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# SHARED LEARNING FORUM: TARGET TRIAL EMULATION (TTE)

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GetReal Institute  
Post-Workshop Report

**3 December 2025** | Online workshop



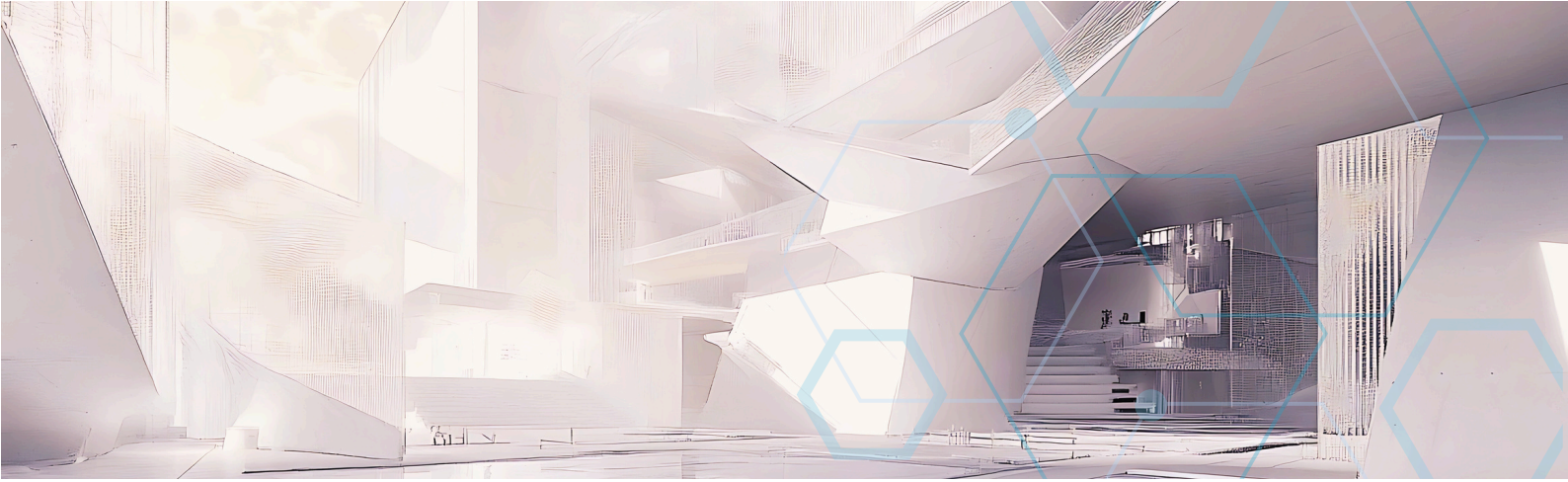


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## FOREWORD



The GetReal Institute's Shared Learning Forum (SLF) was established to provide a impartial, multi-stakeholder space where complex questions around real-world data (RWD) and real-world evidence (RWE) can be explored openly, critically, and constructively. As regulatory authorities, Health Technology Assessment (HTA) bodies, industry, academia, and patient organisations increasingly engage with RWE to inform decisions. The need for shared understanding and practical guidance has never been greater.

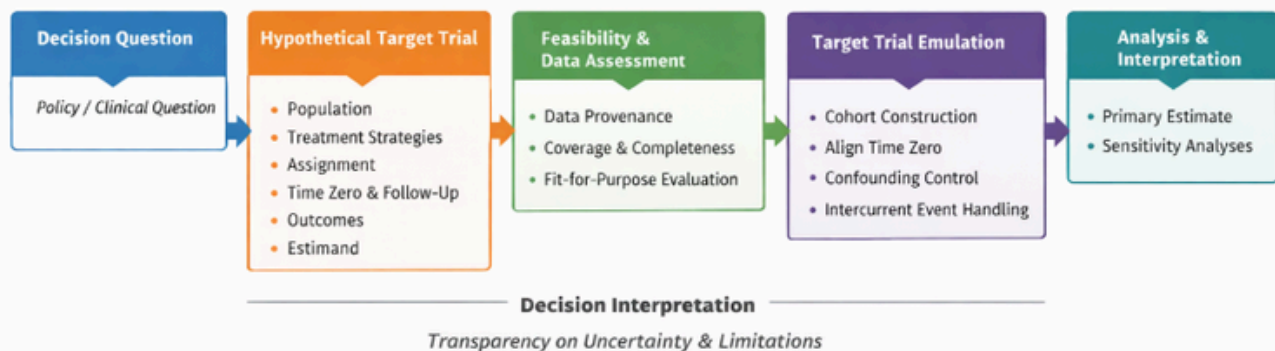
## ABBREVIATIONS

AGENAS	Italian National Agency for Regional Healthcare Services
BfArM	Federal Institute for Drugs and Medical Devices (Germany)
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (United States)
HTA	Health Technology Assessment
HTACG	HTA Member State Coordination Group
JCA	Joint Clinical Assessment
MHRA	Medicines and Healthcare products Regulatory Agency (United Kingdom)
NICE	National Institute for Health and Care Excellence (United Kingdom)
RCT	Randomised Controlled Trial
RWD	Real-World Data
RWE	Real-World Evidence
SLF	Shared Learning Forum
TLV	Dental and Pharmaceutical Benefits Agency (Sweden)
TSI	Technical Support Instrument
TTE	Target Trial Emulation

## INTRODUCTION

This SLF session focused on the principles and application of Target Trial Emulation (TTE), which is a methodological framework that applies the key design features of randomised controlled trial (RCT) design to the analysis of observational data to strengthen causal inference. The choice of topic reflects both the increasing prominence of TTE in the RWE landscape and the recognition that, despite growing interest, the approach remains inconsistently understood and applied in practice.

**Figure 1. From Causal Question to TTE**



Target Trial Emulation requires investigators to explicitly specify the protocol of a hypothetical “target trial”, the RCT that would ideally answer the causal question of interest and then to emulate that protocol as closely as possible using available observational data (Hernán and Robins, 2016). This specification includes eligibility criteria, treatment strategies, assignment procedures, definition of time zero, follow-up, outcomes, the causal estimand, and the analysis plan. By making these elements explicit, TTE promotes design-led causal reasoning and greater transparency, reducing reliance on post-hoc analytical decisions that can undermine causal interpretation.

The Forum’s focus on TTE is closely linked to the expanding role of RWE in healthcare decision-making, including regulatory evaluation, clinical guidance, reimbursement, and health technology assessment (HTA). HTA bodies, regulators, and payers are increasingly required to assess the comparative effectiveness of interventions in settings where RCT evidence may be unavailable, immature, or insufficiently generalisable to routine clinical practice. These decisions are inherently causal, as they depend on counterfactual questions about what would happen to patients if one intervention were used instead of another (Rubin, 2005; Hernán and Robins, 2020).

Unlike RCTs, observational data sources such as electronic health records, registries, and administrative claims do not involve randomised treatment assignment. In real-world settings, treatment choices are influenced by patient characteristics, disease severity, prognosis, comorbidities, and health system factors, many of which are also associated with outcomes. As a result, naïve associations observed in real-world data are vulnerable to confounding, selection bias, and time-related biases such as immortal time bias, and cannot be assumed to reflect causal effects (Hernán et al., 2008; Pearl, 2009). These limitations are particularly consequential for HTA, where relatively small differences in estimated effectiveness may materially affect cost-effectiveness analyses and reimbursement decisions.

Causal inference provides the conceptual and methodological foundation needed to translate observational data into decision-relevant evidence. By clarifying estimands and aligning study design and analysis with the causal question of interest, causal inference frameworks help ensure that RWE addresses the comparative questions faced by healthcare decision-makers, such as intention-to-treat or per-protocol effects over relevant time horizons (Hernán and Robins, 2016). Target Trial operationalises these principles by encouraging investigators to anticipate sources of bias at the design stage and to make assumptions explicit and open to scrutiny.

Despite its conceptual clarity, TTE is often misunderstood. It is sometimes treated as a specific analytical technique rather than a comprehensive design framework or implicitly assumed to deliver RCT-like validity. In practice, the credibility of a TTE depends on strong and transparent assumptions, including adequate measurement of confounding, correct temporal alignment of eligibility, treatment, and follow-up, and faithful correspondence between the target trial specification and the available data (Hernán and Robins, 2020). Empirical evidence indicates that reporting of TTE studies remains inconsistent, prompting the development of dedicated reporting guidance to support transparency and critical appraisal (Hansford et al., 2023; Cashin et al., 2025).

Against this backdrop, the Shared Learning Forum, held on the 3rd of December 2025 convened academics, methodologists, and healthcare decision-makers to introduce TTE, explore practical challenges in applying TTE, share emerging best practices, and identify areas where further guidance and capacity building are needed.

The workshop was framed as a foundational discussion with an explicit interactive component aimed at bridging theory and practice.

## INTRODUCTION TO TARGET TRIAL EMULATION

Manuel Gomes, Professor of Health Economics at University College London, opened the session by providing an introduction to TTE.

He opened by acknowledging the increasing use of RWD to inform regulatory and reimbursement decisions. While RWD offers important opportunities to address evidence gaps when RCTs are infeasible, he stressed that estimating valid treatment effects from RWD remains challenging. These challenges stem from the fact that RWD is not predominantly collected for research purposes and is therefore susceptible to multiple sources of bias, including confounding, selection bias, immortal time bias, misclassification, missing data, and treatment discontinuation.

This shared understanding established the need for approaches that strengthen causal inference primarily through improved study design.

### Why Target Trial Emulation? we do this already

Professor Gomes highlighted that many biases in real-world evidence studies are not inherent to real-world data, but arise from avoidable design decisions, often described as 'self-inflicted biases', including misaligned follow-up and poorly defined treatment initiation.

Although non-randomised studies routinely consider key design elements, such as who is included, what interventions are compared, how follow-up is defined, how outcomes are measured, and how confounding is addressed, these decisions are often made implicitly or inconsistently. Target trial emulation was presented as a framework that brings these design choices to the foreground by requiring explicit specification of the hypothetical RCT that would answer the causal question of interest.



Target trial emulation makes explicit the core design components that must be defined in non-randomised studies, including eligibility criteria, treatment strategies, follow-up, outcome definitions, and approaches to confounding adjustment. Explicit specification of these elements aligns real-world data analyses with the causal question of interest and mirrors fundamental principles of RCT design.

By formalising these elements, TTE shifts the analytical mindset from fitting questions to available data toward designing analyses that reflect meaningful causal contrasts.

### **What's the big deal about Target Trial Emulation?**

Professor Gomes highlighted that the defining feature of TTE is its emphasis on rigorous and transparent study design. Rather than treating observational analyses as fundamentally distinct from trials, TTE seeks to replicate key RCT design principles wherever possible. Target trial emulation emphasises rigorous and transparent study design by explicitly formulating the hypothetical randomised controlled trial that would answer the causal question of interest. By replicating key design principles from randomised trials, TTE aims to clarify causal questions and minimise common pitfalls in real-world data analyses.

He underscored that this explicitness is particularly valuable in regulatory and HTA contexts, where understanding assumptions is as important as the numerical results.

### **The Target Trial Emulation Framework**

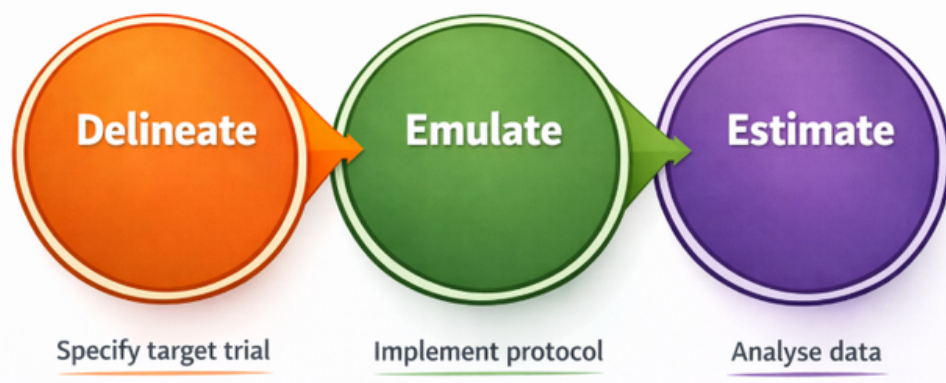
Professor Gomes stated that the definition of time zero and the alignment of eligibility, treatment initiation, and follow-up, as misalignment can introduce immortal time bias.

He then introduced the structured TTE framework, which mirrors the components of a randomised trial protocol. These include eligibility criteria, treatment strategies, assignment procedures, definition of time zero and follow-up, outcomes, estimands, and a pre-specified analysis plan. Once the target trial is specified, the protocol is implemented using RWD, followed by analysis aligned with the predefined estimand and supported by sensitivity or quantitative bias analyses.

The TTE framework consists of three main stages: specification of the target trial protocol (including eligibility criteria, treatment strategies, assignment

procedures, time zero, outcomes, estimands, and analysis plan), implementation of this protocol using real-world data, and analysis of the data with accompanying sensitivity or quantitative bias analyses to assess robustness.

## Figure 2. Key Analytical Stages in Target Trial Emulation



This framework served as the central methodological reference point throughout the workshop.

## The Role of TTE in Real-World Evidence Generation

It is important to stress that TTE does not replace randomisation and cannot fully eliminate residual confounding. Instead, it supports transparency through quantitative bias analysis and explicit communication of uncertainty.

Professor Gomes discussed how TTE fits within the broader ecosystem of real-world evidence generation. TTE was not positioned as a standalone solution, but as a unifying design framework that complements subject-matter expertise, high-quality data sources, appropriate data science tools, and methodological rigor. By making design assumptions explicit, TTE enables more transparent interpretation of RWD-based evidence.

This transparency allows regulators, HTA bodies, and other decision-makers to better judge the credibility, relevance, and limitations of comparative effectiveness estimates derived from RWD.

In closing Professor Gomes stated that TTE brings study design to the forefront of comparative effectiveness research using real-world data. When combined with subject-matter expertise, high-quality data sources, appropriate data science tools, and methodological rigor, TTE supports the generation of transparent, interpretable, and decision-relevant evidence for regulatory, reimbursement, and post-marketing contexts.

## BRIDGING TARGET TRIAL EMULATION AND THE ESTIMAND FRAMEWORK

In this presentation, Daniala Weir, PhD, Utrecht University introduced TARGET-EU, a project bridging target TTE with the estimand framework to strengthen causal inference in non-interventional studies using real-world data. Building on the introduction to TTE, by Professor Gomes the presentation focused on why and how these two frameworks can be bridged in practice to support causal inference in non-interventional studies.

She explained that while RCTs remain the gold standard for evaluating comparative safety and efficacy, they are not always feasible or ethical. In such settings, non-interventional studies play an important complementary role by providing evidence on the safety, effectiveness and use of medicines in real-world clinical practice.

She described how bridging TTE and the estimand framework helps address this challenge by making the hypothetical target trial explicit before analysing real-world data. Target trial emulation provides a structured approach to specifying the trial that would ideally be conducted, while the estimand framework ensures that the treatment effect of interest is clearly defined and aligned with the clinical question. Together, these frameworks support coherence between study objectives, design, analysis, and interpretation, rather than allowing methodological choices to be driven primarily by data availability.

TARGET-EU developed explicit hypothetical target trials for ten diverse case studies. For each case study, feasibility of emulation was assessed using European real-world data sources and the European Medicines Agency's Data Quality Framework to evaluate fitness for purpose. Following this assessment, corresponding TTE protocols were developed using a harmonised template and implemented using a common data model and analytic approach. The case studies span multiple disease areas, including oncology and orphan medicinal products, and involve heterogeneous populations such as adolescents, pregnant women, and older adults, drawing on a range of European healthcare databases.

Dr Weir illustrated the approach using a case inspired by the DECLARE-TIMI 58 dapagliflozin trial. She explained how populations, treatment strategies, outcomes, and intercurrent events were specified in the hypothetical target trial and then operationalised consistently in the real-world emulation. She highlighted the role of the estimand framework in clarifying how intercurrent events, such as treatment discontinuation, treatment switching, addition of

rescue therapy, and death should be handled through pre-specified strategies, including treatment policy, hypothetical, composite, and while-on-treatment approaches. Different strategies were shown to correspond to different scientific and regulatory questions and to give rise to complementary estimands within the same study.

She further noted that while TTE drives methodological rigour in study design and analysis, the accurate measurement of intercurrent events can be more challenging in real-world data, particularly for estimands that rely on censoring at treatment changes. The presentation emphasised the importance of transparently documenting deviations between the hypothetical target trial and its emulation, such as differences in treatment assignment, exposure measurement, and loss to follow-up.

Interim findings from TARGET-EU suggest that the estimand framework and TTE are highly complementary: the estimand framework clarifies what treatment effect is being estimated and how post-initiation events are handled, while TTE provides the methodological structure needed to implement these estimands rigorously using real-world data, supporting transparent and regulatory-relevant non-interventional evidence generation.

The workshops then shifted focus to how HTA bodies use and perceive TTE.

## PERSPECTIVES ON EVIDENCE METHODOLOGY AND UNCERTAINTY IN EU HTA

Marco Marchetti serves as Technology Assessor at the Italian National Agency for Regional Healthcare Services (AGENAS) and as Co-Chair of the HTA Member State Coordination Group. In these roles, he is involved in EU-level and national activities related to the implementation of the EU Health Technology Assessment Regulation (European Union, 2021; European Commission, 2026b). He shared his personal perspective on alternative evidence approaches.

At EU level, the entry into force of the EU Health Technology Assessment Regulation has initiated preparatory and implementation work to establish common methodologies, processes, and governance arrangements for Joint Clinical Assessments (JCAs) and Joint Scientific Consultations (European Union, 2021; European Commission, 2026b; European Commission, 2026c). This includes the development of methodological guidance and procedural rules intended to support consistent assessment of clinical evidence across Member States (European Commission, 2026b; European Commission, 2026a). Implementation has also been supported through implementing acts and associated Commission materials, including factsheets and published updates on operationalisation (European Commission, 2023; European Commission, 2025a; European Union, 2025).

EU-level methodological work also addresses how different forms of clinical evidence may be considered within joint work, including circumstances in which conventional randomised controlled trials are not feasible or available (European Commission, 2026a; European Commission, 2026b; European Commission, 2026c).

Within the EU joint HTA framework, Joint Clinical Assessments are designed to provide a structured and transparent characterisation of the available clinical evidence, including explicit description of uncertainty associated with the evidence base (European Union, 2021; European Commission, 2025a). The outputs of Joint Clinical Assessments are intended to serve as a common scientific basis for Member States and reduce duplication of clinical assessment work, while responsibility for downstream appraisal activities, including economic evaluation, pricing, and reimbursement decisions, remains at national level and outside the scope of EU-level joint clinical work (European Union, 2021; European Commission, 2026b).

At national level, Italy is undertaking reforms to align its HTA system with the requirements, processes, and timelines introduced by the EU Health Technology Assessment Regulation (European Union, 2021; European Commission, 2026b). Italy's national HTA programme for medical devices, coordinated by AGENAS, has been further developed in recent years, including the publication of the Italian National HTA Programme 2023–2025 for medical devices (AGENAS, 2023).

Similar adaptation efforts are underway across Member States as national HTA systems prepare for the implementation of Joint Clinical Assessments under the EU framework (European Union, 2021; European Commission, 2026b). In some cases, reforms are supported through EU instruments aimed at facilitating structural and technical reforms at national level, including the Technical Support Instrument (European Commission, 2021; European Commission, 2025b; European Commission, 2026d).

More broadly, European HTA systems increasingly engage with alternative evidence approaches where randomised controlled trials are not feasible; however, these approaches are generally associated with higher levels of uncertainty compared with conventional trials, requiring careful interpretation and transparent communication of limitations (European Commission, 2025a; European Commission, 2026a).

## HTA PERSPECTIVES ON TARGET TRIAL EMULATION AND REAL-WORLD EVIDENCE

Stephen Duffield, NICE explained that his organisation was among the early adopters of the TTE approach and that, since its initial uptake, there has been a clear push towards greater harmonisation of RWE guidance across regulatory and HTA bodies. He observed that both regulators and HTA institutions increasingly reference target trial concepts, including agencies such as the FDA and EMA, as well as in methodological guidance documents addressing indirect treatment comparisons. He highlighted that coordination-level guidance now explicitly cites the foundational work of Miguel Hernán, reflecting growing methodological consensus.

Stephen noted that one of the principal strengths of TTE lies in its intuitive applicability to common forms of real-world studies, including cohort studies and external control arm designs. He emphasised that the framework's use of randomised controlled trial language has proven particularly valuable for communicating complex observational methods to appraisal committees. When the framework was published in 2022, a central objective was to build trust in high-quality real-world studies by enabling clearer explanation of study design choices, assumptions, and limitations.

Despite this conceptual support, Stephen cautioned that actual uptake of TTE in HTA evidence submissions remains limited. He presented findings from an internal review assessing how frequently submissions explicitly frame causal questions using a target trial approach. The analysis showed that only a small number of studies formally characterise a target trial, even though many implicitly apply its principles. Echoing observations originally made by Miguel Hernán in 2016, Stephen noted that while the target trial concept underpins many big-data analyses, it is still rarely made explicit.

He explained that many submissions apply individual methodological components associated with TTE, such as cohort construction or bias mitigation without fully articulating the target trial itself. This, he argued, represents a missed opportunity to clearly communicate not only how selection bias has been addressed, but also how other forms of bias have been considered and how the estimand has been precisely defined.

Stephen then highlighted an example of good practice drawn from an HTA appraisal comparing Molnupiravir vs no treatment. In this case, investigators used rich, linked health data to explicitly define the target trial, conduct a real-world emulation, and transparently document the methodological challenges

involved. The study incorporated advanced approaches, including sequential trial design and quantitative bias analysis, to explore the impact of measured biases through sensitivity analyses. Importantly, the appraisal committee recognised this work as the highest-quality real-world evidence available at the time, underscoring the practical value of explicit target trial characterisation.

In closing, Stephen reflected on future directions for the field. He noted that, alongside the core principles of TTE, increasingly robust tools and guidelines are now available to support implementation, including guidance that has since been referenced within the NICE real-world evidence framework. He suggested that the next phase of development may involve deeper institutional embedding of these principles, for example through their integration into standard evidence submission templates used by HTA agencies. He concluded by inviting further discussion on how methodological endorsement can be translated into routine and consistent application in HTA practice.

## SWEDISH HTA PERSPECTIVES ON TARGET TRIAL EMULATION

Robert Szulkin, speaking on behalf of TLV, outlined the current Swedish HTA perspective on TTE and its role within evidence assessment. He began by noting that TLV does not currently hold an official position on TTE as a distinct methodological approach. While the agency has referenced the NICE real-world evidence framework in some reports, it does not formally require or request TTE in dossier submissions.

Robert explained that, at present, many TLV assessors are not familiar with the concept of TTE. He noted that this lack of familiarity was initially surprising to him but reflects the current reality within the organisation. Target trial emulations are rarely encountered in submitted dossiers, and assessors continue to show a strong preference for randomised controlled trials. Observational studies, in contrast, are often perceived as challenging to evaluate.

He highlighted several practical difficulties that assessors encounter when reviewing observational evidence. These include the absence of published protocols, a lack of standardisation across studies, and wide variability in the level of documentation provided, ranging from very brief descriptions to extensive reports running to hundreds of pages. By comparison, assessors are far more comfortable with the structured and familiar language of randomised controlled trial frameworks.

Against this backdrop, Robert suggested that TTE could play an important role as a communication tool. By framing observational studies using concepts and terminology aligned with randomised trials, TTE may help bridge the gap between methodological rigour and assessor interpretability, thereby supporting more consistent and transparent evaluation of real-world evidence.

He acknowledged that there is a significant learning curve ahead for TLV in this area and identified a clear need for education and capacity building within assessor teams. Not all assessors currently have the methodological background required to confidently assess TTE or related causal inference approaches, making structured learning and practical exposure essential.

As a concrete step forward, Robert outlined plans for TLV to undertake its own TTE case study within a Swedish context. This work would involve benchmarking and practical application of the methodology, allowing assessors to engage directly with the approach rather than encountering it

only through submissions. He noted that this idea resonated with earlier comments in the session and expressed the view that hands-on experience would be an important step towards building internal understanding and confidence.

## UK REGULATORY PERSPECTIVES ON TARGET TRIAL EMULATION AND REAL-WORLD EVIDENCE

Rachael Williams, Head of Epidemiology at the MHRA, outlined the regulator's approach to novel frameworks and methodologies aimed at improving the quality of evidence submitted to inform regulatory decision-making. She noted that the MHRA has published guidance on the use of real-world data in clinical studies to support regulatory decisions. Although this guidance does not explicitly reference TTE, many of the expectations it sets out are directly applicable to studies adopting the TTE framework.

Rachael explained that her role is primarily focused on the post-authorisation stage, where there are significant opportunities for real-world evidence approaches. She highlighted comparative effectiveness studies, evaluation of performance in routine clinical practice, and the assessment of safety and outcomes in underrepresented populations as areas where traditional randomised controlled trials may be limited and where approaches such as TTE may add value.

She stressed, however, that the acceptability of such studies depends not only on the quality of the study design, where the TTE framework can provide important structure and clarity but also critically on data provenance and data quality. Robust, well-characterised data sources were described as essential prerequisites for credible observational research intended to support regulatory decision-making.

Rachael cautioned against viewing any single methodological framework as a “silver bullet” for observational research. She emphasised that no approach can fully eliminate uncertainty or deliver absolute causal certainty, and that TTE should not be regarded as a panacea for the inherent limitations of non-randomised studies. Instead, she characterised TTE as a useful organising framework that can support transparency, rigour, and clearer communication of study assumptions and limitations.

She noted her support of the use of TTE as a framework, provided it is applied appropriately and underpinned by high-quality data. In this context, she strongly encouraged early engagement with the MHRA through scientific advice procedures for organisations considering the use of TTE in regulatory submissions. She also highlighted the availability of joint scientific advice meetings with NICE, which can be particularly valuable when evidence is intended to support both regulatory and HTA decision-making.

Rachael was speaking in a personal capacity, and her opinions should not be interpreted as reflections of official MHRA policy.

## BFARM PERSPECTIVE ON TTE

Martin Russek, BfARM presented regulatory initiatives focused on the application of TTE approaches to real-world data, with particular reference to activities led by the German medicines regulator (BfArM). The presentation described how target trial based thinking is being used to support methodological development for regulatory and HTA decision-making across the product life-cycle.

A central element of the presentation was the Real4Reg project, a European collaborative initiative running from 2023 to 2026 and coordinated by BfArM. The project involves ten partners across six EU countries and aims to develop, optimise and implement advanced analytical methods for the use of real-world data in regulatory and HTA contexts. The presentation highlighted the use of registry data from Denmark, Finland and Portugal, alongside German claims data, reflecting the range of data sources typically available to regulators.

Within Real4Reg, Use Cases 3 and 4 were described as applying TTE approaches, with a particular emphasis on time-to-event outcomes. These use cases focus on methodological development and learning, exploring how key elements of a target trial, such as alignment with a reference RCT, definition of time zero, follow-up and end points, can be operationalised using real-world data.

The presentation highlighted a replication-based use of TTE, drawing on evidence from the RCT-DUPLICATE initiative, which demonstrated a high level of agreement between randomised controlled trials and corresponding real-world data analyses when target trial principles are applied. This work was presented as an example of how TTE can be used constructively to benchmark real-world evidence against established trial results.

As an illustrative example, a planned study was presented that aims to replicate a randomised controlled trial of diabetes medication effectiveness using real-world data, with an extension to additional safety-related time-to-event end points. This work is informed by the BenchExCal (Benchmark, Expand and Calibration) approach, which provides a structured framework for benchmarking real-world analyses against trial results and exploring the extension of evidence beyond the original trial setting.

Overall, the presentation characterised TTE as a practical framework for structuring and interpreting time-to-event analyses in real-world data, rather than as a purely theoretical exercise. The work was presented as part of a broader regulatory effort to understand how target trial-based approaches can improve the credibility, transparency and regulatory relevance of real-world evidence.



guideline developers or health technology assessment (HTA) agencies, such as NICE. Drawing on his experience, he also shared the value of TTE as a communication tool for engaging clinicians, as it enables complex observational analyses to be framed in trial-like concepts and terms that clinicians readily understand.


A recurring theme in Uwe's remarks was transparency. He argued that, even when studies are of lower quality, the structured nature of TTE makes assumptions and shortcomings explicit and visible to reviewers, thereby supporting scientific rigour and trust. In his view, such transparency is essential for distinguishing robust from poor real-world evidence and for maintaining confidence in observational research.

Reflecting on audience feedback displayed in a word cloud, Mariam noted strong alignment around transparency as a key advantage of TTE. She then steered the discussion towards the importance of case studies and European initiatives designed to support learning and adoption. She invited Seamus Kent, PhD, Erasmus University, to describe the GREG project and its role in disseminating practical examples.

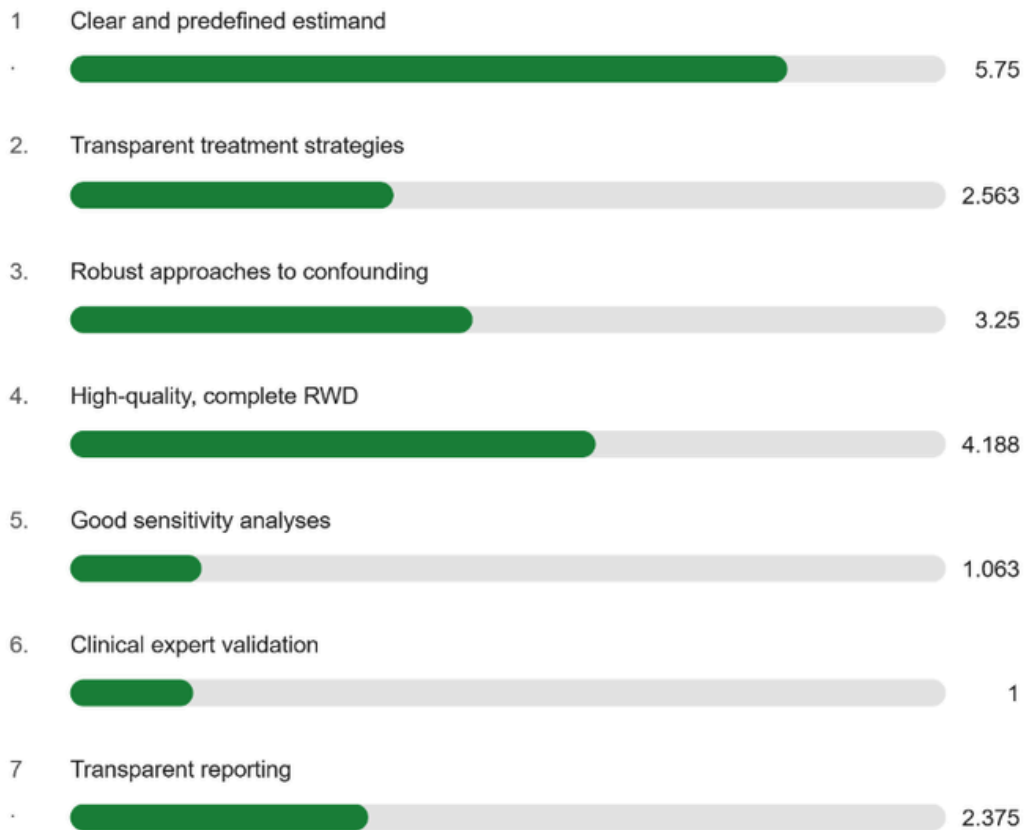
Seamus explained that the project aims to go beyond high-level methodological guidance by collecting and sharing case studies of successful and unsuccessful uses of RWD within a living library. These will provide developers with empirical data on the acceptability of different RWD sources and designs (including TTE) in different contexts. In addition, it will perform analytical use cases addressing common evidence challenges in regulatory and HTA decision making and provide empirical evidence on appropriate data quality, study design and methods.

Stephen Duffield from NICE added that the value of this work lies in testing guidance against real European data sources and real decision contexts. By involving external regulatory and HTA stakeholders, the project aims to directly explore what improves evidence acceptability in practice, thereby translating guidance into more actionable and pragmatic recommendations.

Mariam then introduced a second polling question on features that increase confidence in causal inference from TTE.

 Which features increase your confidence in causal inference from a TTE?

Ranking Poll  16 votes  16 participants



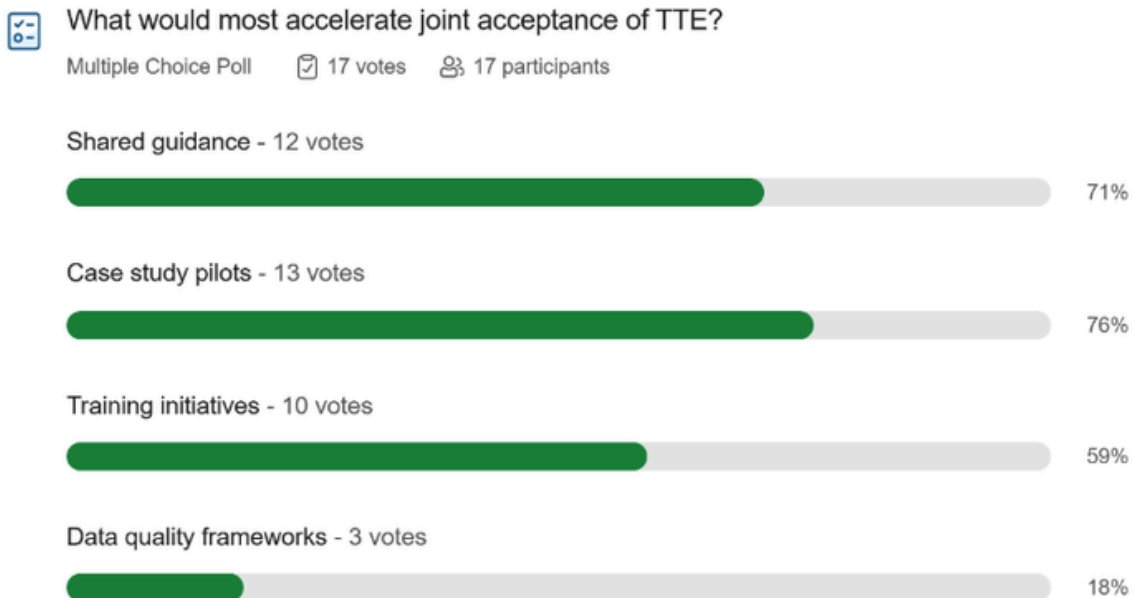
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Directing the response from the poll to Rachael Williams, MHRA. Rachael identified two critical elements. First, she stressed the importance of a clearly defined, pre-specified protocol that explicitly describes the target trial to be emulated, including eligibility criteria, treatment strategies, follow-up, outcomes, causal contrasts, and estimands. She noted that simply stating the use of a TTE approach is insufficient without this level of specification.

Second, Rachael highlighted the central role of high-quality, relevant data sources that adequately capture key variables. While TTE provides a strong design framework, she cautioned that it cannot compensate for poor data quality or inadequate data provenance. These comments were reinforced by Manuel, who noted that although TTE cannot “fix” data limitations, it can help articulate them clearly and support informed trade-offs by decision-makers.

Stephen further pointed to feasibility assessment frameworks, such as those used in large surveillance systems, as useful tools for linking TTE design choices to data availability and analytic feasibility.

The discussion then broadened to consider the role of organisations such as the Get Real Institute, professional societies, and industry groups in promoting awareness and uptake of TTE. When participants were asked what would most accelerate joint acceptance of TTE, a strong preference for action-oriented levers, particularly case study pilots and shared guidance were highlighted.



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Antonia Panayi, Takeda, argued for a joint action plan involving regulators, HTA bodies, industry, and academia to foster shared understanding, align expectations, and promote collective learning. Rachael supported this view, stressing the importance of common definitions and shared understanding of what constitutes good practice, while allowing flexibility for country- and organisation-specific approaches.

On the question of harmonisation between regulatory and HTA bodies, Stephen observed that, despite inherent differences in perspective and evidentiary needs, increasing references to TTE across agencies such as the FDA, EMA, and HTA bodies suggest emerging convergence around a shared methodological language. This, he noted, creates opportunities for joint scientific advice, even where downstream decision criteria differ.

Attention then turned to training and capacity building. It was acknowledged that there is a knowledge gap between different organisations and stakeholders. Manuel and Uwe highlighted the availability of academically

oriented courses, including long-standing training programmes led by Miguel Hernán at the Harvard Chan School of Public Health and the HTADS.org Program at UMIT TIROL, while noting further need for more practical, case-based training focused on applied decision contexts in the regulatory and HTA setting. Uwe emphasised the need for broader dissemination of causal inference concepts, including g-methods for handling time-varying confounding, beyond specialist audiences to a wider range of stakeholders, particularly clinicians and principal investigators.

In closing, Rachael drew attention to a recent training event hosted by the London School of Hygiene and Tropical Medicine, noting that recorded materials are publicly available and may serve as a useful entry point for those seeking to deepen their understanding of TTE.

Mariam concluded the session by acknowledging the complexity of the topic and noted that the Get Real Institute's forthcoming programme will adopt a more topic-based structure, with TTE identified as a priority area. She indicated that future sessions would explore specific subtopics and unresolved questions in greater depth, reflecting the Institute's commitment to advancing understanding and appropriate use of these methodologies.

## PRIORITY DIRECTIONS EMERGING FROM THE WORKSHOP

The Shared Learning Forum highlighted several priority areas where further coordination, guidance, and capacity building could materially support the appropriate and consistent use of TTE in regulatory and HTA decision-making.

### **Advancing practical, decision-focused guidance on Target Trial Emulation**

Participants highlighted the value of moving beyond conceptual discussions of TTE toward more practical, decision-oriented guidance. There was strong support for resources that translate methodological principles into clear expectations for study design, documentation, and transparency, particularly from the perspective of regulators and HTA bodies tasked with evidence appraisal.

### **Expanding access to applied European case studies**

The workshop underscored the importance of real-world examples in building confidence and shared understanding of TTE. Participants emphasised the need for accessible case studies drawn from European data sources and decision contexts, including examples that explicitly document design trade-offs, feasibility constraints, and residual uncertainty, rather than focusing solely on methodological success stories.

### **Strengthening integration between TTE and the estimand framework**

Discussions highlighted growing recognition that TTE and the estimand framework are complementary and mutually reinforcing. Further work to clarify how estimand choices relate to different regulatory and HTA questions and how intercurrent events can be handled in practice using real-world data was identified as an important area for methodological development and shared learning.

### **Building appraisal capacity among regulators and HTA assessors**

A recurring theme was the need to support those responsible for reviewing and interpreting TTE based studies. Participants noted variability in familiarity with causal inference concepts across organisations and jurisdictions, suggesting value in targeted, applied learning initiatives focused on appraisal rather than study conduct, including structured walk throughs of TTE examples and common sources of bias.

### **Encouraging earlier multi-stakeholder dialogue on TTE study design**

The workshop highlighted the potential benefits of earlier engagement between evidence developers, regulators, and HTA bodies when TTE approaches are being considered. Such dialogue could support alignment on study objectives, feasibility, data requirements, and expectations around transparency and uncertainty, helping to reduce misalignment at later stages of decision-making.

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## APPENDIX: SPEAKER AND PARTICIPANT LIST

### Moderator

Mariam Bibi                      The GetReal Institute

### Panelists

Ahmed Elsada	Merck Group
Antonia Panayi	Takeda
Daniala Weir	Utrecht University
Francesca Galea	Johnson & Johnson
Francois Houyez	Eurordis
Jing Wang Silvanto	Astellas
Leo Russo	Independent
Manuel Gomes	UCL
Marco Marchetti	Agenas
Martin Russek	BfArM
Nina Heiss	Merck Group
Rachael Williams	MHRA
Robert Szulkin	TLV
Sascha van Boemmel- Wegmann	Flatiron Health
Seamus Kent	Erasmus University
Stephen Duffield	NICE
Uwe Siebert	UMIT TIROL

## Attendees

Aimée Hamblin	IQVIA
Alban Fabre	Thermo Fisher Scientific
Alice Rouleau	Thermo Fisher Scientific
Amelie Elsaesser	Boehringer Ingelheim
Anila Dede	IQVIA
Barbara Torlinska	Boehringer Ingelheim
Camelia Thompson	Genmab
Camille Jackson	Flatiron Health
Christophe Sauboin	Boehringer Ingelheim
Constanza Andaur	UMCU
Danielle Isaman	Sanofi
Delphine Saragoussi	Sanofi
Emmanuelle Boutmy	Merck Group
Harlan Pittell	Flatiron Health
Irina Degtiar	Boehringer Ingelheim
Isabel Balderas	Boehringer Ingelheim
Jingqiu Zhou	Boehringer Ingelheim
Kellyn Arnold	IQVIA
Kevin Klein	The GetReal Institute
Kshitij Arora	Boehringer Ingelheim
Mandy Smith	Boehringer Ingelheim
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Onyi Diribe	Sanofi
Puja Myles	MHRA
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