time and across healthcare settings, including outcomes such as treatment patterns, adherence, persistence, healthcare utilization, and costs. However, closed claims may have limited longitudinal follow-up due to shorter periods of enrollment with an insurer and studies requiring longer time tracking of >3 years (including

identification, index/baseline period, and follow-up periods) will face issues of reduced sample sizes with increasing study time. Data lags in closed claims also mean that more recent events are not reflected in the data and data extraction for a study will have to be timed accordingly. The data may also be biased towards enrollment characteristics of included health plans and, therefore, an assessment of representativeness and generalizability for a specific use case may be required.

Open Claims

Open claims capture only those claims that are processed through the specified practice management system, which may be limited to a subset of providers or practices. Open claims are nonadjudicated and are pending processing and review or payment. These claims may contain duplicates, and final payments may be missing or misrepresented. However, open claims are available 1 to 2 days after submission.

Due to very short time lags, open claims are valuable for evaluating early access market performance and when coverage across multiple payers is warranted. Open claims databases are also significantly larger and more nationally representative. Although caution must be used since open claims are nonadjudicated and advanced analytical expertise may be required to obtain valid insights.

It is important to note that both open and closed claims do not contain detailed clinical information, including but not limited to lab results and reasons for treatment discontinuation. In addition, utilization of over-the-counter medications and other healthcare services provided but not processed through the insurance will not be captured. Thus, claims data may not be appropriate for addressing clinical research questions.

Electronic Health Records

Clinical research questions may best be addressed using EHRs. EHRs contain detailed clinical information recorded by healthcare providers, such as diagnoses, medications, lab results, vital signs, and clinical notes. Data in an EHR may be structured or unstructured.

Structured Data

Structured data refers to information that is predefined, organized, and stored in fixed fields, including diagnosis codes, procedure codes, medication lists, laboratory values, vital signs, and demographics.

> Not all RWD are created equally. Selecting the right data source is a critical component of integrated evidence planning.

Structured data from EHRs are readily available and valuable for studies where healthcare provider-reported clinical variables are required. Patients can be followed longitudinally within the practice and outcomes such as disease progression can be assessed. However, patients receiving care from different providers and practices, not included in the EHRs, may lead to fragmentation of data. Harmonization of data across different EHR vendors may be challenging and quality and completeness may vary across vendors. It is important to evaluate the variables available and completeness of each of the variables before selecting the appropriate EHR to meet the research objectives.

Unstructured Data

Unstructured data (eg, physician notes, progress reports, and radiology reports) refers to free-text data which are not stored in predefined fields and requires natural language processing or manual review to extract insights.

Unstructured EHR data are valuable when additional clinical data are needed to supplement the data available in the structured EHR.

Specificity and sensitivity of methods used to extract clinical variables from unstructured data may vary. Manual extract by a single data abstractor allows for consistency and continuity but is very time-consuming. The emergence of front-end analytical platforms is allowing for more timely abstraction and analytical flexibility; however, data quality may be compromised in favor of simplicity and efficiency.

Patient registries

Registries are organized systems that collect data on patients with a specific disease, condition, or treatment exposure over time. These may be industry-sponsored, academic, or provider-led. Registries often provide the richest clinical data for a specific population of interest. Data may include detailed clinical assessment, biomarkers, labs, patient-reported outcomes, and long-term follow-up.

These data are best used when evaluating a complex or rare disease that requires more detailed clinical information than provided within an EHR, when the population in an EHR is too small to evaluate, or when the follow-up period in an EHR is too short to evaluate the outcomes of interest. Recruitment techniques, coverage, and minimal required datasets may determine the representativeness, generalizability, and completeness of a registry. Minimal required datasets, where applicable, usually mandate diagnosis and key demographic information and may be sufficient for incidence/prevalence analyses but outcomes and follow-up data may suffer large lags and/or missingness. In many cases, registries are managed by academia, and data access may require specific governance criteria or collaborative academic arrangements.

Other data sources

In addition to claims, EHRs, and registries, there is a growing list of data sources available for research that could be used independently or merged with other available data sources to provide a more holistic view of patients and/or the healthcare system. These include but are not limited to genomic/biomarker data, patient-generated data (including wearables, mobile apps, surveys, and patient-reported outcome measures), and social determinants of health.

Genomic/biomarker data are often obtained through genomic and genetic testing and allow researchers to evaluate genetic markers that may influence disease progression and/or treatment effectiveness. Patient data from wearables and mobile apps generate large-scale continuous data generation across various measures. The measures vary significantly by app

Table. Data Characteristics and Use Cases

Data Source	Strengths	Limitations	Use Cases
Claims – Closed Source	• Longitudinal follow-up • All medical/pharmacy claims during a specified period • Fully adjudicated claims • Actual approved costs	• Lag time ~3 to 6 months • Follow-up limited by duration of eligibility • No clinical details (labs, reason for discontinuation)	• Treatment patterns • Adherence/persistent • Healthcare utilization • Costs
Claims – Open Source	• No lag time • Large sample size • Often times, nationally representative • Capture claims not covered by insurance; cash, discount cards	• Does not represent all claims for a patient only those processed through the specified practice management system • Claims are not adjudicated • Duplicate claims may exist • Final payments may be missing or misrepresented • No clinical details (labs, reason for discontinuation)	• Early access market performance • Healthcare utilization during a visit • Cost of visit
EHR - Structured	• Rich clinical data • Predefined and easily quantifiable • Readily available	• Data quality and completeness vary across vendors • Challenges in harmonizing data across vendors	• Clinical characteristics/ vitals/laboratory results • Overall survival • Treatment patterns
EHR - Unstructured	• Richer source of clinical data • Variables can be defined and abstracted as needed for each unique study	• Ambiguous • Requires manual extraction or advanced techniques such as natural language processing or machine learning • Time consuming to curate	• Disease progression • Overall survival • Treatment patterns • Reason(s) for treatment discontinuation/switching • Adverse events
Patient Registry	• Richest source of clinical data for a specified population	• Representativeness of the population may be limited depending upon recruitment techniques • Incomplete or missing data • Access may be limited due to privacy and data governance guidelines	• Clinical characteristics of complex or rare diseases when the population in an EHR is too small or follow-up period too short
Genomic/Biomarker Data	• Identify and stratify subpopulations	• Representativeness of the population • Limited overlap with claims/EHR/registry data to provide value	• Merged with other data sources to evaluate genetic markers influence on disease progression and/or treatment effectiveness
Patient Generated Data	• Provide patient insights	• Measures vary by app • Frequency of measures vary by user • Subject to patients recall • Representativeness of the population may be limited • Limited overlap with claims/EHR/registry data to provide value	• Merged with other data sources to evaluate treatment preferences and perceived outcomes
Social Determinants of Health	• Factors outside of the typical healthcare setting that may influence treatment and outcomes	• Incomplete or missing data • Limited overlap with claims/EHR/registry data to provide value	• Merged with other data sources to evaluate disparities in healthcare utilization and outcomes

EHR, electronic health record.

and the frequency of measurements varies across users. Surveys and patient-reported outcomes are data collected directly from patients on their health status, preferences, and satisfaction. These measures may come from both validated and unvalidated instruments and are subject to a patient's recall ability. Finally, social determinants of health data (eg, race/ethnicity, income, access to transport) are increasingly being used to understand disparities in access to care and downstream outcomes. Researchers should be aware of and address the limitations of using such data at an aggregate- (eg, county-level) versus patient-level.

Determining if the RWD are fit-for-purpose?

Not all RWD are created equally. Selecting the right data source is a critical component of integrated evidence planning. To generate credible, actionable, and regulatory-grade RWE, it is important to ensure that the RWD are fit-for-purpose. Understanding the differences between data types will help researchers determine the appropriateness of the data to address their research question (see **Table**). Further guidance can be obtained from multiple regulatory and scientific organizations that have released frameworks and guidance documents to help stakeholders assess the fitness of RWD.[3-6] In many cases, a more detailed and targeted fit-for-purpose assessment may have to be conducted by independent experts to match a research question with the best available data source.

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Squaring the Circle? Leveraging Early Access/Compassionate Use Pathways to Provide Market-Specific Real-World Evidence Before Launch

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KEY TAKEAWAYS

Real-world evidence can address clinical trial limitations by demonstrating how a healthcare technology works in the real world, but it is typically generated postlaunch/reimbursement; thus, it may have limited utility for reimbursement bodies making their decisions at launch.

We show how early access programs, which enable patients to access therapies before marketing authorization, have been leveraged to generate country-specific real-world effectiveness data prelaunch and therefore support reimbursement decision making.

The RWE conundrum for payers—great but too late?

Real-world evidence (RWE) is becoming an important focus area in addressing clinical trial data limitations. By leveraging RWE, manufacturers can demonstrate reproducibility of trial data in the clinical setting and alleviate potential safety and tolerability concerns. However, RWE demonstrating the effectiveness of a new therapy can typically only be generated once the product has been authorized. When it comes to reimbursement decisions, however, payers want to see product-specific RWE at launch to inform their decision making.

Could early access programs solve this RWE conundrum?

Early access or compassionate use programs (EAPs or CUPs) provide the opportunity for patients to access therapies prior to marketing authorization under certain criteria. This then allows manufacturers to generate RWE for a product in that market prior to its launch. This article aims to provide an overview of the available EAPs in 6 major European countries (Germany, France, Italy, Spain, the United Kingdom, and The Netherlands) and provide case studies of how EAP-generated clinical effectiveness RWE has been leveraged by manufacturers in HTA assessments to further substantiate their drug's evidence package.

What EAPs exist and how do they vary?

All major European countries offer EAPs through varying schemes. While some markets offer a single access pathway like Germany, Spain, and the United Kingdom, others offer multiple (France, Italy, and The Netherlands). **Figure 1** outlines the available EAPs in the 6 major European markets.

As seen in **Figure 1**, the available EAP schemes vary per country, both in terms of which stakeholder (ie, physicians, manufacturers, or others) can initiate them and on whether they provide reimbursement incentives to manufacturers that partake in such schemes. Typically, applications can

Figure 1. Overview of EAPs/CUPs in Germany, France, Italy, Spain, the United Kingdom, and The Netherlands

Country	Agency	Scheme	Initiated by	Product reimbursed?
	BfarM/PEI	Ordinance on Medicinal Products for Compassionate Use (AHMV)	Manufacturer	No
	HAS	Early Access Authorization (AAP)	Manufacturer	Yes
	ANSM	Compassionate Use Authorization (AAC)	Physician	
		Compassionate Use Framework (CPC)	Ministry of Health	
	AIFA	Law 648/1996	Physician	Yes
		Compassionate Use (Law 94/98)		No
		AIFA National Fund (Law 326)		Yes
	AEMPS	Royal Decree 1015/2009	Physician	Generally No
	MHRA	Early Access to Medicines Scheme (EAMS)	Manufacturer	No
	IGJ	Named Patient Program	Physician	Generally No
	CBG/MEB	Compassionate Use Program	Manufacturer	

Abbreviations: AEMPS, Spanish Agency of Medicines and Medical Products; AIFA, Italian Medicines Agency; ANSM, National Agency for the Safety of Medicines and Health Products; BfarM, Federal Institute for Drugs and Medical Devices; CBG, Medicines Evaluation Board; CUP, compassionate use program; EAP, early access program; HAS, French National Authority for Health; IGJ, Health and Youth Care Inspectorate; MEB, Medicines Evaluation Board; MHRA, Medicines and Healthcare products Regulatory Agency; PEI, Paul-Ehlrich Institute.

be made by either physicians or manufacturers although for some (eg, Spain) it is physician-initiation only. The overall cost of EAPs depends on reimbursement incentives provided, which vary among the countries examined. In 2/6 countries (France and Italy), full reimbursement is offered (although in Italy this is only in select programs). In another 2/6 countries (Spain and The Netherlands), reimbursement is only offered in select cases. Finally, in 2/6 countries (Germany and the United Kingdom), manufacturers must provide their treatments at zero cost. Nonetheless, these avenues provide an opportunity both for patients to access potentially life-saving medication early and for manufacturers to collect product-specific RWE outcomes prior to launch for reimbursement stakeholders.

Case studies—leveraging RWE from EAPs

To further examine the utility and potential limitations associated with leveraging RWE from EAPs to support HTAs, we identified 2 case studies on 2 different therapies that have done this in France and the United Kingdom, asciminib and dupilumab, respectively. **Figure 2** provides an overview of the aforementioned drugs, along with their respective indications and the early access schemes utilized.

Case study 1: Dupilumab *(Dupixent)*—RWE from EAPs moving the needle?

Dupilumab was granted early access via early access to medication scheme (EAMS) in March 2017[1] prior to its European Medicines Agency (EMA) approval in September 2017.[2] It was initially appraised by the National Institute of Health and Care Excellence (NICE) in early 2018, with the initial draft guidance released on March of that year not recommending the drug on the grounds of cost-effectiveness and non-acceptable use of National Health Service (NHS) resources.[3] In the subsequent consultation, supporting follow-up RWE data from the EAMS cohort were submitted, showcasing that dupilumab achieved the primary endpoint at a comparable rate in the United Kingdom's clinical practice as in both its registrational trials.[4] The supporting EAMS data also demonstrated the high unmet need for the indication, with 244 patients enrolling in the scheme in a 6-month period. Discontinuation rates were also included, which were on par with the clinical trial findings, helping support the company's base case model. Finally, both clinicians and patients commented on the use of dupilumab via EAMS, highlighting the clinical benefits of the drug and its impact in their practice and day-to-day life, respectively. Following the final appraisal consultation, NICE overturned its initial decision, recommending dupilumab for its intended indication in August 2018.[5]

Case study 2: Asciminib *(Scemblix)*— Showcasing limitations in RWE from EAPs?

In France, asciminib was granted early access authorization for Ph+ CML-CP via the AAP scheme in April 2022,[6] with its EMA approval following in August 2022.[7] Data collected from the EAP were submitted for the subsequent HTA evaluation of the same indication in November 2022.[8] These included information on the total number of patients that received asciminib via the AAP scheme, their dosage regime, total treatment duration, complete hematological and cytogenic response rate, and adverse event cases, including treatment discontinuations. While the RWE collected from the EAP was included in the Haute Autorité De Santé (HAS) report, it was supplementary in nature, with clear emphasis given to the pivotal trial data for the committee's decision. The drug was eventually granted an SMR important and ASMR IV rating based on the clinical trial evidence submitted.

Lessons learned and future research

The overall outcomes of these 2 case studies demonstrate the unique opportunity EAP schemes offer to manufacturers in terms of RWE collection prior to reimbursement decisions.

> Early access or compassionate use programs provide the opportunity for patients to access therapies prior to marketing authorization under certain criteria.

Manufacturers can demonstrate their drugs' effectiveness, safety, and, moreover, the reproducibility of the pivotal trial in clinical practice. The overall impact of EAP-collected RWE may vary, however, as HTA authorities use their respective methodologies in the overall hierarchy and assessment of such supporting evidence. In the case of asciminib, the manufacturer was able to utilize RWE as supplementary evidence to the drug's clinical trial data. While the HAS report specifically mentioned the RWE collected, there was no further commentary on how these data were perceived or their overall influence in the reimbursement decision. On the contrary, the RWE submitted via the EAMS scheme in the United Kingdom was potentially key in overturning NICE's initial reimbursement decision on dupilumab, as observed in the committee discussion commentary. The EAMS data allowed the manufacturer to both demonstrate to NICE the high unmet need of the indication and support the base case economic model. It is therefore apparent that RWE collected via EAPs can help support a drug's value proposition, even if such evidence is qualitative in nature.

Figure 2. Overview of EAP-enabled RWE collection case studies

Drug	Country	Indication assessed	EAP utilized
Asciminib *(Scemblix)*		Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) previously treated with two or more tyrosine kinase inhibitors	AAP *(Early Access Authorization)*
Dupilumab *(Dupixent)*		Moderate to severe atopic dermatitis in adults who are candidates for systemic therapy	EAMS *(Early Access to Medicines Scheme)*

EAP, early access program; RWE, real-world evidence.

Differing perceptions of RWE highlight a key limitation in utilizing such evidence across markets that offer EAP opportunities. This may, however, change in the future as reimbursement authorities re-examine their assessment methodologies and the importance of RWE in evidence submissions. An additional challenge or barrier to this approach is the lack of reimbursement incentives, which may deter manufacturers from initiating such schemes. The observations of this article were also limited to patients with severe conditions, because EAPs are primarily offered to these patient populations. EAP methodology approaches may also pose difficulties in collecting efficacy data as they are not typically set up for this purpose. Nonetheless, the case studies presented provide an insight into the RWE opportunities that EAPs provide to generate data to support patient access. Further analysis of the impact of such evidence-collection opportunities and the differences in reimbursement outcomes of both EAP-enrolled and non–EAP-enrolled drugs will potentially provide further insights on the importance of utilizing such schemes to address clinical trial limitations and help ensure that patients can access therapies that they need.

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Expert Elicitation Techniques: Informing Application in Health Technology Assessment Decision Making

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KEY TAKEAWAYS

An inevitable level of uncertainty is present in health technology assessment (HTA) due to the intricacies associated with complex products, innovative technologies, and accelerated approval pathways, which can impact HTA decision-making and subsequently patient access to therapies.

Expert elicitation, when applied using best practices, helps reduce this uncertainty by generating evidence where patient data are lacking. Its increasing use in HTA also allows for meaningful stakeholder involvement, ensuring evaluations are relevant, comprehensive, and patient-centered.

Introduction to the benefits of Expert Elicitation

Health technology assessment (HTA) agencies require evidence relating to the burden of illness, comparative effectiveness, cost-effectiveness, and/or the budget impact of new therapies or technologies to assess their value and inform patient access decisions. However, often the required evidence is lacking or can be uncertain due to lack of robust or long-term comparative clinical trial data, challenges in areas like rare diseases with their small and heterogeneous patient populations, or lack of published evidence. In these instances, leveraging the insights of experts who have adequate and appropriate subject knowledge on a particular topic can be useful to elicit key data necessary to inform healthcare decision making.

> Expert elicitation is an evidence-generation technique that, when applied appropriately, can be leveraged to reduce the impact of uncertainty in HTA submissions, provide reliable information, and inform the appraisal in the absence of patient-level data.

The inherent characteristics of the decision-making process for reimbursement and access means that uncertainty is an inevitable element of HTA assessments, since at the time of the evaluation, not all data are available (eg, long-term follow-up data). Expert elicitation is an evidence-generation technique that, when applied appropriately, can be leveraged to reduce the impact of uncertainty in HTA submissions, provide reliable information, and inform the appraisal in the absence of patient-level data.[1] The application of expert elicitation in recent years has become increasingly prominent in value assessments. Previous research has highlighted vast heterogeneity in the methodologies used and a lack of clear guidance on the topic.[2] In addition, there is a lack of evidence available to determine which methods are most appropriate for use in healthcare decision making.[1] Consequently, reference protocols, such as the Medical Research Council (MRC) protocol, have been developed to provide clarity on methods for collecting and using experts' judgements and to consider when alternative methodology may be required in particular contexts.[1]

Recommendations regarding the appropriate use and correct implementation of existing expert elicitation methodologies are required to allow this field to achieve its potential of informing healthcare decisions. As such, a review of literature in MEDLINE exploring the use of expert elicitation methods within HTA was conducted to assess in which contexts elicitation techniques had been used and to identify methodological and practical recommendations included in best practice guidance and HTA guidelines. The learnings were used to develop a framework to inform method selection.

Through the literature review, typical situations where expert elicitation was used were identified. We present here an overview of those potential uses to guide and support appropriate methodological choices across a variety of contexts for those seeking to conduct expert elicitation.

Use of expert elicitation in HTA decision making

The review highlighted that expert elicitation is recognized as an valuable methodology within health economics and outcomes research (HEOR) and is accepted by numerous HTA bodies. The use of expert elicitation was identified in cases where traditional evidence synthesis methods (such as head-to-head comparison and the use of published data) were impractical or insufficient (**Table**).

Acceptability of expert elicitation in HTA decision making

How accepted is expert elicitation currently?

As noted in existing reference protocols, no standard guidelines exist for the conduct of expert elicitation in HTA and on the conditions for the acceptability of the results, but a number of generic guidance documents or reference materials have been developed to help inform appropriate method selection and study design.[1]

Across countries, variation exists as to whether expert elicitation guidance is provided by HTA agencies (**Figure 1**). Most HTA agencies across countries listed provided at least some level of guidance; while some provided extensive details, such as Australia and Portugal, others simply acknowledged the acceptance of expert elicitation techniques in the absence of patient-level data. This is with the notable exception of the United States, where guidance on expert elicitation is not provided nor acknowledged.[3]

Guidelines refer to the use of expert elicitation techniques to inform HTA submissions, with example uses including defining clinical or unmet need, assessing potential alterations to clinical management pathways and algorithms, assessing clinical importance and patient relevance of outcomes, modifying patterns of healthcare resource use, predicting healthcare resource impact, estimating proportions and or probabilities in relation to outcomes of interest, and predicting treatment use following the emergence of a new therapy.[4]

HTA organizations advise that formal elicitation methods must adhere to best practice principles to minimize bias and adhere to validated processes to obtain results with the highest level of objectivity feasible. There is variation in the detail included. For example, in Australia and Portugal, the guidance is prescriptive and includes details relating to design, conduct, expert election, aggregation, and analysis. In contrast, other countries provide minimal details on how to include expert elicitation within HTA. An overview of excerpts from HTA guidelines is presented below in **Figure 2** (detailed guidance from Australia and Portugal have not been listed in this article; however, they can be found in HTA guidelines).[4,5]

Commonalities exist across the recommendations provided in HTA guidelines; for example, the guidelines in France refer to the Australian guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee to outline exemplar methodologies, ranging from questionnaire-based surveys involving a statistical analysis, to the

Table. Overview of expert elicitation methods and example uses

Data type	Aims and methods	Examples *(list not exhaustive)*
Quantitative	Quantitative techniques seek to elicit insights from experts in a quantitative or statistical form, for example, point estimates and probability distributions, and are typically conducted using structured expert elicitation techniques, including (but not limited to) the Sheffield Elicitation Framework (SHELF), Cooke's Classical Model, and the Delphi method.	Utility value derivation, quantifying uncertainty, long-term extrapolations, and real-world dosing patterns and responses
Qualitative	Qualitative techniques aim to obtain descriptive qualitative insights with justifications and/or detailed rationales from experts and leverage techniques including (but not limited to) individual interviews, focus groups, consensus panels, and nominal group techniques. The exact research objective will influence the appropriate choice of elicitation technique.	Strategic planning and feasibility assessments for inclusion in HTA submissions and positioning, validation of nonconventional model inputs, understanding key drivers of uncertainty, burden of illness studies, and consensus derivation

HTA, health technology assessment.

Figure 1. Summary of the availability of guidance on expert elicitation methods across HTA organizations

**Guidance from Germany acknowledges the potential utility of deriving insights from experts leveraging accepted quantitative techniques but does not refer explicitly to expert elicitation. **Refers to use of clinical expert opinion rather than expert elicitation. Figure correct as of May 3, 2025.*
Abbreviations: AOTMiT, Agency for Health Technology Assessment and Tariff System; AUS, Australia; CADTH, Canadian Agency for Drugs and Technologies in Health; CAN, Canada; DE, Germany; ENG, England; FR, France; HAS, Haute Autorité de Santé; HIQA, Health Information and Quality Authority; HITAP, Health Intervention and Technology Assessment Program; ICER, Institute for Clinical and Economic Review; INFARMED, National Authority of Medicines and Health Products; IQWiG, Institute for Quality and Efficiency in Health Care; IRL, Ireland; NICE, National Institute for Health and Care Excellence; NL, Netherlands; Add NOKC, Norwegian Knowledge Centre for the Health Services; NOR, Norway; PBAC, Pharmaceutical Benefits Advisory Committee; POL, Poland; POR, Portugal; SBU, Swedish Agency for Health Technology Assessment and Assessment of Social Services; SCOT, Scotland; SMC, Scottish Medicines Consortium; SE, Sweden; USA, United States of America; ZIN, Zorginstituut Nederland.

qualitative or quantitative summary of interviews across a selected panel of experts. Of note, the latter is in line with the methods outlined in the MRC protocol, suggesting convergence in the preferences of HTA bodies.[4,6] In contrast, some guidelines in Europe lean toward specific methodological directions, such as preference for structured quantitative methodologies in the National Institute for Health and Care Excellence (NICE) guidelines.[7]

How will expert elicitation be perceived in the future?

As the European Commission has adopted a framework of rules and guidance for joint clinical assessments (JCA) as part of its effort to implement the EU health technology assessment regulation, it is currently unclear where expert elicitation will sit within the expert involvement framework. However, it is likely that expert elicitation techniques will gain acceptance provided they follow accepted best practice guidance, such as the MRC protocol, and if guidelines are developed in the future, they will align with existing HTA guidelines.

Application in HTA decision making

As noted above, there is increasing interest in expert elicitation techniques as a means to inform healthcare decision making and reduce the uncertainty inherent to HTA assessments.

Figure 2. Excerpts from HTA guidelines

"In the absence of empirical evidence from randomised-controlled trials, non-randomised studies, or registries, or when considered appropriate by the committee taking into account all other available evidence, expert elicitation can be used to provide evidence. Structured approaches should adhere to existing protocols (such as the Medical Research Council protocol)."

National Institute for Health and Care Excellence, Health Technology Evaluations: the manual, UK (2022)[7]

"In the absence of sufficient data for informing parameter estimates, the elicitation of quantitative input from relevant experts may be useful."

Canada's Drug and Health Technology Agency, Guidelines for the Economic Evaluation of Health Technologies (2017)[8]

"Expert elicitation involves obtaining quantitative values from experts. For example, they mayprovide an estimation of a certain input parameter of an economic evaluation, such as the time an intervention is used, or a distribution of various follow-up treatments. Various structured methods exist for expert elicitation, such as the Sheffield Elicitation Framework (SHELF) method, the Delphi method, and the Cooke method. The use of a structured method is obligatory. These methods start with an individual elicitation, by an interview or questionnaire. A fixed interval method or a variable interval method can be used to request parameter values. In addition to point estimates, these methods also enable to generate a distribution around the parameter values. Various tools are available for requesting estimates from experts. After collecting the estimates of the individual experts, the outcomes must be combined, or aggregated. This can be accomplished through mathematical aggregation or behavioural aggregation. When it comes to mathematical aggregation, the individual estimations are combined using an algorithm. In the case of behavioural application, interaction takes place between the experts in order to generate an outcome through consensus. This can be accomplished through giving feedback on the answers provided by the other experts (the Delphi method), or by organising an expert panel (the SHELF method). Both methods require not only a point estimator to be aggregated, but also a distribution. These distributions must then be included in the deterministic sensitivity analyses and the probabilistic analysis."

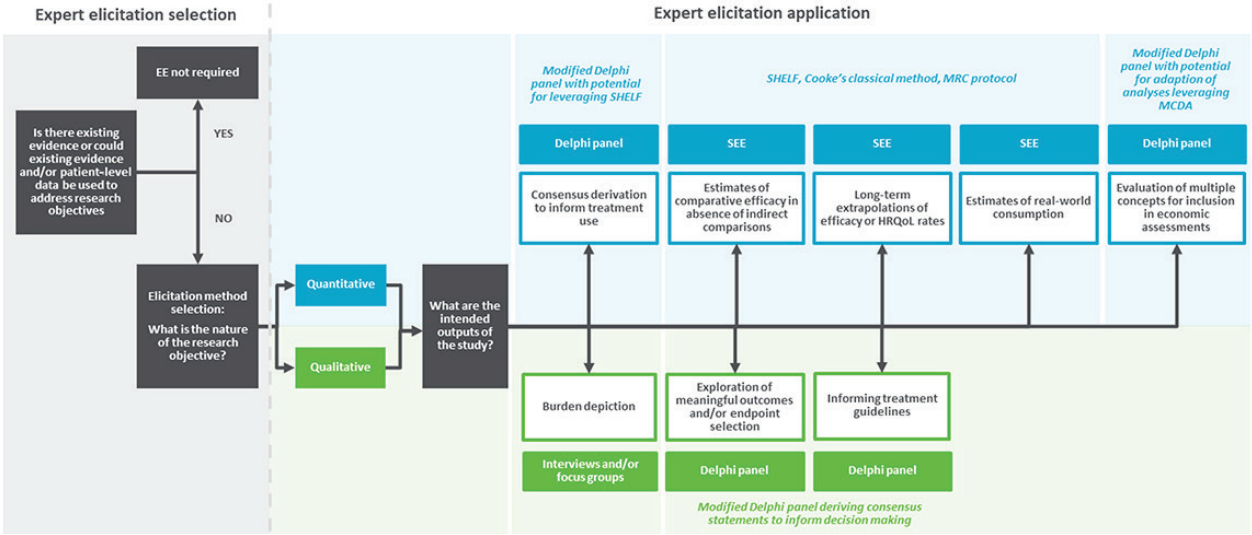
National Health Care Institute, Guideline for Economic Evaluations in Healthcare, the Netherlands (2024)[9]

"Experts' opinions may be used to justify the choice of the data or to justify the relevance of the data or assumptions tested in a sensitivity analysis, so long as the method used to obtain these opinions is detailed (criteria used to select the experts, number of experts approached and who responded, disclosures of potential interests, method used to record the opinions, questions asked, and identification of the data documented through experts' opinions). For quantitative parameters, a formal method of elicitation is preferable."

HAS Choices in Methods for Economic Evaluation Methodological Guidance, France (2020)[6]

Abbreviations: HAS, Haute Autorité de Santé; HTA, health technology assessment; SHELF, Sheffield Elicitation Framework.

Figure 3. Road map of potential uses to help facilitate methodology choices



Abbreviations: EE, expert elicitation; HRQoL, health-related quality of life; MCDA, multi-criteria decision analysis; MRC, Medical Research Council; SEE, structured expert elicitation; SHELF, Sheffield Elicitation Framework.

As uncertainty within technology submissions remains a major challenge for decision makers, techniques—such as expert elicitation—that can help mitigate the level of uncertainty associated with the development of new technologies provide an opportunity for health technology developers to improve the quality of their submissions—provided the studies are conducted and results utilized appropriately.

> It is likely that expert elicitation techniques will gain acceptance provided they follow accepted best practice guidance, such as the Medical Research Council protocol, and if guidelines are developed in the future, they will align with existing HTA guidelines.

To supplement the recommendations and preferences identified within HTA guidelines, we have prepared an overview of potential uses as an elicitation road map (**Figure 3**) to guide appropriate and adequate methodology selection, study design, and implementation across an array of market access research questions, while following best practice principles detailed in published literature.

Call to Action

The wide-ranging requirements needed for HTA submissions to support patient access at an early stage of products' life cycles, combined with the intricacies of challenges encountered in complex indications and innovative types of technologies, leads to the introduction of an inevitable level of uncertainty in HTA decision making.

This uncertainty can often impact HTA decision making negatively or lead to suboptimal decisions as decision makers look to reduce their risk, ultimately reducing patient access to useful therapies. As we continue to aim for earlier patient access to therapies, the uncertainty included in the process is substantial, especially when regulatory pathways are accelerated. Efforts should therefore be made to mitigate the extent of this uncertainty to prevent delays or restrictions to access.

Expert elicitation is an evidence-generation technique that, when applied appropriately, can be leveraged to reduce the impact of uncertainty on HTA submissions to provide stakeholders with reliable information to inform their decision making in the absence of patient-level data. With the increasing use of expert elicitation in HTA decision making, it provides an opportunity for patients and patient representatives to ensure their voices are integrated into evidence-generation activities, making evaluations of new technologies relevant, comprehensive, and patient-centered.

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Evaluation of Pharma-Sponsored Patient Support Programs (PSPs): Why Assessment Is Often the Forgotten Piece of the PSP Lifecycle Jigsaw

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KEY TAKEAWAYS

Comprehensive evaluation of patient support programs (PSPs) by the pharmaceutical industry is rare. When a PSP does not work optimally, it is unclear why; therefore, the ability to assess the value provided to patients, pharma, and payers, and to evolve the approach, is limited.

Behavioral science frameworks can be used to gain a deeper understanding of what prevents organizations from implementing a more comprehensive measurement of PSPs and can guide actionable recommendations to overcome obstacles.

The Challenge and Why It Matters

The purpose of a patient support program (PSP) is to improve the lives of patients by supporting adherence to treatment and self-management of chronic conditions. However, pharmaceutical companies that provide these programs often don't know whether their programs are achieving their objectives. To date, comprehensive measurement of industry-sponsored PSPs is rare, holding back our understanding and curtailing empirically based improvements in program design and opportunities to enhance impact.

Health psychologists and implementation scientists working in the pharmaceutical industry are starting to apply theories, methods, and processes commonly used in public health or academic settings to patient strategy.[1] This has facilitated a greater understanding of the way people behave and cope with a chronic condition.

> Without looking inside the black box of the patient support program, it is more difficult to refine and evolve programs or learn from success and mistakes. Furthermore, without real-world data, it is impossible to demonstrate value and impact.

More importantly, their systematic application of theory to identify modifiable determinants of behavior has enabled the selection of evidenced-based behavior change techniques for use in PSPs. Behavioral scientists strive to adhere to guidelines for complex intervention development[2] while recognizing the need to be flexible and practical. These insight- and evidence-based interventions provide the foundation for the PSP design translated into the program by a wider team of professionals, including content experts, engagement specialists, and graphic designers.

We consider that 3 types of data should be gathered as part of routine service evaluation:

1) Operational data that tell us whether the PSP is running as intended (eg, number of enrollments, time from consent to first contact from PSP staff).

2) Perceptions and experiences of those receiving the program.

3) Data related to the key behavioral outcomes that the program is designed to encourage (eg, treatment adherence, perceptions about condition and treatment).

Data types can be combined to provide a comprehensive understanding of different dimensions of impact. For example, satisfaction with a program can be assessed by self-report questionnaires and operational metrics (eg, numbers of users leaving the PSP early). Improvement in behavioral outcomes can be assessed using a within-participants approach by measuring change over time from enrolment to an appropriate follow-up timepoint.

Building on this routine evaluation, exploring a wider range of clinical and disease-related outcomes is also possible through the setup of protocolized research. Currently, PSP evaluation frequently stops at gathering of operational metrics and the extent to which participants would recommend the program to others. This leaves many unanswered questions:

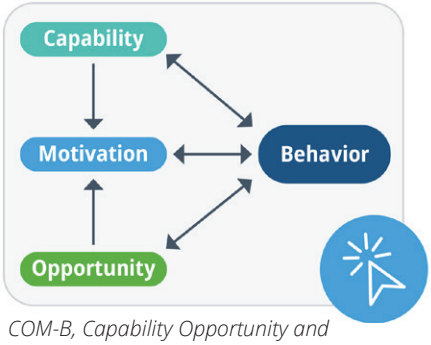
- Is the PSP changing the behavior it was designed to target?
- Is it changing beliefs about treatment and disease?
- Is it improving knowledge?
- Is it building confidence to self-administer treatment?
- Which program asset is most/least effective?
- Are participants engaged and enjoying participation?

Without looking inside the black box of the PSP, it is more difficult to refine and evolve programs or learn from success and mistakes. Furthermore, without real-world data, it is impossible to demonstrate value and impact.

Applying Behavioral Science Change Theory to Understand Factors Contributing to the "Failure to Measure" Phenomenon and Guide Actionable Recommendations

To systematically investigate the barriers to PSP evaluation by the pharmaceutical industry, we applied the Capability Opportunity and Motivation-Behavior (COM-B)[3] framework. We used a practical mixed-methods approach to analyze the perspectives of 23 representatives from international pharmaceutical organizations. The attendees were a self-selected sample of employees from different roles, with varied experience of PSPs, who decided to attend a workshop on PSP evaluation. These perspectives were gathered during workshop group activities. We wanted to build a "bottom-up" understanding of the barriers of evaluation and elicit the perspectives of attendees by facilitating whole-group discussions and small group work. We encouraged discussions to flow naturally, only prompting when conversation stalled. In real time, we classified the barriers described using the COM-B[3] framework and assessed perceptions about evaluation in a short questionnaire.

Figure 2. Visual of COM-B

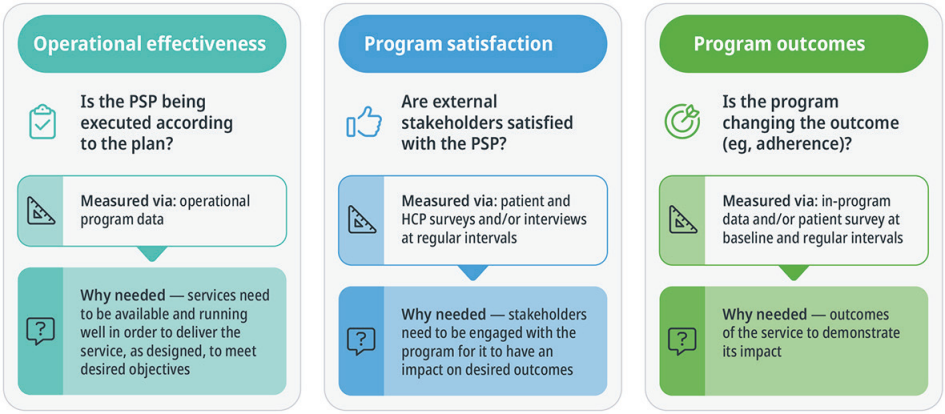


COM-B, Capability Opportunity and Motivation-Behavior.

COM-B 101

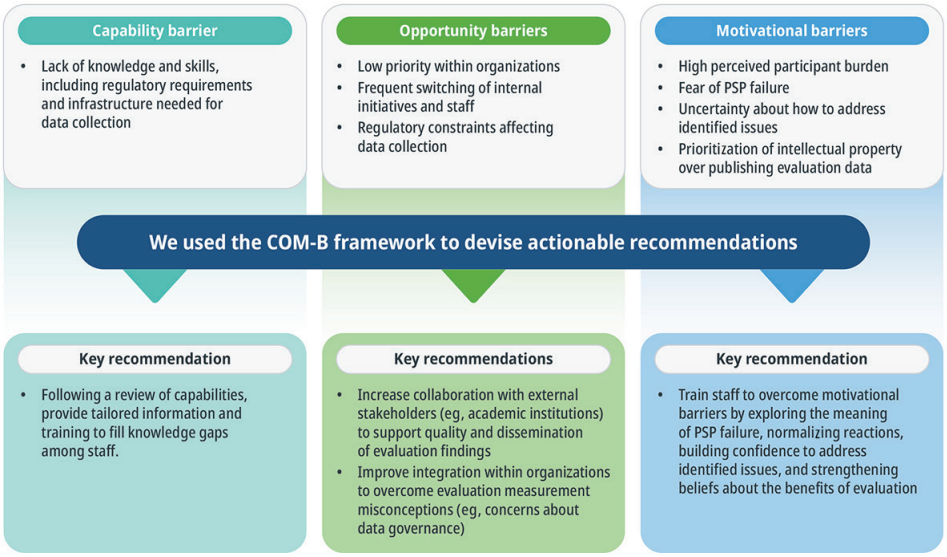
According to the COM-B, a behavior is more likely to occur if an individual has the capability to carry out or "do" the behavior, is motivated, and has the opportunity to successfully enact the behavior. Capability factors include physical and psychological capacity, such as knowledge and skills. Motivation has a wider meaning than its everyday parlance, including all the conscious cognitive brain processes that underpin intention, such as beliefs about the behavior and beliefs about one's capabilities or skills, as well as unconscious phenomena such as routines, habits, and emotions. Opportunity factors include anything outside of the person that can enhance or diminish the likelihood of a behavior happening. This includes things like access to resources, tools, and relationships or support from others. *In a COM-B perspective of the aim to increase physical activity, the person needs to have the knowledge and physical capacity, think activity is worthwhile and likely to achieve benefits, have positive emotional responses and daily routines that increase their chances of success, have access to facilities, and have people around to support by encouraging or joining them in the activity.*

Figure 1. Three data categories recommended for robust PSP service evaluation



PSP, patient support program.

Figure 3. Categorization of Key Barriers and Interventions Classified by COM-B



COM-B, Capability Opportunity and Motivation-Behavior; PSP, patient support program.

Findings

While all attendees recognized the importance of evaluation, the majority (82%) felt they lacked the necessary skills to implement a best-practice approach. Multiple barriers from each COM-B category were described that, at first glance, appeared daunting; however, upon closer inspection, the barriers included those that are more amenable to change.

Attendees lacked **knowledge** about regulation and infrastructure needed for data collection. Key **motivational** barriers to implementing a more thorough evaluation protocol included fears related to the consequences of how PSP metrics would be received both internally and externally, uncertainty about how to address any issues identified, reluctance to increase participant burden by requiring additional surveys, and concerns about sharing intellectual property if data were published. **Opportunity barriers** were significant and included low priority within organizations, frequent shifting of internal initiatives resulting in stopping of funding streams, and movement of staff, stalling momentum.

The application of the COM-B improved understanding of the evaluation barriers faced by those in charge of patient services within pharma, and, more importantly, guided the identification of actionable opportunities to drive change. COM-B is linked to a more detailed framework of domains associated with behavior change (The Theoretical Domains Framework)[4] and a taxonomy of evidenced-based behavior change techniques.[5] We used these to select effective interventions tailored to the barrier type. These recommendations include:

- Provision of tailored information to fill knowledge gaps.
- Training to address fears and misconceptions using case examples and peer experiences.
- Guidance to patient service teams encouraging cross-functional collaboration to develop measurement frameworks.

To address a number of the key barriers, we conducted a pragmatic review of pharma-sponsored PSPs published in peer-reviewed journals[6] and summarized our findings in a factsheet, shared with workshop attendees. The factsheet aimed to address capability barriers by demonstrating what can and has been done, motivational barriers through demonstration of positive outcomes, and opportunity barriers by demonstrating the feasibility of PSP evaluation.

> Robust evaluation is a critical piece in the jigsaw of effective patient-centric service delivery.

Lessons Learned and a Call to Action

Robust PSP evaluation is a critical piece in the jigsaw of effective patient-centric service delivery. Future PSPs are unlikely to benefit from the insights provided by Implementation Science[7] if real-world data are not available to assess how PSPs work in practice. Without it, PSP developers and behavioral scientists are designing at a disadvantage because they must make decisions based on anecdotal experience rather than an empirical evidence base. This analysis uncovered real challenges to PSP evaluation from the perspective of the pharmaceutical industry. Some require significant shifts in organizational structures, while others can be tackled bottom-up with small initiatives that can start to shift the needle. Evaluation strategies that assess program execution, satisfaction with services, and change in behavioral outcomes will provide the data needed to drive ongoing service improvement.

Overcoming the barriers that hinder evaluation of PSPs will help patients experience the full benefit of their prescribed treatment (eg, better adherence and self-management) so pharmaceutical companies can maximize the improvement of patient outcomes from the medicines they develop.

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Accelerating Patient Access to Innovation

Interview With Birgitte Klindt Poulsen, Chair of the Danish Medicines Council

Q&A

Since stepping into the role of Chair of the Danish Medicines Council in early 2025, Birgitte Klindt Poulsen has been navigating the delicate balance between accelerating patient access to innovation and maintaining the rigor of independent, evidence-based evaluation. In this interview, she shares how the Council is embracing real-world evidence, advancing European collaboration, and preparing for the growing complexity of personalized and advanced therapies.

"The mandate of the Council is one I consider both essential and increasingly complex. At its core, our mission is to ensure that Danish patients can access innovative treatments swiftly, but always based on independent, evidence-based evaluations and within the boundaries of cost-effectiveness."

– Birgitte Klindt Poulsen

PharmaBoardroom: What have been your early reflections since stepping into the role of Chair of the Danish Medicines Council, and how are you shaping its strategic direction?

Birgitte Klindt Poulsen: I officially assumed the role of Chair of the Danish Medicines Council in February of this year, following a long-standing involvement with the organization. I joined as a regular member in January 2017 and most recently served as Vice-Chair, which provided a strong basis for stepping into this position. That continuity has been invaluable as it has allowed me to approach the Chairmanship not as a starting point, but as a continuation of a journey already deeply rooted in the Council's values and operations.

The mandate of the Council is one I consider both essential and increasingly complex. At its core, our mission is to ensure that Danish patients can access innovative treatments swiftly, but always based on independent, evidence-based evaluations and within the boundaries of cost-effectiveness. The real challenge lies in maintaining this balance, between acting with the necessary speed to serve patients and applying the analytical depth required to safeguard both clinical and economic soundness. That equilibrium is foundational to our credibility and to the trust placed in us by stakeholders across the healthcare ecosystem.

One of my immediate focuses has been contributing to the formulation of our 2025-2027 strategy, a process that I found particularly meaningful given the weight of the decisions that lie ahead. The strategy reaffirms our role in helping the healthcare system navigate increasingly urgent prioritization demands. Although Denmark is often regarded as a country with strong public health infrastructure, our resources, like those of any system, are finite. We must therefore take seriously our responsibility to guide resource allocation in a way that delivers the greatest

value across disease areas and care levels. As a Council, we see ourselves not merely as assessors of medicines, but as contributors to a more equitable and sustainable model of healthcare delivery, one that serves patients both efficiently and fairly.

PB: How does the 2025–2027 strategy reinforce the Council's mission, and what new priorities are being introduced?

BKP: Our newly launched 2025-2027 strategy reaffirms our commitment to providing timely, evidence-based recommendations for new medicines, balancing the need for rapid patient access with the rigor of independent clinical and economic evaluation. While speed is important, decisions must remain firmly grounded in a thorough assessment of efficacy, safety, and cost-effectiveness. A central priority is strengthening our health technology assessment (HTA) capabilities, both domestically and through our active role in the European Union's HTA framework. As Denmark assumes the EU presidency, we are committed to deepening collaboration on joint clinical assessments while continuing to address national-level policy, organizational, and economic factors.

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Equally important is the need to enhance post-recommendation follow-up. Clinical trial populations rarely mirror Danish patients, so we are investing in more data-driven mechanisms to ensure that our decisions translate into real-world value. Finally, transparency remains essential. We aim to be a clearer, more visible voice in public discussions around prioritization, ensuring that our decisions, and the reasoning behind them, are accessible and trusted by all stakeholders.

PB: In what ways is the Council advancing the integration of real-world evidence into its decision-making processes?

BKP: Denmark possesses a solid foundation for the integration of real-world evidence (RWE), with high-quality healthcare data and strong systems for patient follow-up. Yet despite these advantages, we recognize that our use of RWE remains limited. Unlocking its full potential will require a more concerted effort to strengthen collaboration, not only among domestic clinical and data stakeholders, but also across the Nordic region and the broader European landscape. This objective is already embedded within our current strategic agenda and will be a key area of focus in the coming year.

One of the primary challenges lies in scale. As a relatively small country, Denmark often lacks the patient numbers required to produce robust, timely evidence in areas such as rare diseases or narrowly defined indications. With many of today's new therapies targeting increasingly specific populations, it becomes clear that national data alone are often insufficient. To address this, we are actively pursuing international collaboration to build more comprehensive datasets. In doing so, we aim to ensure that our assessments not only remain methodologically sound but also reflect the realities of clinical practice, ultimately supporting more informed and effective healthcare decision making.

PB: How is the EU HTA regulation influencing the Danish Medicines Council's work, and what contribution can Denmark make at the European level?

BKP: The implementation of the EU HTA regulation is already having a tangible impact on the work of the Danish Medicines Council. Our secretariat has been actively engaged from the outset and is currently participating in joint clinical assessments for new medicines. From an early stage, we recognized the strategic importance of contributing to this evolving framework and made it a priority to ensure Denmark plays an active role in shaping its direction.

Looking ahead, we see this integration as an opportunity to improve both the efficiency and quality of our assessments. Earlier access to shared data and closer methodological alignment across member states will support more robust evaluations, while still allowing national authorities to address local economic, organizational, and policy considerations. The goal is not to replace national assessments, but to enhance them through collaboration.

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With Denmark now assuming the EU presidency in this area, we are well positioned to share our experience and contribute constructively. Our approach ensures that recommendations are not only evidence-based but also implementable in day-to-day clinical practice. The involvement of those directly delivering and receiving care is essential to making our work relevant and usable. Ultimately, our contribution at the European level must remain rooted in that same principle: evaluations that are rigorous, transparent, and able to support meaningful outcomes across diverse healthcare systems.

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