GETREAL INSTITUTE | PUTTING REAL WORLD EVIDENCE INTO PRACTICE

REAL-WORLD EVIDENCE WITH REAL-WORLD CONFIDENCE: **SHAPING THE FUTURE OF HEALTHCARE**

GetReal Conference 2025
Post-Conference Report

1-2 October 2025 | Utrecht, The Netherlands

CONTENT

INTRODUCTION

The GetReal Institute 2025 Conference “Real-World Evidence with Real-World Confidence: Shaping the Future of Healthcare” took place on the 1st and 2nd of October 2025 at the Crowne Plaza in Utrecht, the Netherlands.

The event brought together a vibrant and diverse community of stakeholders from across the healthcare ecosystem, including regulators, HTA bodies, industry, academia, patient organisations, and data service providers. The conference provided a unique platform to explore how Real-World Evidence (RWE) can be generated, shared, and applied with confidence, transparency, and impact.

At a pivotal moment for the field, the conference theme reflected both the maturity of RWE and the responsibility that comes with it - to ensure that the evidence informing healthcare decisions is robust, transparent, and trustworthy.

EXECUTIVE SUMMARY

The GetReal Conference 2025, "Real-World Evidence with Real-World Confidence: Shaping the Future of Healthcare," convened the European real-world evidence (RWE) community at a defining moment for both regulatory and Health Technology Assessment (HTA) decision-making. Across opening remarks, the keynote, and ten interconnected scientific sessions, the conference examined how RWE is reshaping evidence generation and use across the full healthcare decision continuum, from authorisation and benefit–risk assessment to relative effectiveness, pricing, reimbursement, and post-launch.

In the opening remarks, the GetReal Institute emphasised that the growing reliance on RWE across regulatory and HTA contexts brings a shared responsibility. As RWE increasingly informs high-impact decisions on patient access and health system investment, confidence must be earned through transparency, methodological robustness, and early, sustained collaboration between regulators, HTA bodies, payers, industry, clinicians, and patients.

The keynote address from the European Medicines Agency (EMA) highlighted how RWE is now embedded within regulatory science across the medicinal product lifecycle, complementing randomised trials through structured pathways including federated data networks such as DARWIN EU. These activities were framed as equally critical for HTA and payer decision-making, particularly in understanding disease natural history, real-world effectiveness, and safety.

Across the scientific sessions, discussions focused on strengthening the scientific foundations of RWE to meet regulatory and HTA evidence thresholds. Topics included the use of real-world data to inform trial design, the role of pragmatic and hybrid trial designs, and the application of external controls and target trial emulation. While these approaches offer important opportunities, speakers consistently stressed the importance of fitness-for-purpose, transparency, and explicit management of uncertainty.

EXECUTIVE SUMMARY

Later sessions explored how RWE informs decision-making through managed access, pricing, and reimbursement frameworks. Through case-based debate, participants highlighted that RWE can support access in areas of unmet need but cannot compensate for fundamental weaknesses in study design or outcome relevance.

Regulators, HTA bodies, and payers converged on the need for earlier alignment and realistic post-authorisation evidence generation strategies.

The final sessions looked ahead to next-generation RWE strategies, including federated data networks, AI-enabled analytics, and digital health integration. Across these discussions, patient centricity, interoperability emerged as core principles for ensuring that RWE is not only scalable but trusted and decision ready.

Overall, the conference underscored that RWE is now integral to both regulatory and HTA decision-making. Its future impact will depend on coordinated, lifecycle-based evidence strategies that align decision-maker needs, maintain methodological rigor, and support timely, equitable, and sustainable patient access.

Recommendations and Next Steps

The conference highlighted the need to move from discussion to action in the use of RWE across regulatory, HTA, and reimbursement decision-making. Participants emphasised the importance of earlier and more structured multi-stakeholder dialogue to align on evidence needs across the product lifecycle, greater clarity on fit-for-purpose RWE study design and acceptable uncertainty, and continued investment in interoperable data infrastructure and analytical capacity. The discussions also underscored the need to embed patient-relevant outcomes more systematically in RWE and to apply managed access and coverage-with-evidence-development approaches selectively, within clear frameworks and realistic timelines. The GetReal Institute will incorporate these learnings into its 2026 work programme, supporting practical guidance, continued dialogue, and collaborative initiatives to advance confident, decision-ready use of RWE.

OPENING REMARKS

The conference was formally opened by Mariam Bibi, Managing Director of the GetReal Institute, who welcomed participants and set the tone for two days of learning and collaboration.

In her address, Mariam reflected on the evolution of Real World Evidence (RWE) from a promising concept to a central pillar of evidence-based decision-making in Europe and beyond. She emphasised that with this growth comes a shared duty to strengthen the credibility and consistency of RWE through collective efforts and open exchange.

"The title of this year's conference captures where we stand as a community. RWE has matured from an emerging concept to a cornerstone of healthcare decision-making. With that maturity comes responsibility: to ensure that what we produce and how we use it remains robust, transparent, and trustworthy."

Mariam also spoke to the core mission of the GetReal Institute: education and collaboration. She underscored how the conference was designed to bring these two principles to life, through a programme that not only shared the latest advances in RWE but also encouraged participants to learn from one another and build lasting relationships.

"Education and collaboration sit at the heart of the GetReal Institute's mission. This conference was designed to bring both to life - fostering shared learning through our sessions, and creating opportunities to connect, debate, and co-create solutions. I encourage everyone to ask challenging questions, exchange experiences openly, and use these two days to spark new ideas and partnerships that extend well beyond this event."

Her remarks highlighted the Institute's ongoing commitment to cultivating a trusted, collaborative RWE ecosystem, one capable of driving evidence-based health-care that truly reflects the realities of patients and systems.

KEYNOTE - PATRICE VERPILLAT

The keynote address, delivered by Patrice Verpillat, Head of Real-World Evidence at the European Medicines Agency (EMA), provided a comprehensive overview of the agency's evolving role in Real-World Data (RWD) utilisation and the progress made toward embedding RWE in regulatory decision-making.

Patrice began by noting that RWE has moved from a theoretical concept to a fully integrated component of evidence generation: ***"We are in the business of excellent clinical evidence: bigger, better, and more impactful."***

He described how the European healthcare landscape is changing, with RWD now recognised as a possible complement to randomised controlled trials (RCTs) throughout the medicinal product lifecycle. The EMA's work, he explained, is structured around three main pathways for generating RWE:

1. In-house analyses, using RWD sources directly accessible to the EMA;

2. Studies commissioned through framework contracts, enabling targeted RWE generation in response to specific scientific or policy questions; and

3. DARWIN EU, the European federated network for distributed analysis of RWD, launched in February 2022.

DARWIN EU represents a major step forward in the EU's ability to generate RWE rapidly and at scale. The network currently includes 30 data partners across 16 countries, with plans to expand to more than 40 partners by 2026. Together, these partners provide access to data representing over 180 million patients, a critical mass that allows the EMA and the national competent authorities to conduct robust, timely analyses supporting regulatory and safety decisions.

KEYNOTE - PATRICE VERPILLAT

Between February 2024 and 2025, 107 research questions were addressed overall via the 3 pathways, and a large number of them were directed through DARWIN EU, spanning pharmacovigilance, oncology, neurology, and infectious disease. The feasibility rate of these studies increased from 60% to nearly 80% during the period, reflecting the network's growing maturity and efficiency.

Patrice shared specific examples of how RWE is informing regulatory science, including the GLP-1 receptor agonist safety review. The study assessed whether these medicines were associated with an increased risk of suicide or self-harm among patients with type 2 diabetes.

Following a detailed review of the generated RWD and other available evidence, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) concluded that "the results did not support a causal association," and no update to product information was required.

Beyond individual safety assessments, RWE has become an indispensable resource for understanding the clinical context of diseases, supporting study design and validation, and strengthening the overall evidence base available to decision-makers.

KEYNOTE - PATRICE VERPILLAT

Patrice concluded his keynote by outlining five strategic priorities for advancing the use of RWE within the European regulatory system:

1. **Access to Data Sources:** Expanding access to diverse and complementary datasets across Europe.

2. **Acceleration:** Developing strategies to speed up RWE generation without compromising quality.

3. **Regulatory Context:** Anticipating decision-makers' evidence needs early in the lifecycle.

4. **Capacity and Capability:** Building expertise through education, knowledge management, and analytic tools.

5. **Collaboration:** Strengthening partnerships among regulators, HTA bodies, industry, academia, and patients.

He emphasised that while methodological rigor remains essential, progress also depends on shared trust and mutual learning across institutions ***"RWD and RWE play a crucial but complementary role in bridging the gap between clinical trials and real-world practice."***

SESSION 1: REVOLUTIONISING RWD STANDARDS ACROSS THE PRODUCT LIFECYCLE

The opening session of the day moderated by Mariam Bibi, the GetReal Institute examined how Real-World Data (RWD) and Real-World Evidence (RWE) are reshaping decision-making across the entire product lifecycle, from informing clinical trial design and regulatory submissions to supporting reimbursement and post-market surveillance.

The discussion explored three key dimensions:

1. The value of RWE across the product lifecycle
2. The enablers and barriers driving its uptake
3. The impact of emerging technologies on how RWE is generated and applied

Throughout, the session underscored that trust, transparency, and patient engagement are central to advancing RWE adoption globally.

The Value of RWE Across the Lifecycle

The conversation began with a strong focus on the patient perspective. Iain Armstrong (PHA UK) highlighted that lived experience and qualitative insights are too often treated as peripheral data. He argued that emotional honesty and patient-reported experiences provide crucial context for understanding what truly matters to patients in their everyday lives. Over-standardisation, he warned, risks stripping away this human dimension and undermining the relevance of the evidence base.

From the industry perspective, Leo Russo (Pfizer) described how RWE is increasingly being used to inform trial design and patient selection. He pointed to Pfizer's use of trial emulation and electronic health record (EHR) studies to refine eligibility criteria, identify predictors of disease progression, and shape endpoints in areas such as asthma, COPD, and Crohn's disease.

"RWE is underutilised as a tool to simulate trials and shape their design" he said, underscoring how data-driven trial evolution can make research more relevant to real patient care.

SESSION 1: REVOLUTIONISING RWD STANDARDS ACROSS THE PRODUCT LIFECYCLE

Providing the HTA and reimbursement viewpoint, Carlos Martín Saborido (Institutode Salud Carlos III) emphasised the critical role of RWE in contexts such as single-arm trials or when external comparators are required. He highlighted Spain's VALTERMED initiative as an example of how structured frameworks can improve data consistency, quality, and confidence in RWE for decision-making. His message was forward-looking: ***"It's not just about filling today's evidence gaps; it's about generating the data we will need in the next two or three years."***

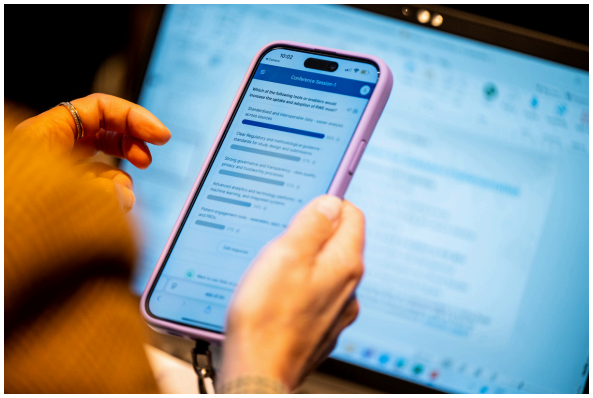
Neil Grubert provided a global policy perspective, noting that regulatory agencies worldwide are increasingly formalising policies for RWE integration. However, he cautioned that Europe may risk falling behind the U.S. in the pace and ambition of RWE adoption. Early and sustained dialogue between regulators, HTA bodies, and industry stakeholders, he argued, is essential to realising RWE's full potential.

Drivers of RWE Uptake

The panel identified trust as the central enabler of RWE adoption, underpinned by robust methodologies, transparency, and governance. Internal company alignment, clear regulatory and HTA guidance, and patient engagement were all recognised as critical to fostering confidence in RWE.

Participants discussed how regulatory and payer expectations for RWE are gradually converging but still diverge in some areas, influencing how companies plan global evidence strategies. Initiatives such as VALTERMED and similar national frameworks were cited as positive steps toward harmonisation.

An interactive audience poll revealed that 68% participants viewed standardised and interoperable data as the most important factor for increasing RWE adoption.



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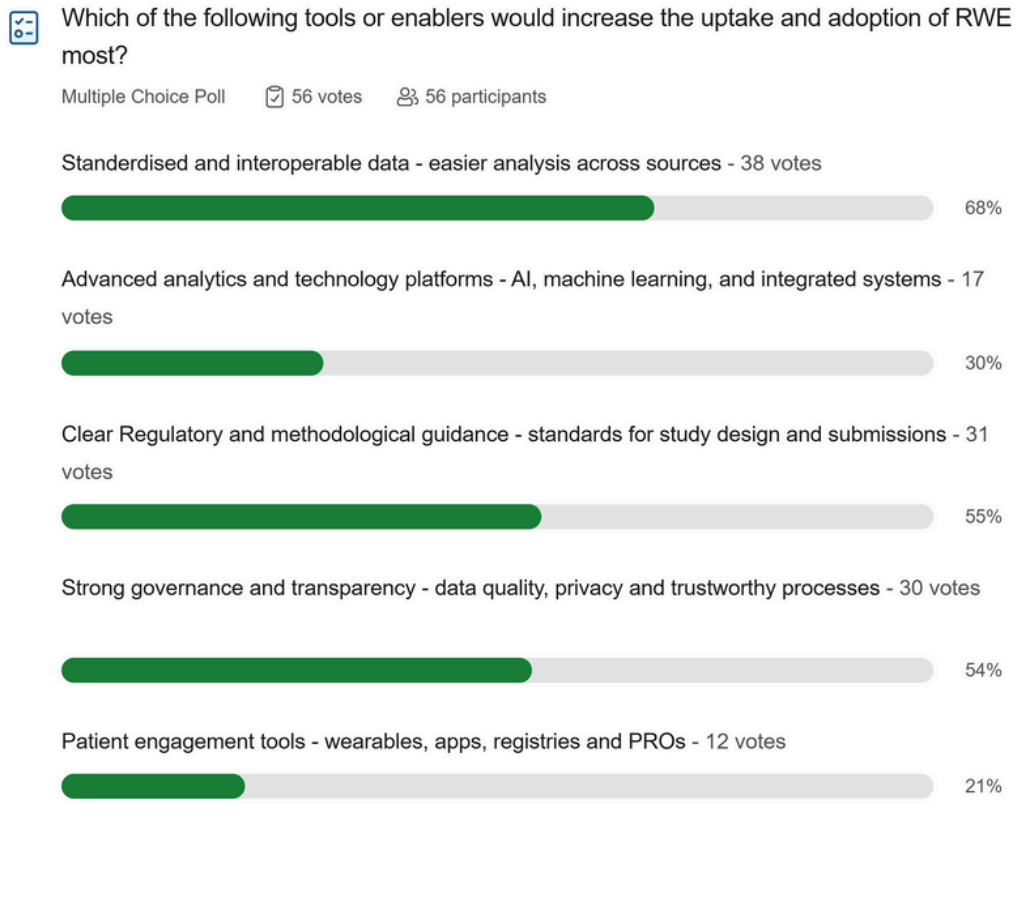

Technology, Integration, and the Future of RWE

In the final part of the discussion, panellists reflected on how technology is reshaping the way RWE is generated and perceived. AI, wearable devices, and integrated health records were seen as key drivers of a more dynamic, flexible, and responsive evidence ecosystem.

Leo noted that advances in data integration are creating more multi-modal data sets which make deeper phenotypes possible, which is crucial because this is often a shortcoming of RWE that is cited by regulators. Iain stressed that technology must capture real-life variability rather than 'smoothing it out', ensuring that patient experiences remain central to the data.

SESSION 1: REVOLUTIONISING RWD STANDARDS ACROSS THE PRODUCT LIFECYCLE

Carlos highlighted that the rapid growth in available data, combined with regulatory openness and the high cost of traditional trials, creates a strong incentive for innovation. Meanwhile, Neil pointed to a growing need for alignment across markets to ensure that progress in one region can translate globally.

Key Takeaways

The session concluded that the promise of RWE lies in its ability to make healthcare decision-making more timely, inclusive, and relevant. Achieving that vision will require coordinated efforts to strengthen data standards, governance, and stakeholder collaboration.

Across all perspectives, there was broad consensus that trust in RWE depends on methodological rigor, transparency, and meaningful patient engagement. Moving forward, the challenge is to balance standardisation with flexibility, ensuring that the data used to shape the future of healthcare truly reflects the lived realities of patients.

SESSION 2: RETHINKING EVIDENCE GENERATION IN INTERVENTIONAL STUDIES: FROM TRIALS TO TREATMENT DECISIONS

Clinical trials and pharmacoepidemiology were once seen as distinct domains, with highly controlled randomised controlled trials (RCTs) on one side and observational studies on the other. As Mira Zuidgeest (University Medical Centre Utrecht) emphasised in her opening remarks, that separation is rapidly dissolving, Real World Data (RWD) and Real World Evidence (RWE) are increasingly embedded within interventional studies, as modern trial designs not only leverage routine data to inform trials but also generate RWD/RWE through pragmatic and hybrid approaches.

This session, chaired by Mira and Iain Armstrong (PHA UK), brought together experts from regulatory bodies, national data infrastructures, and global RWE organisations: Tim Williams (CPRD), Katrien Oude Rengerink (CBG-MEB), and Sascha van Boemmel-Wegmann (Flatiron Health). Together, they explored how RWD can strengthen trials, when RWE-generating trial designs are most useful, and what limitations must be acknowledged to ensure scientific rigor.

The Convergence of Clinical Trials and Real-World Evidence

Mira outlined four key roles for RWD/RWE in interventional research:

1. Informing trial design: using RWD for feasibility, protocol development, and understanding care pathways.
2. Serving as a data source within trials: replacing or supplementing bespoke data collection with routinely captured clinical information.
3. Generating RWE through randomised interventional designs: such as pragmatic trials, registry-based trials, point-of-care trials, and decentralised models.
4. Using RWE alongside trial data: for enrichment, external controls, or contextualising generalisability.

She highlighted that central questions arise around data quality, fitness-for-purpose, robustness of evidence, and acceptability by regulators, HTA bodies, clinicians, and patients.

SESSION 2: RETHINKING EVIDENCE GENERATION IN INTERVENTIONAL STUDIES: FROM TRIALS TO TREATMENT DECISIONS

Rethinking Evidence Generation in Interventional Studies: From Trials to Treatment Decisions - How can we utilise RWD for clinical trials? (Tim Williams, CPRD)

Tim Williams demonstrated how embedded healthcare data can be operationalised throughout the clinical trial lifecycle. CPRD, one of the world's largest primary care EHR databases, includes over 80 million patients for observational studies and more than 18 million patients for trials and clinical studies, with a Median 10 year follow-up and 25% with 20 year follow-up. Representing approximately 25% of the UK population.

"Find, Recruit, Follow Up" Framework

Finding eligible participants

CPRD uses structured EHR data to model inclusion and exclusion criteria, estimate trial feasibility, and identify eligible patient groups by age, gender, ethnicity, and geography. This enables highly targeted site selection and recruitment strategies.

Recruitment through general practitioners (GPs)

GPs play a crucial role: they are the "active care team" and the legal/ethical conduit for contacting patients. Their full clinical records also help validate eligibility elements not directly visible in CPRD's coded data.

Follow-up using linked care data.

Once enrolled, participants' outcomes and safety events can be tracked using linked primary and secondary care data. This approach can reduce participant burden and support real-time surveillance.

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Example: DaRe2THINK Trial

The DaRe2THINK pragmatic trial exemplifies how interventional studies can be effectively embedded in routine primary care:

- With a target of 3,000 patients across ~600 sites (at the time of the conference 1,200 patients had already been recruited).
- Diverse socioeconomic and ethnic representation of GP sites
- Monthly safety monitoring via EHR
- Reduced burden on sites and participants
- Digital infrastructure enabling automated data streaming

The trial illustrates both the potential and the practical challenges, particularly the burden on GPs and the need for dedicated recruitment support.

When Should Trials Generate Real-World Evidence? (Katrien Oude Rengerink, CBG-MEB)

Katrien Oude Rengerink reviewed a continuum of trial designs that blend randomisation with varying degrees of real-world operation. These designs aim to preserve internal validity while increasing representativeness, scalability, and efficiency.

Pragmatic Trials

Designed to assess effectiveness in usual care settings.
Example: the Salford Lung Study, a pre-licensed pragmatic trial in COPD.

Advantages

- Greater generalisability to the studied setting
- Reflect actual prescribing patterns
- Useful for understanding treatment impact across heterogeneous populations

Challenges

- Determining the right timing in development
- Variability in “real-world” practice across regions
- Risk of bias if only one trial arm is pragmatic

SESSION 2: RETHINKING EVIDENCE GENERATION IN INTERVENTIONAL STUDIES: FROM TRIALS TO TREATMENT DECISIONS

Registry-Based Randomised Trials

Leverage disease registries for enrolment, randomisation, and follow-up.
Example: TASTE study enrolling patients and endpoints evaluation through registries.

Advantages

- Broader patient capture
- Efficient data collection
- Potential for longer-term follow-up.

Challenges

- Varying data quality
- Limited registry suitability by disease
- Incomplete capture of endpoints (e.g., patient-reported outcomes).

Point-of-Care Trials

Randomisation embedded into routine clinical practice.
Example: RECOVERY trial during COVID-19, which directly informed regulatory decisions.

Advantages

- Large-scale implementation
- Real-world relevance.

Challenges

- Heterogeneity of care
- Variable documentation quality
- Inconsistent visit timing.

Trials Augmented with External or Virtual Controls

These may reduce placebo allocation or broaden context, but come with risks:

- Population mismatch
- Evolving standards of care
- Selection bias (“cherry picking”)
- Regulatory concerns about methodological rigor.

SESSION 2: RETHINKING EVIDENCE GENERATION IN INTERVENTIONAL STUDIES: FROM TRIALS TO TREATMENT DECISIONS

Katrien emphasised that randomised designs with RWE elements must still meet evidentiary standards appropriate for regulatory and HTA decision-making. They can be ***"the best of both worlds"*** but only when data are comparable, relevant, and robust.

A Real-World Example: External Controls in a Changing Standard of Care (Sascha van Boemmel-Wegmann, Flatiron Health)

Flatiron evaluated whether RWD could augment a global RCT whose standard-of-care changed mid-study. While matching was feasible, several limitations needed to be addressed and taken into consideration:

- RWD were US-based compared to the trial's global population
- Underlying differences in race distribution, certain comorbidities, and clinical practice
- Various degrees of misalignment between structured RCT variables and available RWD elements
- Differences in visit cadence and outcome ascertainment
- Data lags affecting recency and relevance

These challenges created risks of bias that could undermine interpretability.

Strategies to Mitigate Limitations

Sascha proposed practical measures to address limitations:

- Use multinational RWD networks (e.g., DARWIN EU)
- Apply data suitability frameworks early in protocol development
- Strengthen methodological standardisation, including target trial emulation
- Invest in NLP/LLMs for extracting unstructured data from clinical notes
- Prioritise real-time RWD to reflect current practice

Even with these strategies, he noted, external controls are not universally appropriate, particularly when the RWD population diverges meaningfully from the RCT population.

SESSION 2: RETHINKING EVIDENCE GENERATION IN INTERVENTIONAL STUDIES: FROM TRIALS TO TREATMENT DECISIONS

Panel Discussion: Missing Data, Representativeness, and “Fitness-for-Purpose”

Audience questions centred on the challenges of missing data, patient heterogeneity, and assessing when a dataset is not fit for purpose.

Missing data and Lived Experience

Speakers agreed that:

- RWD often lack key information such as patient experience, social determinants, or functional outcomes.
- Tools like patient-reported outcomes, wearables, and qualitative measures must complement structured data.
- Understanding context (care pathways, documentation practices, regional patterns) is essential for interpreting missingness.

Determining When Data Are “Unfit for Purpose”

There is no universal threshold for unfit data. Instead:

- Evidence of mismatch between RWD and the trial population is critical.
- Pilot analyses, validation against RCT results, and data suitability frameworks can support decision-making.
- Regulators recognise context-specificity: a dataset may be fit for exploratory work but not for regulatory submissions.

SESSION 2: RETHINKING EVIDENCE GENERATION IN INTERVENTIONAL STUDIES: FROM TRIALS TO TREATMENT DECISIONS

The panel agreed that the future of evidence generation lies not in replacing RCTs with RWE, but in integrating both to create a more comprehensive, flexible evidence ecosystem.

Key conclusions

- Randomisation ensures internal validity; RWD enhances generalisability/applicability.
- Combining them can support efficient, representative, patient-centred research.
- External controls and hybrid designs hold potential but must be used selectively and transparently to avoid bias. More real-world examples may help to show where they do and do not work.
- Operational challenges remain substantial, especially in recruitment, data availability, and aligning heterogeneous health systems.
- Regulatory acceptance will depend on strengthening standards, including data interoperability, methodological transparency, and fit-for-purpose assessments.

As Mira summarised, the task ahead is clear:

"Stakeholders must work together over the coming years to enhance data quality, advance methodological harmonisation, and build trust in RWD supported interventional research."

SESSION 3 DESIGNING STRONGER RWE STUDIES TO MEET EVIDENCE THRESHOLDS FOR VARIOUS STAKEHOLDERS

This session explored emerging best practices for ensuring that real-world evidence (RWE) generated through externally controlled studies (ECS) and target trial emulation (TTE) meets the rigorous standards needed for decision-making by regulators, HTA bodies, and clinicians.

Moderated by Susan Oliveira (Thermo Fisher Scientific), the discussion centred on two complementary initiatives:

1. The GetReal Best Practice Framework for External Control Studies
2. EU Real4Reg project and the application of target trial emulation

Together, these approaches represent significant progress toward formalising RWE generation across Europe.

The GetReal Institute Framework for External Control studies

Anke van Engen (IQVIA) introduced the Best Practice Framework, developed in collaboration with the Institute's Working Group 2 through extensive review and multi-stakeholder consultation. The framework sets out a seven-step pathway that provides structured guidance from conception to dissemination:

1. Assess the suitability of using an external control approach
2. Define study objectives and clarify decision context
3. Conduct data landscaping and quality evaluation
4. Develop the protocol, including population and endpoints
5. Establish analytic plans aligned with regulatory expectations
6. Execute and analyse results transparently
7. Report and interpret findings with context and limitations

Anke emphasised that the goal is to create a living framework, adaptable to evolving evidence needs and regulatory requirements. It is intended to harmonise understanding of when and how externally controlled studies should be used, addressing a long-standing gap in methodological consistency.

A presentation at ISPOR Europe 2025 will showcase the work to date and a public webinar is planned for Q1 2026. The framework will be updated regularly based on user feedback, practical applications, and alignment with initiatives such as the EMA's Reflection Paper on RWD and the NICE RWE Framework.

SESSION 3 DESIGNING STRONGER RWE STUDIES TO MEET EVIDENCE THRESHOLDS FOR VARIOUS STAKEHOLDERS

Target Trial Emulation and the Real4Reg Project

Martin Russek (BfArM) introduced Target Trial Emulation (TTE) as a structured method to design real-world studies that mirror the features of a randomised controlled trial (RCT). The approach begins with defining an "ideal" hypothetical trial, followed by development of a real-world protocol that replicates the key design elements using available RWD.

Martin illustrated this method through two examples:

- A metformin and cancer study comparing type 2 diabetes patients using metformin with those on other oral medications.
- The EU-funded Real4Reg project, which uses harmonised data from four countries to investigate the cardiovascular effects of SGLT2 inhibitors in adults over 40 with diabetes.

He described how TTE helps avoid biases related to timing, exposure, or patient selection, while clarifying study assumptions and improving transparency. Analytical methods such as Targeted Maximum Likelihood Estimation (TMLE) can strengthen causal inference, though Martin cautioned that "no emulation saves you from critical thinking."

Martin also noted the publication of the TARGET Statement, a new reporting guideline for TTE studies, as a major step toward methodological standardisation.

Challenges and Future Directions

Discussion among panellists and participants focused on the practical and regulatory implications of adopting these methods.

Key challenges include

- Ensuring data completeness, quality, and interoperability across sources.
- Achieving regulatory and HTA confidence in non-randomised study designs.
- Balancing methodological rigor with feasibility in real-world settings.

Martin emphasised that the acceptance of TTE by bodies such as NICE, which already encourages TTE principles in non-randomised studies, will be a critical driver of adoption.

SESSION 3 DESIGNING STRONGER RWE STUDIES TO MEET EVIDENCE THRESHOLDS FOR VARIOUS STAKEHOLDERS

Key Takeaways

The session underscored that externally controlled studies and TTEs are complementary innovations that together enhance the credibility and transparency of real-world evidence. Both approaches support more robust and interpretable analyses, helping bridge the gap between traditional trials and routine clinical practice.

Looking ahead, participants agreed that wider implementation will depend on regulatory alignment, data standardisation, and community learnings.

"Target Trial Emulation doesn't replace randomisation, it helps us think more like trialists when working with real-world data."

POSTER PRESENTATION SPOTLIGHT

Introduction of Research Abstracts and Posters

As part of the 2025 conference programme, the GetReal Institute introduced a call for research abstracts for the first time, expanding opportunities to showcase the breadth of activity across the real-world evidence (RWE) community. Submissions spanned applied case studies, pilot projects, and methodological developments, reflecting the diversity of approaches used to generate and apply RWE. This initiative reinforced the Institute's commitment to advancing best practice, encouraging dialogue, and broadening engagement across the RWE ecosystem.

Fostering Cross-Sector Collaboration

The abstracts and poster track provided a structured forum for exchange between researchers, regulators, HTA bodies, patient representatives, and industry stakeholders. Contributors shared experiences and practical approaches from different perspectives, supporting the Institute's mission to strengthen cross-stakeholder understanding and reduce silos in the generation and use of RWE.

Highlighting Innovation and Best Practice

The call for abstracts highlighted innovative concepts, practical solutions, and emerging methodologies relevant to regulatory, HTA, and broader decision-making contexts. The selected contributions demonstrated how RWE continues to evolve in response to methodological and policy challenges.

Supporting Early Career Engagement

The introduction of a poster track created dedicated opportunities for early-career professionals and students to present their work, engage with senior experts, and expand their professional networks, contributing to capacity building within the RWE community.

POSTER PRESENTATION SPOTLIGHT

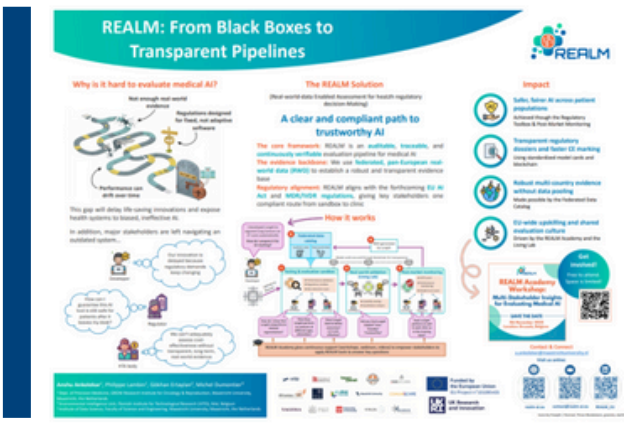
Review and Selection Process

All submitted abstracts were reviewed and scored by the GetReal abstract committee, comprising representatives from across the Institute's membership. Abstracts were evaluated against predefined criteria, including relevance, methodological quality, innovation, and potential impact. Following this process, three abstracts were selected for oral presentation at the conference:

- Repurposing Registries: What is the level of maturity of cancer registries to deliver Real World Evidence to Support Regulatory and Health Technology Assessment decisions. Presenter: Manon Wilpshaar, Utrecht University, The Netherlands

- REALM: From Black Boxes to Transparent Pipelines. Presenter: Anshu Ankolekar, Maastricht University, The Netherlands

- The pilot of the MHRA Real-World Evidence Scientific Dialogue Programme for medicinal products. Presenter: Doaa Elkholly, MHRA, England



POSTER PRESENTATION SPOTLIGHT



Poster Session
A moderated poster presentation and networking session was held on Day 2. This session enabled authors to present their work, receive feedback, and engage in interactive discussion with conference participants.


SESSION 4: SUBMITTING RWE TO REGULATORS, HTAS, RESEARCHERS AND PAYERS

This session brought together representatives from regulatory agencies, Health Technology Assessment (HTA) bodies, payers, and industry to examine how real-world evidence (RWE) can be responsibly integrated into decisions on regulatory approval and reimbursement. The discussion was structured around an illustrative mock case.

The manufacturer, represented by Leo Russo, Pfizer, presented a hypothetical case on Pneumomax, a monoclonal antibody originally authorised for severe asthma. The manufacturer suggested an indication extension for a rare eosinophilic lung disease using an evidence package composed almost entirely of RWE, primarily registry and EHR data derived from patient cohorts in three European countries.

The case was intentionally challenging. Although Pneumomax demonstrated a substantial reduction in hospitalisation rates for the targeted condition, the study design relied on non-concurrent controls, had limited follow-up time, lacked stratification across the disease's substantial heterogeneity, and omitted patient-reported outcomes. These limitations provided fertile ground for stakeholders to debate the evidentiary standards appropriate for high-need areas where traditional randomized trials may not be feasible.

The overarching goal of the session was to pressure-test what constitutes "decision-quality RWE" across the evidence ecosystem and to unpack the practical constraints, methodological concerns, and policy frameworks that would shape the fate of such a submission.

Industry Presentation of the Evidence Package

The session began with the company's presentation of a mock dossier supporting the proposed label extension. Leo emphasised the severe unmet medical need associated with the target disease, a condition with few therapeutic options and substantial morbidity. He highlighted that Pneumomax has a well-established safety profile based on years of clinical use in asthma, which he argued should mitigate concerns about systemic risks in the new indication.

SESSION 4: SUBMITTING RWE TO REGULATORS, HTAS, RESEARCHERS AND PAYERS

The core of the argument rested on a reported 47% reduction in hospitalisation rates among treated patients compared with a composite external control group. Leo stressed that hospitalisation is a concrete, meaningful endpoint directly tied to disease severity and healthcare burden. The data were drawn from three well-established national registries and supplemented by EHR-based outcome capture in two countries.

However, he acknowledged several key limitations. Follow-up was short, approximately eight months on average, limiting assessment of durability of response. The comparator group was non-concurrent, drawn from earlier time periods, raising concerns of secular trends. Furthermore, the disease itself lacks a universally accepted diagnostic definition, complicating cohort ascertainment and stratification.

Leo noted an intention to expand ongoing registries to include symptoms, quality-of-life metrics, and longer-term follow-up if conditional approval were granted, but the current submission relied primarily on hospitalisation reduction as the primary measure of effectiveness.

Regulatory Perspective: Concerns Over Validity and Feasibility

Peter Mol (UMCG & Committee member, CHMP), speaking from a regulatory standpoint, articulated a set of concerns that went beyond mere technical reservations and touched on fundamental principles of regulatory evidence.

At the core of the regulatory critique was disease heterogeneity. The targeted eosinophilic condition encompasses multiple phenotypes and is notoriously difficult to diagnose consistently across centers. Regulators require evidence that a product confers benefit across the population for which it is intended; when the underlying condition is poorly characterised, establishing such benefit becomes significantly harder.

Peter underscored that RWE as the primary basis for new indications remains uncommon within the EU framework. While regulators increasingly rely on RWE for safety monitoring, label expansions in ultra-rare diseases, and contextualising trial evidence, it is rarely used as the only basis for establishing efficacy. In this case, a randomised trial, though difficult, was not demonstrably impossible. Without such a trial, regulators must rely on external controls, and non-concurrent comparators generally carry unresolvable risks of bias.

SESSION 4: SUBMITTING RWE TO REGULATORS, HTAS, RESEARCHERS AND PAYERS

Another regulatory hesitation related to the nature of the endpoint, while hospitalisation is clinically meaningful, it is influenced by multiple non-clinical drivers, including local practice patterns, bed availability, and changes in admission thresholds over time. Because the control arm was drawn from earlier periods, regulators were concerned that system-wide shifts, rather than product benefit, could be responsible for the observed effect.

Finally, Peter raised the issue of evidentiary pathways. Conditional approval in the EU requires a viable plan for confirmatory evidence generation. But if a confirmatory randomised trial is unlikely to be feasible post-approval, then conditional approval is not appropriate. This would place the application instead under "approval under exceptional circumstances," a pathway intended for cases where evidence cannot reasonably be generated. Peter suggested that even this pathway would require stronger justification and clearer articulation of uncertainty mitigation than what was presented.

HTA Assessment Perspective: Tackling Uncertainty and Decision Impact

Reflecting on the evidence from the viewpoint of HTA assessors, Steve Williamson (NICE) and Carole Longson (Independent Senior Adviser, Life Science Policy, HTA and Market Access), discussed the practical challenges of evaluating RWE-heavy submissions for reimbursement decisions. Although the unmet need was acknowledged, both experts emphasised the sheer volume of unresolved analytical questions in the dossier.

From an assessor's perspective, uncertainty was not simply present, it was layered. Evidence uncertainties related to population definition, comparator credibility, time alignment, coding reliability, and confounding adjustment all co-existing even before taking into account the lack of evidence on long-term outcomes. Stephen highlighted that the assessment team would be expected to interrogate each of these evidence uncertainty issues meticulously, inevitably creating a long list of technical requests to the manufacturer. Many of these queries, such as validation of diagnostic pathways or justification of exclusion criteria, had not been anticipated or addressed in the submission.

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Carole explained that for HTA committees, uncertainty is only tolerable when it is actionable. In this case, the limited follow-up, absence of quality-of-life data, and reliance on a single endpoint severely constrained the committee's ability to judge both the magnitude and relevance of benefits. Such gaps complicate not only the clinical assessment but also the economic model. The model in this submission required extensive extrapolation, and several key parameters were effectively unanchored, leaving cost-effectiveness ratios highly unstable.

When asked whether managed access, an option frequently used for oncology products, could be a viable route, Carole was cautious. Managed access requires that new evidence generated during the access period has real potential to change the decision. The HTA panel questioned whether any type of incremental data collection from the proposed registries could resolve the most fundamental concerns, such as disease heterogeneity and comparator alignment.

Payer Perspective: Balancing Practical Need with Evidence Standards

The payer perspective, provided by Sahar Barjesteh van Waalwijk van Doorn-Khosrovani (Associate Professor, LUMC & National Payer's Evaluation Committee, CieBAG), added a critical dimension by highlighting the operational realities of funding decisions. Payers in the Netherlands often encounter this condition through prior-authorisation requests submitted by clinicians seeking off-label use of therapies. These requests serve as a real-world indicator of unmet need, one that may not be fully visible in regulatory or HTA settings.

However, Sahar drew a clear distinction between academic off-label evidence generation and industry-sponsored submissions. When a manufacturer seeks a funded indication extension for a still-protected product, payers expect a high evidentiary standard because the request involves a substantial financial commitment from the public budget. In this case, she noted that the current evidence package was too thin to support an unconditional reimbursement decision.

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Sahar acknowledged that hospitalisation is a "hard" endpoint but also highlighted how infrequent these events are in the disease area. Large reductions in rare events can appear dramatic without materially altering patient pathways. This nuance further complicated the value proposition. Yet, unlike regulators, payers have more flexibility to employ managed entry agreements (MEAs) or coverage with evidence development, particularly when unmet need is visible in clinical practice.

Sahar described two national platforms in the Netherlands, one for oncology drugs (the Drug Access Program) and one for orphan indications (Orphan Access Program), where structured data collection accompanies conditional coverage. These platforms involve master protocols, standard data elements, defined reassessment timelines, and cost-sharing for data generation. She suggested that a similar approach could be viable for Pneumomax, but only if the manufacturer committed to a more rigorous evidence-generation plan than what was currently proposed.

Audience Reaction and Poll Results

Following the panel deliberations, participants were invited to vote on whether the evidence presented should support regulatory approval or reimbursement. Only a small minority favoured full approval; the majority opted for "approval with conditions," reflecting a shared belief that unmet need should be recognised but that the current evidence base is insufficiently robust. Approximately one-third of respondents chose outright rejection, a result likely driven by concerns about the risk of harm and the ethical implications of approving a therapy without strong evidence of meaningful benefit.

Audience comments highlighted the risk of setting expectations too early in the treatment journey. When patients with severe conditions are offered therapies that ultimately prove ineffective, trust in the system erodes, and patients may become reluctant to participate in further trials of new treatments or data collection efforts.

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Evidence Generation Responsibilities and Sustainable Access Models

A recurring theme through the discussion was the question of who should bear responsibility for generating additional evidence. Regulators emphasised that while manufacturers typically fund post-authorisation studies, societal resources are always implicated, both directly through public funding of healthcare and indirectly through opportunity costs.

HTA experts stressed that managed access schemes are resource-intensive for assessment bodies, requiring dedicated staff, infrastructure, and governance mechanisms. They cautioned that such schemes should be reserved for products where further evidence can genuinely reduce uncertainty and not merely delay an inevitable negative decision.

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The payer perspective added a pragmatic counterpoint: clinical demand and unmet need can justify early access, but only within a transparent framework with predefined expectations. In addition to the often cited NICE/NHS England Cancer Drug Fund and Innovative Medicines Funds managed access initiatives, the Dutch access platforms described during the session illustrate a viable mechanism for balancing early availability with the discipline of structured evidence generation. These models also avoid direct financial relationships between manufacturers and clinicians, preserving the integrity of data collection.

Industry Reflections and the Path Forward

In closing remarks, industry representatives acknowledged the need for more proactive and detailed planning around uncertainty mitigation. They committed to re-evaluating the choice of comparator groups, strengthening time alignment, and exploring pragmatic trial designs embedded within existing registries. They also expressed willingness to collaborate with HTA bodies and payers earlier in the development process to ensure that data collected in routine practice align with decision-maker needs.

Across the panel, there was broad agreement that earlier, multi-stakeholder scientific advice, bringing together regulators, HTA bodies, payers, clinicians, and patients, will be critical to avoid misaligned expectations and to shape data collection strategies that are feasible, meaningful, and sustainable.

Conclusions

The session revealed a fundamental tension that lies at the heart of modern evidence-based decision-making: RWE can be highly valuable, yet it cannot compensate for fundamental limitations in study design when used as a stand-alone basis for regulatory approval or reimbursement.

SESSION 4: SUBMITTING RWE TO REGULATORS, HTAS, RESEARCHERS AND PAYERS

Stakeholders uniformly recognised the severity of unmet need but their views differed in how much uncertainty they were willing to tolerate. Regulators emphasised methodological rigor and feasibility of confirmatory evidence; HTA assessors focused on actionable uncertainty and decision impact; payers emphasized operational realities and the importance of structured access pathways; and industry highlighted feasibility constraints and the imperative to serve patients with no alternatives.

Ultimately, the discussion underscored that RWE can support but not replace other forms of robust evidence generation. It also highlighted the increasing need for coordinated, cross-sector approaches to evidence planning, particularly in areas where traditional trials are infeasible. The mock case served its intended purpose by illuminating both the promise of RWE and the structural limitations that must be addressed to make RWE-driven decisions both scientifically defensible and socially acceptable.

SESSION 5: THE FUTURE OF RWE-BASED HTA, PRICING & REIMBURSEMENT MODELS

Session 5 was a continuation from session 4 and explored how real-world evidence (RWE) is reshaping health technology assessment (HTA), pricing, and reimbursement models across Europe, particularly in the context of growing uncertainty around novel and precision medicines.

The session focused on how managed entry agreements (MEAs) and structured post-launch evidence generation can support access to innovation while maintaining sustainability and predictability for health systems.

The session opened with presentations from Tarang Sharma (WHO) and Steve Williamson (NICE), followed by a panel discussion.

Tarang, Technical Officer for the Novel Medicines Platform (NMP) and HTA at WHO/Europe, presented the WHO/Europe Novel Medicines Platform. She noted that WHO/Europe spans 53 countries, including the EU27, the UK, candidate accession countries, and Central Asia, highlighted a growing focus on novel treatments and precision medicine.

Establishment and Purpose

Launched in March 2023, the NMP is a multisector forum supporting structured dialogue on access to novel medicines. It is similar in spirit to initiatives such as the GetReal Institute, being a multi-stakeholder, convening payers, HTA bodies, regulators, ministries, industry associations, civil society, patient groups, and international partners such as OECD and the European Commission. More than 150 stakeholders have registered.

Its core aim is to create a shared space for public–private collaboration to improve access to innovative treatments.

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Objectives

Stakeholders agreed on five objectives:

1. Formal collaboration enabling countries and partners to work collectively, with flexibility for countries to choose their representatives (HTA body, payer, regulator, or ministry).
2. Transparency, clarifying what information can be shared across stakeholders and where legal limits apply.
3. Solidarity, ensuring all countries receive the support needed to address complex access challenges collectively, regardless of their size or resources.
4. Sustainability, identifying ways to manage the high cost of innovative medicines without undermining health system budgets.
5. Antimicrobials, in response to stakeholder demand for a dedicated workstream on antibiotic access and incentives.

Focus on Managed Entry Agreements

Tarang focused on one project in particular: developing principles and tools for managed entry agreements (MEAs). Chaired by NICE with technical support from a WHO Collaborating Centre at Utrecht University and led by Tarang from the WHO Secretariat, the project sought to create shared principles for agreements between developers and payers when uncertainty about a new treatment is high.

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Development Approach

A literature review helped produce initial draft principles. These were refined through:

- Expert consultation
- Discussions with patient groups, academics, industry, clinical professionals regulators, HTA bodies and payers.
- Academic peer review
- Broad consultation across all NMP stakeholders

The principles were also tested in practice:

- Moldova, which is planning to adopt MEAs to expand access to innovative therapies. WHO, NICE, and Utrecht provided hands-on capacity building with the ministry, procurement body, and HTA agency.
- Greece, which is preparing a Reimbursement Innovation Fund and plans to pilot elements of the framework.

Additional Country Examples (UK, Italy, France)

Tarang also noted examples informing Greece's approach and illustrating how countries are operationalising MEAs and RWE-based reimbursement:

- United Kingdom – Greece is looking to the UK's *Innovative Medicines Fund* and experience with conditional reimbursement pathways that link managed access with evidence development.
- Italy (AIFA) – Italy's *Innovative Medicines Fund* and long-standing system of AIFA registries provide structured mechanisms for outcome-based and conditional reimbursement, including data collection tied to real-world use.
- France (HAS) – France's experience with registries overseen by HAS shows how routine data can support conditional reimbursement, monitoring, and iterative decision-making.

These examples illustrate how established data systems and dedicated innovation funds help countries implement MEAs more effectively.

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Emerging Principles

Key draft principles include:

- Standard HTA as the preferred route; MEAs should be used only when necessary.
- Simplicity over complexity, avoid heavy data or administrative burdens.
- Time-limited agreements, ideally 2–5 years, with opportunities to learn and adapt.
- Clear assessment and exit terms defined from the outset.
- Collaborative roles across developers, clinicians, patients, and country authorities.
- Regular evaluation and monitoring throughout the agreement.

For outcome-based MEAs:

- Use existing data systems and registries wherever possible.
- Ensure transparency about what information can be shared legally and practically.
- Align with developments such as the European Health Data Space, which will make aspects of registry data more interoperable and accessible.

MEA Complexity Scale and Framework

Tarang presented a scale from standard reimbursement to financial MEAs, mixed models, and outcome-based agreements such as coverage with evidence development or pay-for-outcome structures. Increased complexity corresponds to greater uncertainty and higher expected clinical value.

A four-phase MEA framework, selection, contracting, implementation/ monitoring, and managed exit, was also developed. Each phase includes checklists and practical tools to support decision-making.

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Conclusion

Tarang concluded by recognising the significant contributions from participating countries and stakeholders. The MEA work exemplifies the NMP's mission: producing practical, consensus-based tools that help countries across the WHO European Region improve access to innovative treatments while managing uncertainty and budget impact.

Managed Access at NICE

Steve Williamson, Associate Director of Managed Access at NICE, provided a clear explanation of how NICE uses Managed Access to handle uncertainties that prevent immediate routine commissioning. His talk outlined how feasibility assessments determine whether real-world evidence (RWE) can realistically resolve these uncertainties and support early access to innovative therapies in the NHS.

Purpose of Managed Access

Managed Access is NICE's framework for enabling early patient access to promising medicines while generating additional evidence to address unresolved clinical and economic questions. It applies to treatments with clear potential but significant, resolvable uncertainty. The framework relies on the Cancer Drugs Fund (CDF) and Innovative Medicines Fund (IMF), which have evolved from politically driven access schemes into structured funding mechanisms for cancer and non-cancer medicines, particularly in rare diseases. Both operate under fixed budgets to ensure sustainability.

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Core Principles

Steve emphasised that strong guiding principles ensure consistency. To qualify for Managed Access, a treatment must:

1. Address an unmet need and show credible benefit;
2. Have uncertainties that can be resolved within a reasonable timeframe;
3. Present at least one plausible ICER within range, otherwise, additional evidence will not solve the cost-effectiveness barrier.

Although MA is often described as lasting up to five years, typical agreements run just over two. Longer durations occur when evidence is based on early-phase or single-arm trials. All eligible patients must have access during MA, which can be infeasible for very large populations, Alzheimer's was cited as an example. A significant manufacturer obligation is that, if NICE's final recommendation is negative, patients already on treatment continue at the manufacturer's expense, a factor that influences company behaviour, especially for chronic therapies.

When Managed Access Is Considered

A NICE committee must first issue a negative routine commissioning decision before MA is explored. Only when additional evidence could resolve the key uncertainties does the MA pathway open. NICE's Managed Access team then advises the committee on feasibility and realistic data-collection expectations, ensuring MA is used selectively and not as a default middle option.

Feasibility Assessment

The feasibility assessment is central to determining whether MA is workable. NICE's technical team examines every uncertainty in the clinical and economic evidence and assesses whether RWE, extended follow-up, or both could address them. This involves engagement with clinicians, registries, payers, and manufacturers. Practical issues, clinical workload, data-capture capacity, infrastructure readiness, and systemic constraints, are key considerations. Findings are summarised in a colour-coded assessment built from a comprehensive spreadsheet mapping uncertainties to potential evidence solutions.

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Lessons and RWE Considerations

Successful MA agreements typically rely on ongoing clinical trials, with RWE used to supplement, not replace, core evidence. Agreements are more effective when data demands are minimal, registries already exist, and outcomes such as survival and quality of life can be reliably captured. Steve warned against viewing MA as a way to avoid negative decisions; the uncertainty must truly be solvable. He also shared the technical factors NICE weighs when judging RWE suitability, including data provenance, completeness, linkage, bias, outcome clarity, and analytic timelines.

Exits from Managed Access

Most MA agreements have exited with positive NICE recommendations, with only a few leading to negative outcomes or product withdrawals. This high success rate demonstrates the value of a disciplined, feasibility-driven approach.

Conclusion

Steve offered a transparent account of how NICE balances early access with evidence rigor and financial stewardship. His focus on feasibility, stakeholder alignment, and principled criteria highlighted the sophistication of the Managed Access framework and its importance in using RWE to support reimbursement and innovation in the UK.

Panel Discussion Summary

The panel explored the feasibility and value of implementing structured national frameworks for managed entry agreements (MEAs) and post-launch evidence generation, reflecting on the examples presented earlier in the session. Christine Leopold (Utrecht University) opened by noting that despite the complexity of such frameworks, evidence from countries like England suggests they often lead to positive decisions, prompting the question of whether more systematic approaches could be adopted across national health systems.

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Usefulness of Frameworks and Implementation Challenges

Sahar Barjesteh van Waalwijk van Doorn-Khosrovani emphasized that these frameworks are essential preparation tools for countries facing waves of new and evolving technologies. However, she raised concerns about the administrative burden placed on clinicians, particularly regarding additional data collection, which may hinder successful implementation. This challenge resonated with earlier discussions about the need to align clinical and policy expectations around data use.

Adding an industry perspective, Leo Russo highlighted the value of detailed frameworks even when they differ across countries. While acknowledging limitations posed by national variability, he noted that simply having structured approaches can support convergence and potential cross-country alignment over time.

Toward Convergence on Uncertainties and Evidence Needs

Christine and Tarang both underscored the growing opportunity for harmonisation through European regulatory developments. Tarang noted that the new Joint Scientific Consultation mechanisms under the EU HTA Regulation allows for coordinated input from 27+ countries on both clinical trial design and post-launch evidence generation. This creates new avenues to agree on uncertainties, relevant endpoints, and data collection needs early in development. Countries beyond the EU, including accession candidates, are closely following this model, signalling potential for broader regional alignment.

Long-Term Vision: Embedding Learning Into Health and Life Sciences Systems

Carole Longson stressed that MEA frameworks are becoming indispensable given the increasing uncertainty surrounding new medicines, particularly with precision therapies and smaller populations. Drawing on experience with the Cancer Drugs Fund and NICE, she argued for a future where learning processes are embedded throughout the product lifecycle. In such a system, uncertainties would be mapped earlier, managed entry decisions would be informed by real-world data generated in routine care, and the role of real-world evidence (RWE) would shift from peripheral to central.

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Balancing Innovation with Practical Realities

Peter offered a measured regulatory perspective, supporting the move toward personalised medicine while cautioning against overcomplexity. He emphasized that drug development is already costly and demanding, and systems must avoid creating barriers that reduce predictability for developers. Peter advocated for maintaining strong evidence standards for large-population indications, while using RWE more flexibly in small-population or precision-medicine contexts. He also requested clarification on whether MEA assessments are carried out at the individual patient level or based on aggregated cohort data.

Experiences With Patient-Level Versus Cohort-Level Approaches

Steve clarified that NICE's managed entry agreements assess outcomes at the cohort level, ensuring broad access while analysing anonymised aggregated data. Sahar added insights from the Netherlands, where early attempts at patient-level pay-for-performance proved impractical. The Dutch now rely on cohort-based evaluations during defined test phases, assuming clinicians discontinue ineffective therapies without formal patient-by-patient verification.

Future Directions: Building Systems That Enable Individual-Level Outcome Tracking

Carole and Tarang both argued that while patient-level performance-based models may not feasible today in many countries, they should remain an aspirational goal. Tarang highlighted Greece's current efforts to build a new innovation fund alongside health-system digitalisation, an example of how smaller countries investing in modern infrastructure may enable individualized outcome tracking, particularly for ultra-rare and ATMP therapies.

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Conclusion

The discussion underscored strong support for national MEA and RWE frameworks as essential tools for managing uncertainty and enabling access. At the same time, panellists highlighted persistent challenges: administrative burden, infrastructure gaps, national fragmentation, and the need to preserve predictability in drug development. Despite these barriers, there was clear alignment around a long-term vision for a health and life sciences system in which early alignment on uncertainties, coordinated evidence generation, and eventual patient-level outcome data form the foundation for more adaptive, responsive decision-making.

SESSION 6: NEXT-GENERATION RWE STRATEGIES FOR REGULATORY DECISION-MAKING

The session, moderated by Melinda Hanisch (MSD), examined how real-world evidence (RWE) has evolved from a concept used mainly to contextualise or address safety concerns through post-authorisation studies, to one increasingly applied in benefit/risk assessment as a whole, including disease natural history and use and effectiveness of medicines. Melinda highlighted the impact of federated data networks such as DARWIN EU and of the forthcoming European Health Data System, which offer new opportunities despite some current challenges with data fragmentation and quality. She also noted that demand for RWE now extends beyond the regulatory environment to HTA bodies, payers, patients and healthcare providers, reinforcing the need for next-generation strategies.

The panel featured Catherine Cohet (EMA), Peter Mol (UMCG & CHMP), and Daniala Weir and Lourens Bloem (Utrecht University).

Catherine presented use cases of EMA-led real-world data studies and how RWE from these studies inform EMA committees. She described a study characterising RSV disease burden in adults aged fifty and older, which supported CHMP discussions on unmet need and established baseline outcomes for future vaccine effectiveness studies. She then outlined work undertaken during the 2022 mpox public health emergency, where limited clinical evidence for a repurposed vaccine drove the need for rapid real-world effectiveness data. To address this need, evidence was generated from both prospective data collection in Germany and secondary use of data from the US. When the outbreak declined before sufficient data could be gathered, a retrospective target trial emulation approach enabled comprehensive effectiveness and safety evidence to be available to support the EMA Emergency Task Force, including for readiness in case of future public health crises.

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Catherine also summarised a study in DARWIN EU which supported closing safety signals of insomnia, erectile dysfunction, and increased blood pressure in migraine patients treated with CGRP antagonists, and a study exploring a suicidality signal in patients with chronic skin conditions treated with doxycycline, which confirmed that currently available evidence does not support an association. Additional studies included a DARWIN EU natural-history study of juvenile polymyositis and dermatomyositis that informed the paediatric investigation plan by showing availability of sufficient patient numbers for controlled trials; an HTA-triggered analysis of immunotherapy outcomes in non-small cell lung cancer, which aligned with expectations from clinical trials; a proof-of-concept study on the utilisation of *Pelargonii radix* herbal preparations for respiratory indications; and a pharmacogenomics study exploring the risk of muscle symptoms associated with statin use in relation to genetic variants, demonstrating the capacity of DARWIN EU to leverage data from biobanks. She concluded with an overview of ongoing EMA projects ranging from routine drug utilisation studies to complex causal inference studies, feasibility work in several therapeutic areas, methodological initiatives, and continued vaccine monitoring and emergency preparedness activities.

Daniala introduced Target EU, a project combining target trial emulation with the estimand framework to strengthen causal inference in non-interventional studies. She explained that while RCTs remain the gold standard, well-designed real-world studies can address questions where trials are infeasible. Target EU developed hypothetical target trials for ten case studies, assessed data-source feasibility using EMA's quality framework, and created emulation protocols to be executed using a common data model. The case studies span multiple disease areas, include oncology and orphan products, and make use of diverse European datasets, including studies involving pregnant and elderly populations.

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Daniala illustrated the approach using a case inspired by the DECLARE-TIMI 58 dapagliflozin trial, explaining how populations, treatments, outcomes and intercurrent events were defined consistently between the hypothetical trial and its real-world emulation. She noted that the estimand framework clarifies how to handle intercurrent events, while target trial emulation drives methodological rigour. Interim findings suggest the two frameworks are highly complementary.

The final presentation, from Lourens, addressed the role of RWE in managing uncertainty across the decision-making lifecycle. Lourens emphasised that all regulatory decisions involve uncertainty and described how oncology medicines authorised between 2011 and 2022 carried a median of six unresolved uncertainties at approval, particularly in cell and gene therapies and conditional approvals. These uncertainties stemmed in most cases from limited or no data, and concerns about data validity. In this context, post-authorisation trials intended to resolve uncertainties are often delayed or inconclusive, and some medicines later fail to demonstrate expected benefits.

Lourens noted that HTA bodies and clinical societies such as ESMO and ASCO frequently judged oncology medicines to have unproven benefit at approval, especially those authorised via expedited pathways. He highlighted increasing calls for research on treatment optimisation, including dosing and treatment sequences in real-world settings. He argued for timely, robust, transparent real-world studies, alongside reproducible methods and data sharing, and questioned whether regulators should play a broader role in facilitating generation of RWE on treatment optimisation.

SESSION 6: NEXT-GENERATION RWE STRATEGIES FOR REGULATORY DECISION-MAKING

During the panel discussion, speakers explored how to help non-specialists, including patients and the public, understand the opportunities and challenges of RWE. Peter Mol emphasised the value of robust methodological approaches and leveraging lessons learnt. Daniela highlighted the importance of education and open and transparent sharing of protocols and code. Catherine underlined the role of regulatory and non-regulatory guidance, communication and stakeholder involvement, pointing to initiatives such as EMA's patient experience data reflection paper and the ICH M14 guideline. Lourens stressed the need for harmonisation across organisations to avoid conflicting or duplicative guidance and expressed interest in future enhanced mechanisms for integrating new evidence into product labels as foreseen in the new European general pharmaceutical legislation.

SESSION 7: AI & RWE: INNOVATION MEETS EVIDENCE ACROSS THE PRODUCT LIFECYLE

Artificial intelligence (AI) is emerging as one of the most consequential forces reshaping the real-world evidence (RWE) ecosystem, from the transformation of clinical data into analysable variables to the redesign of health technology assessment (HTA) processes and internal regulatory operations. During this session, moderated by Stephen Duffield of NICE, experts from academia, industry, and healthcare systems explored the promise and challenges posed by AI in RWE across the product lifecycle. Their reflections, demonstrations, and methodological perspectives revealed a field undergoing rapid expansion, yet still grounded in the enduring principles of scientific rigour, data quality, and human oversight.

1. Opening Context: The Shift from Human-in-the-Loop to Human-at-the-Helm

Stephen began by acknowledging the pervasive presence of AI not only in healthcare but across society, noting that even those attempting to avoid the technology find it “encroaching on all of our lives.” From the vantage point of HTA bodies such as NICE, AI must be confronted directly: its usefulness, its risks, and the transformations it may bring must be understood proactively rather than reactively.

In outlining NICE’s current stance, Stephen described three distinct domains in which AI is set to play a role. First, there is AI used in the evidence submitted to NICE, such as in algorithmically curated datasets. Second, AI may be incorporated into the technologies that NICE evaluates, for example within software-as-a-medical-device or diagnostic products. Third, AI increasingly influences the internal operations of the organisations themselves.

To manage this rapidly evolving landscape, NICE has developed both a Statement of Intent and a Position Statement. The Statement of Intent articulates the challenges and opportunities AI presents setting out an approach to develop further guidance and collaboration in this area, while the Position Statement provides interim guidance on how to approach submissions that involve AI, recognising that formal methods manuals may be slower to update and less able to keep pace with technological change. Stephen also introduced, for the first time publicly, an update to NICE’s Real-World Evidence Framework, which includes best practice principles for reporting and validating AI methods that have been used to transform unstructured data into structured data for analysis. This reflects a growing prevalence of algorithmically curated variables within datasets submitted for HTA.

SESSION 7: AI & RWE: INNOVATION MEETS EVIDENCE ACROSS THE PRODUCT LIFECYLE

Stephen outlined that future trajectories may move "from human-in-the-loop to human-at-the-helm," ways of working, where AI is no longer a peripheral helper but a central instrument whose use must be guided firmly by human expertise and governance.

Extracting Structured Evidence from Clinical Narratives: AI in Hospitals and Evidence-Generating Medicine

The session then turned to the practical application of AI in healthcare settings, beginning with Calum Yacoubian (IQVIA). Over the last decade, natural language processing (NLP) and, more recently, LLM-augmented workflows have become instrumental in converting the vast corpus of narrative clinical notes into structured variables that can support research, registries, and quality improvement.

Calum demonstrated how hospitals are already using NLP and agentic AI systems to restructure electronic health records (EHRs). He highlighted the fundamental problem: many of the most clinically meaningful details, such as tumour staging, histopathological descriptors, functional assessments, treatments, and temporal relationships reside exclusively in free-text form. Structured fields, such as ICD-10 codes, are blunt tools that obscure nuance and often cannot even differentiate cancer subtypes. The example of lung cancer illustrated this vividly: even distinguishing non-small cell from small cell disease in structured data can be unreliable, let alone detailed staging or biomarker information.

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In the live demonstration, Calum showed synthetic oncology medical records being converted into structured CRF-style output fields. The AI system identified relevant variables, indicated whether information was explicit, inferred, or missing, and provided structured fields for downstream use. Inferred information was flagged transparently, enabling humans to review the logic or seek additional documentation. The system also demonstrated how multiple specialised models operate together: an "agentic" architecture determines which model to use for each information request, selecting among ontology-based tools, rule-based NLP, or LLM components. Calum argued that hybridisation is essential, asserting that combining models "gets the most accurate answers," a principle reflected across many institutions now deploying similar systems.

The demonstration also illustrated the system's capacity to generate clinical documentation, such as referral letters, from medical context. Calum stressed that while these capabilities are remarkable, they do not eliminate the need for humans. Instead, AI should reduce administrative burdens, improve accuracy, and enable more timely evidence generation. He echoed a phrase that resonated throughout the session: "AI is there to make people's lives better."

The broader vision Calum presented is one in which hospitals evolve from evidence-based medicine to evidence-generating medicine, creating "living" data ecosystems that continuously supply insight. This shift, he suggested, will become foundational for research, registries, regulatory submissions, and future HTA processes.

Scaling Oncology Curation Through LLMs: Depth, Breadth, and Analytical Transformation

Melissa Estevez (Flatiron Health) provided a detailed view of how LLMs are enabling oncology data curation at scales that were previously unimaginable. Flatiron now uses ML/LLMs to curate over 40 unstructured variables across a dataset of 950,000 breast cancer patients. The breadth of this dataset allows researchers to examine small subpopulations, emerging biomarkers, and nuanced treatment patterns without sacrificing clinical granularity.

SESSION 7: AI & RWE: INNOVATION MEETS EVIDENCE ACROSS THE PRODUCT LIFECYLE

Melissa emphasised that LLMs allow Flatiron to maintain depth while expanding scale. New variables, such as ctDNA testing details, can be incorporated rapidly and then applied across pan-tumour datasets. Earlier, adding such variables required substantial manual abstraction pipelines. Now, once an LLM model is built, the organisation can immediately scale it to hundreds of thousands of records.

The practical impact of this capability is evident in predictive modelling and digital twin applications. In a lung cancer project, Flatiron sought to model survival outcomes for patients receiving standard-of-care treatment, while accounting for shifts in treatment patterns following the approval of immunotherapy-plus-chemotherapy combinations. Specifically, in time periods where chemo plus immunotherapy became preferred standard-of-care, some patients continued to receive chemo alone, raising concerns about time-dependent confounding by indication. Using LLMs, Flatiron was able to rapidly extract potential confounders such as autoimmune comorbidity information from the patient charts. This variable, absent from the standard data model, was essential for improving the accuracy and interpretability of the predictive model.

Melissa emphasised to the importance of validation. Traditional machine learning metrics such as sensitivity and precision, while important, paint only a partial picture. It is not sufficient to know that a model is “85% accurate” without understanding the context of the remaining 15%. If a metastatic diagnosis date is wrong by two days, the impact is minimal; if it is wrong by six months, downstream analyses, such as treatment sequencing, may be substantially distorted. Hence, Flatiron’s approach incorporates three validation layers: benchmarking model performance against human abstractors, conducting patient-level consistency checks (including temporal logic and cross-field coherence), and performing replication analyses comparing clinical outcomes calculated from LLM-curated data to those derived from human-curated datasets.

Melissa stressed that validation must be risk-based. Not all use cases require the same level of scrutiny, and methodological expectations should be aligned with the intended downstream use of the data.

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Data Engineering as the Primary Constraint: Linking, Cleaning, and the Burden of Real-World Data

While the capabilities of AI are expanding rapidly, Ashwin Kumar Rai (Thermo Fisher Scientific) drew the audience's attention back to a fundamental bottleneck: data quality and engineering. Ashwin noted that despite the excitement around LLMs and agentic AI, the core barrier in healthcare remains the difficulty of obtaining, cleaning, linking, and standardising real-world data. He highlighted a persistent gap between clinical and administrative coding practices, which results in divergent narratives between EHR entries and claims records. For instance, clinicians document diagnoses and treatments for clinical purposes, while claims personnel may use different codes oriented toward reimbursement.

Temporal alignment poses another challenge. Services recorded in EHRs may only appear in claims databases months later, complicating linkage efforts and corrupting patient journey reconstruction. Ashwin estimated that most of the time in an AI project is spent preparing data, not developing models. He emphasized that while models can be built in a matter of hours, the real work and the majority of project time is spent locating, cleaning, harmonising, and validating the data.

Ashwin also explained that general-purpose LLMs, while impressive, must be adapted to domain-specific content to be reliable. Without appropriate training data, oversight, and governance structures, their outputs may be unstable or misleading. Trust, he insisted, is the essential ingredient. Organisations must cultivate trust incrementally by starting with small, low-risk projects that demonstrate value quickly. He also noted that deploying models within institutional environments such as behind firewalls can mitigate many privacy and governance concerns, though robust oversight and model governance remain essential.

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AI for HTA: Abstraction, Comparability, and the Emergence of Computable Guidance

Turning from evidence generation to evidence assessment, Jan-Willem Versteeg (Utrecht University) described two major areas in which the use of AI in HTA processes are being studied/developed. First, AI is being used to abstract information from HTA reports, guidance documents, and methodological manuals. This supports comparative HTA research by enabling cross-agency comparisons of the evidence requirements, analytical approaches, and decision rationales used in different jurisdictions. For comparative researchers, policymakers, and industry teams seeking to understand how their evidence packages may be judged in different markets, this type of abstraction tool is potentially transformative.

The second application involves making HTA recommendations machine-readable. As part of a collaboration with the Dutch National Healthcare Institute, Jan-Willem is developing computable recommendations that can be linked to clinical databases. This linkage would allow real-world monitoring of whether HTA-recommended starting and stopping rules are being followed, whether real-world outcomes align with trial expectations, and when new evidence signals the need for reassessment. He argued that this approach would allow HTA bodies to prioritise re-evaluations more systematically and create a foundation for “living HTA,” in which assessments are updated dynamically as data evolve.

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Concerns from the Field: Feasibility, Access, and Cultural Barriers

During the discussion period, a European regulator shared the experience of attempting to use an NLP algorithm for data abstraction across seven hospitals in the Netherlands. Despite the modest nature of the task, it took two years to secure participation from those hospitals. Even once the system was deployed, validation revealed that while many outputs were correct, the model was "not very clever," requiring substantial manual review. The regulator asked how organisations such as IQVIA overcome institutional hesitancy, particularly given concerns about allowing AI algorithms, especially LLMs, access to hospital data.

Calum acknowledged that scepticism remains widespread, particularly in Europe. He clarified that many hospitals are more comfortable with models that operate within their secure environments rather than in external cloud systems. He argued that the risks associated with using AI tools inside hospitals' own privacy boundaries are often lower than the risks of traditional paper-based workflows. He noted, however, that acceptance will grow only as organisations see clear evidence of value and as guidelines for AI-derived evidence become better established.

Final Reflections: How Organisations Should Begin and Where the Field Is Headed

At the conclusion of the session, panellists offered practical advice for organisations seeking to begin using AI. Ashwin emphasised the need to start with manageable projects that deliver quick results and to ensure that data infrastructure is robust before attempting more complex applications. Calum cautioned against treating AI as a hammer searching for nails; organisations should begin with clear problems that matter to their clinicians or researchers, particularly those that reduce workload burdens at clinical sites.

Melissa pointed to the future direction of AI-enabled evidence generation: the integration of multiple data modalities, text, structured EHR fields, genomics, imaging, and more, into unified embedding spaces that allow models to reason across previously disconnected data types. This shift, she suggested, will move AI's role from data extraction to a deeper role in analysis itself.

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Jan-Willem advised HTA organisations to begin by building internal literacy, mapping out their existing knowledge and processes, and identifying simple tasks where AI can add value. Starting small, he argued, is essential for building trust, especially in environments that must uphold high standards of methodological transparency.

Conclusion

The session revealed a RWE landscape in rapid transition. AI has already become integral to how unstructured clinical data are transformed into structured research variables, how oncology datasets are curated at scale, and how predictive models expand the analytical possibilities available to researchers. It is beginning to permeate HTA processes through automated abstraction and the development of computable recommendations. At the same time, significant challenges remain: data quality, linkage, governance, validation, reviewer training, and the cultivation of institutional trust.

What emerged most clearly is that while AI's capabilities are accelerating, the principles of rigorous evidence generation and assessment remain unchanged. As Stephen remarked, AI may come to redefine how evidence is generated, assessed, and applied, but "the principles of good science remain exactly the same." The task ahead is to ensure that the methods, governance structures, and regulatory frameworks evolve rapidly enough to guide AI toward responsible, transparent, and decision-grade use throughout the healthcare ecosystem.

SESSION 8: ADVANCING PATIENT-CENTRIC REAL-WORLD EVIDENCE AND DIGITAL HEALTH INTEGRATION

The panel session moderated by Mariam Bibi from the GetReal Institute brought together three experts, patient advocate and clinician Iain Armstrong (PHA UK), digital health and RWE leader Ian Bonzani (IQVIA), and patient experience research specialist Kevin Marsh (Thermo Fisher Scientific). Across their presentations, dialogue, and audience discussion, a central theme emerged: although patient centricity is widely referenced across research and real-world evidence generation, it is still too often a slogan rather than a lived practice. The session therefore set out to interrogate what genuine patient centricity requires, how it can be operationalised, and how digital health and patient preference science can help shift the field from rhetoric to meaningful reform.

The session opened by asking the audience to submit the first word or phrase that came to mind when encountering "patient centricity." The responses, ranging from PROs, quality of life, empathy, equity, what matters to the patient, and voice, reflected both the diversity of interpretations and the lack of consensus around the term. This set the scene for a panel discussion aimed at examining patient centricity not as a vague aspiration but as a tangible set of commitments.

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Iain Armstrong began with a critique of what currently passes for patient centricity. He argued that it is too often reduced to tokenism, where patients are given visibility but not influence. Iain Armstrong explained that "being seen is not the same as being heard, and being heard is not the same as being listened to and trusted." He described a recurring pattern in research in which patients are invited into discussions but their contributions are not treated as evidence. Iain Armstrong emphasised that this is ethically problematic, given that participation in research requires substantial emotional effort and investment from patients. If their insights do not meaningfully shape the research, then the system has failed them.

For Iain, genuine patient centricity is a mindset rather than a method. It requires designing studies with patients rather than for them and embedding emotional security into every interaction. He highlighted the importance of recognising that people engage with healthcare from multiple identities and that real-world data should encompass emotional and social dimensions, not only clinical variables. Iain Armstrong criticised the long-standing tendency to treat qualitative data as "soft," arguing instead that it must be treated as rigorous evidence, particularly when the goal is to understand how patients live with and interpret their conditions and treatments.

To illustrate the consequences of misaligned outcome measurement, Iain Armstrong recalled a pivotal moment from his qualitative research. A 74-year-old woman participating in a study told him, "I don't just get up in the morning to survive. I get up in the morning to engage in life." This comment changed Iain Armstrong's clinical practice because it highlighted how traditional survival-oriented endpoints overlook what truly matters to patients. He argued that research must be reshaped so that outcomes align with how patients define meaningful improvement, not simply how clinicians, HTA bodies or regulators define it.

Turning to the practical challenge of embedding patient sentiment into research, Kevin Marsh argued that the field has reached a consensus on the importance of patient involvement but has not yet solved the problem of implementation. Kevin presented evidence from an internal survey of 150 scientists assessing the current state of patient experience data. The findings

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demonstrated that while patient-reported outcomes are increasingly integrated into studies, patient preference data remain significantly underutilised. Kevin noted that both the FDA and EMA conceptualise patient experience through two streams: outcomes and preferences. The field has made progress on outcomes but remains far behind on systematically capturing patients' assessments of treatments, their tolerance for side effects, and the trade-offs they are willing to make. Such data are sparsely collected, despite their potential to influence adherence, uptake, persistence, and ultimately real-world effectiveness.

He further explained that the two most common obstacles to collecting preference data are cost and time. Traditional preference studies are lengthy and expensive. Kevin argued that one way to overcome this barrier is to embed preference-related questions into existing RWE infrastructures rather than conduct standalone studies. He highlighted his team's ongoing work with the PPD-CorEvitas obesity registry, where patient assessments, adherence behaviours, and choice-based experiments are being integrated directly into the registry. This will allow stakeholders to predict patterns of uptake and persistence, enabling treatment development and policy decisions to be guided by real-world patient behaviour rather than assumptions.

In discussing how preference data are used by decision-makers, Kevin contrasted regulatory and HTA environments. He observed that the FDA has been the global leader in encouraging the use of patient preference data and that the EMA is increasingly showing interest, supported by the publication of new guidance on patient experience data. In contrast, HTA bodies remain much more resistant. According to Kevin, the European HTA environment is characterised by normative barriers, including long-standing centrality of public preferences in treatment valuation, based on the often misplaced assumption that patient adaptation to their conditions and undervalue certain clinical outcomes. He argued that the HTA system is "not ready" for systematic use of patient preference data, though he suggested that future harmonisation across Europe may be more achievable if patient perspectives are incorporated more explicitly.

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Ian's presentation shifted the conversation toward the role of digital health technologies in capturing patient experience. He cautioned against treating digital health as a monolithic concept, explaining that it includes a diverse set of tools such as digital outcome assessments, wearable-derived biomarkers, and platforms for decentralised study participation. Each serves different functions, and their effective use depends on matching the right technology to the right purpose.

Ian reviewed the rapid growth of digital measures across therapeutic areas, noting that the field has expanded beyond simple activity tracking into more complex domains such as voice, gait, and sleep. Regulators and payers are showing increasing openness to these measures, although the field has also learned from past instances of excessive or inappropriate adoption of digital tools. He characterised the current landscape as a period of "enlightenment," in which enthusiasm is tempered by recognition of the need for rigorous endpoint selection, clear purpose, and strong data governance.

A core message from Ian was that digital technologies can make research more accessible by enabling decentralised and virtual participation. Patients can complete assessments from home, and study teams can monitor compliance and identify emerging issues more quickly. However, he emphasised that digital tools cannot replace the human infrastructure required for high-quality research. Successful implementation requires support from investigators, nurses, data managers, and technical teams. Without these "wrap-around" services, digital studies risk poor compliance, unusable data, and patient frustration.

An important theme running throughout the session was the challenge of informed consent. An audience question described a decision aid developed for a metastatic lung cancer study, which proved far more effective than traditional consent forms. Kevin acknowledged that although sponsors have attempted to make consent materials more patient friendly, the impact has been limited. He reiterated that study teams are constrained by time pressure and by an inability to quickly integrate patient-friendly insights into trial design. Iain added that consent documents often prioritise protecting ethics committees and institutions rather than informing patients. He also highlighted that consent processes frequently occur too quickly, undermining patients' ability to reflect or decline participation. Ian agreed and noted that while consent forms may be slow to change due to regulatory constraints, multimedia tools such as videos can enhance understanding and navigation.

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Geographical differences further complicate patient engagement. Kevin observed that while regulators in the US have been proactive in expecting patient preference data, this has not always translated into widespread practice in other regions, including parts of Asia-Pacific. Ian added that operational and regulatory constraints differ substantially across countries. These variations can limit follow-up, restrict communication, and create barriers that ultimately undermine the patient experience, even when technology could help.

As the session drew to a close, each panellist offered reflections on how the field should move forward. Iain stressed that patient involvement must be continuous. Studies should not end only with academic publications but with patient-facing summaries that close the feedback loop. Ian encouraged the field to collect richer forms of patient experience data in RWE studies rather than relying solely on clinical trial instruments. Kevin concluded by urging researchers to collect comprehensive and standardised patient data wherever possible so that insights can be reused and interpreted consistently across studies and geographies.

The session as a whole reinforced three overarching imperatives. First, patient centricity must be experienced by patients as meaningful involvement, not performative inclusion. Second, digital technologies can broaden engagement and improve data collection, but they must be chosen and implemented with precision and with full operational support. Third, evidence generation must reflect what patients genuinely value, not because it is fashionable to claim so, but because such evidence improves decisions, equity, and outcomes across the healthcare system.

SESSION 9: FROM REAL-WORLD DATA TO DECISION-GRADE REAL-WORLD EVIDENCE

Session 9 explored the practical and methodological steps required to transform real-world data (RWD) into real-world evidence (RWE) robust enough to support regulatory and HTA decisions. Moderated by Leo Russo (Pfizer), the session featured perspectives from Catherine Cohet (EMA), Susan Oliveria (Thermo Fisher Scientific), and Martin Russek (BfArM).

Although each speaker approached the topic from a different angle - regulatory, industry, and methodologically, common themes emerged throughout: the primacy of transparency, the importance of feasibility assessments and data quality, the need for study designs driving selection of suitable data sources, and the growing need for global convergence in RWE standards.

EU/international guidance and good practice to support reliable and relevant RWE (Catherine Cohet)

EMA Reflection Paper on Use of RWD in Non-Interventional Studies (NIS) (2025)

Catherine began by outlining the main components of the EMA RWE Reflection Paper. The document clarifies how RWD should be used in descriptive and causal non-interventional studies and emphasises the importance of feasibility assessments, consideration of the target trial and estimand frameworks, and the identification and mitigation of bias and confounding.

She underscored that transparency in design, execution, and reporting, is essential for regulatory trust, and recommended structured data quality assessments using tools such as the EMA Data Quality Framework (DQF).

ICH M14: First Harmonised Guideline on Non-Interventional Safety Studies

Catherine then discussed ICH M14, the first harmonised global guideline dedicated to non-interventional safety studies. While focused on safety, many of its principles extend to effectiveness and drug utilisation research. The guideline describes an iterative approach to study development, to guide investigators through defining the research question, selecting an initial study design, and refining the protocol as feasibility insights emerge.

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She highlighted the guideline's strong emphasis on transparency, documentation of decisions, and strict pre-specification of design and analysis characteristics. Catherine also noted the definition of the term "fit-for-use" in the guideline (often also referred to as "fit-for-purpose", to emphasise alignment between the data at hand and the intended analytic use.

EMA Data Quality Framework (DQF)

Catherine described the DQF, adopted in 2023, as a structured approach for evaluating whether data are suitable for regulatory purposes. The framework's five dimensions: reliability, extensiveness, coherence, timeliness, and relevance provide a set of criteria for assessing data limitations and strengths.

She explained that the DQF includes metrics, checklists, and visual tools, along with an RWD-specific addendum. EMA is currently reviewing public feedback ahead of an updated version expected in 2026.

RWD Catalogues: Transparency Infrastructure

Catherine also introduced the HMA-EMA Catalogues of RWD Sources and Studies, which include more than 250 data sources and more than 3,000 studies. These catalogues are intended to strengthen reproducibility by linking studies to the data sources they rely on and to replace and enhance the EU PAS Register.

The catalogues remain in active development, and an ENCePP special interest group is developing use cases to support their use by researchers.

International Collaboration and Harmonisation

Catherine concluded by situating EMA's efforts within a broader global context. She described collaborations through the International Coalition of Medicines Regulatory Authorities (ICMRA). She also outlined the ICH E23 concept paper, which seeks to harmonise terminology and principles for assessing RWE, particularly effectiveness studies, and noted that revisions to GVP Module VIII are underway to align with ICH M14.

Her final point was that RWE guidance is expanding rapidly across organisations, with challenges around clear terminology and alignment being addressed.

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Industry Perspective: Applying Frameworks in Real-World Studies (Susan Oliveria, ThermoFisher)

Practical Realities of Implementing Multiple Frameworks

Susan provided an industry view, grounded in her experience leading teams conducting post-marketing safety studies, regulatory-support analyses, and studies using both primary and secondary RWD sources. She emphasised the difficulty of meeting the expectations of multiple regulatory bodies simultaneously.

Her core message was pragmatic: each study must be approached on its own terms. Frameworks are useful, but they do not eliminate the practical constraints and data limitations researchers encounter.

“Show Your Work”

Susan’s central recommendation “Show your work” captured the value of exhaustive documentation. She explained that successful submissions are often those that provide meticulous detail: complete descriptions of data sources and feasibility results, explicit definitions of external comparators, clear justification of design decisions, and comprehensive sensitivity analyses.

She observed that many strong submissions include what she described as “almost a little bit of overkill,” reflecting the high premium regulators place on transparency.

Quality Management Systems for RWE

Susan also described how principles from clinical trial quality management systems (QMS) can be adapted to RWE generation. A QMS for RWE would formalize processes, require systematic documentation, and ensure decision traceability going significantly beyond checklist-based approaches. She argued that such systems enhance reproducibility and organisational discipline.

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Foundational Methodology: Design Before Modelling (Martin Russek, BfArM)

Martin delivered a clear methodological message: strong analysis starts with strong design. He cautioned against overemphasis on complex statistical methods at the expense of foundational decisions.

Prioritising Study Design

Martin stressed that well-constructed study design is the most important determinant of credible RWE. Analytical sophistication is of little value without clear methodological intent and explicit pre-specification.

When Advanced Methods Matter

He acknowledged that advanced causal inference tools have appropriate applications, such as when effect sizes are small or confounding structures complex. However, even the most sophisticated methods cannot compensate for flawed design or biased data.

Common Red Flags

Martin pointed to recurring issues in published RWE studies: methods that appear improvised, insufficient description of machine-learning techniques, and absence of clear evaluation criteria. He echoed Catherine and Susan in calling for explicit, pre-specified analytic approaches.

Panel Discussion and Audience Engagement

Pre-Specification as a Critical Weakness

Peter Mol, speaking from the audience, emphasised that failure to pre-specify external control selection and analyses remains a major credibility issue. He noted that constructing external comparators after knowing the trial results severely undermines trust.

Susan added that when post hoc analyses are necessary, they must be explicitly labelled as such and accompanied by updated statistical analysis plans and sensitivity analyses.

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Alignment Between Regulators and HTA Bodies

Carole Longson raised concerns about limited HTA involvement in ICH guideline development. She argued that misalignment between regulatory and HTA frameworks creates inefficiencies and reduces HTA influence within companies. Her comment reinforced the principle of "globalise the evidence, localize the decision."

Catherine acknowledged that HTA participation in M14 was limited but noted increasing collaboration in Europe, for example through the EMA Network Data Steering Group.

The Pace of Guideline Development

Participants observed that the rapid increase in guidance documents, combined with inconsistent terminology, creates challenges for both regulators and industry. Catherine responded that initiatives such as M14, E23, the DQF update, and the GVP VIII revision aim to address these issues, though full harmonization remains a work in progress.

Key Takeaways

Transparency and Pre-Specification

Transparency was repeatedly described as essential. Lack of pre-specification, especially for external controls, was highlighted as a major room for improvement.

Frameworks as Tools, Not Formulas

Speakers emphasized that frameworks support thinking but do not replace scientific judgment.

Feasibility is key

Both EMA and ICH M14 reinforce the need for iterative feasibility assessments to support robust study design.

Systematic Data Quality Evaluation

The DQF provides a structured approach across reliability, extensiveness, coherence, timeliness, and relevance, key for decision-grade evidence.

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Design Before Analytical Complexity

Robust study design must precede advanced models. Causal methods cannot correct for inadequate data or design.

Quality Management Systems Support Rigor

Applying QMS principles to RWE strengthens reproducibility and accountability.

Global Convergence Is Important but Incomplete

ICH initiatives represent progress, but stronger HTA involvement and clearer terminology remain needed.

Conclusion

Across all presentations and the panel discussion, the session reinforced that decision-grade RWE depends on transparency, rigor, and careful documentation at every stage. Early and iterative feasibility assessments, systematic evaluation of data quality, and strict pre-specification were highlighted as cornerstones of credible RWE.

Methodological frameworks are helpful but cannot replace scientific reasoning, and strong study design must always come before analytical complexity. Finally, while global collaboration is increasing, further integration of HTA perspectives and harmonized terminology will be essential to truly align expectations for RWE across regulatory and reimbursement environments.

SESSION 10: MULTI-STAKEHOLDER "HOT SEAT" DEBATE - STRENGTHENING RWE ACCEPTABILITY

The final session of the conference, moderated by Charlie Nicholls (Sanofi), focused on the question: **how can we make RWE more acceptable?** Building on discussions throughout the two-day event, the "Hot Seat" session explored the practical challenges of translating RWE from promise to impact.

Charlie highlighted that while methodologies, data sources, and relevance have been widely discussed, moving RWE into today's decision-making context, strengthening regulatory and HTA submissions, and ultimately enhancing patient care is rarely straightforward. Expectations, data quality, methodological approaches, and decision maker scrutiny all vary, creating a complex landscape for investigators.

The session aimed to learn from both successes and failures, focusing on the lived experiences of RWE investigators. Panellists shared insights into the challenges and barriers encountered in study design and data generation and discussed strategies to overcome issues of acceptability. The goal was to identify how RWE studies can be strengthened meaningfully, providing robust evidence to help inform healthcare decision-making.

The discussion featured four experts: Peter Mol (University Medical Centre Groningen), Frauke Naumann-Winter (BfArM), Pamela Dobay (Biogen), and Finlay MacDougall (IQVIA), each bringing unique regulatory, HTA, industry, and operational perspectives to the conversation. The theme the good, the bad and the ugly was used to illustrate challenges and discuss opportunities and best practice.

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The Good the Bad & the Ugly

Opening the session, Peter Mol offered the regulator's perspective on "ugly" studies, describing the challenges that regulators face when evidence is generated under real-world constraints. In areas such as rare diseases and oncology, conventional trials are frequently impractical, making alternative approaches, like biomarker-driven cohorts or historical comparisons necessary. He explained that as patients transition quickly to newer treatments, trials struggle to retain participants, eroding the robustness of their findings. In these circumstances, investigators turn to RWD to fill evidentiary gaps, raising difficult questions about how much flexibility is possible without undermining the integrity of regulatory and HTA assessments and revise decisions based on failed or inconclusive trials.

Frauke warned against situations where sponsors attempt to salvage an underpowered or failed trial by turning to whatever retrospective data happen to be available. She noted that these efforts may rely on incomplete biomarker information or inconsistent datasets and begin far too late to meaningfully address the underlying evidentiary gaps. In her view, only very specific circumstances allow the expectation that existing data sources fully answer a specific regulatory question without prior preparation (e.g. objective outcome measures in a homogeneous target population). Post-hoc analyses typically cannot compensate for the lack of prospective planning.

She emphasised the need for early interaction with regulators, on how already available data could inform on knowledge gaps and whether or how intentional data collection could enrich existing data so that RWE complements, rather than attempts to repair, a flawed trial.

Pamela introduced the concept of "funky data," which she used to specifically describe RWD generated in disease registries that are eventually used in regulatory studies that may not have been originally intended to answer the proposed question. She described two forms of ugliness: (1) collecting data without understanding its purpose, resulting in irrelevant or poorly structured variables and/or data collection, and (2) stakeholders not accepting the limitations in their dataset, which leads to distrust, due to lack of transparency. She emphasised that unacknowledged limitations reduce the usability of real-world data for patient-focused evidence generation.

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Finlay highlighted that RWE studies are often designed from an academic perspective, working with sponsors highlights the substantial rigor that goes into protocol development, statistical analysis planning, and overall study design, however even the best-laid plans can shift once confronted with real data. Feasibility is particularly difficult to determine upfront, especially in complex areas such as precision oncology. Key variables, such as biomarkers not routinely collected in clinical practice, may require for example retrospective tissue testing and data linkage, introducing constraints related to sample viability, availability and data access. As these limitations emerge, study designs often need to be adapted, sometimes shifting from comparative to descriptive analyses. Differences in clinical practice and endpoint implementation across contributing countries add further complexity. As a result, feasibility often remains uncertain until late in the study, and original plans frequently prove harder to execute than anticipated.

Discussion and Outlook

Navigating methodological best practice and operational realities.

Charlie outlined the "hygiene factors" emphasised in current guidance, namely, the use of pre-specified protocols, prospective registration, and the concerns sometimes raised about iterative adjustments to study designs as if this might be mistaken for "looking under the hood" and seeking desired results. He noted, as with Finlay's example, that feasibility assessments frequently require precisely this type of exploratory examination, creating an inherent tension between methodological best practice and operational realities.

Peter described two examples illustrating how data limitations can undermine planned RWE analyses. In a multi-country Horizon Project study of the off-label use of rituximab in Multiple Sclerosis, four registries initially appeared suitable, but one dataset lacked essential information on treatment retention, forcing its exclusion and reducing the analysis to three registries leading to protocol adjustments and a significant delay in execution. A second example involved a haematology–oncology dataset submitted as an external control. Missing information on patients who left the healthcare system for stem-cell transplantation an important prognostic factor and required retrospective adjustments, which in turn eroded confidence that the external control population was truly comparable. In that case, the evidence was ultimately judged insufficient. Peter explained how early dialogue and transparent explanation of feasibility findings are therefore essential.

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Timing and Early Integration

Frauke stressed that many challenges arise because feasibility exploration begins too late. For promising products, early engagement, often in parallel with early clinical development is crucial. She pointed to patient preference studies as an example where insights gathered before designing the evidence strategy would have far greater impact than those conducted at the end.

Clarifying What "Good" Looks Like

Pamela welcomed the EMA's data quality framework ad updated reflection paper on non-interventional studies, both of which illustrate what "good" data quality and documentation look like. She emphasised the importance of understanding real limitations that only emerge during actual analysis, particularly when sponsors cannot directly access the data. The new guidance, she said, enables clearer articulation of uncertainty and more realistic expectations between sponsors and data custodians.

The Reality of Registries

Finlay described frequent mismatches between registry claims and reality, often discovered only after extensive due diligence. Aspirational coverage estimates, limitations in variable availability, incomplete site participation, and data management and analytical resource constraints were cited as recurring pitfalls. Catalogues or data inventories, he argued, must incorporate lived experience rather than presenting overly optimistic portraits of data availability.

HTA and JCA Timelines: A New Source of Pressure

When asked about the constrained timelines under the EU Health Technology Assessment (HTA) Regulation and Joint Clinical Assessment (JCA), Peter noted the difficulty of obtaining aligned viewpoints from HTA bodies, who themselves are overwhelmed by JCA preparations. Finlay added that compressed timelines create a situation where sponsors must predict PICO requirements in advance, a "PICO guessing industry" because there is no time to generate new evidence once JCAs begin.

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The discussion moved toward how governance and infrastructure can improve evidence acceptability. All panellists agreed on the importance of pre-specified protocols, robust feasibility assessments, and early dialogue with regulators and HTA bodies.

Pamela highlighted the role of dataset quality metrics to benchmark data readiness for decision-making, while Finlay pointed to synthetic datasets as promising tools for testing study feasibility without compromising patient privacy. Both approaches were seen as bridges to transparency and efficiency.

In their final reflections, the panel converged on three priorities:

1. Plan early and seek advice. Align data collection with decision needs from the start.
2. Foster shared understanding among regulators, HTA bodies, industry, and academia.
3. Keep the patient outcome in focus. Acceptability rises when RWE delivers real-world relevance.

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Panel Reflections on How the GetReal Institute Can Enhance Acceptability

Panellists highlighted the Institute's role as a trusted, independent platform for cross-stakeholder dialogue and emphasised several priorities to strengthen acceptability of RWE:

- Sustain the community and momentum. The Institute provides a valuable EU-based forum for regulators, HTA bodies, industry, and researchers to engage outside large conferences. Maintaining this collaborative space and building on ongoing EU and IHI projects was seen as essential.
- Identify "lowest-hanging-fruit" use cases. Rather than approaching trial emulation and other RWE applications case by case, the panel suggested focusing on areas with clear preconditions for success, such as population characteristics and endpoint definitions to develop horizontal learnings and more consistent regulatory uptake.
- Maintain a shared focus on patient benefit. The Institute's strength as a collegial, "safe space" was noted. Ensuring alignment on common goals and stakeholder expectations, grounded in patient needs, will support meaningful progress.
- Build shared understanding of operational realities. Greater transparency around how RWD is generated, its constraints, timelines, and the trade-offs between speed, cost, and evidentiary quality: could improve scientific dialogue and expectations. Working through real examples together was proposed as a practical next step.

Collectively, the panel emphasised that strengthening shared understanding, focusing efforts where RWE can have the most immediate impact, and sustaining an inclusive community will help further enhance RWE acceptability.

CLOSING REMARKS

The GetReal Conference 2025 marked a pivotal moment in the evolution of real-world evidence (RWE) in Europe. Across two days of in-depth discussion, debate, and practical case exploration, the conference demonstrated that RWE is no longer a peripheral or experimental input into healthcare decision-making. It is now firmly embedded across the regulatory, HTA, reimbursement, and post-authorisation landscape.

At the same time, the discussions underscored that wider use of RWE brings heightened responsibility. Confidence in real-world evidence cannot be assumed; it must be earned through transparent methods, robust study design, clear articulation of uncertainty, and sustained multi-stakeholder collaboration. Throughout the scientific sessions, participants consistently emphasised that RWE is most impactful when it is planned early, aligned to clearly defined decision contexts, and generated with an explicit understanding of how it will be interpreted by regulators, HTA bodies, payers, clinicians, and patients.

The conference also highlighted that innovation in evidence generation, whether through pragmatic and hybrid trials, external control studies, federated data networks, AI-enabled analytics, or managed access frameworks, does not reduce the need for methodological rigor. Rather, it demands greater clarity around fitness-for-purpose, governance, and the limits of what RWE can and cannot resolve.

Importantly, patient centricity emerged not as a rhetorical ambition but as a practical imperative. Without systematic integration of patient-relevant outcomes, lived experience, and real-world treatment pathways, even technically sophisticated RWE risks falling short of decision-maker and societal expectations.

Taken together, the GetReal Conference 2025 reinforced a shared conclusion: the future impact of RWE will depend less on the volume of data generated and more on the quality of collaboration, alignment, and trust that underpin its use. The challenge ahead is not whether RWE will be used, but how confidently, consistently, and responsibly it will inform decisions that shape patient access and health system sustainability.

CLOSING REMARKS

Recommendations and Next Steps

1. Strengthen Early Multi-Stakeholder Alignment Across the Lifecycle
Evidence strategies should be shaped through earlier and more structured dialogue involving regulators, HTA bodies, payers, industry, clinicians, and patients.

2. Embed Fitness-for-Purpose as a Core Design Principle
RWE studies must be explicitly designed around the decision they aim to inform, with transparent discussion of limitations.

3. Invest in Data Infrastructure, Interoperability, and Capability
Continued investment is needed in interoperable data systems, federated networks, and analytical capacity.

4. Use Innovative Study Designs Responsibly and Transparently
Innovative approaches must be accompanied by rigorous methodological standards and clear reporting.

5. Apply Managed Access and Coverage-with-Evidence Development Selectively
Managed access frameworks should be reserved for situations where additional evidence can genuinely reduce uncertainty.

6. Systematically Integrate Patient-Relevant Outcomes
Patient-reported outcomes and lived experience should be embedded more consistently in RWE strategies.

The GetReal Institute will integrate the insights and priorities emerging from the Conference into its 2026 research programme. This will include translating key learnings into targeted research activities, methodological guidance, and collaborative initiatives aimed at strengthening the generation and use of decision-ready RWE across regulatory, HTA, and reimbursement contexts.

APPENDIX: SPEAKERS LIST

Anke van Engen	IQVIA
Ashwin Kumar Rai	Thermo Fisher Scientific
Calum Yacoubian	IQVIA
Carlos Martín Saborido	Instituto de Salud Carlos III
Carole Longson	Independent Adviser
Catherine Cohet	European Medicines Agency
Charlie Nicholls	Sanofi
Christine Leopold	Utrecht University
Daniala Weir	Utrecht University
Delphine Saragoussi	Sanofi
Finlay MacDougall	IQVIA
Frauke Naumann-Winter	BfArM
Iain Armstrong	PHA UK
Ian Bonzani	IQVIA
Jan-Willem Versteeg	Utrecht University
Katrien Oude Rengerink	CBG-MEB
Kevin Marsh	Thermo Fisher Scientific
Leo Russo	Pfizer
Lourens Bloem	Utrecht University
Mariam Bibi	The GetReal Institute
Martin Russek	BfArM
Melinda Hanisch	MSD
Melissa Estevez	Flatiron Health
Mira Zuidgeest	University Medical Center Utrecht
Neil Grubert	Independent Consultant
Pamela Dobay	Biogen
Patrice Verpillat	European Medicines Agency
Peter Mol	UMCG & Committee Medicinal Products for Human Use
Sahar Barjesteh van Waalwijk van Doorn-Khosrovani	CZ/LUMC

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Sascha van Boemmel-Wegmann	Flatiron Health
Stephen Duffield	NICE
Steve Williamson	NICE
Susan Oliveria	Thermo Fisher Scientific
Tarang Sharma	WHO
Tim Williams	Clinical Practice Research Datalink