GETREAL INSTITUTE | PUTTING REAL WORLD EVIDENCE INTO PRACTICE

WEBINAR REPORT

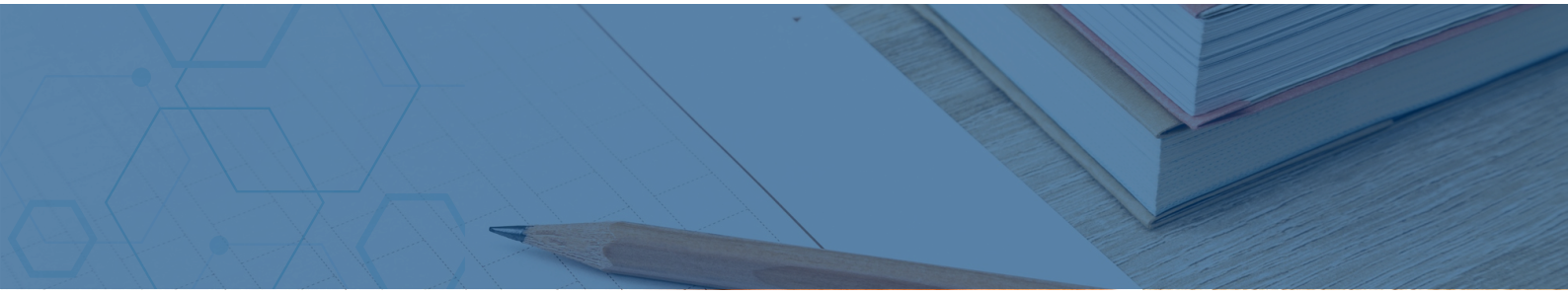
EXTERNAL CONTROL STUDIES: **WHAT DOES IT TAKE TO GET REAL?**

4 March | 14:00 - 15:00 CET | Webinar

Facilitated by
Mariam Bibi, PhD | GetReal Institute

Presenters
Wim Goettsch, PhD | Zorginstituut Nederland & Utrecht University
Anke van Engen, MSc | IQVIA

CONTENTS



SPEAKERS

FACILITATOR

Mariam Bibi, PhD

Managing Director
The GetReal Institute

PRESENTER

Wim Goettsch, PhD

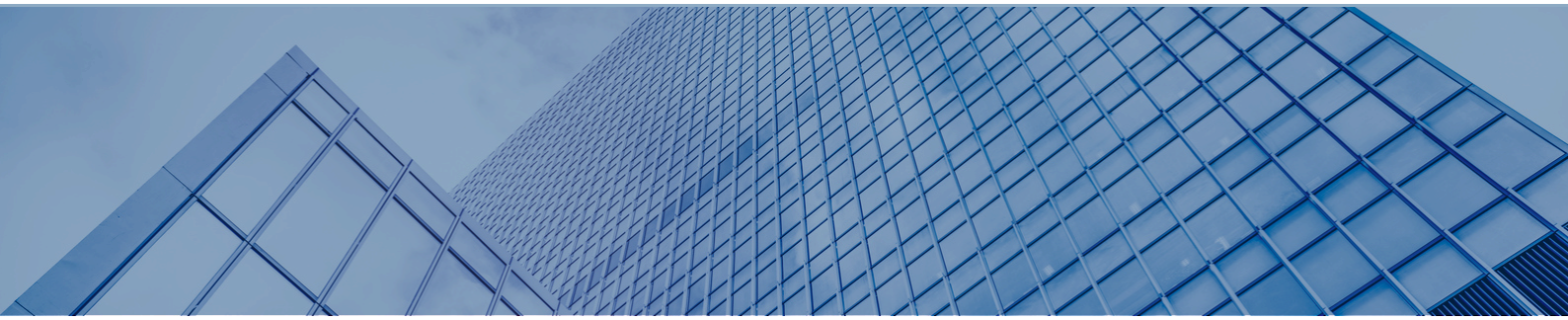
Professor HTA of Pharmaceuticals & Special Advisor HTA
Utrecht University & Zorginstituut Nederland (Dutch National Healthcare Institute)

Wim shared his personal perspectives, not from ZIN or Utrecht University. The work presented was partly funded by H2020-HTx through the EU Horizon 2020 program and The GetReal Institute.

PRESENTER

Anke van Engen, MSc

VP, Global CoE Leader - Health Economics, HTA, Value & Access
IQVIA



LIST OF ABBREVIATIONS

ATMP	Advanced Therapy Medicinal Product
ASMR	Amélioration du Service Médical Rendu (improvement in medical benefit)
CMPH	Committee for Medicinal Products for Human Use
CONSORT	Consolidated Standards of Reporting Trials
DataSAT	Data Source Assessment Tool (NICE)
EC	External control
EPAR	European Public Assessment Report
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
HAS	Haute Autorité de Santé (French National Authority for Health)
HARPER	HARmonized Protocol Template to Enhance Reproducibility
HTA	Health technology assessment
IMI	Innovative Medicines Initiative
IPD	Individual patient data
IPD-RWD	Individual patient data from real-world data sources
ISPE	International Society for Pharmacoepidemiology
JCA	Joint Clinical Assessment
MAIC	Matched adjusted indirect comparison
ML-NMR	Multilevel network meta-regression
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
PICO	Population, Intervention, Comparator, Outcome
PICOT	Population, Intervention, Comparator, Outcome, Time
RCT	Randomised controlled trial
RWD	Real-world data
RWE	Real-world evidence
SAT	Single-arm trial
SPIFD	Study Protocol and Information for FDA submissions
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
STaRT-RWE	Structured Template and Reporting Tool for Real-World Evidence
ZIN	Zorginstituut Nederland (Dutch National Healthcare Institute)

INTRODUCTION

On 4 March 2026, the GetReal Institute convened an on-line webinar entitled **External Control Studies: What Does It Take to Get Real?** The session brought together academics, regulators, Health Technology Appraisal (HTA) professionals, and industry representatives to address one of the methodological challenges in contemporary evidence generation: **how to design, conduct, and report externally controlled (EC) studies rigorously and transparently.**

Although randomised controlled trials (RCTs) remain the gold standard for assessing treatment efficacy and safety, certain conditions make it difficult to conduct adequately powered trials. In these cases, single-arm trials (SATs) and non-randomised studies are often pursued, yet their lack of a control group limits causal inference. External control groups, drawing on real-world data (RWD), are increasingly used to generate comparative evidence when RCTs are impractical or unethical. However, as Wim Goettsch observed in opening the session, it remains unclear to what extent these EC studies are fit for purpose. In response, the GetReal Institute developed an External Control Best Practices Framework to help stakeholders determine when, whether, and how to design and execute such a study.

This report summarises the two presentations, the discussion points raised, and the key conclusions from the session. It is intended as an accessible reference document for those working in or alongside the field of real-world evidence generation.

PART 1: SINGLE-ARM TRIALS AND EXTERNAL CONTROLS: A HTA PERSPECTIVE

Wim Goettsch, Professor Health Technology Assessment of Pharmaceuticals at Utrecht University and Special Advisor at Zorginstituut Nederland, opened the webinar with personal perspectives on the methodological and policy landscape around SATs and external controls.

The Growing Complexity of HTA

HTA bodies across Europe face an increasing volume of medicines for which the standard evidentiary benchmark, data from RCTs is unavailable or insufficient. This is particularly pronounced for Advanced Therapy Medicinal Products (ATMPs), orphan medicines, and oncology treatments with histology-independent or tumour-agnostic indications. A core insight from the HTx Horizon2020 research project was that most challenges in the HTA of complex health technologies stem from data insufficiencies rather than from the complexity of the technologies themselves, and that as the number of complex technologies grows, so does the urgency for new methods and policies to guide HTA decision-making.

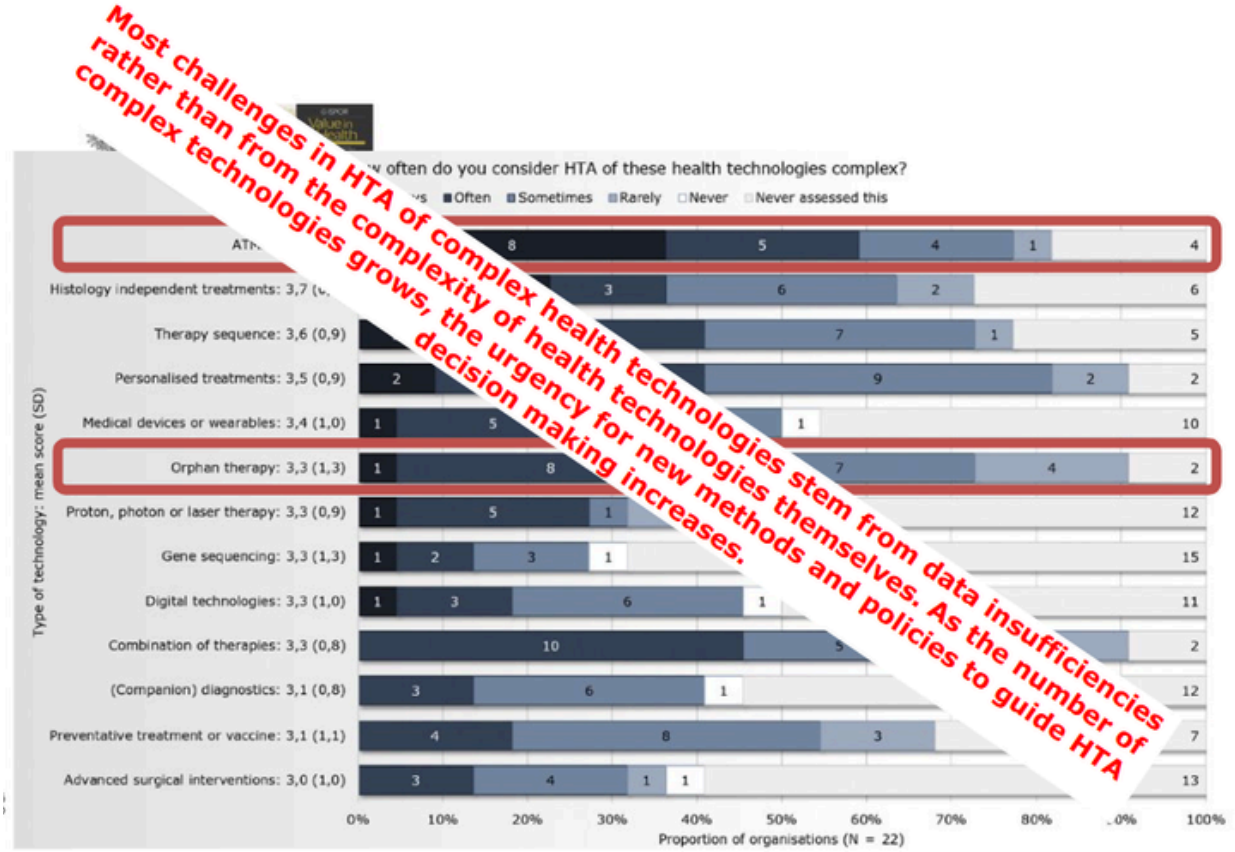


Figure 1. Highlights that challenges arise primarily from data insufficiency, not from inherent technological complexity.

These challenges also exist at the supranational level through the EU Joint Clinical Assessment (JCA) process, which commenced in 2025 for oncology and ATMP products. All 13 compounds on the live JCA list at the time of the webinar (data extracted on 2 March 2026) were ATMPs, oncology treatments, or orphan products, vividly illustrating how central the challenge of evidence insufficiency is to the European HTA landscape. Two relevant guidance documents from the EU HTA Member State Coordination Group were also highlighted: the Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons, and the accompanying Practical Guideline, both of which are shaping assessor expectations for comparative evidence.

A Review of Methods, Guidelines, and Practice

Wim described the systematic review by Hogervorst MA, Soman KV, Gardarsdottir H, Goettsch WG, and Bloem LT, published in Value in Health (2025; 28(1):161–174), which examined analytical methods for comparing uncontrolled trials with external controls drawn from real-world data. The review covered three layers: the peer-reviewed scientific literature, regulatory and HTA guidelines, and the actual content of EPARs (2015–2020) and HTA reports (2015–2023) from England, France, Germany, the Netherlands, and EUnetHTA.

The methodological framework that emerged, aligned with ISPE good pharmacoepidemiology practice, organises requirements around three pillars: (1) research design grounded in target trial emulation, including defining the estimand and choosing an individual patient data (IPD) data source that closely mirrors the uncontrolled trial arm; (2) data analytic methods focused on selecting and preparing cohorts for comparison, performing statistical comparative analyses, conducting sensitivity analyses, and undertaking quantitative bias analysis; and (3) transparency through a priori protocol registration, quality assurance, detailed reporting of results, and archiving.

Figure 2. A visual summary of the stepwise methodological approach for comparing uncontrolled trials with external controls derived from individual patient real-world data, based on the good pharmacoepidemiology practices guideline of the International Society for Pharmacoepidemiology (ISPE).[34] In bold are the elements that were described in the scientific literature; the orange/red elements are the focus of the rest of the results.

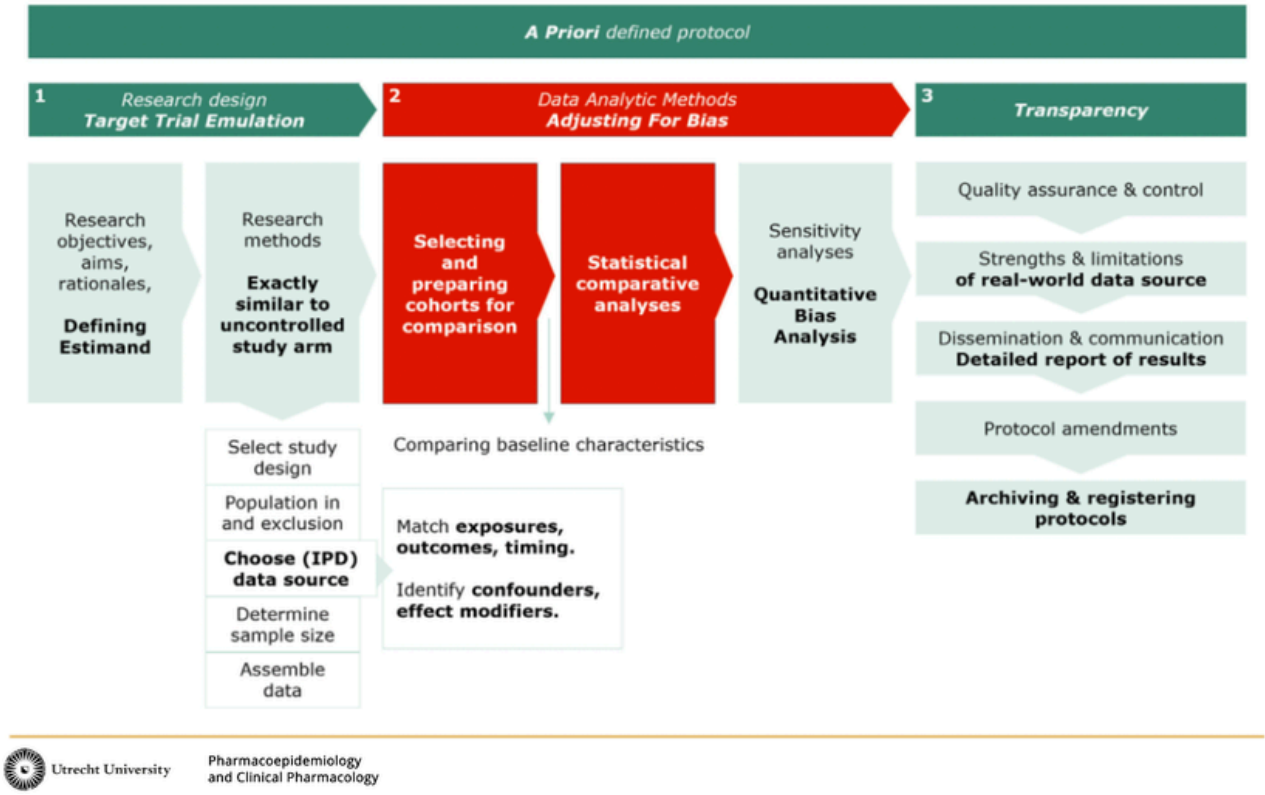


Figure 2. A visual summary of the stepwise methodological approach for comparing uncontrolled trials with external controls from individual patient real-world data, based on ISPE good pharmacoepidemiology practice guidelines.

The Gap Between Aspiration and Reality

The review revealed significant divergence between recommended and actual practice. In 50% of HTA assessments, RWD was used as a comparator, but in the majority of cases only summary-level data was available rather than IPD. There were large variations between agencies in how external controls were considered, and the exact methods used, data source, and matching approach; regression adjustments were frequently not described. For aggregate data, naive comparisons remained commonly used, and methodologically sounder approaches were often not applied even when IPD was available. The literature described preferred methods, such as multilevel network meta-regression (ML-NMR), that differed substantially from those actually used in regulatory and HTA assessments.

Key Finding: *A significant gap exists between the preferred methods described in the scientific literature and those actually used in regulatory and HTA assessments. Descriptions in regulatory and HTA reports are often so brief that it is difficult to assess what biases remain unaddressed.*

Wim's recommendations included: establishing standardised definitions to resolve the use of distinct terminology across the field; developing guidelines on consistent reporting of methods and data; reducing the discrepancy between the willingness to use sophisticated methods and the trust in their correct use and interpretation; and ensuring that externally controlled studies emulate RCT design as closely as possible, making full use of IPD from comparative methods wherever access permits.

PART 2: A PRACTICAL FRAMEWORK FOR EXTERNALLY CONTROLLED STUDIES USING REAL-WORLD DATA

Anke van Engen, VP and Global CoE Leader for Health Economics, HTA, Value and Access at IQVIA, presented the GetReal Institute's EC Best Practices Framework: a practical, stepwise framework for the design, conduct, and reporting of externally controlled studies based on real-world individual patient-level data (IPD-RWD).

Several HTA bodies have recently issued guidance on EC study requirements, however none comprehensively addresses all aspects of EC study design and execution. Furthermore, these guidelines lack consensus across key methodological domains. The aim of this framework was therefor to operationalise key principles for EC study conduct into a structured, multi-stakeholder informed process integrating both methodological guidance and regulatory and HTA expectations into an actionable toolkit designed to provide harmonised guidance in determining when to consider an EC study using real world IPD, as well as in the design, conduct, and reporting of such studies

The GetReal EC framework was developed by and for various stakeholders, highlighting key requirements from regulators, HTA bodies, academia, industry, and patients.

It was developed through a targeted review of regulatory and HTA guidance, a peer-reviewed literature synthesis, three multi-stakeholder workshops (each with 20–25 participants representing regulators, HTA bodies, academia, industry, and patients), and confirmation through an expert focus group of 6-8 members, followed by final validation review with GetReal Institute members.

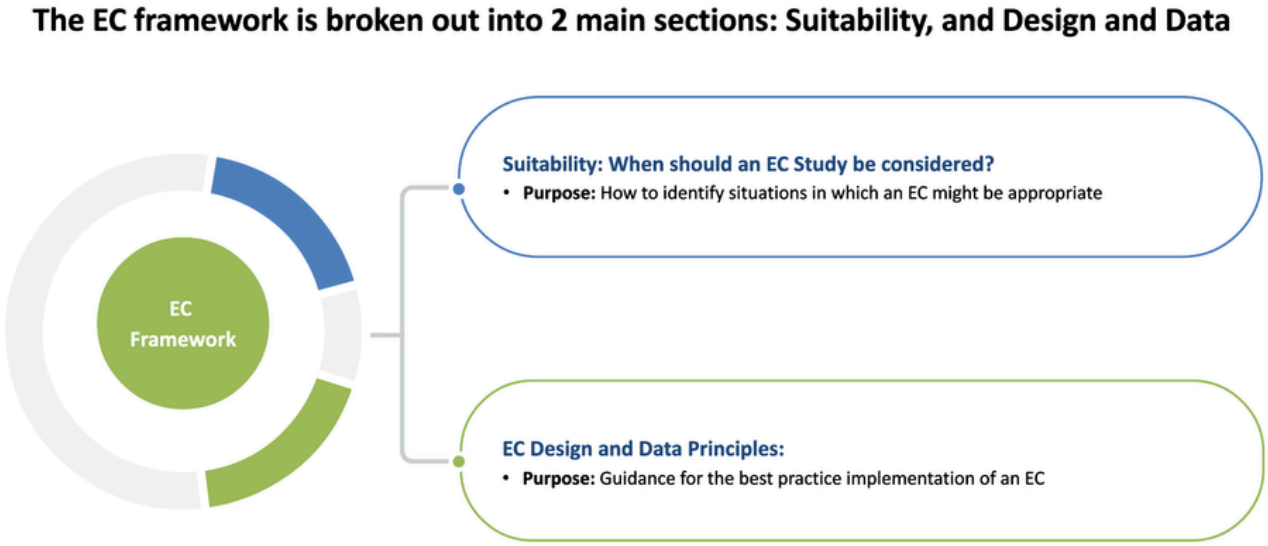


Figure 3. The EC framework is structured around two main sections: Suitability (when to consider an EC study) and EC Design and Data Principles (how to implement one in best practice).

Part 1 of the Framework: When Should You Consider an EC Study?

The first component is a five-question suitability decision tree designed to help sponsors determine systematically whether an EC study is the appropriate evidence generation approach and if not, what alternatives to consider.

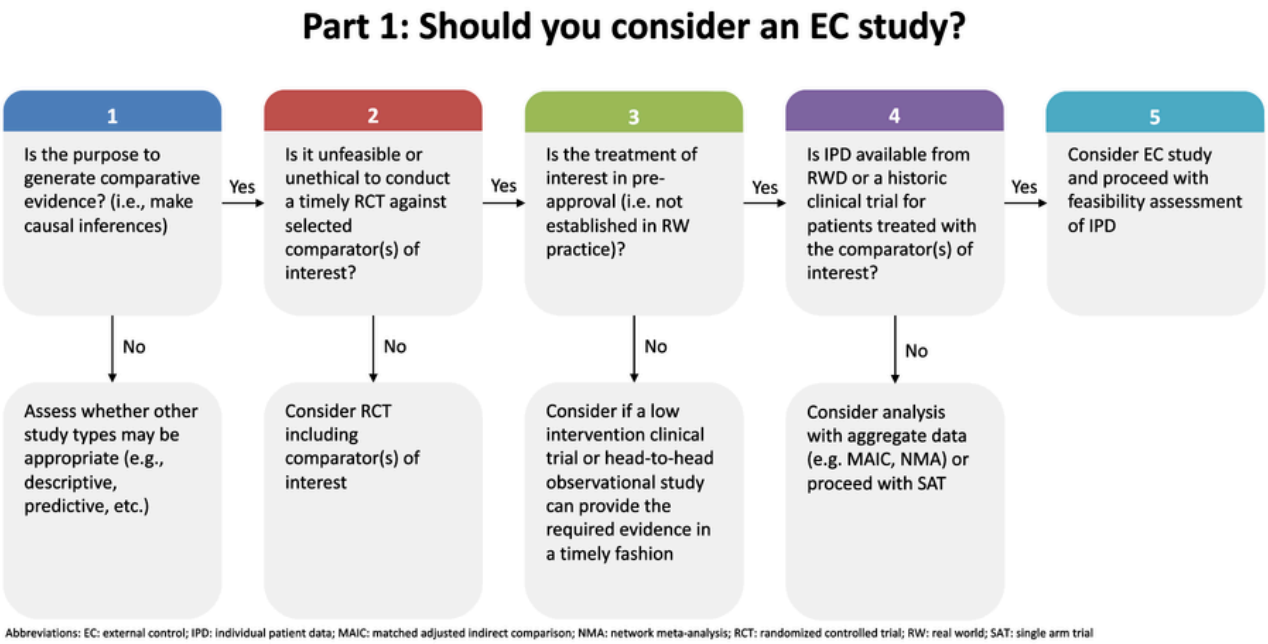


Figure 4. The EC suitability decision tree. Five sequential questions guide users to determine whether an EC study using real-world IPD is appropriate, or whether alternatives such as a head-to-head RCT, observational study, MAIC/NMA, or SAT alone may be better suited.

The five questions are: (1) Is the purpose to generate comparative evidence i.e., to make causal inferences? (2) Is it unfeasible or unethical to conduct a timely RCT against the selected comparators of interest? (3) Is the treatment of interest in pre-approval status? (4) Is IPD available from RWD or a historic clinical trial for patients treated with the comparators of interest? If all four questions are answered affirmatively, the framework recommends proceeding to (5) a feasibility assessment. If any answer is no, specific alternatives are recommended.

Figure 5 describes the most common situations when EC studies can help inform decision-making.

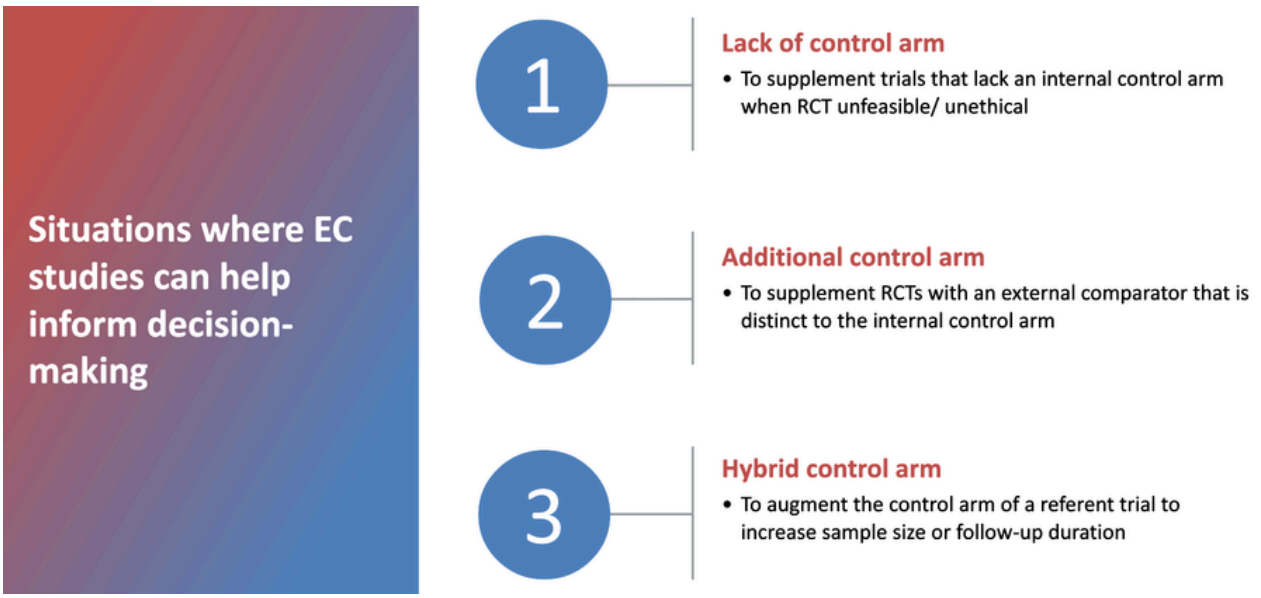


Figure 5. Describes the most common situations when EC studies can help inform decision-making.

Part 2 of the Framework: A Seven-Phase Operational Process

The second component is a seven-phase operational process providing best-practice guidance for EC study implementation. Phases 1-4 are explicitly iterative: feasibility constraints frequently require revisiting objectives and design parameters before proceeding.

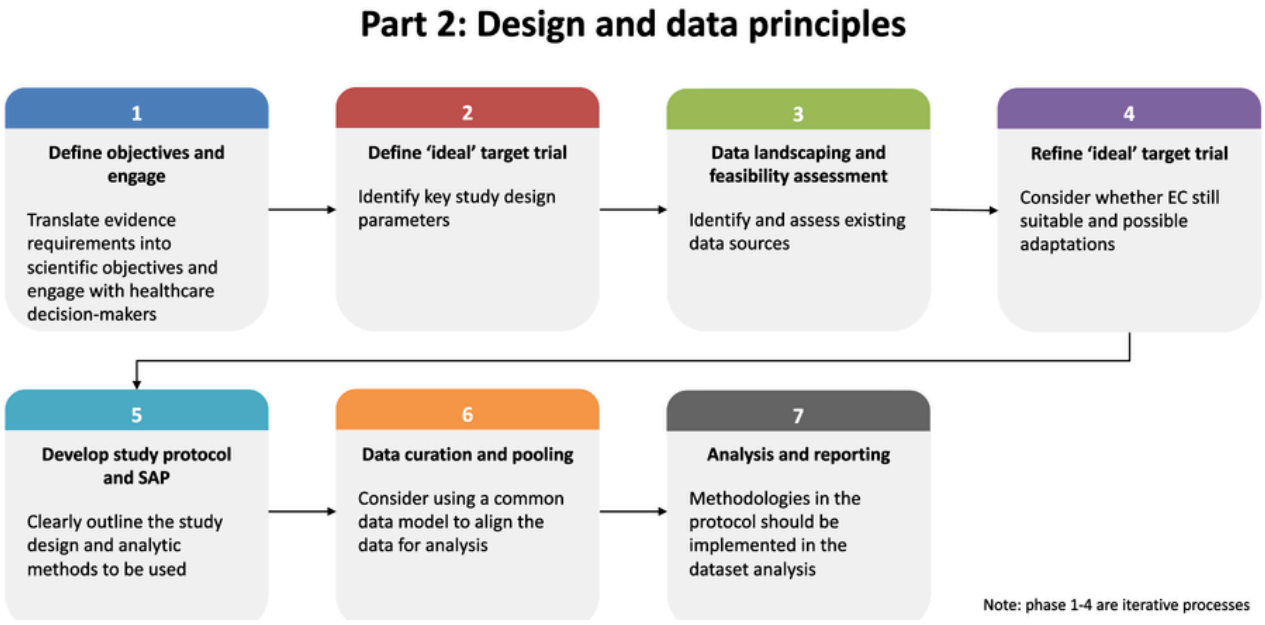


Figure 6. The seven-phase operational process for EC study design and conduct.

The first phase is to translate the sponsors' evidential needs into well-defined scientific objectives using frameworks such as PICOT and target trial emulation. To facilitate this process, early engagement with key healthcare decision makers and key opinion leaders is recommended, for example through joint scientific consultation with EU HTA bodies.

Phase 2 is to define the 'ideal' target trial a priori and identify key study design parameters using the target trial emulation and PICO frameworks, facilitating selection of the most appropriate study design.

Phase 3 undertakes systematic data landscaping, evaluating candidate sources qualitatively and quantitatively using tools including NICE's DataSAT and SPIFD, and engaging regulators and HTA bodies to confirm external validity.

Phase 4 refines the target trial following feasibility assessment, identifying adaptations and evaluating trade-offs, documenting all sources of bias including unmeasured confounding and missing data, with a comprehensive, unambiguous protocol.

Once the feasibility of the EC study has been established, a full study protocol and statistical analysis plan (SAP) should be developed in phase 5 detailing how bias, confounding, and missing data will be addressed, using frameworks such as STaRT-RWE, HARPER, NICE RWE Framework, and CHMP Missing Data guidance.

Phase 6 addresses curation and pooling of data, ensuring high-quality RWD through a common data model with documented processes.

Phase 7 implements analysis in a secure environment and reporting, drawing on CONSORT, STROBE, and other reporting guidelines to produce outputs tailored for healthcare decision-makers.

QUESTION AND ANSWER SESSION

Following the two presentations, Mariam facilitated a structured Q&A session drawing on questions submitted in advance and from the live audience.

Are There Successful Examples of EC Studies Supporting Reimbursement Decisions?

Both speakers acknowledged that robust, decisive examples remain rare. Wim noted he was not aware of cases where an EC study was the single decisive factor in a positive reimbursement recommendation; in cases where products were reimbursed despite limited RCT data, effect sizes may be large enough that EC analyses could serve as corroboration. Anke highlighted the TOSCA RWE study for Libtayo (cemiplimab) in cutaneous squamous cell carcinoma in France, which contributed to an improved Amélioration du Service Médical Rendu (ASMR) rating in the HAS assessment.

How Can Trust in New Methodologies Be Increased?

Anke emphasised that early, transparent engagement with HTA and regulatory bodies, explaining design rationale, documenting the data landscape process, and proactively addressing data availability challenges, is critical. Wim identified complementary pathways: sponsors should genuinely assess whether an RCT is truly infeasible before defaulting to a SAT; joint scientific consultation provides a structured pre-commitment alignment opportunity; and the field needs more validation research demonstrating how advanced methods perform in specific contexts.

> **Key Message:** *Early engagement with Regulatory and HTA bodies through joint scientific consultation is one of the most valuable steps sponsors can take to improve the likelihood that EC study evidence will be accepted and acted upon effectively.*

What Internal Capabilities Are Required?

Both speakers were emphatic that EC studies are fundamentally interdisciplinary. Expertise across clinical development, epidemiology, real-world data science, statistics, regulatory affairs, market access, and health economics must be coordinated from the earliest planning stages. Wim noted that regulatory and HTA activities have historically been siloed, and that for smaller companies in particular, early cross-functional alignment is a precondition for success rather than a luxury.

How Will the EU JCA Process Approach Evidence from Single-Arm Trials?

Wim clarified that JCA assessors work with what sponsors submit, if that is a SAT with an EC, that is what is assessed. Quality and transparency are the most controllable determinants of how evidence is received: IPD availability, methodological appropriateness, and reporting completeness all matter. Anke noted that sponsors must first pass the JCA completeness check, and that a well-designed EC study addressing the relevant PICO provides a far stronger foundation than no comparative data or a naive unadjusted comparison.

CONCLUSIONS AND NEXT STEPS

The EC framework offers a structured, actionable approach to improve IPD-RWD-based EC study design, conduct, and reporting, strengthening credibility, optimising resources, and aligning with evolving regulatory and HTA expectations.

The webinar underscored the urgency of the challenge posed by single-arm trials and externally controlled studies in modern HTA. As the volume of ATMPs, orphan medicines, and complex oncology products entering assessment continues to grow, the need for clear, consistently applied, and methodologically rigorous approaches to external control evidence has never been more pressing.

The GetReal Institute EC Best Practices Framework represents a meaningful step forward: a practical, multi-stakeholder-informed toolkit that translates methodological principles into operational guidance. It helps sponsors determine when EC studies are appropriate, and supports systematic planning, design, and reporting in line with evolving regulatory and HTA expectations. The framework is explicitly designed as a living document, the field is evolving rapidly, and The GetReal Institute is committed to updating it as evidence and guidance develop.

> **Next Steps:** *The framework manuscript is in near-final preparation for peer-reviewed publication. The Institute hopes the framework will be taken into account into updates of forthcoming EU HTA coordination group guidance documents.*

ABOUT THE GETREAL INSTITUTE

The GetReal Institute is dedicated to advancing the adoption and integration of real-world evidence in healthcare decision-making across Europe and beyond. Its origins are rooted in over a decade of structured, EU-supported research: the Institute evolved from two influential programs supported by the Innovative Medicines Initiative (IMI): the GetReal Project (2013 - 2017) and the GetReal Initiative (2018 - 2021), which together demonstrated how robust real-world data collection and synthesis could be incorporated earlier into pharmaceutical development and healthcare decision-making.

Established in May 2021 as a Dutch non-profit membership association, the GetReal Institute was designed to act as an incubator and design lab for strategies and tools to clarify scientific and operational uncertainties in RWE approaches and methods.

As an independent, multi-stakeholder, non-profit forum, the Institute unites partners from across Europe and beyond to advance the use of real-world evidence in healthcare decision-making, contributing to the development of RWE methods and informing research practices, regulatory frameworks, health technology assessment, clinical implementation, and patient-centred decision-making. Its membership reflects this cross-sector ambition: the community includes decision-makers, public and private researchers, patients, clinicians, data custodians, and technology developers, all working collectively to shape the evidence agenda and drive meaningful change across the healthcare ecosystem.

With over a decade of experience at the forefront of the RWE landscape, the GetReal Institute is an independent voice on real-world evidence. It is uniquely positioned to convene the right stakeholders, surface the most pressing challenges facing the field, and where the need is greatest conduct and support targeted research that moves the science forward. Its influence spans regulatory policy, health technology assessment, and clinical practice, making it an indispensable force in shaping how evidence is generated and used across European healthcare.

For further information on the Institute's work on external control studies and real-world evidence methodology, visit www.getreal-institute.org.

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