

2026 GETREAL CONFERENCE

Translating Real-World Data into Decision-Ready Evidence: Bringing Data, Methods, and Decision Context Together

CONFERENCE REPORT

GetReal Conference 2026
29-30 June 2026 | Utrecht, Netherlands

CONTENT

Introduction	01
Executive Summary	02
Opening Remarks	05
Keynote Address	07
Session 1: Understanding the Decision Context: What do Regulators, HTAs & Payers Actually Need?	13
Session 2: Data Foundations: Assessing Fitness for Purpose Across the Evidence Lifecycle	23
Session 3: Parallel workshops	35
Session 4: AI & Machine Learning: Accelerating the translation of RWD into decision ready evidence	37
Poster Presentations	41
Session 5: Real-World Evidence in Action: Key Results and Policy Lessons from the MetReal Project Cluster	46
Session 6: EU Joint Clinical Assessment: One Year In, what have we learned?	57
Session 7: Meeting Long Term Follow Up Obligations: Challenges and Opportunities for Post Approval Evidence Generation	69
Session 8: Closing Panel: Translating Learnings into Commitments	77
Closing Remarks	86
Appendix A: Speaker list	
Appendix B: Abbreviations list	



INTRODUCTION



The GetReal 2026 Conference, **"Translating Real-World Data into Decision-Ready Evidence: Bringing Data, Methods, and Decision Context Together"**, took place on **29 and 30 June 2026** at the Crowne Plaza Utrecht, the Netherlands.

Bringing together regulators, Health Technology Assessment (HTA) organisations, payers, industry, academia, patient organisations and data partners from across Europe and beyond, the conference focused on one central question: how can real-world data be translated into evidence that is credible, decision-ready and capable of informing healthcare decisions? Through a keynote presentation, expert panel discussions, case studies, workshops and interactive sessions, delegates explored the scientific, methodological and practical considerations needed to achieve this ambition.

The conference took place at a significant point in the evolution of the real-world evidence (RWE) landscape. **As regulatory and HTA expectations continue to develop, the challenge is no longer simply to demonstrate the value of RWE, but to ensure that it is generated, evaluated and applied in ways that are transparent, robust and fit for purpose.** Reflecting this shift, the 2026 programme examined the data foundations, analytical methods, governance frameworks and collaborative approaches needed to support a evidence package capable of meeting the needs of multiple decision-makers across the product lifecycle.

Throughout the two-day programme, speakers and participants shared practical experiences, emerging methodologies and lessons from across the healthcare ecosystem. Together, they highlighted the progress already being made while recognising that continued collaboration, methodological innovation and stakeholder alignment will be essential to embedding decision-ready evidence into routine regulatory, HTA and payer decision-making.

EXECUTIVE SUMMARY

The GetReal Conference 2026, Translating Real-World Data into Decision-Ready Evidence: Bringing Data, Methods, and Decision Context Together, brought together regulators, HTA organisations, payers, industry, academia, patient organisations and data partners to examine how real-world data can be translated into evidence that is credible, transparent and fit for purpose. Across the two-day programme, a consistent message emerged: the debate has moved beyond whether RWE has value. **The priority now is understanding how it can be generated, assessed and used to support real healthcare decisions.**

The keynote set the direction for these discussions by challenging a rigid application of traditional evidence hierarchies. Randomised Controlled Trials (RCTs) remain fundamental, but increasingly personalised treatments, rare diseases and advanced therapies mean that decision-makers are often required to work with different forms of evidence and residual uncertainty. Rather than viewing RCTs and RWE as competing approaches, the conference highlighted their complementary roles within an evidence ecosystem in which evidence is generated throughout the product lifecycle and judged according to its fitness for purpose.

Decision context matters. Regulators, HTA bodies and payers may consider the same evidence but ask different questions of it. Discussions demonstrated growing convergence around the characteristics that create confidence in RWE: transparent and well-understood data sources, appropriate study design, methodological rigour, reproducibility, capture of clinically important variables and explicit characterisation of uncertainty. The challenge is therefore not to eliminate uncertainty, but to understand which uncertainties matter for a particular decision, whether they are acceptable and how they can be addressed through further evidence generation.

Fitness for purpose must be assessed in relation to the question being asked. Europe's expanding data infrastructure, including federated networks, DARWIN EU and the European Health Data Space, is creating significant opportunities for evidence generation. **However, greater availability of data does not automatically produce better evidence.** Common data models and federated networks can make data quality easier to assess systematically, but understanding provenance, completeness, clinical context and the limitations of individual datasets remains essential. Close collaboration with those who understand the data is therefore as important as the infrastructure through which those data are accessed.

Methodological innovation must be accompanied by transparency, validation and implementation. This was particularly evident in discussions of Artificial Intelligence (AI) and emerging analytical approaches. New technologies have considerable potential to support evidence generation, but their value for regulatory and HTA decision-making will depend on whether methods can be understood, validated and reproduced, and whether governance develops alongside technological capability. Across the programme, speakers repeatedly emphasised the importance of testing new approaches in practice rather than considering methodological development in isolation.

Evidence generation increasingly needs to be planned across the lifecycle. The first experience of EU Joint Clinical Assessment reinforced the need to consider regulatory, HTA and market access requirements earlier in development rather than treating HTA as a downstream activity. Comparative evidence, external controls and RWE strategies should be anticipated during study design, with earlier dialogue between developers and decision-makers helping to identify evidence needs before important uncertainties become embedded in submissions.

The same principle extends beyond approval. Experience with cell and gene therapies demonstrated that authorisation is increasingly one stage in a continuing evidence-generation process. Long-term follow-up, registries, natural history studies and other sources of RWE can address uncertainties around durability, long-term safety, effectiveness in routine practice and patient outcomes. Delivering this evidence over many years, however, requires sustainable infrastructure, consistent data collection, patient engagement and collaboration across organisations and countries.

The MetReal Cluster demonstrated the scale of European methodological innovation already underway, while also highlighting that scientific advances alone will not change decision-making. Better understanding of healthcare data, more efficient data access, transparent and reproducible methods, and environments in which regulators, HTA organisations and researchers can test new approaches together were identified as important conditions for translating research into practice.

Across all sessions, collaboration emerged as a prerequisite for progress rather than an additional consideration. Decision-ready evidence cannot be created by data holders, methodologists, industry or decision-makers working independently. It requires earlier and sustained engagement between regulators, HTA bodies, payers, researchers, industry, patients and data partners, alongside greater willingness to share not only successful approaches but also lessons from studies that have not delivered as intended.

Taken together, the conference pointed towards a more mature phase for RWE. **The task ahead is not simply to generate more real-world data or develop more sophisticated methods, but to connect the right data, appropriate methods and a clear decision context from the outset.** Doing so will be central to moving RWE from promising applications towards a routine, trusted and decision-relevant component of healthcare decision-making.



OPENING REMARKS

The GetReal Institute 2026 Conference was formally opened by Mariam Bibi, Managing Director of the GetReal Institute, who welcomed delegates to Utrecht and introduced the conference theme, **Translating Real-World Data into Decision-Ready Evidence: Bringing Data, Methods, and Decision Context Together**. Her opening address reflected on the progress made in advancing the use of RWE while challenging delegates to consider how the field must now evolve to meet the changing needs of healthcare decision-makers.

Bibi reflected on the evolution of discussions at previous GetReal conferences, noting that much of the focus had been on demonstrating the value of RWE across the product lifecycle. While this had been essential in building confidence in the role of RWE, she argued that the field has now reached a new stage of maturity. The challenge is no longer whether RWE has a place in healthcare decision-making, but how it can be generated, evaluated and applied in ways that support regulatory, HTA and payer decisions.

"Rather than talking about the value of real-world evidence, this year we're focusing more on its use and what that looks like in practice."

She explained that this shift in thinking underpins the 2026 conference theme. Producing decision-ready evidence requires more than access to high-quality data or increasingly sophisticated analytical methods. It also requires a clear understanding of the context in which evidence will be used and the decisions it is intended to inform. Throughout the conference, delegates would therefore explore how data, methods and decision context can be brought together to generate evidence that is credible, transparent and fit for purpose.

The scientific programme was structured to examine the full evidence pathway, beginning with the evidence needs of regulators, HTA organisations and payers before exploring the practical foundations of evidence generation, including data infrastructure, data quality, patient engagement, artificial intelligence, advanced analytical methods, EU Joint Clinical Assessment and post-approval evidence generation. Together, the sessions demonstrated how these elements contribute to the development of decision-ready evidence across the product lifecycle.

Bibi acknowledged the Conference Committee, speakers, moderators, members, partners and sponsors whose continued support had made the conference possible. She noted that the strength of the programme lay not only in the breadth of expertise represented, but also in the willingness of stakeholders from across the healthcare ecosystem to engage in open, constructive dialogue around shared challenges.

Emphasising the interactive nature of the conference, Bibi encouraged delegates to participate actively throughout the two-day meeting by asking questions, challenging assumptions and sharing their own experiences. She highlighted that some of the most valuable insights emerge through discussion between different stakeholder groups rather than formal presentations alone.

"Please do ask questions, engage with the speakers and use this as an opportunity to ask questions that you probably would not have the opportunity to ask in your day-to-day roles."

Collaboration was a central theme of the opening address. As an independent multi-stakeholder organisation, the GetReal Institute provides a forum where regulators, HTA organisations, payers, industry, academia, patient representatives and researchers can work together to address common evidence generation challenges. Bibi argued that producing decision-ready evidence is not solely a methodological challenge. It also depends on sustained collaboration between those generating evidence and those responsible for interpreting and applying it within healthcare decision-making.

"I fundamentally believe that as a community, we will progress a lot quicker if we build these collaborative relationships."

Looking beyond the conference itself, Bibi encouraged delegates to help shape the future direction of the Institute's work. She explained that discussions over the following two days would inform future Topic Groups, collaborative initiatives and research priorities, ensuring that the Institute continues to address the practical challenges facing the real-world evidence community.

Bibi's opening remarks established the central message that ran throughout the conference: decision-ready evidence cannot be achieved through better data or better methods in isolation. It requires these elements to be considered alongside the context in which healthcare decisions are made. This principle provided a consistent framework for the discussions, debates and case studies presented over the two-day meeting.

KEYNOTE ADDRESS

The Year Everything Changed: Towards a New Era of Evidence Driven Decision Making for Therapeutic Interventions

Opening the scientific programme, **Carole Longson**, Independent Adviser and former Director of the Centre for Health Technology Evaluation at the National Institute for Health and Care Excellence (NICE), challenged delegates to reconsider one of the fundamental principles underpinning evidence-based medicine: how healthcare evidence should be evaluated, in an era of increasingly personalised, data rich healthcare. Rather than presenting a new methodological framework, Longson argued that the changing nature of healthcare requires a corresponding evolution in how evidence is generated, assessed and applied. Her keynote provided the conceptual foundation for the conference, encouraging delegates to move beyond traditional debates about evidence hierarchy towards a broader discussion centred on evidence that is fit for purpose.

Longson opened by posing a question that framed the keynote and would resonate throughout the conference.

"Does the traditional evidence hierarchy remain fit for purpose in an era of increasingly personalised, data rich healthcare?"

She acknowledged that the traditional evidence hierarchy has served healthcare well for many decades. Randomised Controlled Trials (RCTs) remain one of the most reliable methods for establishing treatment efficacy, providing strong internal validity through randomisation and carefully controlled study designs. Systematic reviews and meta analyses continue to play an essential role in evidence based medicine. However, she argued that while the principles underpinning the hierarchy remain valid, the healthcare environment in which decisions are now made has changed considerably.

Today's therapeutic landscape is increasingly characterised by precision medicine, advanced therapy medicinal products, cell and gene therapies, and treatments developed for rare diseases or highly stratified patient populations. These innovations frequently reach regulators and health technology assessment (HTA) bodies supported by evidence packages that differ substantially from those seen only a decade ago. Conducting large comparative trials may be impractical because eligible patient populations are small, while randomisation may present ethical or practical challenges where

early evidence suggests substantial clinical benefit. Consequently, decision makers are increasingly required to make important decisions despite residual uncertainty.

Rather than describing these evidence packages as weaker than traditional evidence, Longson encouraged delegates to recognise that they are fundamentally different.

"The challenge we face is not necessarily that the evidence is poor or inadequate. The evidence is different."

This distinction formed one of the keynote's central messages. Longson argued that continuing to evaluate contemporary evidence using frameworks developed for a different era risks overlooking information that is highly relevant to modern healthcare decision making. Instead of focusing primarily on where evidence sits within a traditional hierarchy, greater emphasis should be placed on whether it is capable of answering the questions facing those responsible for regulatory, HTA and reimbursement decisions.

She suggested that this requires a subtle but important change in perspective. Rather than asking ***"What type of evidence is this?"***, stakeholders should increasingly ask ***"How useful is this evidence?"*** This shift moves the discussion away from categorising evidence according to study design alone and towards understanding its contribution to decision making.

Longson explained that this change has important implications across the product lifecycle. Different decision makers seek different answers from evidence. Regulators may focus primarily on benefit and risk, HTA bodies on comparative effectiveness and value, while payers and healthcare systems often require evidence relating to long term effectiveness, healthcare resource utilisation and outcomes achieved in routine clinical practice. No single study design can answer every question, and no single evidence hierarchy adequately reflects these differing evidence needs.

Throughout the keynote, Longson returned repeatedly to the concept of **fitness for purpose**, arguing that this should become the organising principle for evidence assessment. The question facing decision makers is not whether a particular study occupies a specific position within a hierarchy, but whether the evidence generated is sufficiently reliable, transparent and relevant to support the decision being made.

Importantly, she emphasised that adopting a more flexible approach to evidence generation should not be interpreted as lowering evidential standards. On the contrary, greater flexibility demands greater scientific rigour. Careful study design, high quality data, transparency of methods and appropriate analytical approaches remain fundamental to producing credible evidence. The challenge is therefore not to relax standards, but to ensure that methodological expectations remain appropriate to the decision context.

Longson argued that uncertainty should also be viewed differently. For innovative therapies, particularly those addressing areas of high unmet need, uncertainty is often an inevitable consequence of scientific innovation rather than evidence failure. Waiting until every uncertainty has been eliminated is rarely possible and may unnecessarily delay patient access to potentially valuable treatments. Instead, uncertainty should be recognised, characterised and managed transparently through appropriate evidence generation strategies.

Her discussion represented a clear shift away from viewing evidence generation as a process of identifying a single definitive answer. Instead, she described evidence as a means of progressively reducing uncertainty throughout the product lifecycle. This requires a broader understanding of how different sources of evidence can work together to support increasingly informed decisions as new information becomes available.

By the midpoint of the keynote, Longson had established the central argument that would underpin the remainder of her presentation. While the principles of evidence based medicine remain unchanged, modern healthcare requires a more integrated approach to evidence generation, where different sources of evidence contribute to different stages of decision making. She therefore turned her attention to how randomised controlled trials and real-world evidence can work together within an evolving evidence ecosystem to support regulators, HTA bodies and payers throughout the product lifecycle.

Rejecting the suggestion that healthcare faces a choice between randomised trials and real world evidence, Longson described the two approaches as complementary rather than competing.

"The future is not RCT or RWE. The future is RCT and RWE working together."

Randomised controlled trials, she explained, remain fundamental for establishing treatment efficacy and continue to provide the strongest evidence of causal effect under controlled conditions. However, they are rarely

capable of answering every question that decision makers face. Information relating to long term effectiveness, durability of response, treatment sequencing, safety in routine clinical practice, outcomes in broader patient populations and healthcare resource utilisation often only becomes available once a medicine is used in routine care. In these circumstances, real world evidence provides an opportunity to complement clinical trial findings by addressing questions that emerge after regulatory approval.

Longson argued that this requires evidence generation to be viewed as a continuous process rather than a series of isolated studies undertaken before and after market authorisation. As medicines progress from development through regulatory approval and into routine clinical practice, the uncertainties facing regulators, HTA bodies and payers inevitably change. Evidence generation strategies should therefore anticipate how those uncertainties will evolve and identify the most appropriate methods for reducing them over time. Rather than expecting a single study to answer every question, evidence should be generated incrementally, with each study contributing to a broader understanding of treatment value.

Drawing on her experience at NICE, Longson illustrated how this approach is already influencing healthcare decision making. She highlighted managed access agreements, including the Cancer Drugs Fund and the Innovative Medicines Fund, as examples of how healthcare systems are increasingly managing uncertainty rather than avoiding it. These mechanisms enable patients to access promising therapies while additional evidence is generated in routine clinical practice to address important remaining uncertainties. In doing so, they demonstrate that evidence generation increasingly extends beyond initial regulatory approval and becomes an integral part of the product lifecycle.

This, she suggested, represents an important evolution in the relationship between evidence generation and decision making. Uncertainty should not automatically prevent patient access where there is a reasonable expectation of clinical benefit. Equally, uncertainty should not be ignored. Instead, it should be explicitly recognised, transparently communicated and addressed through carefully planned evidence generation. Success therefore depends upon early dialogue between developers, regulators, HTA bodies and healthcare systems to ensure that evidence generation strategies remain aligned with future decision making needs.

Longson also discussed the growing role of external control arms and other non randomised approaches in supporting evidence generation where conventional comparative trials may not be feasible. While recognising that

these approaches present important methodological challenges, she argued that they also offer valuable opportunities to address questions that cannot always be answered through randomised studies alone. The focus should therefore be on improving the design, conduct and evaluation of these studies rather than dismissing them because they do not fit within traditional evidence hierarchies.

She acknowledged that wider use of real world evidence inevitably raises concerns regarding bias, confounding, missing data and data quality. These challenges, however, should stimulate continued methodological innovation rather than reinforce reliance on historical approaches alone. Advances in study design, analytical methods and data governance are steadily improving the credibility of real world evidence and increasing confidence in its application to healthcare decision making.

Reflecting on the progress made over recent years, Longson suggested that the discussion surrounding real world evidence has itself matured.

"The debate has therefore shifted from not whether RWE should be used, but how it should be used."

This shift, she argued, represents a far more productive conversation. Rather than debating the legitimacy of real world evidence, the emphasis should now be on ensuring that evidence is generated transparently, evaluated consistently and applied appropriately within the context of the decisions it is intended to support. Achieving this will require continued collaboration across the healthcare ecosystem together with ongoing investment in methodological development, data quality and scientific capability.

Returning to the question that had opened her keynote, Longson concluded that the future of evidence assessment should move beyond a rigid hierarchy towards an integrated evidence ecosystem that draws on multiple complementary sources of evidence while maintaining scientific rigour. What ultimately matters is not whether evidence comes from a clinical trial, a registry, an external control arm or routinely collected healthcare data, but whether it is capable of reducing uncertainty and supporting better decisions for patients.

"What matters is not simply where evidence sits on the pyramid. What matters is whether it is fit for purpose."

In closing, Longson challenged delegates to consider the role they each play in shaping this future. Delivering decision ready evidence will require methodological innovation, investment in high quality data infrastructure, early engagement between stakeholders and a willingness to move beyond long established assumptions about how evidence should be generated and evaluated.

"Are you ready to build that future?"

Longson's keynote established the intellectual framework for the conference and introduced themes that would recur throughout the subsequent scientific sessions. Discussions on decision context, fitness for purpose, lifecycle evidence generation, methodological transparency and the complementary roles of randomised controlled trials and real world evidence all reinforced a central message that resonated across the two day meeting: as healthcare decisions become increasingly complex, decision ready evidence depends not on choosing between different forms of evidence, but on bringing together the right data, appropriate methods and a clear understanding of the context in which evidence will be used.



SESSION 1: UNDERSTANDING THE DECISION CONTEXT: WHAT DO REGULATORS, HTAS & PAYERS ACTUALLY NEED?

Moderator: Christine Leopold, Utrecht University

Panel: Alexandra Pacurariu, EMA; Niklas Hedberg, TLV; Sahar Barjesteh van Waalwijk van Doorn-Khosrovani, LUMC/CZ; Ramiro Gilardino, HTAi Dynamic HTA Working Group; Francesco Pignatti, EMA; Leo Russo, Independent Adviser.

Session overview

The first session of the conference addressed one of the key challenges in modern evidence generation: how can a single evidence package satisfy the differing needs of regulators, health technology assessment (HTA) bodies and payers?

Building on the conference keynote, which challenged traditional approaches to evidence hierarchies, the discussion shifted the focus away from whether real-world evidence (RWE) has value and towards a more practical question: **what evidence do decision-makers actually need?**

Bringing together representatives from the European Medicines Agency (EMA), national HTA organisations, payers and the international HTA community, the session explored how RWE is currently being used in initial submissions, where it is already influencing decisions and what barriers continue to limit its wider adoption. Through audience polling, expert presentations, panel discussion and an interactive mock case study, the session demonstrated that while different stakeholders increasingly share common expectations around evidence quality, each continues to evaluate evidence through a distinct decision-making lens.



Where is RWE making the greatest impact today?

The discussion began with an interactive Slido poll asking delegates where they believed RWE currently has the greatest impact in initial submissions.

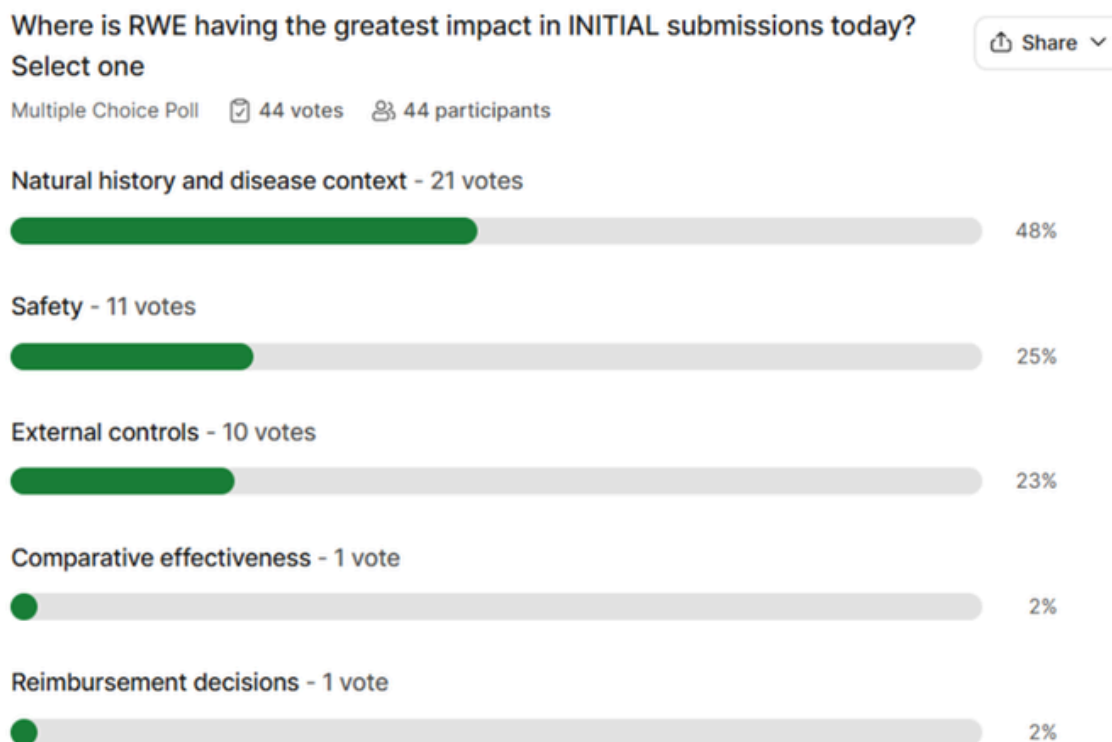


Figure 1: Audience response to where RWE is having the greatest impact in initial submissions

The audience identified natural history and disease context and safety as the areas where RWE is already making the greatest contribution, followed by external control arms, comparative effectiveness and reimbursement decisions.

The panel broadly agreed with these findings.

From the regulatory perspective, Alexandra Pacurariu explained that safety remains one of the most mature applications of RWE because routinely collected healthcare data are well suited to pharmacovigilance and causal safety studies. Regulators also increasingly rely on RWE to understand disease natural history, to validate company claims regarding clinical trial feasibility, frequency of the disease or standard treatments and support activities such as orphan designation and paediatric assessments. He noted, however,

Representing the HTA perspective, Niklas Hedberg agreed that observational evidence has become well established for safety evaluation because it follows different methodological principles from efficacy assessment. He noted

however, that disease burden and natural history evidence often play an equally important role in reimbursement decisions by providing the context needed to judge the value of new treatments.

From the payer perspective, Sahar Barjesteh van Waalwijk van Doorn-Khosrovani described how RWE is routinely used to understand epidemiology, healthcare utilisation and unmet medical need. She illustrated this using an example where real-world data had informed reimbursement of genomic testing for patients with carcinoma of unknown primary by demonstrating poor prognosis and limited treatment options.

Looking ahead, Ramiro Gilardino suggested that RWE is evolving beyond contextual information towards supporting treatment comparisons and reducing uncertainty in decision making. Gilardino argued that the more important shift is not what RWE is used for at launch, but whether decision systems are designed to learn from evidence as it matures post-launch.

Similarly, Francesco Pignatti highlighted the significant potential for external control arms, particularly in oncology, where many regulatory decisions continue to rely on evidence from single-arm studies.



Understanding what regulators need

Pacurariu then provided an overview of how RWE is used across the different scientific committees within the EMA, emphasising that there is no single regulatory requirement. Instead, different committees require different forms of evidence depending on the regulatory question being addressed.

What is of interest to regulators?

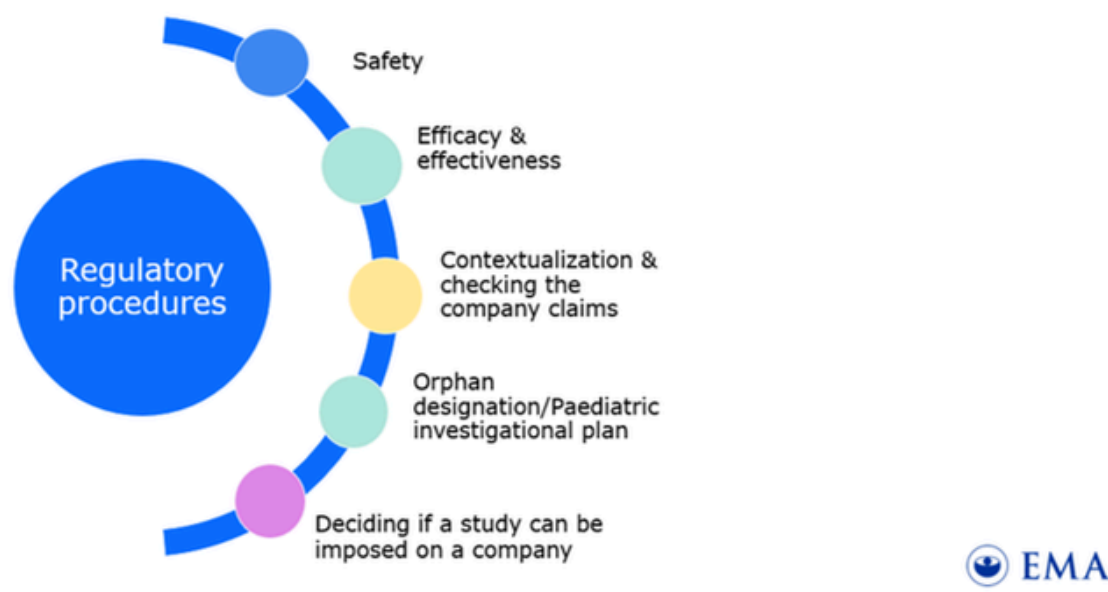


Figure 2. Regulatory areas of interest for real-world evidence. Source: EMA.

Examples included:

- Pharmacovigilance Risk Assessment Committee (PRAC) using RWE to investigate safety signals and assess effectiveness of regulatory interventions;
- the Committee for Medicinal Products for Human Use (CHMP) using RWE to understand disease natural history, treatment pathways and prevalence of the disease
- PDCO seeking evidence on treatment patterns and outcomes in children, where randomised trials are often difficult or impossible; and
- COMP relying on epidemiological evidence to confirm disease prevalence and rarity.

Although these applications differ considerably, Pacurariu identified three characteristics that consistently increase the likelihood of RWE contributing successfully to regulatory submissions:

- **Data that can be trusted**, supported by robust quality assessment;
- **Data that can be understood**, with transparent descriptions of data provenance and study methodology; and
- **Data sources that are demonstrably fit for purpose**, ensuring that the available information can answer the research question being asked.

Using an example from DARWIN EU, she illustrated the practical challenges of identifying suitable data sources. An initial search across 25 datasets for a rare cancer study ultimately resulted in only six datasets that were sufficiently suitable for analysis, with further limitations caused by incomplete treatment information and missing tumour staging. The example demonstrated that although Europe is rapidly expanding its data infrastructure, identifying genuinely decision-grade datasets remains a significant challenge.

Moving beyond data quality

The second audience poll asked delegates to identify, in a single word, the biggest challenge facing RWE in initial submissions.



Figure 3. Audience response to the biggest challenges facing the use of RWE in initial submissions

The dominant responses included:

- Data quality
- Trust
- Access
- Credibility
- Methodology
- Fit for purpose

While these responses reflected familiar concerns, the subsequent panel discussion challenged whether data quality itself remains the principal obstacle.

Pignatti argued that successful external control arms depend on more than simply collecting large volumes of data. Confidence in the findings depends on complete capture of important prognostic variables, minimising missing data and understanding the clinical context in which the data were collected. Achieving this requires much closer collaboration between researchers, registry holders and clinicians than has traditionally existed.

Pacurariu reinforced this message, explaining that genuine improvements in data quality often occur through conducting studies rather than discussing them. Working directly with data holders enables specific problems to be identified and progressively addressed, improving the quality of future datasets.

Hedberg offered perhaps the most provocative perspective of the session. While agreeing that data quality is essential, he argued that the field risks becoming trapped in a decades-long debate about quality without agreeing what constitutes evidence that is sufficiently reliable for decision making. Rather than continuing to seek perfect datasets, he suggested that regulators, HTA bodies and researchers need shared principles that define acceptable levels of uncertainty. Without such agreement, debates about data quality alone are unlikely to move the field forward.

Governance, transparency and trust

The discussion then shifted from data quality to governance.

From the payer perspective, Barjesteh van Waalwijk van Doorn-Khosrovani highlighted that sponsors typically select the datasets, define inclusion criteria, conduct the analyses and interpret the findings. While this reflects current practice, it also introduces opportunities for bias. She argued that analyses informing reimbursement decisions should be reproducible across independent datasets rather than relying solely on one favourable analysis.

To illustrate this point, she described the experience of **darvadstrocel**, where encouraging observational evidence following regulatory approval was later contradicted by the results of a controlled randomised trial. Although multiple real-world studies had suggested positive outcomes, the subsequent randomised evidence failed to demonstrate benefit, ultimately leading to withdrawal of the product. The example served as an important reminder that observational evidence, while valuable, must always be interpreted within its methodological limitations.

Gilardino extended the discussion internationally, observing that countries vary considerably in both their tolerance of uncertainty and their ability to generate post-launch evidence. He noted that the infrastructure gap is closing, but the governance gap, specifically, accountability for initiating and enforcing post-launch reassessment, has not kept pace.

Applying the principles: a mock case study in regulatory and HTA decision making

The second half of the session moved from discussing principles to applying them in practice through a fictional but realistic oncology submission. Designed as a joint regulatory and HTA scientific advice exercise, the case illustrated the complexities of developing a single evidence package capable of satisfying multiple decision-makers with different evidential requirements.

The fictional submission involved a novel PD-L1 inhibitor for patients with relapsed or refractory Merkel cell carcinoma whose disease had progressed following previous immunotherapy. As is often the case in rare cancers, conducting a conventional randomised controlled trial was considered operationally difficult because of the small patient population and lack of available treatment options.

The evidence package consisted of a Phase II single-arm study involving 92 patients recruited from Europe and the United States. Primary and secondary endpoints included objective response rate, progression-free survival, overall survival, duration of response, quality of life and safety. To strengthen the submission, an external control arm had been constructed using three complementary real-world data sources: oncology electronic health records, a European patient registry and academic chart review. Target trial emulation principles had been applied throughout the study design, supported by pre-specified sensitivity analyses intended to minimise bias and improve the validity of the comparisons.

Audience perspective

Delegates were invited to assess the fictional submission before hearing the views of the expert panel.

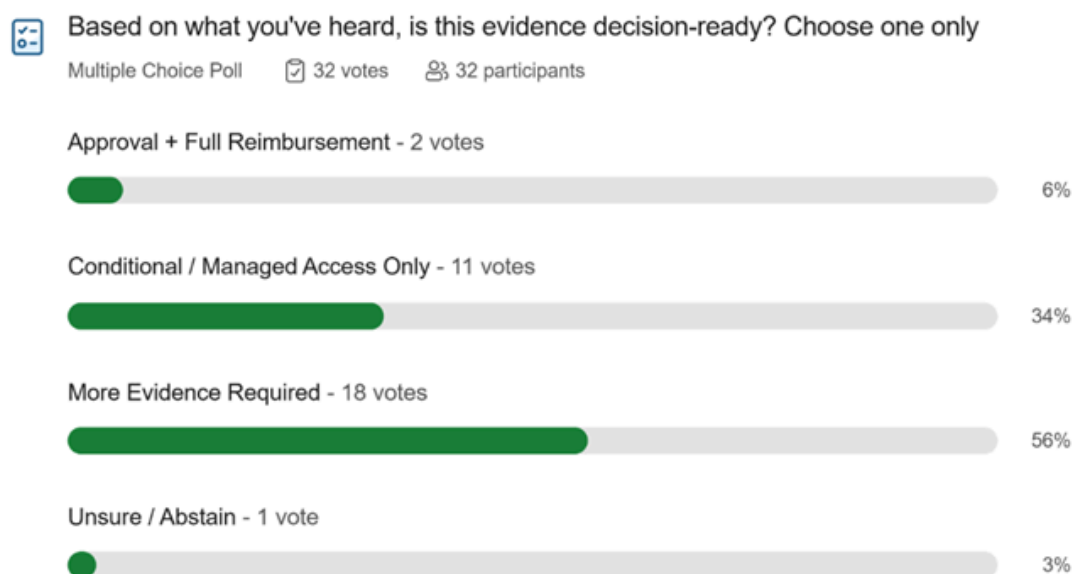


Figure 4: Audience interpretation of mock evidence submission

The polling results demonstrated that delegates themselves recognised the complexity of the scenario. While many viewed the results as encouraging, opinions differed regarding whether the evidence would be sufficient for both regulatory approval and reimbursement. The audience responses reflected one of the central messages of the session: identical evidence may be interpreted differently depending on the decision being made.

How regulators viewed the evidence

The regulatory panellists explained that rare diseases inevitably require greater flexibility than more common conditions. Where conventional randomised studies are not feasible, external control arms can provide valuable contextual evidence. However, flexibility does not remove the need for methodological rigour.

Discussion focused on patient selection, completeness of prognostic variables, management of missing data and transparency of analytical methods. The panel emphasised that confidence depends not simply on the size of the dataset but on whether clinically important variables have been consistently captured and whether the methods used to generate the external control are fully transparent.

The panel also noted that regulators increasingly expect sponsors to provide detailed descriptions of their underlying data sources, enabling assessors to understand how the evidence has been generated and whether it is genuinely fit for purpose.

The HTA perspective

HTA representatives approached the same evidence package through a different decision framework.

While recognising the challenges of evidence generation in rare diseases, they emphasised that reimbursement decisions require confidence not only that a treatment demonstrates clinical benefit but also that comparative effectiveness can be estimated with sufficient certainty.

Hedberg returned to his earlier argument that discussions should move beyond data quality towards agreement on acceptable uncertainty. Rather than continually seeking perfect evidence, decision-makers need shared principles describing when evidence is sufficiently trustworthy to support reimbursement decisions.

The payer perspective

From the payer perspective, governance and reproducibility remained central themes.

Barjesteh van Waalwijk van Doorn-Khosrovani argued that confidence in observational evidence depends upon independent reproducibility rather than favourable findings alone. She emphasised that different datasets analysed independently should produce broadly consistent conclusions before decision-makers can confidently rely on RWE for reimbursement decisions.

The earlier example of darvadstrocel reinforced this point, illustrating how positive observational studies may not always predict the results of subsequent randomised trials.

External control arms: considerable opportunity but high expectations

A recurring theme throughout the discussion was the growing importance of external control arms.

Pignatti observed that externally controlled studies have the potential to influence a substantial proportion of oncology regulatory decisions, particularly where single-arm trials remain unavoidable. However, their value depends on complete capture of important prognostic factors, minimisation of missing data and clinically meaningful treatment effects.

Maintaining high-quality registries also presents practical challenges. Disease classifications evolve, treatment pathways change and new prognostic variables emerge over time. As a result, maintaining decision-grade datasets requires continuous collaboration between clinicians, registry holders, researchers and regulators.

Managing uncertainty rather than eliminating it

Perhaps the strongest message to emerge from the case study was that decision-making is fundamentally about managing uncertainty rather than eliminating it.

Throughout the discussion, panellists repeatedly returned to questions such as:

- Which uncertainties matter most for the decision being made?
- Are those uncertainties acceptable given the unmet clinical need?
- Can remaining uncertainty be addressed through post-authorisation evidence generation?
- How much confidence is required for regulatory approval compared with reimbursement?

These discussions reinforced the keynote message that evidence should not simply be judged according to its place within a traditional hierarchy but according to whether it is sufficiently reliable, transparent and relevant to inform the decision being made.

Conclusions

The session demonstrated that the conversation around RWE has evolved considerably. Rather than debating whether observational evidence has value; regulators, HTA bodies and payers are increasingly focused on understanding what constitutes evidence that is sufficiently credible to support decisions.

Although different stakeholders continue to evaluate evidence through different decision contexts, there was notable convergence around the characteristics that inspire confidence. Across the discussion, panellists consistently highlighted the importance of transparent data sources, datasets that are genuinely fit for purpose, reproducible analytical methods, comprehensive capture of clinically important variables and clear reporting of uncertainty.

The mock case study illustrated that producing decision-ready evidence is not about generating different evidence packages for different stakeholders. Instead, it requires understanding the different questions each decision-maker is trying to answer and designing evidence generation strategies capable of addressing those questions from the outset.

As the opening scientific session of the conference, the discussion established many of the themes that were revisited throughout the following two days: trust, transparency, methodological rigour, fitness for purpose and the need for closer collaboration between data holders, researchers, regulators, HTA bodies and payers. Together, these themes underpin the continuing transition from generating real-world data to delivering genuinely decision-ready evidence.

SESSION 2: DATA FOUNDATIONS: ASSESSING FITNESS FOR PURPOSE ACROSS THE EVIDENCE LIFECYCLE

Moderator: Seamus Kent, Erasmus University Rotterdam

Panel: Alexandra Pacurariu, EMA; Dmitry Etin, EHDS expert, etza GmbH; Daniala Weir, Utrecht University; Radek Wasiak, Adigens Health

Session overview

The second session of the conference turned to the foundations of real-world evidence: the data itself. Opening the session, Seamus Kent observed that Europe is investing heavily in health data infrastructure, pointing to electronic health record linkage initiatives, disease registries, federated networks, DARWIN EU, TARGET-EU and the European Health Data Space (EHDS) regulation as examples of an increasingly rich landscape of resources for evidence generation. Building this infrastructure, he argued, is only the first step: the greater challenge is ensuring the data can be accessed and used effectively, and that they are genuinely fit for purpose for the question being asked.

Kent framed fitness for purpose as context-dependent rather than a fixed property of a dataset, varying across the evidence lifecycle from understanding disease burden and treatment patterns, through regulatory and HTA decision-making, to post-authorisation monitoring. Four short presentations, on federated data networks, DARWIN EU, the EHDS and TARGET-EU, set the scene for a panel discussion involving all four presenters alongside Radek Wasiak.



Building Europe's federated data networks

Kent opened with a presentation on federated data networks (FDNs), defined broadly as collections of data sources that can be analysed collectively while data holders retain control of their own data. The federated approach is not new, having long been used in regulatory contexts such as the US FDA's Sentinel Programme, but it has gained renewed momentum in Europe, in part because of the success of the EHDEN project, which built a network of around 200 European data sources mapped to a common data model (OMOP) and laid the foundations for the EMA's DARWIN EU real-world data network.

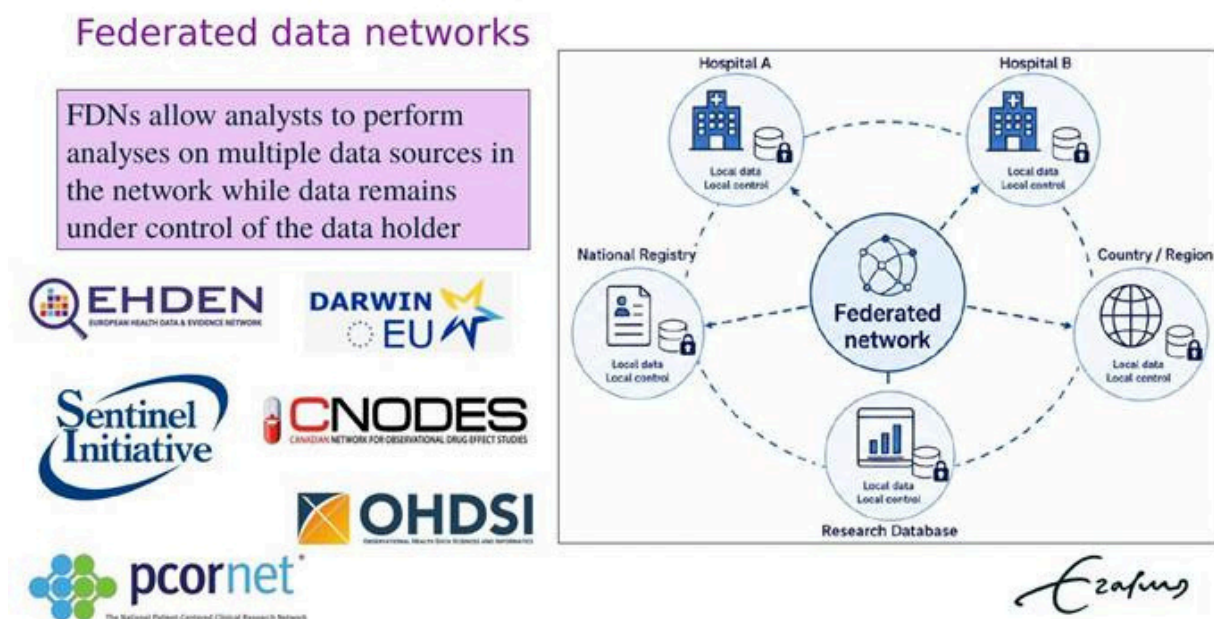


Figure 1. Federated data networks for real-world data analysis

Kent was explicit that federated networks and common data models do not, by themselves, improve data quality, but they allow that quality to be better understood. The EHDEN portal illustrates how: population, exposure and data-content metadata support initial screening of candidate sources, while cohort-defining code enables more detailed feasibility exploration of populations, exposures, outcomes, follow-up and governance, supporting common data quality assessment tools aligned with frameworks such as the EMA's. This, Kent argued, allows more systematic and consistent fitness-for-purpose assessment at scale.

He also set out the limitations: a common data model does not remove the need to understand the underlying local data, metadata does not capture everything, phenotype definitions may not transfer consistently across sources, and partner engagement and governance arrangements vary considerably. These challenges, he noted, are not unique to federated networks but apply to any use of external data assets. FDNs create the opportunity for more systematic feasibility assessment and improved evidence quality, without changing the underlying quality of the data itself.

DARWIN EU's growing scale and complexity

Pacurariu presented on DARWIN EU's progress in its fourth year. 107 research topics were logged between February 2025 and February 2026, 92 through DARWIN EU and 15 through EMA framework contracts, a 49% increase on the previous reporting period; 43 studies have been completed and 45 are ongoing. She attributed part of this growth to a learning curve on both sides, with requesters, including regulators and EMA colleagues, becoming more experienced in framing feasible requests.

Diverse and rich data and European representativeness

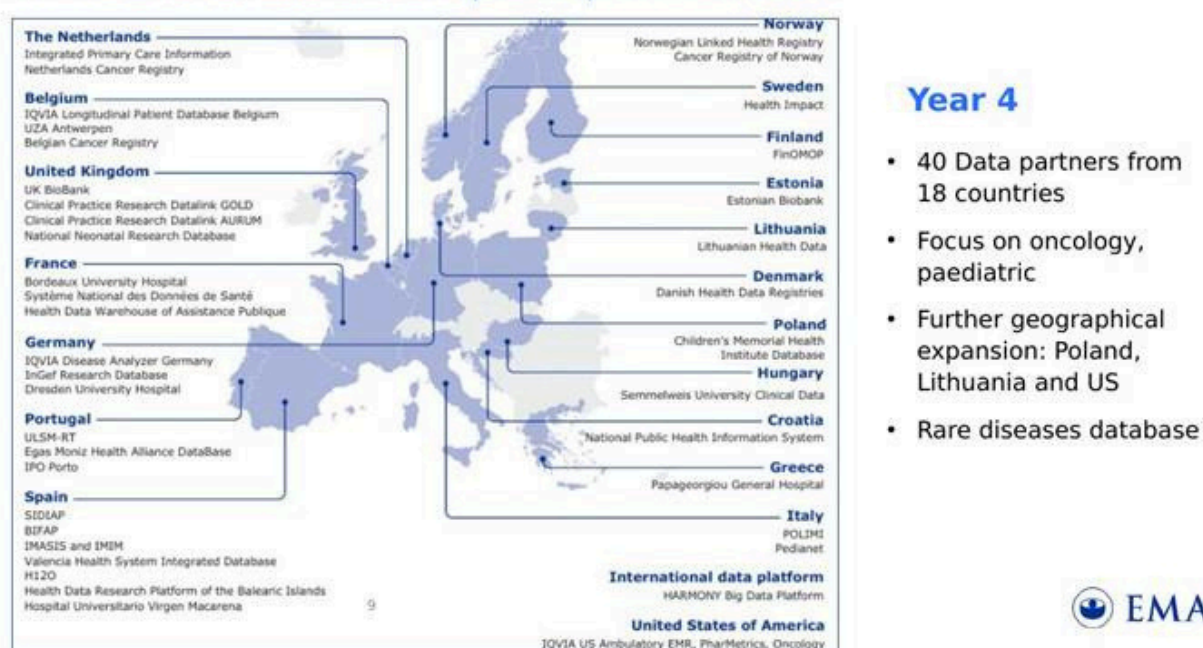


Figure 2. Data sources and geographical coverage of the DARWIN EU network

Growth has come alongside increased complexity and quality, Pacurariu explained. The median number of data partners per study has doubled from three to six, complex studies have doubled compared with the previous year, and two particularly complex studies were run in pregnancy and oncology, alongside dedicated studies under EMA framework contracts for rare diseases and special populations. Data quality has also improved through better mapping and completeness, dedicated mapping for conditions or medicines of interest such as oncology and pregnancy, and a new quality issue tracker with periodic monitoring; where errors are detected during a study, the network can sometimes correct it within the study itself, though this takes additional time.

Around 30% of studies now have a direct impact on regulatory procedures, which Pacurariu described as a high bar given the combined demands of data quality, methodology and speed; 44% improved clinical or methodological understanding outside a specific regulatory decision, and 15% supported

regulatory preparedness, primarily around drug shortages and vaccine safety. Examples of scientific and public health impact included a study on non-small cell lung cancer and immunotherapy, in which real-world results aligned with clinical trial findings, and two studies conducted with Cystic Fibrosis Europe on the clinical characteristics and monitoring of patients with cystic fibrosis, both methodologically demanding given the extent of missing data and high number of variables required for the study.

On requesters, Pacurariu noted that the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) had been the leading requester for the past three years but has now been overtaken by internal EMA teams, reflecting closer collaboration across pharmacovigilance, clinical therapeutic areas and RWE teams. Drug utilisation, disease epidemiology and safety remain the most common request types, alongside a growing shift towards feasibility and design exercises. By therapeutic area, nervous system disorders are now the most researched area (21%), having climbed from fourth place previously, followed by oncology (15%), anti-infectives (13%) and cardiovascular disease (13%). The network now comprises 40 data partners across 18 countries, with recent expansion into Poland and Lithuania and the acquisition of US oncology and general-purpose data, alongside a new rare disease database and a continued focus on oncology and paediatric populations.

The promise and limits of the EHDS

Etin presented on the state of play for secondary use of data under the EHDS. He explained that the EHDS was conceived primarily to support cross-border data exchange, to improve care and to help innovators, researchers and policymakers make use of collected data, with certain patient rights provisions added late in the proposal and negotiations phase; this shift though allowed the regulation to impact national infrastructure directly, not only cross-border exchange.

He noted that the Commission's own pre-launch impact assessment estimated a value of around EUR 11 billion over ten years, of which EUR 5.4 billion is attributed to secondary use and over EUR 3.4 billion to research and innovation outcomes, figures the Commission itself has cautioned are impossible to measure directly. He contrasted this with the global real-world evidence market, estimated at USD 3 to 6 billion a year and already larger and growing faster than the modelled EHDS estimate, questioning how ambitious the Commission's assessment really is relative to market reality.

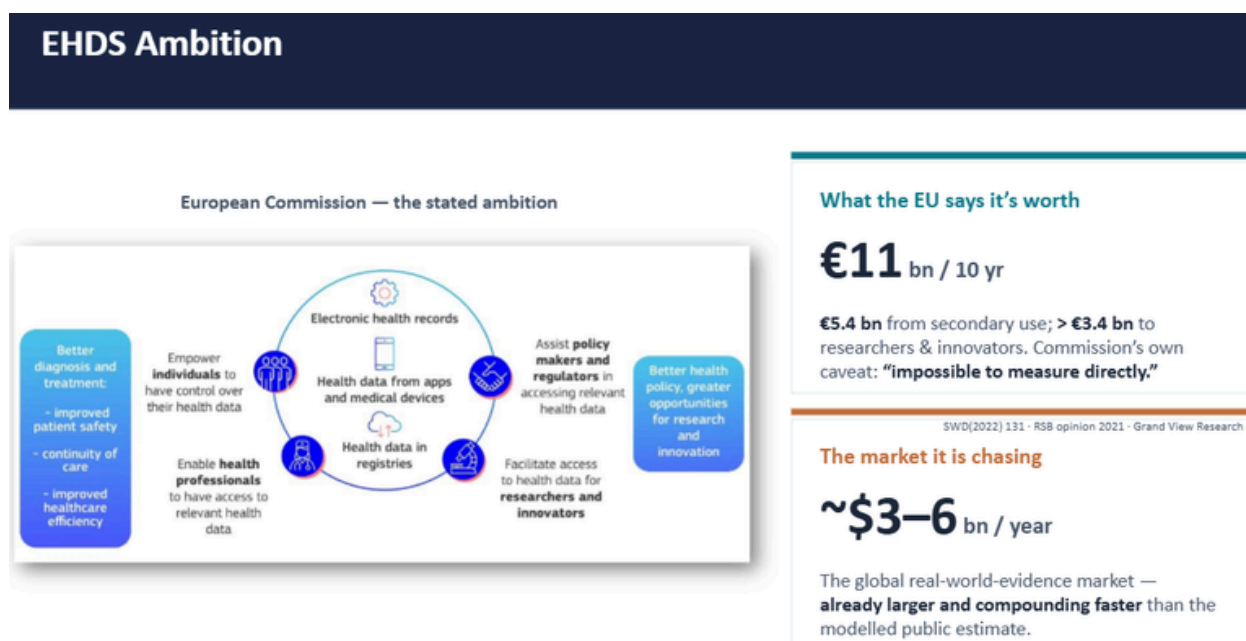


Figure 3. Ambition and expected benefits of the European Health Data Space

Etin set out the regulation's staged timeline:

- Regulation (EU) 2025/327 entered into force on 26 March 2025;
- general application begins in 2027, when implementing acts, digital health authorities and contact points are due and all Member States must have designated their Health Data Access Bodies ;
- main rollout of most Article 51 data categories and operational data holder duties follows by 2029;
- the remaining data categories, including genetic, omic, clinical trial and cohort data, follow by 2031; and
- third-country access provisions apply from 2035.

The first implementing act was adopted in April 2026. A small number of others, including the metadata description standard, are already in the adoption process or out for public consultation, with more in preparation.

EHDS milestones and obligations

Regulation (EU) 2025/327, in force from 26 March 2025, staged application through 2035.



Figure 4. EHDS implementation milestones and obligations

Secondary use, Etin explained, is deliberately less prescriptive than primary use: the access process itself is set out in the regulation and overseen by national Health Data Access Bodies, but the only genuinely normative technical standard is the metadata standard for dataset discovery, HealthDCAT-AP, alongside a forthcoming Data Quality and Utility Label. Data standards and technical design are left to be agreed between stakeholders, a deliberate choice: because secondary use, by definition, involves data collected for purposes unknown at the point of collection, a single content standard cannot realistically be mandated in advance. He pointed to DARWIN EU's convergence on the OMOP common data model as an example of standardisation achieved through procurement incentives and community adoption rather than regulatory mandate, alongside national decisions such as use of HL7 FHIR in specific Austrian use cases, and frameworks developed through projects such as TEHDAS2.

He closed by distinguishing 'fit for purpose', a concept held by the data holder describing what a dataset could plausibly be used for, from 'fit for use', the data user's assessment of whether a specific purpose is actually feasible with that dataset. As the distance between data holders and data users grows, for example as the EHDS introduces more intermediary bodies, it becomes harder for data users to assess suitability from metadata alone; closing this gap depends on direct dialogue between data holders and data users, something Etin suggested the EHDS does not yet actively promote.

Testing feasibility within TARGET-EU

Daniala Weir presented on the feasibility assessment process developed and applied within TARGET-EU, a project commissioned by the EMA through a framework contract. The project's two objectives were to improve understanding of the opportunities, challenges and limitations of using target trial emulation with real-world data to support regulatory decision-making, and to examine the advantages and challenges of combining target trial emulation with the SDM framework for comparative effectiveness and therapy studies.

TARGET-EU selected ten case studies of regulatory interest where real-world data is increasingly used in decision-making. For each, the project team developed an estimand and protocol for a hypothetical target trial, using the ICH E9(R1) addendum and a modified ICH M11 template, before conducting a full three-step feasibility assessment based on the EMA's data quality framework: first assessing the quality of the data infrastructure and governance, second the intrinsic quality of the specific database, and third the relevance of the data to the case study, that is, whether the data needed were actually captured. Each case study was then assessed as feasible, feasible with limitations, or not feasible, before target trial emulation protocols were developed using a modified HARPER template; analysis of all ten case studies is ongoing.

Weir described several practical constraints encountered because feasibility was assessed in parallel with protocol design, before any data cuts were available. The team had to rely on prior knowledge and the expertise of data experts and access providers, which varied considerably by case study, creating uncertainty around sample size estimates. Data experts and access providers found it difficult to answer some sections of the feasibility assessment without a more fully developed target trial protocol, and confounder lists were not yet finalised at the point the feasibility assessment was conducted, making it difficult to confirm whether key confounders were captured in a given dataset.

Reflecting on lessons learned, Weir said the project would sequence its approach differently if repeated: first specifying the estimand and key target trial elements, then conducting a light feasibility check to confirm that the target population, exposure, outcome and key variables are present in adequate sample size, then developing a protocol outline for the emulation and engaging data experts and access providers, and only then conducting the full three-step feasibility assessment before a final feasibility decision.

Where does the biggest challenge lie?

Ahead of the panel discussion, Kent polled the audience on the biggest challenge to generating decision-relevant evidence in Europe today, offering five options: determining whether data are fit for purpose, identifying suitable data sources, navigating access and governance requirements, timelines for obtaining data, and generating evidence that meets decision-makers' needs.

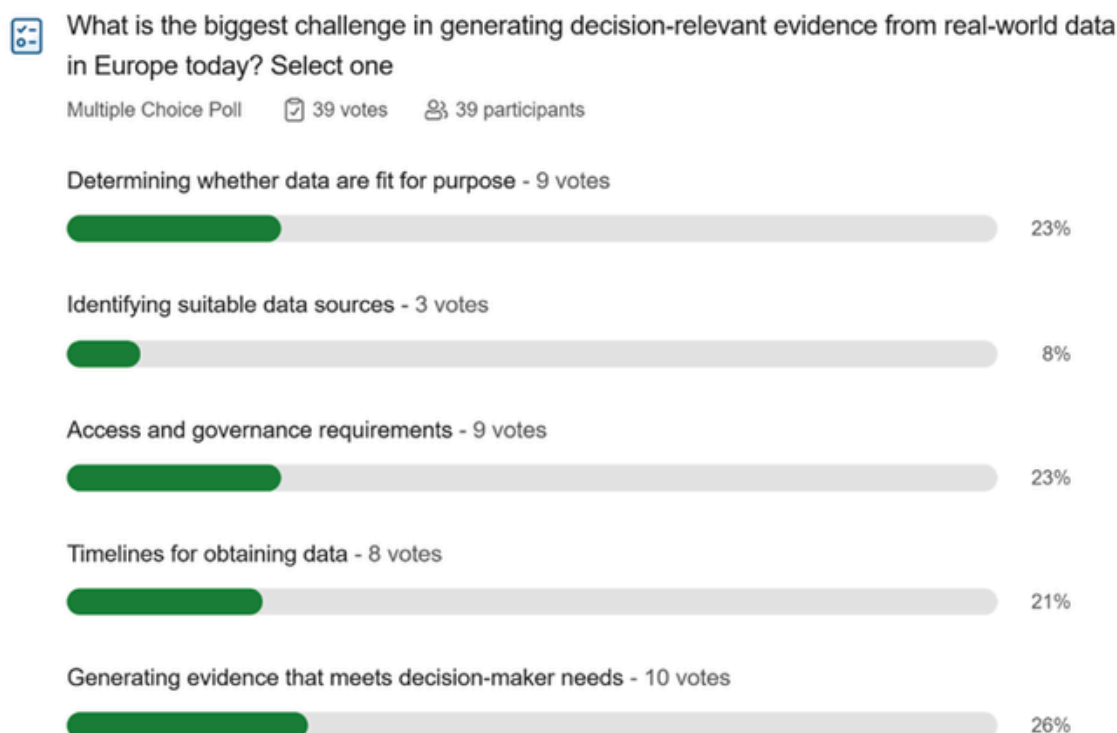


Figure 5. Audience views as to the biggest challenges in generating decision-relevant evidence from RWD in Europe

Invited to respond, Radek Wasiak suggested there is no single standout issue: identifying suitable data sources is an overarching challenge that runs through the others, generating evidence that meets decision-makers' needs is closely linked, and doing all of this in a timely way remains a constant challenge. He connected this to the earlier presentations, noting that federated access, as described by Kent, addresses data privacy concerns, and that DARWIN EU, as described by Pacurariu, demonstrates how this can work at scale across many data sources. He argued that the lessons from DARWIN EU should now be applied to the EHDS as it develops, warning that the RWE community risks missing a narrow window to influence design choices and to avoid repeating known mistakes, such as requiring a pre-specified protocol before feasibility has been established. He praised TARGET-EU's reflective approach to sequencing feasibility work as a genuine example of best practice, and argued that fitness-for-purpose assessment is not a single step but a series of iterative assessments moving between study design and data characteristics.

Asked by Kent whether his organisation prefers to work with data it already knows well, Wasiak said this depends on the research question and that researchers should avoid restricting themselves prematurely. He described the practical trade-offs involved in deciding how much to ask of data holders, how quickly answers can be obtained, and the cost implications of delay for drug developers responding to regulator or HTA requests. His preference, he said, is to work with data that is good enough to support an initial view, while continuing to look for ways to improve feasibility assessment more broadly, citing faster data access and processing in the US and parts of Asia as a benchmark Europe could learn from.

What does the EHDS actually add?

Kent asked Etin what the EHDS adds, given existing initiatives such as EHDEN and other federated or secure data environments. Etin said the EHDS's core value lies in its scale and its mandatory nature: a union of 450 million people is, in his view, collectively stronger than the sum of individual member states, echoing existing collaboration between smaller Nordic countries that pool resources to create meaningful datasets. The more significant shift, he argued, is structural: today, access to good data is effectively locked to organisations with existing relationships, such as large pharmaceutical companies, major academic centres or university spin-offs, leaving startups and small research groups largely dependent on lower-value open datasets. Because the EHDS's 17 secondary-use data categories cover almost all health data, designated data holders will, in effect, no longer be able to withhold access, which Etin described as the regulation's most important practical change, even though it does not resolve questions of data quality or of what to do with the data once access is granted.

Comparing DARWIN EU and TARGET-EU

Kent asked Pacurariu whether DARWIN EU's approach to fitness-for-purpose assessment differs from TARGET-EU's, given that DARWIN EU studies are often characterisation or drug utilisation studies while TARGET-EU focused specifically on comparative effectiveness. Pacurariu said the challenges are very similar: access is needed before a dataset can be properly understood, but a protocol is needed to request access. She noted DARWIN EU's advantage of an established relationship with its network, built up over around 100 studies over four years, which reduces surprises. She described a new enhanced feasibility assessment the network is piloting: a simple descriptive study used to test data suitability rather than to answer a research question directly, which at least provides real counts rather than estimates. She also raised fragmentation as a further constraint: with data split across many hospitals, a rare disease study might only have a handful of patients per site, and small-number privacy masking rules can make even that limited data difficult to use.

Kent then asked whether the same evaluation framework applies to externally conducted studies submitted by companies during the regulatory process. Pacurariu said this remains a work in progress. What does translate externally is the EMA's data quality framework and its catalogue of data sources, though she felt the catalogue is underused, in part because not all data holders update their records regularly (DARWIN EU partners are required to do so at a new data-quality feature is being added to the catalogue, though metadata, she cautioned, will never fully substitute for hands-on assessment).

Are standards communicated clearly enough?

Asked whether evidence and data standards are communicated clearly enough by regulators, HTA bodies and payers, Wasiak said the expectations themselves are generally clear, but the practical path to meeting them is not, a gap he said he regularly helps drug developers bridge. He argued that treating any dataset as fit for purpose across all possible studies is a flawed assumption, and that fitness for purpose needs to be assessed case by case, ideally through a quick, repeatable reassessment process rather than a one-off assessment, while still meeting the short timelines needed to bring treatments to patients. He noted that what pre-specification means in a real-world evidence context is itself not well defined, and cautioned against assuming that everything can, or should, be pre-specified in advance.

Kent suggested the challenge may run deeper still, questioning whether the field yet knows what level of data quality it actually needs for different use cases. Wasiak responded that the field is evolving, pointing to the EMA's annual DARWIN EU updates as evidence of a system responding to what drug developers are doing in practice rather than a static one, and framed this iterative learning as a core reason the conference itself remains valuable.

A cautionary tale from the audience

An audience member raised a historical example from the Netherlands, where a cancer registry appeared to show one hospital achieving much better survival outcomes, which on closer inspection reflected that hospital selectively screening and treating healthier, earlier-stage patients rather than a genuine difference in care quality. They asked how the panel would prevent similar misleading conclusions, for example a false impression that one country is outperforming another on survival for a given cancer type, once more data becomes broadly available.

Pacurariu said the most readily available safeguard is genuinely representative national data collected without restricted patient selection, citing Nordic and Dutch national registries, built on legal mandates to record patient data regardless of how a patient responds to treatment, as a strong, if imperfect, example given issues of missing data.

She acknowledged that hospital-level selection bias of the kind described will continue to occur and that she did not have a general solution for it.

Etin argued that an abundance of data always carries risk, but that the more useful question is can be done with the data available, since in practice data will likely never be as complete as researchers would like. He noted that benchmarking was one of the EHDS's stated objectives, intended to help policymakers work more efficiently, though he cautioned that exposing apparently poor hospital performance is not necessarily helpful if the underlying comparison is flawed, and that Europe is still far from the abundance of data the EHDS ultimately promises.

Wasiak closed by arguing that Europe's starting position is such that meaningful improvement is achievable: drawing on his experience of the US data environment two decades ago, he said data fragmentation remains the central problem to solve, and that resolving it would make it far easier to judge which data are genuinely good quality. He credited the EHDS, with beginning to shift Europe toward a mandatory model for secondary data access, which he predicted would substantially change how research is conducted, expressing hope for eventual access to a pooled dataset spanning the EU's roughly 450 million citizens.

Working with the data experts who know it best

Invited to close, Weir emphasised the continued importance of working closely with data experts and access providers throughout the research process. Researchers, she said, may work across many different databases, but it is the specialists embedded in each dataset who understand its intricacies and the appropriate way to work with it. Whatever changes lie ahead for European data infrastructure, she argued this need for direct collaboration between researchers and data experts is unlikely to diminish, and should remain the starting point for any new study.

Conclusions

Across the presentations and panel discussion, several consistent themes emerged. Federated networks and common data models, as Kent and Pacurariu both illustrated through EHDEN and DARWIN EU, do not by themselves improve data quality, but they make that quality easier to assess systematically and at scale. Etin's distinction between fit for purpose, a data holder's description of a dataset, and fit for use, a data user's assessment of feasibility for a specific study, recurred throughout the session and reinforced the panel's shared view that fitness for purpose cannot be assessed once and applied universally, but must be revisited case by case as research questions evolve.

Both Weir and Pacurariu illustrated the practical cost of assessing feasibility before a protocol is finalised, and DARWIN EU's enhanced feasibility pilot and TARGET-EU's proposed re-sequencing point towards a shared emerging solution: earlier, lighter feasibility checks ahead of full protocol development. Finally, while the EHDS was widely welcomed as a structural step forward, notably in making data access effectively mandatory for designated holders, panellists were consistent in flagging that access alone does not resolve data fragmentation, quality or usability, and that direct dialogue between data holders and data users remains essential regardless of how the regulatory landscape evolves.



SESSION 3: PARALLEL WORKSHOPS

Interactive Workshops

Two parallel interactive workshops provided participants with the opportunity to explore key methodological and practical challenges in RWE through structured discussion and cross-stakeholder exchange.

1. Target Trial Emulation: From Framework to Submission

Moderators: Radek Wasiak, Adigens Health; Xabier Garcia de Albeniz, Adigens Health; Daniala Weir, Utrecht University; Antonia Panayi, Takeda; Leo Russo, Independent Adviser; Manuel Gomes, University College London (UCL)

The Target Trial Emulation workshop explored the Target Trial Framework (TTF) as a structured approach to strengthening the design and conduct of non-interventional studies using real-world data. The session introduced the key stages of the framework, from defining the estimand and specifying the hypothetical target trial through to assessing data feasibility, developing the emulation protocol and statistical analysis plan, executing the analysis and transparent reporting.

The workshop also considered why the TTF is gaining momentum and what is needed to support its rigorous and consistent application. Drawing on early findings from stakeholder interviews, participants considered current challenges including retrospective application of the framework, alignment with estimand thinking, data fitness for purpose, sensitivity analyses, training needs and practical constraints associated with data access.

Through breakout discussions, participants explored gaps in knowledge, tools and standards and considered how the framework could evolve to better support the needs of regulators, HTA bodies, clinicians and industry.

A dedicated white paper on the Target Trial Framework, incorporating the stakeholder interviews and insights generated through the workshop, will be published separately by the GetReal Institute.

2. Patient Voice in Real-World Evidence for Decision Making in Oncology

Moderators: Iyar Mazar, Pfizer; James Turnbull, IQVIA; Marieke Heisen, Patvocates; Mariam Bibi, The GetReal Institute

The Patient Voice workshop explored how patient perspectives can be embedded more meaningfully throughout the RWE lifecycle, from study design and outcome selection through to the interpretation and use of evidence in regulatory and HTA decision making. The session emphasised the importance of moving beyond consultation towards meaningful patient partnership, recognising the distinct contribution that patient experience and expertise can make to the relevance and value of RWE.

Using a hypothetical oncology case study, participants worked in mixed stakeholder groups to identify where patient perspectives had been absent or insufficient within an RWE study and how patient engagement could have been incorporated more effectively. Discussions focused particularly on the selection of patient-relevant outcomes, the role of patient-reported evidence alongside clinical endpoints, and opportunities to involve patients earlier in evidence generation.

Groups then identified practical points within the evidence-generation and decision-making process where patient engagement could have the greatest impact, including who should be responsible and what form that engagement should take. The workshop reinforced the value of involving patients from the outset so that RWE captures not only clinical outcomes, but also the outcomes and experiences that matter to patients.

The insights and recommendations generated through the Patient Voice workshop will be developed further in a separate GetReal Institute white paper, exploring how patient perspectives can be more meaningfully embedded in RWE generation and decision making.



SESSION 4: AI & MACHINE LEARNING: ACCELERATING THE TRANSLATION OF RWD INTO DECISION READY EVIDENCE

Moderator: Shaun Rowark, NICE

Panel: Kathi Seidl-Rathkopf, Flatiron Health; Michel Dumontier, Maastricht University; Casper Safalou, UMCU; James Gwinnutt, IQVIA

Session overview

Artificial intelligence (AI) is rapidly transforming healthcare research, yet its successful adoption depends on more than technological innovation alone. Moderated by Shaun Rowark, this session explored how AI and machine learning are beginning to reshape the generation of Real World Evidence (RWE) across the product lifecycle, while examining the scientific, methodological and ethical considerations required to ensure that AI generated evidence is trusted by regulators, HTA bodies and healthcare decision makers.

Reflecting on the previous day's discussions, Rowark observed that many of the challenges surrounding AI mirror those already encountered in the evolution of RWE. Rather than focusing on the technical capabilities, the session examined how AI can be implemented responsibly, how confidence in AI generated evidence can be established, and how these technologies can strengthen the production of decision ready evidence. Drawing on examples from NICE, he described how natural language processing is already being used to extract clinically meaningful information from poorly coded medical health records and highlighted opportunities for AI across evidence generation, evidence synthesis, dossier preparation and, potentially, evidence review itself.

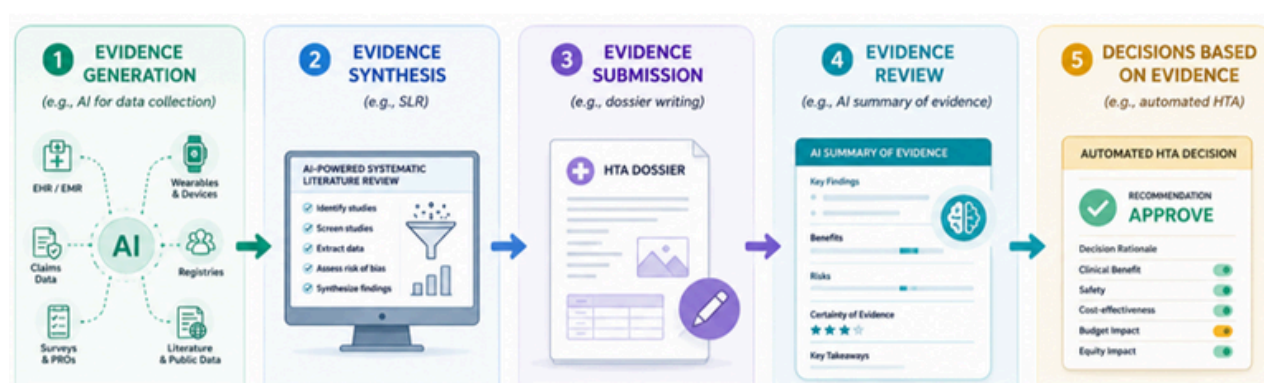


Figure 1. AI across the evidence lifecycle. Source: NICE.

Kathi Seidl-Rathkopf opened by demonstrating how AI is transforming the curation of oncology real world data. She explained that much of the information required for oncology research exists within unstructured clinical documentation rather than coded fields within electronic health records. Traditionally this information has required labour intensive manual abstraction, limiting both the scale and speed of data generation. By combining large language models with clinical expertise and robust quality assurance, Flatiron Health has now unlocked unstructured information from millions of patient records, creating research ready datasets capable of supporting large scale oncology research.

Seidl-Rathkopf emphasised that increased efficiency alone is insufficient. Confidence in AI generated data depends upon rigorous validation and transparent quality assurance. She introduced the Validation of Accuracy for LLM and ML Extracted Information and Data (VALID) framework, developed to assess reliability, fairness and fitness for purpose throughout the data lifecycle. The framework evaluates variable level performance, verifies clinical plausibility and benchmarks AI extracted data against established research findings. Using progression free survival across fourteen tumour types as a case study, she demonstrated close agreement between AI extracted and manually curated datasets, illustrating how structured validation can provide confidence in AI generated real world data.

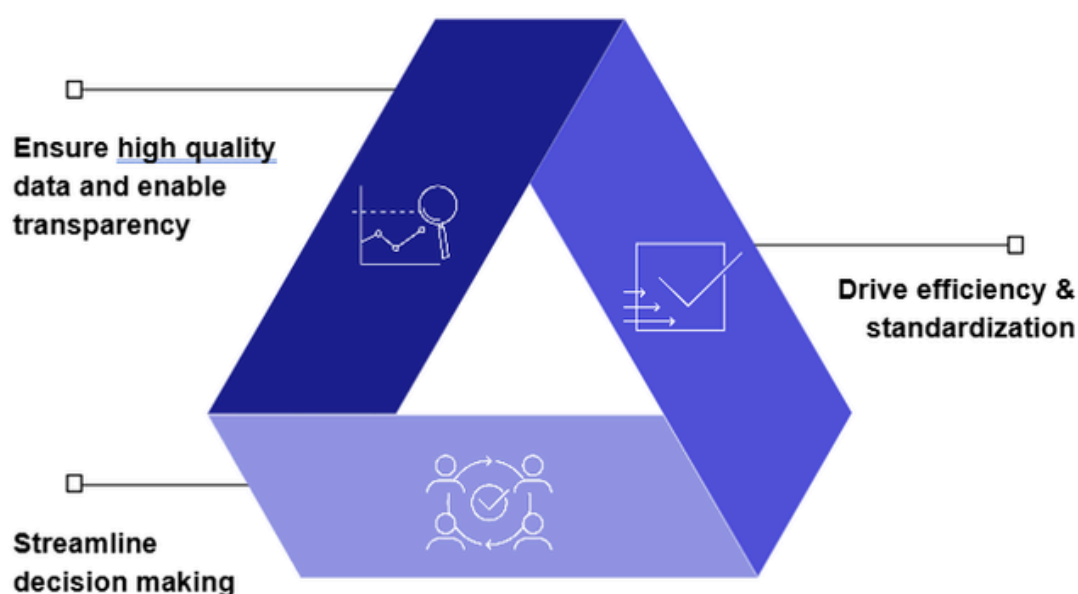


Figure 2. VALID (Validation of Accuracy for LLM and ML Extracted Information and Data) framework

Caspar Safarlou then explored AI from an ethical perspective. He challenged delegates to move beyond treating ethics as a checklist of obligations, such as protecting patient privacy or performing patient participation, and instead ask what underlying value each obligation actually serves. Protecting privacy, he argued, is not a standalone duty in itself but matters in part because it builds the trust needed to sustain patient participation in research; naming that underlying value gives clearer purpose to research practice than compliance alone. He applied the same reasoning to patient involvement, arguing that patients can contribute unique experiential knowledge that cannot be deduced from clinical data or researcher expertise alone. This value-based perspective, he suggested, should also underpin responsible AI implementation.

Safarlou also encouraged greater precision when discussing concepts such as bias. Rather than treating bias as a single problem, he distinguished between statistical bias, selection effects, publication bias and prejudice, noting that each represents a different challenge requiring different methodological responses. Without this clarity, discussions around responsible AI risk becoming too broad to guide meaningful scientific practice.

James Gwinnutt demonstrated how AI is already supporting activities across the evidence lifecycle. Applications now extend from literature reviews and evidence synthesis to medical record abstraction, terminology coding, statistical programming and scientific writing. AI is particularly effective at processing large volumes of unstructured text, enabling repetitive tasks to be completed more efficiently while allowing researchers to focus on scientific interpretation and decision making. He stressed that AI should augment rather than replace scientific expertise and that organisations should adopt a risk-based approach, selecting the right technology for the right task and demonstrating measurable benefit before implementation.

Michel Dumontier considered the future of AI within regulatory science. Drawing on work within the REALM regulatory sandbox, he argued that AI systems must be evaluated independently across a wide range of use cases to understand both where they perform well and where important limitations remain. Looking further ahead, he suggested that increasingly autonomous AI systems may eventually design studies, generate evidence, prepare regulatory submissions and evaluate their own outputs. While deliberately provocative, this perspective challenged delegates to consider how governance, accountability and validation frameworks should evolve as AI capabilities continue to develop.

The panel discussion reinforced that trust remains central to the successful adoption of AI within healthcare research. Speakers consistently returned to themes of transparency, reproducibility, validation and human accountability. While AI systems may increasingly automate technical activities, responsibility for evidence quality remains with researchers and organisations deploying these technologies. Human oversight therefore evolves from performing individual tasks towards designing robust systems, establishing governance and ensuring appropriate safeguards remain in place.

Audience questions focused on reproducibility, regulatory acceptance and the future relationship between AI and scientific decision making. Delegates questioned how confidence in AI-generated evidence can be maintained as language models continue to evolve and agentic approaches become more widely used. They also asked whether increasingly autonomous systems could ever satisfy regulatory expectations. Panellists emphasised that confidence should be built through transparent workflows, independent validation and reproducible methodologies, rather than assumptions about the underlying technology. Discussion also explored AI's potential to improve clinical trial design, optimise data collection and enhance evidence generation while maintaining scientific rigour.

Looking ahead, speakers anticipated wider adoption of smaller language models operating securely within healthcare organisations, AI assisted clinical documentation to improve the quality of routinely collected data, and increasing integration of AI throughout the evidence generation lifecycle. Although opinions differed regarding the extent to which AI may eventually automate elements of research, there was broad agreement that the principles underpinning trustworthy evidence remain unchanged.

The session concluded that **the challenge is no longer whether AI should be used in RWE, but how it can be implemented responsibly to strengthen evidence generation while maintaining scientific rigour, transparency and public trust.** Reflecting the wider conference theme, AI was presented not as an end in itself, but as a powerful enabling technology capable of helping translate data into decision-ready evidence.



POSTER PRESENTATIONS

Moderator: Susan Oliveria, Thermo Fisher Scientific

Showcasing Real-World Evidence Research

Building on the introduction of research abstracts and posters at the 2025 conference, the 2026 programme continued to provide a platform for sharing research and methodological developments from across the real-world evidence (RWE) community.

The poster programme showcased research addressing practical and methodological questions relevant to the generation and use of RWE. All abstracts selected through the review process were presented as posters in the dedicated poster hall, giving delegates the opportunity to explore the research throughout the conference and engage directly with presenters.

The poster hall complemented the main scientific programme, creating an additional space for researchers and delegates to exchange perspectives, discuss emerging work and make connections across the RWE community.

Review and Selection

Abstract submissions were reviewed by the GetReal Institute abstract committee, comprising representatives from across the Institute's membership. Submissions were assessed against predefined criteria, including relevance to RWE, methodological quality, innovation and potential impact.

Following the review, selected abstracts were invited to present their work as posters in the conference poster hall. Three abstracts were additionally selected for oral presentation as part of the Poster Presentation Spotlight, providing an opportunity to showcase selected research within the main conference programme.

Poster Presentation Spotlight

The three selected posters for oral presentations were:

- Contribution of Real-World Evidence for the Orphan Medicines Approvals in the European Union between 2000 and 2025 | Lisbon University | Presentor: Luisa Bouwman
- Automated Study Feasibility Using Agentic Artificial Intelligence to Rapidly Identify Fit-for-Purpose Secondary Data | ThermoFisher Scientific | Presentor: Mark Yates
- From Trials to Routine Care: Evaluating CPMS Identifier Recording in UK Primary Care EHRs | Clinical Practice Research Datalink | Rachana Tank

The spotlight gave the selected presenters an opportunity to share their research with the wider conference audience and highlight its relevance to current RWE practice. Bringing these presentations into the main programme enabled delegates to hear directly from the researchers and consider the implications of their work across different decision-making contexts.

Supporting Research Exchange

The poster programme continues to support the GetReal Institute's role as a multi-stakeholder platform for RWE. Combining a dedicated poster hall with selected oral presentations provided different opportunities for research to be shared and discussed, while increasing the visibility of work taking place across the RWE community.

Together, the poster hall and Poster Presentation Spotlight broadened the scientific content of the conference and provided a forum for sharing emerging research, practical applications and methodological developments alongside the main conference sessions.

The following three pages feature the spotlight posters selected for oral presentation.



Contribution of Real-World Evidence for the Orphan Medicines Approvals in the European Union between 2000 and 2025

Luísa Bouwman^{1,2} · Diogo Almeida^{1,2} · Carla Jonker³ · Hubert Leufkens^{1,4} · Bruno Sepodes^{1,2} · Carla Torre^{1,2}

¹Faculdade de Farmácia, Universidade de Lisboa, Portugal | ²Research Institute for Medicines (iMED.Ulisboa), Portugal | ³Medicines Evaluation Board, Utrecht (The Netherlands) | ⁴Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands.



BACKGROUND

Orphan medicinal products (OMPs) face challenges aligning with traditional randomized control trials (RCT) pathways. RWD/RWE can provide critical complementary evidence — yet their systematic contribution to EU OMP approvals over 25 years had not been comprehensively characterised.

OBJECTIVE

Assess the contribution, role and temporal trends of RWD/RWE in regulatory decision-making for OMP marketing authorisation approvals in the EU (2000–2025), across both pre- and post-authorisation phases.

METHODS

Population: All 311 orphan medicinal products (OMPs) approved by EC (Jan 2000–Dec 2025)

Data source: European Public Assessment Reports (EPARs) from the EMA website

Pre-authorization screening: Keyword search per EPAR; RWD classified as 'main', 'supportive', or 'not known'

Post-authorization screening: PAMs in Annex II conditions, SOBs, and RMP category 1–3 activities screened for RWD/RWE

Extraction: Data source type, study design, main objective, and role in benefit-risk assessment

QC: 25% random sample checked by second author; full check for critical variables; consensus by 3 researchers

KEY FINDINGS AT A GLANCE

311
OMPs approved
EU 2000–2025

81%
MAAs containing
RWD/RWE

512
Total RWD sources
identified

21%
RWD as main/pivotal
evidence

Figure 1. Annual OMPs approved (dark green) and OMPs with RWD identified in pre- or post-authorisation phase (light green), EU 2000–2025. In 2000 no OMPs have been approved.

Pre-authorization RWD sources (N=280)

Early Access Programs36.1%

Case reports / Nat. History Studies22.5%

Electronic Health Records16.8%

Post-marketing experience from other regions10.7%

Registries8.2%

Not clear/Other5.7%

Role of RWD in Pre-authorization

Main / Pivotal evidence21.1%

Supportive — Efficacy36.8%

Supportive — Safety28.2%

Supportive — Efficacy & Safety3.9%

Not known / Not specified10.0%

RWE in Main Evidence

Corresponding to 41 OMPs

73% Non-oncological indications

56% Non-small molecules

59% Conditional MA/approval under exceptional circumstances

53% of main-evidence RWD sources were external controls — primarily from EHRs (n=16), natural history studies (n=6) and patient registries (n=5).

Post-authorization RWD sources (N=232)

Registries (disease, patient, product, pregnancy)66.8%

Electronic Health Records / eCRF/patient surveys23.3%

Not clearly specified7.8%

Early Access Programs1.3%

Claims data0.9%

POST-AUTHORISATION STUDIES (N=232)

Additional Pharmacovigilance Activities in the Risk Management Plan (RMP)
N= 223; 96%

Category 3 (required)43.9%

Not specified (pre-2012)24.7%

Category 1 (imposed condition)17.5%

Category 2 (specific obligation)13.9%

CONCLUSIONS

Post-authorisation Efficacy Studies
N= 9; 4%

>80% of OMP MAAs contain RWD/RWE — confirming it as an essential component of OMP regulatory evaluation

68% of pre-auth RWD is **supportive**; main evidence RWD particularly relevant for ATMPs and non-standard MAAs

Early Access Programs most common **pre-auth** RWD source (36%), yet data collection remains largely unstructured

Registries dominate **post-auth** phase (67%); prospective cohorts most common study design (93.5%)

Lack of Harmonisation standardised EPAR terminology and documentation needed to improve RWE interpretability

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Automated Study Feasibility: Leveraging Agentic AI to Rapidly Identify Right Fit Secondary Data

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Background

- Identifying appropriate data sources for real-world evidence is increasingly challenging as research questions demand granular clinical, temporal, and biomarker data. At the same time, the number and diversity of available real-world data (RWD) sources, across electronic health records, registries, claims, and linked datasets, has expanded rapidly across regions.
- The Professional Society for Health Economics and Outcomes Research (ISPOR) task force guidance emphasizes transparent, reproducible evaluation of data source suitability; however, feasibility assessments often rely on manual processes and fragmented institutional knowledge. There remains a need for scalable approaches that can operationalize ISPOR principles in a consistent and practical way across diverse data sources.
- This approach aligns with ISPOR principles of transparency, reproducibility, and fitness-for-purpose in real-world data selection.

Objectives

- This poster describes the development of a structured metadata catalogue and explores the use of an agentic artificial intelligence (AI) interface to operationalize transparent, reproducible data source selection.

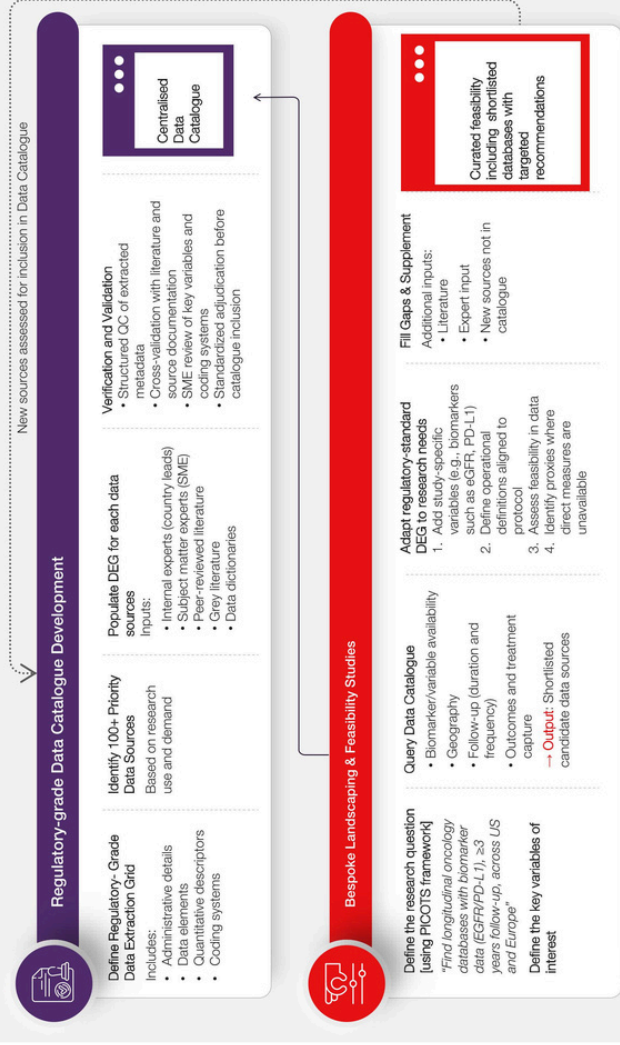
Framework Development and Insights

- Data source catalogue development followed a reproducible workflow using a unified data element grid (IDG) template, harmonized from internal knowledge and EWA catalogue metadata. For initial development, 100 commonly used claims and electronic health record (EHR) databases were prioritized. DEGs were curated by subject-matter experts using a structured extraction process, with independent review by a second knowledgeable reviewer.
- This structured metadata foundation enables systematic and reproducible interrogation of data sources and forms the basis for AI-assisted querying.
- Adding an AI-assisted querying layer to curated metadata enables a more standardized, efficient, and reproducible approach to identifying fit-for-purpose data sources. The process for framework development is outlined in **Figure 1**.

AI-Powered Data Source Recommendations

- An AI agent-based interface is under development to interpret study requirements in line with ISPOR-ISPE good practice for real-world data studies, align them with catalogue metadata, and generate standardized, transparent recommendations for data source suitability. The AI does not generate knowledge; it operationalizes expert-curated metadata.

Figure 1. Framework for Systematic Data Catalogue Development and Bespoke Landscaping



Abbreviations: DEG = data extraction grid; EGFR = epidermal growth factor receptor; PD-L1 = programmed death ligand 1; POCOTS = population, intervention, comparator, outcome, time, and setting; nRFS = real-world progression free survival; OC = quality control; SME = subject matter expert.

References

- Berger ML, et al. *Value Health*. 2017;20(8):1003-1008.
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Disclosures

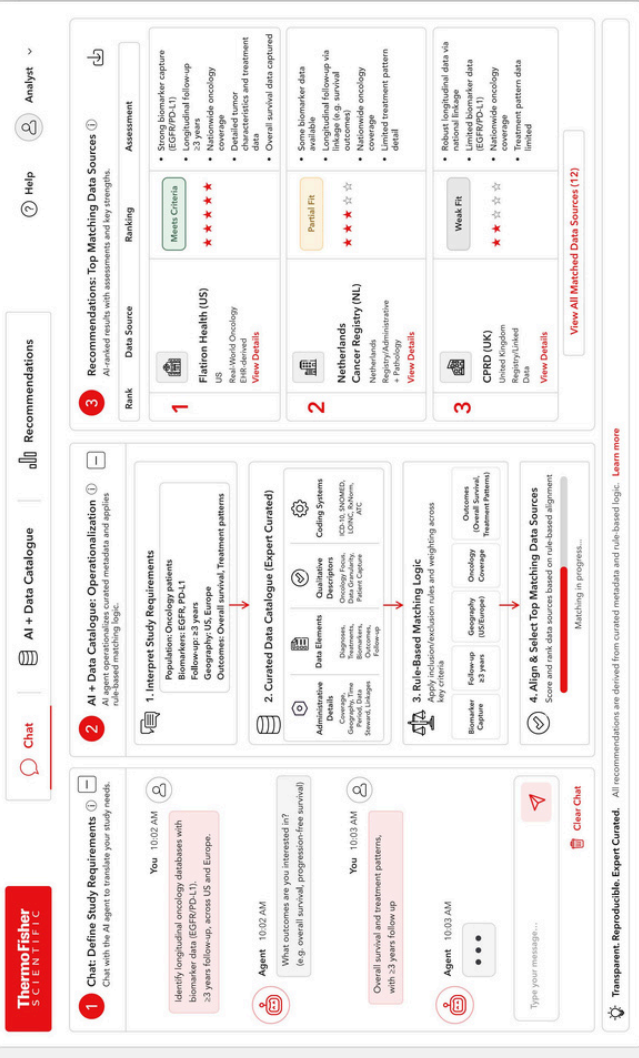
The authors are employees of PPD™ Evidera™ Real-World Data & Scientific Solutions, Thermo Fisher Scientific, and report no other relevant financial relationships.

- The planned front-end interface will allow non expert users to enter study requirements in free-text form, which are then cross checked against catalogued metadata to present data recommendations to the user. A prototype is illustrated in **Figure 2**.
- While this approach shows clear potential, development and early prototyping identified several practical challenges around standardization, accounting for complex study designs and data heterogeneity, usability, and automation.
- These findings are directly informing refinement of the metadata catalogue and highlighting where additional standardization and training data are needed to improve performance.

Conclusions

- A harmonized metadata foundation combined with an AI-driven interface provides a scalable approach to operationalizing ISPOR principles for data source selection supporting greater transparency, reproducibility, and confidence in real-world evidence studies.
- As the field continues to evolve, high-quality background data remain critical. The model will improve with further refinement and expanded data, but human expertise remains essential to guide interpretation and appropriate use.
- Ongoing work focuses on improving classification of complex data sources, expanding catalogue coverage, and evaluating the impact of AI-assisted feasibility assessments on study planning efficiency and decision quality.

Figure 2. AI Agent-Enabled Study Recommendations



Abbreviations: AI = artificial intelligence; ATC = Anatomical Therapeutic Chemical; CPDR = Clinical Practice Research Datalink; EGFR = epidermal growth factor receptor; ICID-10 = International Classification of Diseases, 10th Revision; LOINC = Logical Observation Identifiers, Names, and Codes; NL = Netherlands; PD-L1 = programmed death ligand 1; SNOMED CT = Systematized Nomenclature of Medicine—Clinical Terms.

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Medicines & Healthcare products
Regulatory Agency

From Trials to Routine Care: Evaluating CPMS Identifier Recording in UK Primary Care EHRs

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INTRODUCTION

Longitudinal electronic health records (EHRs) are used to support healthcare decision making. Clinical Practice Research Datalink (CPRD) contains UK-wide coded, pseudonymised primary care EHRs and currently supports two clinical trials with recruitment and safety monitoring. One challenge is identifying RCT participation and linking trial cohorts to routine care for post-trial follow up. In UK primary care, SNOMED codes capture research activity, while the Central Portfolio Management System, a national portfolio recruitment system, assigns unique portfolio study identifiers (CPMS IDs). If CPMS IDs are reliably recorded in routine care, alongside trial participation codes, this could enable study specific linkage in CPRD and support follow up beyond trial end. We assessed the completeness of CPMS IDs recorded in CPRD for two studies with known enrolment.

Objective: To assess the completeness of CPMS ID recording in CPRD for two pragmatic trials with known enrolment.

METHODS

We assessed recording of trial participation in CPRD data for two UK pragmatic trials: DaRe2THINK (cardiovascular) and Asymptomatic (respiratory).

Using the March 2026 Aurum build of CPRD data we extracted records with SNOMED codes indicating any trial activity (e.g. consent, invitation). We then identified records containing trial-specific CPMS IDs, and restricted analyses to codes corresponding to participation-related pathway milestones only (e.g. enrolment, follow-up). Observed counts were then compared with known enrolment totals for each trial.



RESULTS

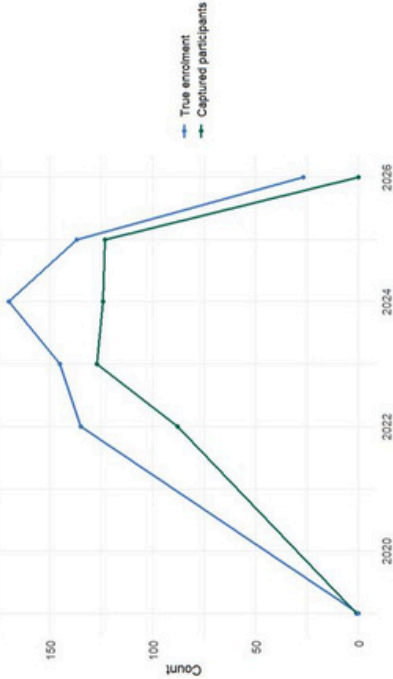
When examining overall representation of CPMS IDs in CPRD data, compared to the reference period of 2016- November 2025, CPRD CPMS IDs represented 32.8% of the 18,912 trials reported by the CPMS system.¹

Completeness of DaRe2THINK and Asymptomatic CPMS ID recording in CPRD Data

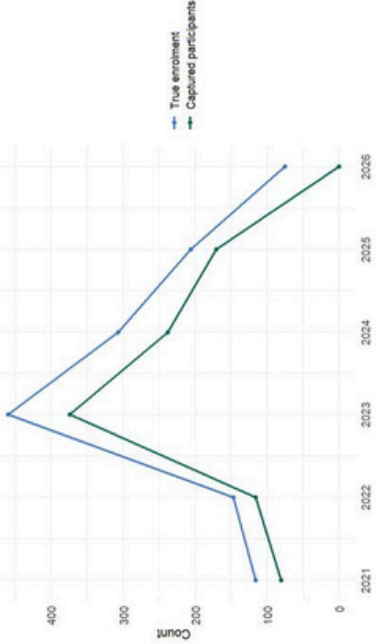
Study	Known enrolled	CPMS ID recorded	% completeness
Asymptomatic	614	455	74%
DaRe2THINK	1,313	813	62%

Most frequent SNOMED Participation Events	
Participant in research study	24%
Patient entered into trial	19%
Consent given to participate in research study	18%
Patient consented to clinical trial	16%
Referral for participation in clinical trial	6%
Consent given to review medical record in research study	5.5%

Asymptomatic: Trends in Captured Participants vs True Enrolment



DaRe2Think: Trends in Captured Participants vs True Enrolment



¹ (UK Clinical Research Delivery key performance indicators: data to November 2025 (data tables))

CONCLUSIONS

Completeness of CPMS ID recording in CPRD primary care was variable across the studies examined. While study-level linkage and extended follow-up are feasible when CPMS IDs are available, overall sensitivity may be enhanced by jointly leveraging SNOMED codes alongside CPMS identifiers. The observed variability in recording is likely multifactorial. Differences in study teams and their operational practices may influence how consistently CPMS IDs are captured and entered into primary care records. In addition, variation in patient populations may play an important role: for example, studies involving more vulnerable populations may have closer clinical oversight and more diligent documentation in primary care, leading to higher completeness of recording. However, the use of CPMS identifiers and SNOMED codes for post-trial follow-up may also raise governance challenges, particularly around whether such identifiers can be routinely used for secondary follow-up beyond the original trial context, and how this aligns with consent, data access permissions, and regulatory approvals. Standardising CPMS recording practices across studies and settings could therefore strengthen the utility of EHR data for post-trial follow-up and improve the assessment of longer-term safety outcomes.

SESSION 5: REAL-WORLD EVIDENCE IN ACTION: KEY RESULTS AND POLICY LESSONS FROM THE METREAL PROJECT CLUSTER

Moderator: Michel Dumontier, Maastricht University, REALM project

Panel: Peter Mol, CBG-MEB, More-EUROPA project; Martin Russek, BfArM, Real4Reg project; Carole Longson, HTA expert and Evidence Based Practice Expert

Session overview

This session brought together representatives from the Horizon Europe MetReal Cluster to showcase progress across six collaborative research projects advancing the generation and use of real-world evidence (RWE) for regulatory and health technology assessment (HTA) decision-making. Rather than presenting the projects in isolation, the session focused on common methodological challenges, practical solutions and emerging policy lessons across the Cluster.

Opening the session, Michel Dumontier, Distinguished Professor of Data Science at Maastricht University and Coordinator of the REALM project, described the growing importance of real-world data in European research. Healthcare systems now generate vast amounts of data from sources including electronic health records, patient registries and digital health technologies, and regulators, HTA organisations, clinicians and patients increasingly recognise its potential to inform healthcare decision-making. The challenge, he explained, is no longer how to generate real-world data, but how to transform it into robust, transparent and reproducible evidence that can be trusted for regulatory and HTA decision-making.

Dumontier explained that the MetReal Cluster brings together six Horizon Europe projects examining this challenge from complementary perspectives, spanning data quality, methodological standards, study design, AI, analytics, regulatory science and governance. Together, the projects represent one of Europe's largest coordinated investments in real-world evidence and, although each has a distinct scientific focus, share a common ambition to improve the use of real-world and synthetic data for regulatory and HTA decision-making.

Setting out the session's structure, Dumontier explained that delegates would first hear an overview of the six projects from Peter Mol, followed by Martin Russek summarising the Cluster's cross-project recommendations. These would then be explored through an interactive Slido exercise before discussion by an expert panel representing regulatory, HTA and research perspectives.

Dumontier concluded by posing the overarching question that framed the session:

What will it take for real-world evidence to become a routine, trusted component of healthcare decision-making across Europe over the next five years?

Overview of the MetReal Cluster

Mol opened by introducing the MetReal Cluster's six Horizon Europe projects, which began in 2023 and are now in their fourth year, with many starting to deliver results. His presentation gave an overview of each project before drawing together common methodological themes and practical lessons.

To frame the discussion, Mol referred to the widely recognised paper by colleagues from the European Medicines Agency (Arlett et al., 2022), which set the ambition of establishing the value of **trustworthy real-world evidence** by 2025. He suggested this ambition remains highly relevant, posing three questions that continue to underpin the Cluster's work: what real-world data can contribute, how it can be trusted, and how it can be used appropriately to answer questions faced by regulators, HTA bodies and other decision-makers?

Mol then introduced each of the six projects, highlighting how they address different but complementary aspects of strengthening the use of real-world evidence.

More-EUROPA (more-europa.org) focuses on improving the use of patient registries for regulatory and HTA decision-making. Well-curated registries are one of the closest forms of real-world data to clinical trial data, Mol explained, given the greater curation and standardisation they undergo compared with many routinely collected healthcare datasets. The project is developing methods to identify suitable registries, strengthen federated analyses, and build the knowledge and skills regulators and HTA organisations need to confidently evaluate registry-based evidence.

Real4Reg (www.real4reg.eu) is developing AI methods, analytical standards and guidance for regulatory and HTA use of real-world data across the product lifecycle. During the presentation, Mol also emphasised that where external control arms are intended to complement single-arm trials, they should be planned prospectively as part of the overall evidence strategy rather than constructed retrospectively.

Mol then introduced **REALM** (www.realm-ai.eu/), which is establishing a collaborative test environment for evaluating software as a medical device and AI-enabled healthcare technologies. He highlighted its collaborative nature, bringing regulators, industry and researchers together in a test environment that evaluates innovative approaches while encouraging iterative dialogue between stakeholders throughout development.

Turning to **INSAFEDARE** (www.insafedare.org), Mol described how the project is developing methods and assurance frameworks to support the safe and trustworthy use of both real-world and synthetic data in regulatory decision-making. He explained that synthetic data may help address privacy and governance challenges while retaining analytical value for selected regulatory applications.

Mol next introduced **REDDIE** (www.reddie-diabetes.eu), which is investigating how real-world data can complement randomised controlled trials in diabetes research, exploring national registries, machine learning, target trial emulation and tools to identify data sources fit for specific research questions, while examining how such evidence can be generated to meet regulatory and HTA standards.

Finally, **Oncovalue** (oncovalue.org), which is investigating how routinely collected oncology data from European cancer centres can be transformed into high-quality real-world evidence using AI-based methods. The project aims to improve assessment of the real-world effectiveness and value of cancer therapies for clinicians, regulators and HTA decision-makers.

Throughout, Mol emphasised that evidence generation should begin with a clear understanding of the research question and decision to be informed, rather than starting with the available data, a principle underpinning many of the methodological developments presented across the Cluster.

Drawing together common themes, Mol highlighted methodological developments strengthening the generation and interpretation of real-world evidence, including external control arms, target trial emulation, common data models, federated data analysis, synthetic data and AI, emphasising the importance of assessing whether data are fit for purpose, improving interoperability, and enabling secure analyses across distributed sources.

Mol argued that establishing the value of real-world evidence should begin with a clear understanding of the regulatory or HTA decision to be informed, and that RWE is often most valuable when it complements rather than replaces randomised controlled trial evidence. While advances such as target trial emulation, pragmatic registry-based studies and AI-supported methods offer important opportunities, their success ultimately depends on selecting the right data and applying it appropriately.

Looking beyond methodology, Mol stressed that wider adoption of real-world evidence will depend on building trust through practical implementation as much as scientific innovation. Across the Cluster, projects are supporting this through training, tools to help identify appropriate data sources, regulatory sandboxes, and earlier engagement between researchers, regulators and HTA organisations. He also highlighted prospective study planning, including designing external control arms at the outset, and registering study protocols in the HMA-EMA Catalogues of real-world data sources and studies as important steps towards transparency and routine use of real-world evidence.

Mol concluded that the MetReal projects have generated a wealth of methodological innovation that will continue to inform regulators and HTA organisations, but that successful adoption will require continued collaboration across the research community, regulators, HTA bodies and initiatives such as the GetReal Institute to translate these advances into routine decision-making.

From Project Findings to Cross-Project Recommendations

Building on Mol's overview, Russek shifted the focus from individual project outputs to the collective lessons emerging across the Cluster, explaining how regular collaboration between the six projects had enabled common challenges, shared experiences and practical recommendations to be identified.

Project representatives had met regularly to exchange experiences and discuss common challenges, and towards the end of 2025 these discussions became more structured, aiming to identify recurring themes and translate them into recommendations for those shaping the future use of real-world evidence. The resulting recommendations were organised around three stakeholder groups: European policymakers, health data access bodies and data holders, and the wider real-world evidence community.

Before presenting the recommendations, Russek reflected on common challenges, many relating to accessing and using healthcare data. Despite increasing data availability, obtaining access often remained lengthy and

administratively complex, with multi-country research frequently constrained by differing governance processes, limited cross-border access, and difficulties linking datasets across organisations, continuing to delay research and limit opportunities for evidence generation.

Methodological challenges were equally apparent, including missing data, differing coding systems between countries, heterogeneity in multi-database study results, and the need for further research into issues such as time-varying confounding. Infrastructure also remained a constraint: secure analysis environments often lacked the flexibility required for modern methods, while limited computational resources restricted the use of AI and other intensive approaches.

Although significant, Russek highlighted practical solutions already emerging: Real4Reg has developed software supporting target trial emulation and addressing time-varying confounding; Oncovalue is applying AI to structure information from oncology clinical notes; More-EUROPA and REDDIE have both developed machine learning tools to help identify appropriate data sources; and INSAFEDARE is developing frameworks to assess synthetic data quality before use. These examples show many Cluster-identified challenges are already being addressed through practical innovation.

Recommendations for European policymakers

Russek began with recommendations for European policymakers, focused on creating an environment that enables continued development and application of high-quality real-world evidence. Key priorities included continued investment in computational infrastructure, support for federated data analysis, improved standardisation and translation of metadata, and ensuring knowledge from publicly funded research is shared beyond scientific publications to support implementation and policy development.

Recommendations for health data access bodies and data holders

The second group of recommendations targeted organisations managing and providing access to healthcare data, aiming to make data more accessible, transparent and easier to use for research. Priorities included clearer information on available data sources, secure programming environments using realistic synthetic data for study preparation, shared best-practice examples of successful access applications, harmonised application forms, aligned study protocol templates, and more streamlined approval pathways, collectively reducing administrative burden and enabling more timely evidence generation.

Recommendations for the real-world evidence community

Russek concluded with recommendations for the wider real-world evidence community, focused on strengthening methodological capability and public trust: developing more computationally efficient methods, further research into multi-database heterogeneity, and improved communication with patients and the public, involving patients more actively in research design, helping citizens understand how and why their data are used, and being transparent about data protection and governance. Maintaining this trust, he emphasised, is essential if real-world evidence is to realise its full potential.

Russek explained that the recommendations would be published after the conference and encouraged delegates to follow the Cluster's ongoing work, before handing back to Dumontier, who invited the audience to prioritise the recommendations via Slido ahead of the panel discussion.

Audience Prioritisation of the Recommendations and Panel Discussion

Following Russek's presentation, Dumontier invited delegates to rank the recommendations via Slido according to which they believed would have the greatest impact across the three stakeholder groups. As results appeared live, Dumontier invited the expert panel to reflect on the audience's priorities and what would be required to translate them into routine practice.

Recommendations for European policymakers

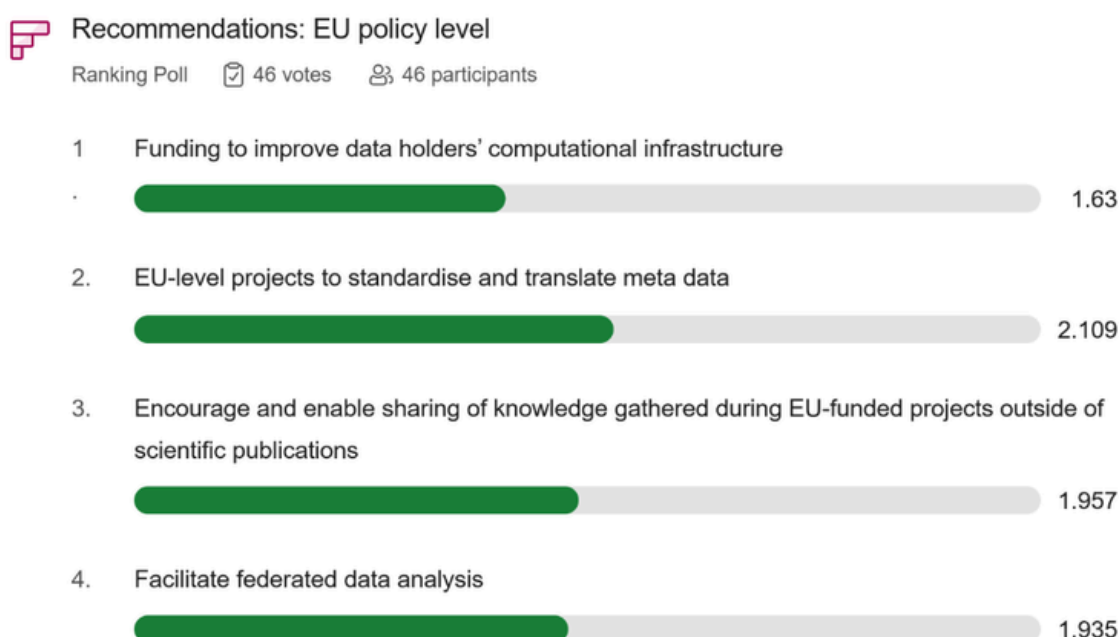


Figure 1. Audience prioritisation of recommendations for European policymakers

The first discussion focused on recommendations for European policymakers. While rankings showed broad support across all proposed actions, Dumontier noted particularly strong support for federated data analysis, standardisation and translation of metadata, sharing publicly funded research beyond scientific publications, and investment in computational infrastructure.

Responding, Carole Longson, suggested that the greatest challenge lies not in generating methodological research but in translating its outputs into policy and routine practice. Europe has invested considerably in methodological innovation, she argued, but stronger mechanisms are now needed to ensure regulators and HTA organisations systematically adopt the findings of publicly funded research.

Responsibility for implementing research findings should not rest solely with researchers, she suggested; policymakers, regulators and HTA bodies should demonstrate how they intend to use publicly funded research to improve decision-making, strengthening the connection between research and policy to maximise the impact of investment through programmes such as Horizon Europe.

A second theme focused on the increasing alignment between regulatory and HTA decision-making: although traditionally viewed as separate, both increasingly rely on the same evidence base, so future policy sandboxes should support both rather than operating independently. Drawing on REALM's work with software and AI-enabled technologies, she suggested similar collaborative approaches could extend to medicines and other healthcare technologies, creating a more direct route from research to implementation.



Recommendations for health data access bodies and data holders



Recommendations: HDABs & data holders

Ranking Poll



37 votes



37 participants

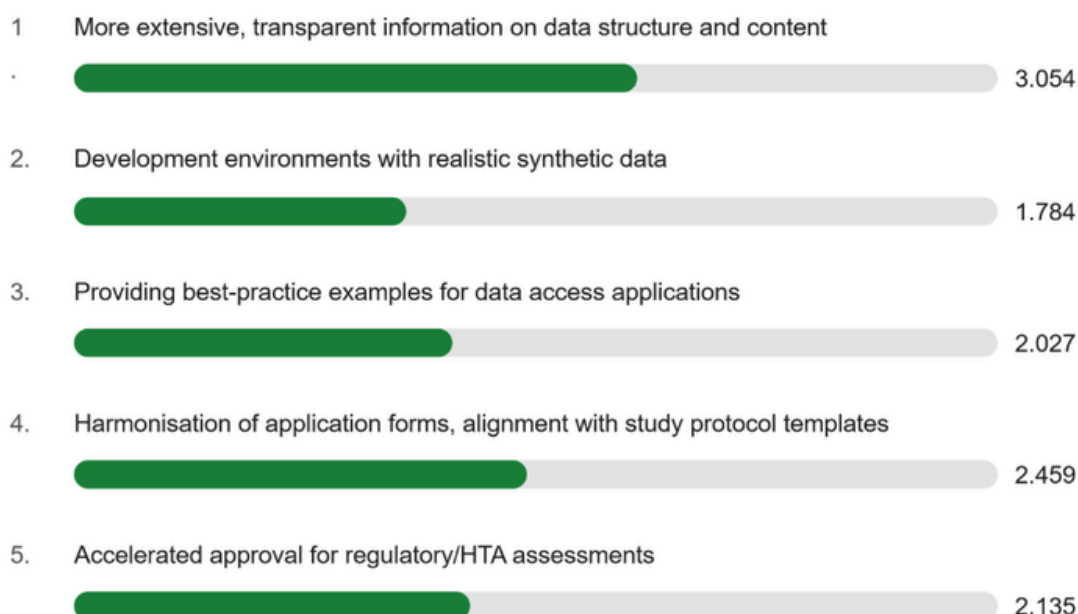


Figure 2. Audience prioritisation of recommendations for Health Data Access bodies and data holders

The second poll focused on organisations managing and providing access to healthcare data, covering improved transparency around available data sources, realistic synthetic data environments for study preparation, shared best-practice examples of successful applications, harmonised application forms, aligned study protocol templates, and accelerated approval pathways for regulatory and HTA studies.

Longson again emphasised that while each recommendation addressed important technical and operational barriers, the broader challenge remained ensuring policymakers fully embrace real-world data as legitimate evidence for healthcare decision-making. Medicines regulators have made considerable progress here, she noted, whereas some HTA organisations remain more cautious; greater policy acceptance would help many of the practical recommendations be implemented more effectively.

Dumontier then invited Mol to identify the recommendation he believed would have the greatest impact on regulatory acceptance. Mol argued the priority should be improving understanding of the data themselves: what is available, how it was collected, and whether it suits the research question, with understanding of disease natural history becoming particularly important where randomised evidence is unavailable. He also highlighted the need to address confounding, immortal time bias, and differences between outcomes measured routinely in practice versus in clinical trials.

Recommendations for the wider real-world evidence community



Recommendations: RWD community

Ranking Poll  34 votes  34 participants

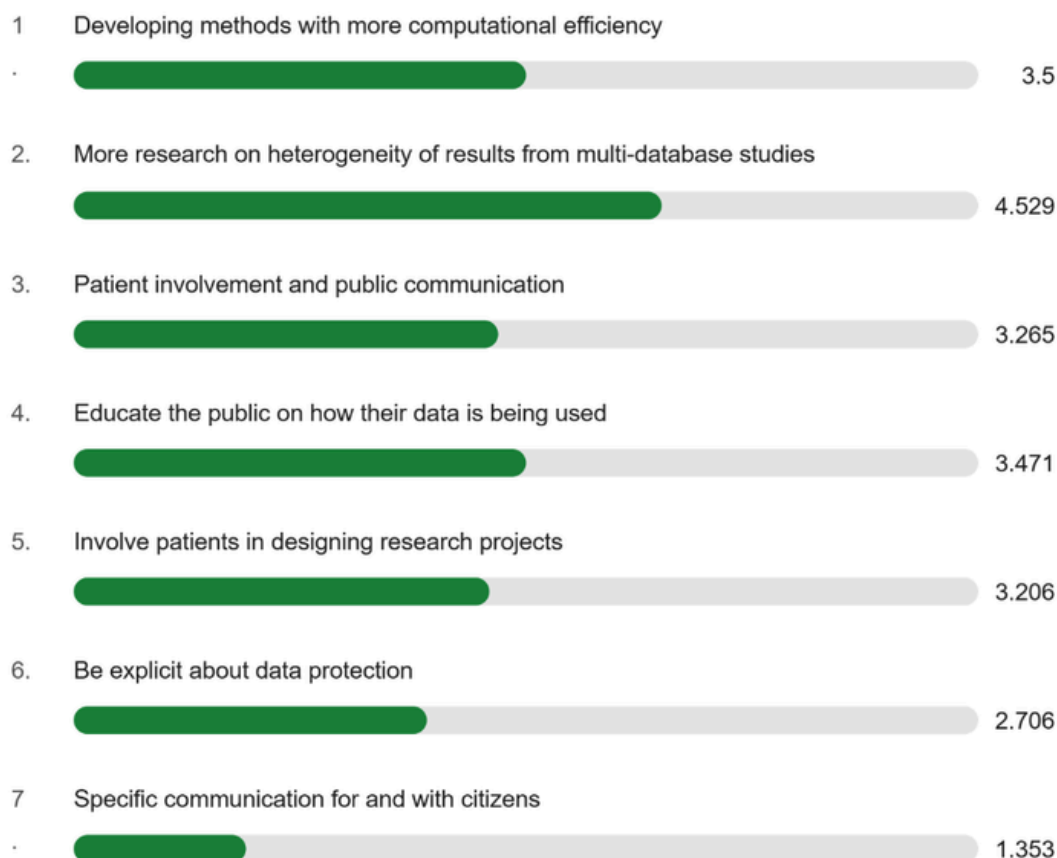


Figure 3. Audience prioritisation of recommendations for the wider Real World Evidence community

The final Slido exercise focused on recommendations for the wider real-world evidence community, including methodological research, patient involvement and public communication.

Russek welcomed the audience's prioritisation of further research into heterogeneity across multi-database studies, noting that understanding why results differ between data sources is essential for strengthening confidence in real-world evidence. Greater understanding, he suggested, would improve researchers' ability to interpret findings, predict variation between datasets, and identify the data sources most likely to generate reliable evidence.

Asked which recommendations could be implemented most readily, Russek argued that improving communication with patients and the public is something the research community can begin immediately, communicating directly with patients and citizens about how healthcare data are used, why

they are valuable, and how privacy and data protection are maintained, rather than relying solely on publications and regulatory submissions. Building public understanding, he suggested, is fundamental to maintaining trust.

Final reflections

To conclude the session, Dumontier invited each panellist to identify the single recommendation they believed would have the greatest impact if implemented.

Mol selected better understanding of the data, arguing that confidence in real-world evidence depends first on knowing what data are available, how they were generated, and whether they are fit for purpose. He also highlighted the importance of improving communication with patients, many of whom remain unclear how their healthcare data are used.

Longson selected policy sandboxes, arguing that regulators and HTA organisations should work together to evaluate methodological innovations and commit to translating successful approaches into routine policy and decision-making processes.

Russek identified improving data access as the single greatest opportunity for advancing real-world evidence. More efficient access to healthcare data, he argued, would accelerate research, encourage innovation, and ultimately strengthen the evidence available for regulatory and HTA decision-making.

Bringing the discussion to a close, Dumontier reflected that despite different perspectives, the panel had converged around three priorities: improving knowledge and quality of healthcare data, enabling more efficient access to it, and creating collaborative policy environments through regulatory and HTA sandboxes, important foundations for translating the Cluster's methodological advances into routine decision-making across Europe.

Session Conclusions

The MetReal Cluster session demonstrated how coordinated, multi-project research is helping address the methodological, technical and policy challenges of generating robust real-world evidence for regulatory and HTA decision-making, illustrating the breadth of activity across the six Horizon Europe projects to strengthen the quality, transparency and acceptability of real-world and synthetic evidence.

A recurring theme was that methodological innovation alone will not realise the full potential of real-world evidence: success also depends on selecting fit-for-purpose data, transparent and reproducible methods, evidence generation grounded in the decision to be informed, and trust built through transparency, early engagement and stronger communication with patients and the public.

These recommendations reflected the collective experience of six Horizon Europe projects, identifying practical actions for policymakers, health data access bodies, researchers and the wider real-world evidence community, underpinned by the same three priorities the panel identified.

The discussion reinforced that advancing real-world evidence is not solely a scientific challenge but also one of implementation. As Europe invests in initiatives such as the European Health Data Space, the MetReal Cluster's work provides a practical foundation for translating methodological advances into routine decision-making.

Looking ahead, continued collaboration between researchers, regulators, HTA organisations, data holders, patients and policymakers will be essential if real-world evidence is to become a routine, trusted, decision-relevant component of healthcare decision-making across Europe.



SESSION 6: EU JOINT CLINICAL ASSESSMENT (JCA): ONE YEAR IN, WHAT HAVE WE LEARNED?

Moderator: Christine Leopold, Utrecht University

Panel: Anne Willemsen, Chair of the Joint Clinical Assessment (JCA) Subgroup, ZIN; Niklas Hedberg, TLV, Co-Chair of the EU HTA Coordination Group; Tarang Sharma, Policy and HTA Expert; Sascha van Bommel-Wegmann, Flatiron Health, Martin Parkinson, Thermo Fisher Scientific.

Session overview

Less than 18 months after the EU HTA Regulation became applicable, Europe's first JCA, a report on the paediatric brain cancer treatment tovorafenib, had been published. While only a single report was available at the time of the conference, the panel agreed it already offered valuable insight into how the system is operating in practice, and what developers, HTA bodies and evidence generators can learn as implementation continues.

Moderated by Christine Leopold, the session brought together experts in European HTA, evidence methodology and industry to examine the first experience of the JCA process: what the inaugural report reveals about evidence expectations, how RWE contributes within the wider evidence package, and how manufacturers may need to rethink evidence generation strategies to meet the requirements of the new European framework. Throughout, speakers were clear that the first JCA should not be read as a definitive template for future assessments, but as the start of an iterative learning process that will continue to evolve as more assessments are completed.



One year of the JCA

To set the scene, Willemsen, Chair of the JCA Subgroup and senior advisor at Zorginstituut Nederland, gave an overview of progress since the Regulation came into force. Eighteen JCAs had been initiated: sixteen ongoing, one published and three discontinued. One discontinuation followed withdrawal of the corresponding marketing authorisation application; the other two reflected submissions that failed to meet the requirements laid down in the HTA Regulation.

Willemsen highlighted that around a third of the eighteen assessments involved advanced therapy medicinal products (ATMPs), while roughly half already carried an orphan designation, despite mandatory inclusion of orphan products not commencing until 2028. She suggested this showed the new framework was already being tested across some of the most scientifically complex and evidence-challenging therapeutic areas.

She also pointed to the breadth of European participation achieved during implementation: assessors and co-assessors had been drawn from 15 Member States and 18 HTA organisations, with patient, carer and clinical experts contributing to every assessment undertaken so far.

“It really is a European endeavour, and not only for the big Member States.”

Understanding what a JCA is and what it is not

Before turning to the lessons from the first published assessment, Willemsen clarified one of the most important principles underpinning the new European framework: a JCA is not a European reimbursement decision.

Although both regulators and HTA bodies evaluate evidence for new medicines, they do so from different perspectives. Where the EMA focuses primarily on whether a medicine's benefits outweigh its risks, the JCA evaluates the relative clinical effectiveness and relative safety of a technology against the treatment options currently available across Europe.

Willemsen explained that the JCA is limited to the clinical domains defined within the HTA Regulation. It does not assess cost-effectiveness, determine added therapeutic value or make recommendations on reimbursement; those decisions remain the responsibility of individual Member States through their own national appraisal processes.

“We don't make any conclusions, we don't give any advice on reimbursement, so there's no positive or negative outcome in the JCA.”

This distinction is fundamental. The JCA provides a common scientific assessment that national HTA agencies can use, but it does not replace their independent decision-making; it aims instead to reduce duplication by creating a shared evidence base, while pricing, reimbursement and healthcare priorities continue to differ across Europe, Member States may also differ in the types of evidence they are prepared to accept.

Central to the process is the Population, Intervention, Comparator and Outcomes (PICO) framework: policy questions agreed before the evidence is assessed and designed to reflect what Member States need rather than the evidence a manufacturer has developed. Because healthcare systems differ in comparator availability, patient population and decision basis (clinical added value versus cost-effectiveness), PICO(s) inevitably vary across Europe. Rather than eliminating that variation, the JCA is built to represent it within a single assessment. Willemsen was clear that the starting point for every assessment is the question decision-makers need answered, not the evidence available; success depends on how well a submission addresses the PICO(s), not simply on how much evidence it contains.

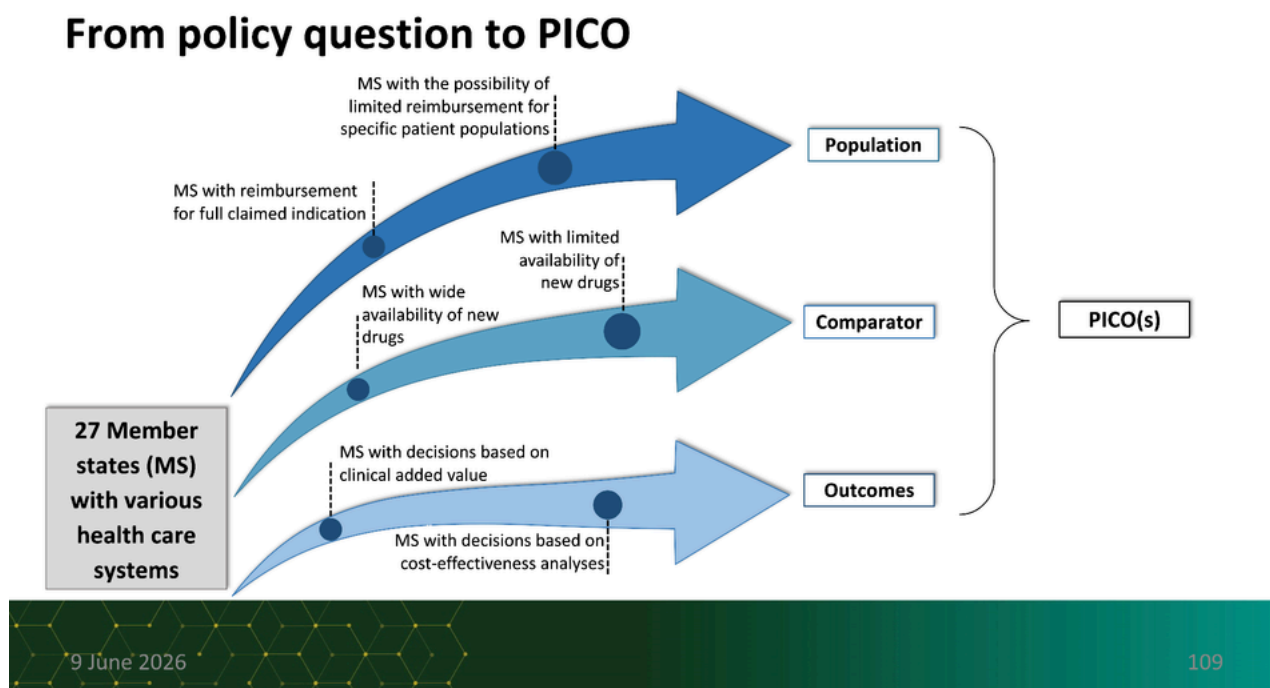


Figure 1. From policy question to PICO: how variation across 27 Member States converges into a single PICO framework

The first JCA: revealing evidence gaps as much as evidence

Turning to the tovorafenib report itself, Willemsen encouraged delegates to look beyond its conclusions and consider what it revealed about the evidence-generation process. With only one report available, she cautioned against drawing broad conclusions about future assessments, but argued it already shows the types of evidence HTA bodies expect, where gaps are most likely to arise, and how manufacturers can prepare better submissions.

Because PICO questions are established before the available data are reviewed, assessments inevitably identify situations where evidence is incomplete or unavailable. In these circumstances, Willemsen stressed, manufacturers should not simply state that evidence does not exist, but explain clearly why it could not reasonably be generated, supported where appropriate by systematic literature reviews, feasibility analyses or methodological reasoning.

“It's up to the industry to really argue and justify where evidence is available, or where evidence is not available.”

Willemsen also reflected on practical lessons from the early assessments. Some submission dossiers contained incomplete sections or omitted information assessors expected to see, making it hard to tell whether evidence had genuinely been considered or simply not presented. These experiences have already informed the guidance: the Coordination Group is now publishing an evolving Questions and Answers document, which clarifies common areas of uncertainty far more quickly than a formal guideline revision would allow.

New guidance on transparency and publication has followed the same logic. Published assessment reports are now accompanied by the manufacturer's submission dossier and supporting documentation, with clear rules on what counts as commercially confidential information. Willemsen suggested this openness is a significant opportunity for future applicants, allowing manufacturers to learn directly from earlier submissions and understand evolving evidence expectations.

Key take aways

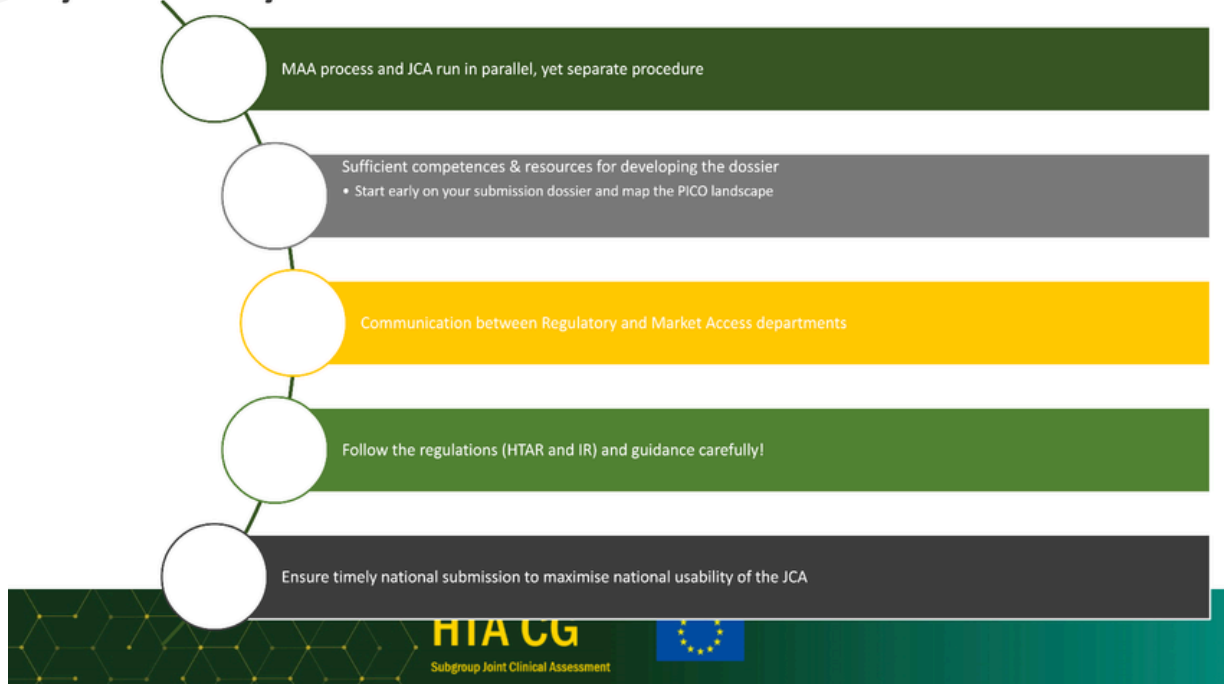


Figure 2. Key take-aways for health technology developers: parallel but separate MAA and JCA procedures, resourcing, cross-departmental communication, and timely national submission

Planning for HTA begins long before submission

Asked by Leopold what advice she would give developers in the room who are only now starting to prepare a submission, Willemsen turned to the practical implications of the new process. Although the JCA and EMA procedures run in parallel, they remain separate processes with different dossiers and evidence requirements, and their timelines overlap almost completely, leaving little opportunity to generate additional evidence once regulatory review is underway.

This, she argued, fundamentally changes how companies need to approach evidence generation. Rather than treating HTA as a downstream activity that follows regulatory approval, manufacturers should begin considering HTA requirements while designing pivotal trials: anticipating likely PICO questions, exploring comparative evidence, and considering pragmatic studies or indirect comparisons at an early stage.

“Think of HTA as early as you can. Do not only focus on the regulatory aspect.”

She also stressed close collaboration between regulatory and market access teams throughout development and encouraged manufacturers to submit national reimbursement dossiers as soon as possible after JCA publication, since delay increases the risk that new evidence will emerge and reduce the report's and submission dossier's relevance to national decision-making.

Panel discussion: where does real-world evidence fit within the JCA?

Following Willemsen's overview, Leopold pressed the panel on whether methodological expectations for evidence, and for real-world evidence in particular, were becoming any clearer in practice. That question turned the discussion to one of the most anticipated topics of the session: what role does real-world evidence currently play within Joint Clinical Assessments, and how might that evolve as the framework matures?

Niklas Hedberg cautioned against reading the limited use of RWE in the first published report as a lack of interest from HTA bodies. The current guidelines, he explained, contains no dedicated section addressing real-world evidence; instead, it enters the assessment through a number of routes depending on the research question and the product's lifecycle stage.

“There is no specific rule or place for real-world evidence in the regulation,” he explained, pointing to scientific consultations, future reassessments, voluntary HTA activity and the overall clinical evidence package as the channels through which RWE can currently contribute. As experience with the Regulation grows, he anticipated these opportunities would continue to develop, although the immediate priority remains embedding the mandatory JCA process successfully.

Tarang Sharma reinforced this point, arguing that methodological expectations for real-world evidence are already clearer than sometimes recognised. Existing guidance does not create a separate pathway for RWE, but neither does it exclude it: observational evidence is assessed alongside randomised evidence, provided it is appropriate for the research question and supported by robust methodology. As more JCAs are published, alongside the Coordination Group's Q&A documents, developers will gain an increasingly detailed picture of the evidence and methodological standards expected across different scenarios.

Both panellists emphasised that the JCA represents only one stage of the broader European HTA pathway. While it provides a common clinical assessment, reimbursement decisions continue to be made nationally, where additional evidence, including real-world evidence, often plays a more prominent role alongside economic evaluation and country-specific considerations. The recurring theme: real-world evidence is not a separate category of evidence with different standards, but one component of a broader evidence package, judged on its fitness for purpose, methodological quality and ability to answer decision-makers' questions.

From submission to strategy

Having explored how the first JCA is being implemented, the discussion turned to what the new framework means for developers more broadly, Leopold steering the panel from Martin Parkinson's early manufacturer reaction into a closer, more technical read of the report from industry itself. Sascha van Bommel-Wegmann offered that reading, reflecting on how sentiment has shifted since the Regulation's introduction: from initial uncertainty and concern towards a growing acceptance that JCAs are now an integral part of European evidence generation.

Drawing on the tovorafenib report, he cautioned against treating it as a template, describing it instead as an important stress test for both manufacturers and HTA bodies, the first real indication of how the framework performs in practice.

One striking observation: while the number of PICO questions (eight, across three patient populations) appeared manageable, the availability of comparative evidence was much more limited. Of the eight, only two ultimately carried comparative data into the final assessment, leaving considerable uncertainty around relative effectiveness, particularly for a product approved on the basis of single-arm studies.

Van Bommel-Wegmann set out what that uncertainty looked like in practice. Overall survival could not be estimated; the only outcome reaching nominal statistical significance, progression-free survival, actually favoured the comparator; objective response was inconclusive; and there was no comparative data at all on quality of life or symptom control. Descriptive safety data suggested numerically more serious and severe adverse events on the studied treatment than on the comparator. The message the report sends to member states, he said, is dominated by uncertainty rather than demonstrated benefit. ***“For a rare paediatric cancer approved on uncontrolled data, a relative-effectiveness assessment may be structurally unable to demonstrate the benefit that regulators and clinicians nonetheless recognise,”*** he said, describing this as the central tension the first report exposes.

Van Bommel-Wegmann suggested this illustrates a broader methodological tension: regulators may accept uncontrolled evidence at the point of approval for rare-disease or oncology treatments, but demonstrating comparative clinical effectiveness for HTA purposes is a considerably higher bar, one the new framework will continue to confront.

Planning comparative evidence years before submission

Throughout the discussion, one message emerged consistently: evidence strategies must begin much earlier than they have historically. Van Bommel-Wegmann argued that comparative analyses and external control arms should be planned at the point of study design, when opportunities to identify suitable comparator datasets, secure individual patient data and define robust analytical methods remain available, not shortly before submission. Where indirect comparisons are anticipated, prognostic variables and effect modifiers should be identified in advance, analytical approaches pre-specified, and sensitivity analyses planned well ahead of filing; work left until the end of development risks producing evidence unlikely to withstand JCA-level scrutiny.

A particular lesson from the first report, he added, was the need for greater transparency where evidence cannot be generated: developers should demonstrate that feasibility work has been done, rather than simply acknowledging the gap.

“JCA readiness is a multi-year evidence strategy problem,” not a documentation exercise completed shortly before approval.

First JCA Report: Message & Take-aways

First JCA Report: Outlook

Several notable take-aways, but most importantly: HTDs need to anticipate IQWiG-grade scrutiny regardless of which member states act as (co-)assessors.


PICO spread is not, on its own, the binding constraint

- Rather: the availability of usable comparative evidence for each question.
- HTDs should map, as early as trial design, which PICOs their evidence can realistically support and which they cannot. Be candid about the proportion that will go unaddressed!


Single-arm assets structurally disadvantaged

- JCA's relative-effectiveness framework requires a deliberate indirect comparison strategy built early and to a high standard:
 1. Secure access to comparator individual patient data where possible
 2. Pre-specify the estimand
 3. Conduct rigorous prognostic and effect-modifier identification
 4. Plan credible sensitivity analyses.
- The JCA report shows that an under-powered MAIC (even in rare diseases) will be heavily discounted
- Where external control arms are considered, the feasibility work should be done years ahead, not at the point of submission.


Expect IQWiG-grade methodological scrutiny

- ...regardless of which member states assess a given product
- Resource the JCA accordingly!


HTDs must carry value arguments into each national process

- The JCA confers no benefit rating of its own
- A JCA dominated by uncertainty does not foreclose access, but it shifts the burden squarely back onto country-level dossiers and price negotiations



Ramagopalan SV, Ransley AJ. J. Comp. Eff. Res. (2026) doi:10.57264/icer-2026-0117

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Figure 3. Building evidence for the JCA begins at trial design: single-arm assets, indirect comparison strategy and value arguments that must be planned years ahead

Learning from the first discontinued submissions

The panel also reflected on the three JCAs discontinued during early implementation. One followed withdrawal of the corresponding marketing authorisation application. The other two assessments were discontinued because the submitted dossiers failed to meet the Regulation's evidence requirements. Van Bommel-Wegmann suggested these cases are as instructive as the published report: reviewers cited inadequate systematic literature searches, PICO questions left unaddressed, insufficient documentation of study selection and weaknesses in evidence synthesis.

The message for manufacturers, he argued, is that demonstrating the absence of evidence requires the same scientific rigour as presenting positive findings; gaps must be supported by robust methodological reasoning, not unsupported statements.

Panel discussion: integrated evidence planning is becoming essential

Building on these themes, Parkinson reflected on how the JCA is reshaping evidence planning across the pharmaceutical industry, describing it as a genuine change-management exercise for manufacturers used to letting individual national markets set their own requirements. Many organisations had already begun adopting integrated evidence planning, bringing clinical development, regulatory affairs and market access together earlier in the product lifecycle, but how consistently this happened varied considerably by company. The introduction of JCAs, he said, has made that discipline systematic across the industry rather than a matter of individual practice, and has made it increasingly difficult to treat HTA evidence generation as a separate activity following regulatory considerations.

The companies best placed to respond, he suggested, are those starting to think about evidence requirements as early as Phase II, once an asset looks likely to progress, deciding not only which outcomes the pivotal trial itself should generate but also what additional evidence, from external data sources or routine clinical practice, will need to be produced alongside it. Assessing at this early stage what the likely P's, C's and O's, of the potential future scope of a JCA allows informed decisions to be taken throughout the clinical and additional evidence generation plans. Starting this early carries its own risk given normal attrition rates, but leaving these decisions until later leaves companies with far less room to manoeuvre once the JCA and EMA timelines begin running in parallel.

Parkinson also pointed to comparator evidence as an area needing more attention, and not only on quality grounds. He described cases where a JCA submission had to rely on a competitor's data published only as a conference abstract, since the company preparing the dossier had no control over when, or whether, that evidence entered the public domain. He suggested this points to a wider publication timing issue across the industry: unless comparator evidence is made available early and consistently, sponsors attempting indirect comparisons will keep running into gaps they cannot control themselves.

He also highlighted the implications for business development. As companies acquire external assets or enter licensing agreements, these decisions are often made under considerable time pressure, and understanding the strength of an asset's existing evidence package is becoming an increasingly important part of that due diligence; some companies are already building in checks and balances specifically to flag JCA implications as results of on-going evidence development activities. Products acquired without that consideration, he warned, may need substantial additional investment before they can successfully navigate the European assessment process.

Looking ahead: creating a learning health technology assessment system

Speaking earlier from a national reimbursement perspective, Hedberg had already drawn a distinction that shaped much of the later discussion: scientific uncertainty and decision uncertainty are not the same thing. Because pricing and reimbursement bodies also weigh price when reaching a decision, an agency such as TLV can sometimes accept a considerable degree of scientific uncertainty, including data that would elsewhere be considered vague or non-traditional, provided the resulting decision uncertainty, in effect the price being asked, remains reasonable. The closer a submission gets to the actual payment decision, he noted, the wider that gap between scientific and decision uncertainty tends to become.

As the session drew to a close, Leopold turned the discussion towards how the system is likely to evolve, prompting Hedberg to argue that the greatest opportunity lies in engaging much earlier in the development pathway. Joint Scientific consultations (JSCs), supported by European horizon scanning activities, have the potential to strengthen dialogue between developers and HTA bodies before pivotal studies are underway, helping ensure clinical development programmes are better aligned with the needs of European health systems. He also expressed hope that the framework would encourage developers to give European evidence requirements greater weight during trial design, rather than focusing predominantly on expectations outside Europe.

“We hope that the needs of Europe... are valued higher than they historically have been in setting up the clinical trials.”

Sharma described Joint Scientific Consultations as one of the most important opportunities created by the new Regulation, encouraging developers to use them not only to discuss trial design but to seek advice on the additional evidence, including patient experience data and other forms of real-world evidence, that may be needed to support future HTA decisions. This earlier dialogue, she suggested, has the potential to improve both the relevance and quality of future evidence packages, reducing uncertainty later in the assessment process.

Willemsen echoed this, reminding delegates that parallel JSCs involving both EMA and HTA bodies are already available; while uptake has so far been limited, she encouraged manufacturers to make greater use of the opportunity, allowing regulatory and HTA evidence requirements to be considered together from the earliest stages of development. Parkinson suggested that broader sharing of learning from these consultations, echoing how regulatory scientific advice has evolved, could help companies without direct access build consistency across future submissions and accelerate learning across the wider evidence-generation community.

Key messages

Although only one Joint Clinical Assessment had been published at the time of the conference, the discussion showed that important lessons are already emerging for regulators, HTA bodies and developers alike. The panel agreed the first JCA should be viewed as the beginning of an evolving process, not a definitive model, but one that already signals the standards of transparency, methodological justification and evidence quality expected under the new framework.

A recurring message was that HTA can no longer be treated as a downstream activity undertaken after regulatory approval. Regulatory, clinical and market access considerations increasingly need to be integrated throughout the product lifecycle, with comparative evidence, external controls and real-world evidence strategies considered from the earliest stages of study design. Real-world evidence itself is not assessed by a separate standard, but on whether it is fit for purpose, methodologically robust and able to answer the questions decision-makers need addressed.

As more JCAs are completed, speakers expect these expectations to sharpen, giving developers greater certainty while strengthening the consistency of evidence used to support healthcare decisions across Europe. Rather than providing all the answers, Europe's first JCA has laid the foundations for a shared learning process, one the panel agreed should now translate into earlier collaboration and better-planned evidence generation.

SESSION 7: MEETING LONG TERM FOLLOW UP OBLIGATIONS: CHALLENGES AND OPPORTUNITIES FOR POST APPROVAL EVIDENCE GENERATION

Moderator: Lourens Bloem, Utrecht University

Speakers: Christine van Hattem, Utrecht University; Lourens Bloem, Utrecht University; Andreas Schuil, Orchard Therapeutics

Panel: Peter Mol, Andreas Schuil and Marieke Heisen, Patvocates.

Session overview

For many innovative medicines, regulatory approval marks the beginning rather than the end of the evidence journey. This session explored how post approval evidence generation, particularly through long term follow up studies and RWE, can reduce the uncertainties that remain after authorisation. Using advanced therapy medicinal products (ATMPs) including gene therapies as a case study, the speakers examined how regulators, HTA bodies, industry and patients/patient organisations each contribute to building the evidence needed to support confident decision making throughout a medicine's lifecycle.

Introducing the session, Lourens Bloem explained that although the presentations would focus on gene therapies, the challenges discussed are relevant across many therapeutic areas. As medicines increasingly reach patients with limited long term evidence, robust post approval evidence generation is becoming essential to understand long term safety, effectiveness and value in routine clinical practice.

The session demonstrated that while regulators and HTA bodies often assess the same clinical evidence, they do not always identify the same uncertainties or require the same additional data. Long term evidence generation is therefore becoming increasingly important to address unanswered questions, support reimbursement decisions and provide greater confidence in the real world performance of innovative therapies. Throughout the presentations and panel discussion, speakers highlighted the growing importance of high quality registries including sustainable funding models, meaningful patient involvement and collaboration across stakeholders. Such efforts are essential to support evidence generation beyond the point of regulatory approval and, as emphasised by patient representatives, beyond the period for which formal evidence generation activities are mandated.

Understanding uncertainty at the point of approval

The first presentation was delivered by Christine van Hattem, who examined how uncertainties in the evidence supporting cell and gene therapies are assessed by European regulators and HTA bodies. Her work compared the evidence reviewed by the European Medicines Agency with assessments undertaken by HTA organisations in Germany, France, the United Kingdom and the Netherlands, focusing on the initial authorised indications for cell and gene therapies.

Van Hattem explained that the study included all cell and gene therapies authorised in Europe up to December 2024 for which at least one HTA assessment had been published by July 2025. Data were extracted from publicly available regulatory and HTA reports, allowing the team to compare the clinical evidence used and the uncertainties identified by each organisation. Of the 29 authorised therapies identified, 23 had been assessed by at least one HTA body using largely the same evidence considered by the EMA.

The analysis found that both regulators and HTA bodies frequently relied on evidence from single arm studies, often supported by additional sources such as observational studies, external controls, historical controls and natural history studies. However, despite reviewing similar evidence packages, the organisations did not always identify the same uncertainties.

Long term efficacy emerged as one of the most consistently recognised uncertainties across both regulatory and HTA assessments. In contrast, HTA bodies were more likely than regulators to highlight uncertainty around effectiveness in routine clinical practice and the availability of quality of life evidence. Differences were also observed in the emphasis placed on long term safety, reflecting the distinct perspectives and decision making responsibilities of regulators and reimbursement agencies.

Van Hattem concluded that these findings reinforce the importance of post approval evidence generation. Long term follow up studies and high quality real world evidence have an essential role in addressing the uncertainties identified during both regulatory and HTA assessments, enabling earlier patient access while continuing to strengthen the evidence base after authorisation. Rather than viewing approval as the end of evidence generation, she suggested it should increasingly be seen as the beginning of a continuous process of evidence development.

Meeting long term follow up obligations in practice

Building on Van Hattem's presentation, Bloem shared findings from his own research examining the practical challenges of delivering long term follow up studies for gene therapies. While these studies are now a well established component of post authorisation evidence generation, he noted that there is surprisingly little empirical evidence describing how they perform in practice or the obstacles encountered during their implementation.

Bloem's study reviewed all gene therapies authorised in Europe up to the end of 2024, the majority of which had orphan designation and many of which had received conditional marketing authorisation or other forms of accelerated regulatory approval. Of the authorised products, almost all had long term follow up requirements in place, with most relying on registry based studies to generate evidence after approval. To understand how these studies were progressing, the research team analysed regulatory assessment reports to identify the practical issues raised during their conduct.

The analysis identified several recurring themes. Study design and planning remained a significant challenge, particularly as follow up studies often continue for 15 to 20 years while standards of care, treatment pathways and regulatory expectations continue to evolve. Maintaining high quality data throughout these extended timeframes also proved difficult, requiring consistent data collection, robust governance and ongoing oversight.

Operational challenges were equally important. These included identifying eligible patients, recruiting participants across multiple countries, retaining patients throughout lengthy follow up periods and minimising loss to follow up. Bloem also highlighted the complexity of coordinating multinational studies, where differences in healthcare systems, data collection processes and regulatory requirements can make implementation particularly demanding.

Beyond operational considerations, the research highlighted broader governance challenges. These included maintaining alignment with evolving regulatory requirements, obtaining appropriate consent for long term participation, ensuring transparency around data use and establishing clear responsibility for the management of registries. Bloem noted that these issues become increasingly important as studies continue over many years and involve multiple stakeholders across different healthcare systems.

Concluding his presentation, Bloem emphasised that long term follow up studies should not simply be viewed as regulatory obligations. Understanding the practical challenges associated with their delivery is essential if they are to generate robust, decision relevant evidence that addresses the uncertainties identified at the time of authorisation and supports future regulatory and HTA decision making.

Learning from practice: Industry experience of post approval evidence generation.

The final presentation was delivered by Andreas Schuil, who shared practical experience of generating post approval evidence for atidarsagene autotemcel (Libmeldy), an autologous gene therapy for metachromatic leukodystrophy, a rare inherited neurodegenerative disease. His presentation demonstrated how long term follow up, registry data and real world evidence are already supporting regulatory commitments and reimbursement decisions, while also illustrating the practical challenges of generating evidence for ultra rare diseases.

Schuil explained that the evidence supporting Libmeldy extended well beyond the pivotal clinical trial. Compassionate use programmes, hospital exemption data and natural history studies all contributed to the overall evidence package submitted to regulators. Because these data were generated at a single treatment centre using consistent protocols, they could be integrated to provide a more complete understanding of the therapy's effectiveness. Even after regulatory approval in 2020, evidence generation continued through ongoing clinical studies and long term follow up, with successive data cuts supporting reimbursement submissions across Europe.

One of the clearest messages from Schuil's presentation was that different HTA bodies can reach different conclusions despite reviewing very similar evidence, echoing the presentation of Van Hattem.. Using Libmeldy as an example, he described how the same dataset was considered sufficient by the United Kingdom's HTA process, while additional evidence was requested by Dutch assessors before reimbursement could be agreed. Five years after European authorisation, reimbursement discussions were still continuing in some countries, highlighting the variation that remains across national decision making processes.

Schuil also described the complementary roles of two different long term evidence generation programmes. Orchard Therapeutics operates a company led long term follow up study involving treated patients, while an independent academic registry, the MLD Initiative, captures data from both treated and untreated patients across specialist centres. Importantly, both registries were

designed collaboratively so that clinicians collect a common set of data elements, reducing duplication while improving the consistency and usefulness of the resulting evidence.

Reflecting on the lessons learned, Schuil argued that independent registries provide important advantages by increasing confidence in the credibility of the evidence and creating datasets that can support future regulatory and HTA assessments for multiple products and manufacturers. He emphasised that smaller, well curated datasets are often more valuable than larger datasets with substantial missing information. However, he also highlighted the ongoing challenge of securing sustainable funding for independent registries, noting that maintaining high quality evidence generation over many years remains one of the greatest barriers to long term success.

Panel discussion: Creating sustainable evidence beyond approval

Opening the panel discussion, Bloem shifted the focus from methodology to the people who ultimately make long term follow up studies possible. He asked whether patients see value in participating in these studies and, if not, what needs to change to encourage sustained engagement. The discussion brought together perspectives from patient advocacy, regulation and industry, highlighting that successful evidence generation depends as much on trust and collaboration as it does on study design.

Marieke Heisen argued that patients are willing to contribute their data, but participation depends on a clear value exchange. Rather than viewing registries solely as research tools, patients need to see how participation benefits them directly, whether through improvements in their own care, better monitoring of their condition or opportunities to report outcomes that matter to their daily lives. She noted that symptoms such as fatigue, sleep disturbance and treatment burden are often best captured through patient reported data, making patients active partners in evidence generation rather than passive participants. Moreover, patients are committed for the long term. When registries are co-designed with the community, they can improve participant retention and data completeness while creating opportunities for patient organisations to (co-)lead the initiative. This can enable data collection to continue beyond industry's formal commitments, ensuring that the registry remains a valuable source of evidence for advocacy efforts.

Drawing on experience from the More-EUROPA project, Peter Mol described how patient organisations have helped improve understanding of registries through simple educational materials explaining why data are collected and how they contribute to research and healthcare decision making. He

explained that patients are generally more willing to contribute data when they understand its purpose and can see how it may improve care for themselves or future patients. Mol also noted that caregivers often play a central role in supporting participation, particularly for people living with rare diseases or conditions that limit their ability to contribute independently.

Schuil added that, in rare paediatric diseases such as metachromatic leukodystrophy, caregivers are often highly motivated to contribute because they have seen the devastating consequences of untreated disease. He also highlighted that discussions with families do not always align with the outcomes prioritised by HTA bodies. For example, parents frequently place greatest importance on preserving cognition and communication, whereas some assessments continue to focus primarily on disability measures. He suggested that greater alignment between regulators, HTA bodies and patient priorities could strengthen future patient-relevant evidence generation and decision making.

The discussion then turned to the practical barriers to sustaining long term follow up studies. An audience poll identified funding and sustainability as the single greatest challenge, ahead of patient retention, infrastructure and data quality. Panellists agreed that maintaining high quality registries over many years requires secure, long term investment, particularly for rare diseases where patient numbers are small and commercial incentives may diminish over time.

What is the biggest barrier to successful long-term follow-up studies?

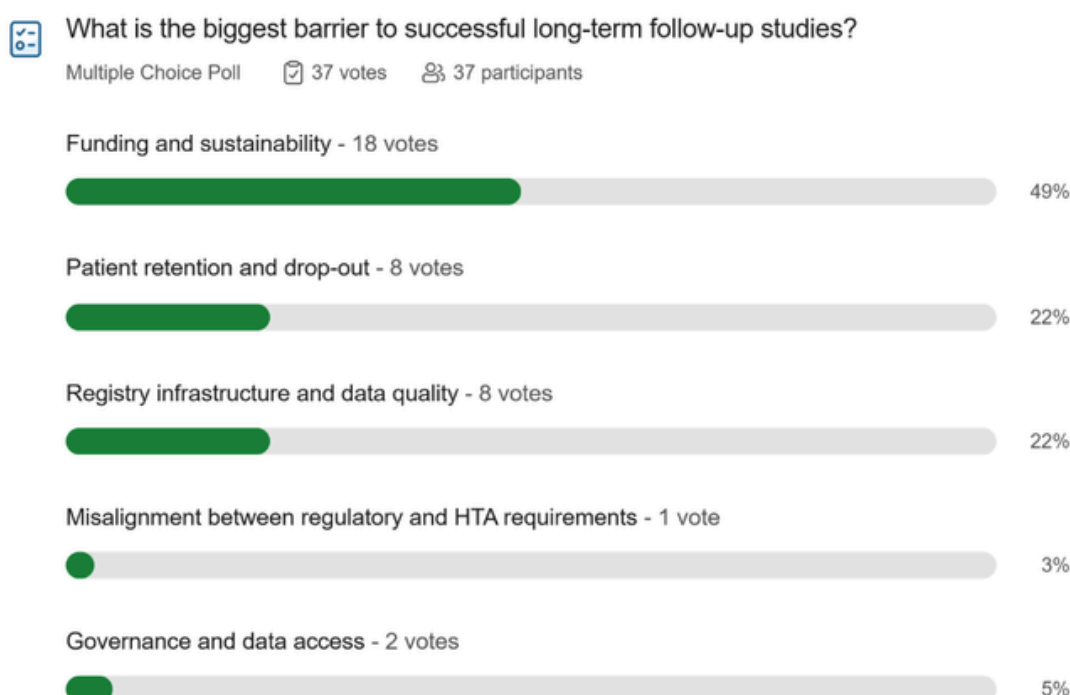


Figure 1. Audience poll: biggest barriers to successful long-term follow-up studies

Several possible approaches were discussed. Heisen highlighted successful patient led registries that have remained active because patient organisations have an enduring commitment to improving care. Mol argued that registries should be developed collaboratively, bringing together regulators, industry, registry owners and patients from the outset to ensure that data collection remains both feasible and capable of supporting regulatory and HTA decision making. Schuil suggested that government funded independent registries could provide the most sustainable long term model, improving both credibility and accessibility while ensuring that data support multiple therapies rather than individual products.

The panel also considered the potential role of the European Health Data Space (EHDS), also referring back to previous sessions earlier during the day. While recognising its future promise, the speakers agreed that significant work remains to improve infrastructure, interoperability, governance and public confidence before it can routinely support the complex evidence needs of long term follow up studies. Patient involvement was stressed repeatedly as particularly important to building trust and ensuring that future data sharing initiatives reflect the priorities of the communities they are intended to serve.

Key takeaways

Bringing the session to a close, Bloem invited each panellist to summarise, in a single word or phrase, what they believed should define the future of long term follow up studies. Their responses reflected the collaborative spirit that had characterised the discussion and reinforced the need to move beyond identifying barriers towards developing practical, sustainable solutions.

Schuil called for a change in mindset, encouraging the community to focus less on what cannot be achieved and more on making the best possible use of the evidence already available. Referencing themes introduced during the conference keynote, he argued that the field should move away from a hierarchical view of evidence and instead recognise the complementary value of different evidence sources when they are generated using robust methods, , especially in the context of rare diseases.

Mol agreed in principle, emphasising that high quality real world evidence generated through well designed registries can play an increasingly important role in reducing uncertainty after authorisation. However, he reiterated that perspectives on evidence generation must remain realistic, recognising that

existing registries may not capture every variable requested by regulators or HTA bodies but can still provide valuable decision relevant evidence when designed appropriately.

Heisen concluded by calling for co created, sustainable registries, highlighting the importance of treating patients as equal partners throughout the evidence generation process. She argued that meaningful patient involvement should extend beyond data contribution to include participation in the design, governance and long term development of registries and evidence generation programmes.

The discussion concluded that long term follow up should no longer be viewed solely as a regulatory requirement following market authorisation. Instead, it represents a shared responsibility across regulators, HTA bodies, industry, clinicians and patients to generate the robust, real world evidence needed to reduce uncertainty and facilitate patient access to safe and effective therapies. Achieving this will require sustainable registry funding models, trusted independent registries, greater collaboration across stakeholders and continued investment in data quality. While significant challenges remain, the session demonstrated that there is growing consensus on both the importance of long term post approval evidence generation and the practical steps needed to strengthen it in the years ahead.



SESSION 8: CLOSING PANEL: TRANSLATING LEARNINGS INTO COMMITMENTS

Moderator: Mariam Bibi, GetReal Institute

Panel: Páll Jónsson, National Institute for Health and Care Excellence (NICE); Manuel Gomes, University College London; Peter Mol, CBG-MEB and CHMP; Finlay MacDougall, IQVIA and Charlie Nicholls, Sanofi

From discussion to delivery: defining the next chapter for real-world evidence

Session overview

The closing session of the GetReal Institute Conference 2026 looked beyond the scientific programme to ask a more fundamental question: what must the RWE community do next to ensure progress translates into better healthcare decision making?

Over the previous two days, delegates had explored advances in data access, federated research networks, artificial intelligence, target trial emulation, Joint Clinical Assessment (JCA), regulatory science and patient engagement. Rather than revisiting those discussions, the closing panel sought to identify where the greatest opportunities now lie to accelerate implementation and where the GetReal Institute can make the greatest contribution over the coming years.

Opening the discussion, Mariam Bibi challenged the panel to consider whether the RWE community risked becoming trapped in familiar conversations around data quality, trust and implementation. While acknowledging the significant progress made in recent years, she questioned whether stakeholders wanted to be discussing the same barriers five years from now or whether the time had come to focus on practical solutions that move the field forward.

She invited the panel to reflect not only on the current state of decision-ready evidence but also on how the Institute's research programme should evolve. Current priorities include artificial intelligence in healthcare decision making, target trial emulation, patient engagement and the patient voice, surrogate endpoint validation and continued development of the External Control Framework. However, she emphasised that these priorities are intended to evolve alongside the needs of regulators, HTA bodies, industry, academia and patients, ensuring the Institute continues to address the most pressing challenges facing RWE generation.

The discussion that followed reflected a notable shift in the maturity of the RWE landscape. Rather than calling for more methodological frameworks or additional guidance, panellists consistently argued that the next phase must focus on implementation, demonstrating how existing approaches can be applied consistently, transparently and at scale to support healthcare decisions.

From developing methods to implementing them

A recurring theme throughout the conference had been the rapid evolution of methodological guidance. Frameworks for target trial emulation, external controls, study reporting and evidence generation have matured considerably over recent years, providing researchers with a far stronger methodological foundation than existed only a few years ago.

Charlie Nicholls argued that this progress has created genuine momentum across stakeholder groups. Regulators, HTA bodies, industry and researchers increasingly share a common ambition to generate more robust and decision-relevant evidence. The challenge now is ensuring these methods can be implemented effectively under the practical constraints of real-world research.

Using target trial emulation as an example, Nicholls explained that while the framework provides an excellent structure for designing observational studies, evidence generation rarely follows a perfectly linear path. Early feasibility assessments inevitably evolve as researchers gain a deeper understanding of available data, and unforeseen limitations often emerge only after detailed analyses begin. Rather than viewing these changes as methodological weaknesses, he suggested the community should develop practical guidance that helps researchers manage such adaptations transparently while maintaining confidence in the evidence generated.

Peter Mol agreed that target trial emulation has made an important contribution by encouraging researchers to think more explicitly about how observational studies relate to the clinical trials that decision makers are accustomed to evaluating. Framing studies around the hypothetical trial helps align observational research with established regulatory and HTA thinking, making evidence easier to interpret and assess.

At the same time, he cautioned against expecting any single methodology to eliminate uncertainty completely. Observational research will always face challenges associated with residual confounding and bias, and where randomised controlled trials remain feasible they continue to provide the highest level of evidence. Rather than replacing trials, approaches such as

target trial emulation strengthen the quality and transparency of observational research, particularly in situations where conventional trials cannot realistically be undertaken.

Together, these perspectives reflected an important shift in the conversation. The community is no longer asking whether appropriate methodological frameworks exist. Instead, the priority has become demonstrating how those frameworks can be implemented consistently and credibly across increasingly complex evidence generation settings.

Closing the credibility gap through implementation

Bibi challenged the panel to consider where the remaining credibility gap lies if methodological guidance has advanced so substantially. Rather than identifying shortcomings in existing frameworks, panellists consistently returned to the importance of practical implementation.

Manuel Gomes argued that greater confidence in RWE will be built through experience rather than additional guidance alone. One area he identified as particularly valuable was benchmarking, where observational studies are compared against established randomised trial results. The objective is not simply to reproduce identical findings but to understand what different data sources are capable of answering, where their limitations lie and how those limitations should influence future study design. Such exercises, he suggested, help build confidence by making the strengths and weaknesses of individual datasets more transparent.

He also highlighted the importance of planning evidence generation prospectively wherever possible. Designing studies earlier in the development pathway provides greater control over patient selection, outcome measurement and study conduct, strengthening both scientific credibility and stakeholder confidence. Although retrospective analyses will continue to play an important role, integrating prospective RWE planning into wider evidence generation strategies offers greater opportunities to address future regulatory and HTA questions.

Finlay MacDougall recognised that such ambitions often collide with the operational realities of product development. Timelines, organisational structures and commercial pressures frequently dictate when evidence generation activities begin, limiting opportunities for ideal study planning. Rather than treating these constraints as obstacles to be overcome privately, he argued they should become part of a more open dialogue between stakeholders.

Reflecting on discussions throughout the conference, MacDougall observed that one of the most valuable outcomes had been exposing the assumptions that different stakeholder groups often make about one another. Regulators, HTA organisations, industry, contract research organisations and data custodians all operate within different constraints, yet those constraints are not always fully understood across the wider evidence ecosystem. Greater transparency around these realities, particularly through collaborative work on real studies facing genuine operational challenges, would help bridge understanding far more effectively than theoretical examples alone.

He suggested that following evidence generation from protocol development through to decision making would allow stakeholders to understand why studies sometimes change direction, how feasibility assessments evolve and what practical compromises become necessary. Learning from real implementation, rather than idealised scenarios, would ultimately strengthen confidence across the RWE community.

Understanding different evidence needs rather than assuming alignment

A recurring message throughout the conference was that regulators, HTA bodies, industry and researchers are becoming increasingly aligned in their expectations for high-quality evidence. However, the closing discussion highlighted that important differences remain and that recognising these differences is just as important as pursuing convergence.

Building on discussions from the JCA session earlier in the conference, MacDougall reflected that one of the most valuable outcomes of the past two days had been exposing the assumptions that different stakeholder groups often make about one another. Regulators, HTA bodies, pharmaceutical companies, contract research organisations and data custodians all approach evidence generation from different perspectives and operate under different constraints. These differences are not always visible and can lead to unrealistic expectations about what evidence can be generated, when it can be delivered and how it will ultimately be used.

He pointed to discussions around external comparators as an example. While these studies are increasingly important for HTA, particularly within the evolving JCA landscape, their role within regulatory decision making is often different. Understanding these distinctions earlier in the evidence generation process would enable more realistic study planning and reduce the risk of misaligned expectations between stakeholders. Rather than assuming that evidence requirements have fully converged, the discussion suggested that greater transparency around differing objectives, timelines and constraints is needed to support more effective collaboration.

Páll Jónsson echoed this perspective from the HTA standpoint. Reflecting on NICE's experience developing its RWE Framework and subsequent methodological guidance, he suggested that the community now has a good understanding of what constitutes high-quality RWE. The challenge is no longer defining best practice, but understanding when particular types of evidence are fit for purpose for specific decisions.

He explained that NICE is increasingly applying real-world analyses within live technology appraisals and clinical guideline development, allowing committees to build practical experience of interpreting more complex evidence. This includes exploring newer methodologies such as target trial emulation alongside artificial intelligence and advanced analytical approaches. Rather than relying solely on theoretical frameworks, these real-world applications are helping generate practical use cases that demonstrate where different forms of evidence can most effectively support decision making.

Jónsson also encouraged the community to look beyond medicines. Medical technologies have historically relied far less on randomised controlled trials, requiring decision makers to work with a broader range of evidence from the outset. Programmes such as NICE's Early Value Assessment demonstrate how uncertainty can be managed pragmatically while supporting innovation and timely patient access. He suggested that many of these lessons could help inform wider approaches to RWE across medicines, particularly as healthcare technologies become increasingly data driven.

Collectively, the discussion reinforced that progress will depend not on forcing all stakeholders towards identical evidence requirements, but on developing a better understanding of where their needs align, where they differ and how evidence generation strategies can be designed to address both. Greater collaboration earlier in development, combined with continued opportunities for joint scientific advice and shared learning, was seen as essential for reducing unnecessary divergence while recognising that different decision contexts will continue to require different types of evidence.

Moving beyond the randomised controlled trial versus RWE debate

One of the most thought-provoking discussions centred on how the RWE community can move beyond framing evidence generation as a choice between RCTs and RWE. Instead, panellists argued that the focus should be on identifying the most appropriate evidence to answer the question being asked.

Bibi challenged the panel to consider what would be required to change the prevailing narrative within healthcare decision making, where RCTs are often viewed as the default standard against which all other evidence is judged. While acknowledging the importance of randomised trials, she questioned how the community could encourage decision makers to adopt a broader view of evidence, reflecting the message delivered in Carole Longson's keynote that different decisions require different forms of evidence.

Jónsson observed that this shift is already underway. HTA organisations are increasingly assessing non-randomised evidence, including external comparator studies, particularly where conventional trials cannot address all of the uncertainties relevant to reimbursement decisions. Rather than viewing these approaches as exceptional, he suggested the community should recognise that they are becoming an increasingly important part of routine evidence generation and should continue to refine how they are applied in practice.

Mol emphasised that this evolution should not be interpreted as diminishing the importance of randomised trials. Particularly for medicines entering clinical use for the first time, carefully controlled clinical studies remain essential for establishing safety and efficacy. However, he argued that healthcare decision makers increasingly face situations where traditional trials alone cannot answer all the questions that matter. Rare diseases, paediatric conditions and long-term effectiveness all require evidence that extends beyond the clinical trial setting.

In these situations, the objective should not be to replicate RCTs, but to generate the highest quality evidence possible using the data available. This requires studies to be planned from the earliest stages of development, with external controls and other observational approaches considered proactively rather than retrospectively. Prospective planning, improved data quality and continued methodological rigour would all help increase confidence in RWE, but ultimately acceptance would develop through experience and repeated demonstration of what these approaches can and cannot achieve.

The discussion also highlighted that the regulatory use of RWE should not be viewed as uniform or fully established. From the CHMP perspective, Mol noted that while there is growing recognition of the role RWE can play, its acceptance remains highly dependent on the decision context and the question the evidence is intended to address. This is becoming increasingly important as regulators encounter more rare disease developments and other settings where conventional evidence generation may be particularly challenging. Rather than applying a single standard to RWE, a more

differentiated approach is therefore needed, considering the relevance, strengths and limitations of the available data in relation to the specific regulatory scenario.

Gomes reinforced that achieving this cultural shift requires commitment from both evidence generators and evidence users. Decision makers should increasingly move from asking whether RWE can be used to asking how it can best be used to answer specific questions. Equally, sponsors have a responsibility to demonstrate that they are genuinely embracing contemporary methods rather than simply applying familiar approaches under new labels. He encouraged greater transparency in reporting methodologies such as target trial emulation so that decision makers can clearly understand how studies have been designed and why particular methodological choices have been made.

Nicholls agreed that industry has embraced the growing role of RWE across the medicine development pathway. He described how real-world evidence is increasingly informing decisions long before regulatory submission, from identifying patient populations most likely to benefit from treatment to supporting trial design and preparing for future HTA requirements. Looking ahead to Joint Clinical Assessment, he highlighted the challenge of generating evidence for multiple comparators where historical trial data may not exist, reinforcing the need for innovative yet scientifically robust approaches.

However, he also cautioned that progress is unlikely to occur uniformly across Europe. While some regulators and HTA organisations have become increasingly familiar with newer methodologies, others remain at different stages of adoption. As a result, studies that are considered methodologically robust by one assessor may receive greater scrutiny elsewhere. Continuing education, collaboration and practical experience will therefore be essential if confidence in modern RWE methodologies is to develop consistently across the wider decision-making community.

Taken together, the discussion reflected an important change in emphasis. The future of evidence generation is not about replacing randomised controlled trials with real-world evidence but about using each source of evidence where it adds the greatest value. As healthcare questions become increasingly complex, decision-ready evidence will depend on selecting the right methods for the right questions and applying them with transparency, rigour and a clear understanding of their respective strengths and limitations.

A roadmap for the GetReal Institute and the wider RWE community

Bringing the discussion to a close, Bibi invited each panellist to look beyond the conference itself and identify where the GetReal Institute could make the greatest contribution over the next 12 to 18 months. Rather than reflecting on what had already been achieved, the conversation focused on the practical actions needed to accelerate the adoption of decision-ready RWE and ensure the Institute's future work addresses the needs of the wider community.

While the recommendations reflected the different perspectives represented on the panel, several common themes emerged.

Gomes encouraged the Institute to continue doing what it does best: bringing together stakeholders who would not ordinarily have the opportunity to work closely together. However, he argued that future discussions should extend beyond those already convinced of the value of RWE. Engaging a broader range of decision makers, including those who remain cautious or sceptical about the role of real-world evidence, would be essential if wider consensus is to be achieved. Dialogue alone would not be sufficient. He stressed that scepticism should be met with robust examples of good practice, demonstrating where carefully designed and transparently conducted RWE studies have successfully informed healthcare decisions. Building confidence, he suggested, depends on allowing decision makers to see high-quality evidence applied in practice rather than simply discussing its potential.

Mol reinforced the importance of continuing to convene the right mix of expertise around real-world challenges. He encouraged the Institute to focus on practical case studies that illustrate both what RWE can answer and where its limitations remain. By openly exploring the strengths, weaknesses and methodological considerations associated with different approaches, the community can continue to build confidence through shared learning rather than theoretical debate.

Nicholls returned to the implementation challenges discussed earlier in the session. He suggested there remains an opportunity for the Institute to produce practical discussion papers addressing issues that existing guidance does not fully resolve, particularly around feasibility assessments, protocol adaptations and the operational realities of conducting RWE studies. Rather than developing entirely new methodological frameworks, such work could help researchers navigate the complexities that inevitably arise when translating theory into practice.

From an HTA perspective, Jónsson encouraged the Institute to accelerate work on practical use cases that demonstrate how RWE can support real decision making. He emphasised the importance of maintaining a clear focus on targeted, high-impact questions while ensuring that the Institute complements, rather than duplicates, the work of other initiatives. Drawing together evidence and lessons from across different projects would maximise the value of collaborative research and help translate emerging methodologies into routine practice.

MacDougall concluded by highlighting what became one of the defining messages of the discussion: the importance of learning not only from success, but also from failure. He argued that the community should be more willing to examine studies that did not achieve their intended objectives, exploring why particular approaches were unsuccessful, what constraints influenced study design and what lessons could be applied in future. Although such reflections can be uncomfortable, understanding why evidence generation falls short can be just as valuable as celebrating examples of good practice. Creating opportunities for these conversations would help the community avoid repeating the same mistakes and accelerate collective learning.

Taken together, these recommendations outlined a clear direction for the GetReal Institute. The discussion suggested that its future role extends beyond facilitating dialogue to enabling implementation by bringing together diverse perspectives, generating practical guidance, sharing real-world experiences and fostering collaborative learning across the evidence ecosystem. In doing so, the Institute is well placed to help shape not only the next phase of its own research programme, but also the wider evolution of decision-ready RWE across Europe.



CLOSING REMARKS

The 2026 GetReal Institute Conference closed with a clear message: the challenge is no longer simply to demonstrate the potential value of real-world evidence, but to ensure that it can be generated and used in ways that meet the needs of healthcare decision makers.

Across the conference, discussions repeatedly returned to the importance of bringing data, methods and decision context together. High-quality data and robust methods remain essential, but neither is sufficient in isolation. Evidence needs to be designed with a clear understanding of the decision it is intended to inform, the uncertainties that matter to different stakeholders and the standards against which it will ultimately be assessed.

The discussions also highlighted how quickly the environment is evolving. Developments in data access and infrastructure, artificial intelligence, EU Joint Clinical Assessment and the growing use of real-world evidence across the product lifecycle are creating new opportunities, while also raising important questions around transparency, reproducibility, validation and acceptability.

A recurring theme was the value of dialogue across stakeholder groups. Regulators, HTA bodies, researchers, industry, patients and data partners bring different perspectives and requirements to evidence generation and use, but many of the challenges identified during the conference are shared. Addressing them will require greater clarity around expectations, continued methodological development and, importantly, opportunities to test approaches in practice and learn from their application.

The GetReal Institute will continue to provide an **independent, multi-stakeholder platform** for this work. Our independence allows us to bring together different perspectives while taking a clear, evidence-informed position on the issues that matter for the generation and use of real-world evidence. Through our scientific programme, we will continue to challenge current practice, identify where greater alignment is needed and work with our community to develop practical approaches that can support better healthcare decision making.

We would like to thank all of our speakers, moderators, workshop leads, delegates, sponsors and partners for their contribution to the 2026 Conference. The quality of the discussion reflected the expertise and openness of those who participated, and the insights generated across the two days will help shape the Institute's priorities and work programme as we look ahead to 2027.

APPENDIX A: SPEAKER LIST



Carole Longson /
Independent Adviser



Alexandra Pacurariu /
European Medicines
Agency



Andreas Schuil / Orchard
Therapeutics



Anne Willemsen / JCA & ZIN



Antonia Panayi / Takeda



Caspar Safariou / UMC
Utrecht



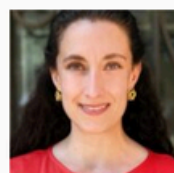
Charlie Nicholls / Sanofi &
GetReal Board Member



Christine Leopold / Utrecht
University & GetReal Board
Chair



Christine van Hattem /
Utrecht University



Daniala Weir / Utrecht
University



Dmitry Etin / Advisor



Finlay MacDougall / IQVIA



Francesco Pignatti /
European Medicines
Agency (EMA)



Ilyar Mazar / Pfizer



James Gwinnutt / IQVIA



James Turnbull / IQVIA



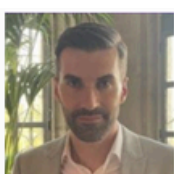
Kathi Seidl-Rathkopf /
Flatiron Health



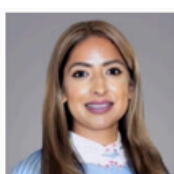
Leo Russo / Independent
Advisor



Lourens Bloem / Utrecht
University



Manuel Gomes / University
College London (UCL)



Mariam Bibi / The GetReal
Institute



Marieke Heisen / Patvocates



Martin Parkinson / Thermo
Fisher Scientific



Martin Russek / BfArM



Michel Dumontier /
Maastricht University



Mira Zuidgeest / UMCU &
GetReal Board Member



Niklas Hedberg / TLV



Páll Jónsson / NICE –
National Institute for Health
and Care Excellence &
GetReal Board Member



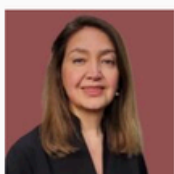
Peter Mol / UMCG & CHMP,
CBG-MEB



Radek Wasiak / Adigens
Health



Ramiro Gilardino / HTAI
Dynamic HTA Working
Group



Sahar Barjesteh van
Waalwijk van Doorn-
Khosrovani / LUMC, CieBAG



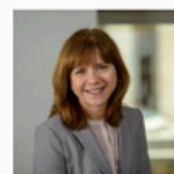
Sascha van Boemmel-
Wegmann / Flatiron Health



Seamus Kent / Erasmus
University Rotterdam



Shaun Rowark / NICE –
National Institute for Health
and Care Excellence



Susan Oliveria Thermo
Fisher & GetReal Board
Member



Tarang Sharma / Evidence
to Policy



Xabier Garcia de Albeniz /
Adigens Health

APPENDIX B: ABBREVIATIONS LIST

Abbreviation	Full form
AI	Artificial intelligence
ATMPs	Advanced therapy medicinal products
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices, Germany)
CBG-MEB	College ter Beoordeling van Geneesmiddelen – Medicines Evaluation Board (the Netherlands)
CHMP	Committee for Medicinal Products for Human Use
CZ	CZ (Dutch health insurer)
EHDEN	European Health Data & Evidence Network
EHDS	European Health Data Space
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (United States)
FDNs	Federated data networks
HARPER	HARmonized Protocol Template to Enhance Reproducibility
HMA	Heads of Medicines Agencies
HTA	Health Technology Assessment
HTAi	Health Technology Assessment international
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

JCA(s)	Joint Clinical Assessment(s)
JSCs	Joint Scientific Consultations
LLM	Large language model
LUMC	Leiden University Medical Center
MAA	Marketing authorisation application
ML	Machine learning
MLD	Metachromatic leukodystrophy
NICE	National Institute for Health and Care Excellence
PICO(s)	Population, Intervention, Comparator and Outcomes
PRAC	Pharmacovigilance Risk Assessment Committee
RCT(s)	Randomised controlled trial(s)
RWD	Real-world data
RWE	Real-world evidence
TLV	Tandvårds- och läkemedelsförmånsverket (Dental and Pharmaceutical Benefits Agency, Sweden)
TTF	Target Trial Framework
UK	United Kingdom
US	United States
VALID	Validation of Accuracy for LLM and ML Extracted Information and Data
WHO	World Health Organization
ZIN	Zorginstituut Nederland (National Health Care Institute, the Netherlands)