White Paper

Bridging the Evidence Gap

External comparator studies from design to reimbursement

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Executive summary

Pharmaceutical and biotech sponsors face increasing pressure to generate robust comparative evidence in indications where Randomized Controlled Trials (RCTs) are ethically, operationally, or practically infeasible, including rare disease, oncology, and pediatric populations. External Comparator (EC) studies — single-arm trials augmented with comparator cohorts drawn from Real-World Data (RWD) — have evolved from a niche workaround to a recognized evidence pathway, offering a defensible alternative when RCTs cannot deliver timely or feasible answers. For sponsors, the central question is no longer whether EC studies are acceptable, but how to design and execute them to withstand regulatory and Health Technology Assessment (HTA) scrutiny as evidentiary expectations continue to rise across FDA, EMA, MHRA, and EU Joint Clinical Assessment contexts.

The commercial and strategic implications are significant. Sponsors who engage EC planning early — aligning data source selection, endpoint definitions, and statistical approaches with regulatory expectations before the SAT is fully enrolled — consistently achieve better outcomes than those who treat EC studies as a post-hoc remediation. Conversely, late or poorly designed EC studies have been a source of HTA rejection in Germany, France, and increasingly at the EU JCA level, where the methodological bar is higher than most sponsors anticipate. The window between regulatory approval and HTA reimbursement is where EC study quality most often determines commercial access outcomes.

For innovators in rare disease and oncology especially, the message is clear: EC studies, properly executed, can eliminate evidence delays, accelerate patient access, and deliver comparative data that supports both approval and reimbursement — but only if they are planned with the same rigour as the trials they support.

This whitepaper provides the scientific, methodological, and policy foundation sponsors need to make EC studies a deliberate and defensible component of development strategy. It covers data source selection, fit-for-purpose standards, causal inference methodology, global regulatory evolution, and the emerging role of AI, federated models, and OMOP harmonization.

Key takeaways:

- EC studies have added value compared to traditional Single-Arm Trials. For life sciences sponsors, this means access to defensible comparative evidence in indications where an RCT is not feasible — supporting both regulatory approval and HTA reimbursement.
- Regulatory harmonization is going to increase and standardize EC evidence. For example, The **EMA's Draft Concept Paper on External Controls** and the **MHRA's 2025 draft guideline** mark a shift toward formalized global standards for using external control arms in regulatory decision-making.
- Global progress is sustained by data models and methodologies, such as OMOP, which allow decentralized collaboration without compromising patient privacy.
- AI is poised to play a greater role across the data life cycle and selection of patient comparators in real-world datasets.

Background/context

External comparator terminology explained

An External Comparator (EC) study is typically a Single-Arm Trial (SAT) which is augmented by a comparator cohort external to the trial, either from prior trials but more frequently from real-world data (RWD, e.g., registries, EHR, or claims data). Randomized Clinical Trials (RCTs) can be augmented with external data as well (called hybrid/augmented RCTs).

We discourage using RCT terminology like *arms or groups*, as these terms do not reflect the observational character of EC studies. Instead, the observational term of *cohorts* is appropriate to use. Further, although the term *External Control Study* is valid, it could imply that the study is conducted in a fully controlled manner as RCTs are, where the research is not only controlled by a control treatment (potentially placebo) but also by detailed written protocol specifications of measurement and diagnostic procedures, visit times, highest data management and monitoring standards, identical eligibility criteria and same data temporality, regions and site types across the RCT groups. We use the term *External Comparator study*, which is more modest and avoids this misconception. However, in the rare case that the EC study is pre-specified before the SAT starts, and there is just a single trial protocol which also outlines the EC study part, the term *Externally Controlled Trial*, as introduced by the US Food and Drug Administration (FDA), should be used. A full discussion of EC study terminology is available.[1]

Appropriate use case of EC studies

For sponsors developing therapies in rare disease, oncology, and pediatric populations, the strategic question is rarely whether an RCT is preferred — it is what evidence can be generated when an RCT is not feasible, not ethical, or not timely enough to support patient access. EC studies are increasingly the answer. When starting to discuss EC study use cases, it should be stressed that an RCT remains the first choice and "gold standard" for establishing causal relationships. RCTs are the routine requirement for market approval of most but not all drugs in countries with a highly developed regulatory system. Generally, whenever it is possible and ethical to do an RCT, it should be performed.

However, conducting an RCT may not be possible in some situations, especially for rare diseases and rare populations. For example, the number of needed RCT patients may be known to be impossible to reach for generating statistically robust findings, or randomization of patients at the terminal illness stage may be unethical when a potentially life-saving drug is being tested. Researchers may also come across other limitations like difficulties in logistics, follow-up, and budget constraints because of high costs per patient.

Regulatory bodies, such as the FDA or the EMA have acknowledged that strong therapeutic effects can occasionally eliminate the requirement for RCTs, as demonstrated by the market approval of drugs, particularly within oncology, without RCT data. The FDA has approved at least 45 drugs based on external data and 20 of the approved drugs were based on retrospective natural history and 5 were based on prospective natural history.[2] In this sense, RCTs and EC studies constitute different design options to generate the appropriate level of evidence for concrete study needs, i.e., the EC design is a valuable addition to the design toolbox for the right use case.

In a situation where an RCT is not feasible and the only option is an uncontrolled trial, the question is what additional evidence can be made available to support decision making. This is when EC studies may be considered as a valuable or even best option. Because they provide additional evidence by bridging the gap generated by the missing internal control group, they bring in true *added value* compared to a traditional SAT: they deliver more information than a SAT alone and are therefore more informative.[3]

The use of EC studies has evolved over recent decades alongside the growing availability of high-quality RWD. Regulatory authorities, including the FDA, began releasing draft guideline on how to conduct EC studies.[4]

Oncology has been a leading therapeutic area for the early adoption of EC studies, due to pressing unmet needs and smaller target trial-eligible populations (e.g., biomarker subpopulations). According to a 2022 analysis by Mishra-Kalyani et al., at least 45 oncology medication approvals since 2000 have included some type of EC data, notably for uncommon or life-threatening tumors where RCTs would be impractical or unethical.[5] Another recent systematic review found that the FDA frequently accepted EC studies (between 2017 and 2022) for non-oncologic rare disease applications. 70% of these applications for drug licensing included Real World Data (RWD).

As EC study uptake increases, their adoption is variable across geographies (Table 1). This variation can be seen in the level of support and commentary provided by the stakeholders (e.g., regulators, HTA bodies) and is often aligned with the region's maturity in Real-World Evidence (RWE) usage, and how well digital infrastructure is available to accommodate RWE programs.

Table 1: Regional support for external comparators

REGION	STAKEHOLDER SUPPORT AND COMMENTARY	RWE MATURITY	INFRASTRUCTURE: LEVEL OF ACCOMMODATION	UPTAKE
U.S.	High	High	Strong	High
EU	Moderate	High	Mixed	Moderate
Asia-Pacific	Low	Varied	Developing	Low
LATAM/Africa	Minimal	Low	Weak	Minimal

As mentioned earlier, in the United States, the FDA has indicated relatively strong support for EC studies, particularly in rare disease and oncology but also in situations of expedited or breakthrough treatment designations. This openness is aided by a strong digital infrastructure and a sophisticated regulatory framework for RWE. Health Technology Assessment (HTA) organizations in the United States, such as Institute for Clinical and Economic Review (ICER), Friends of Cancer Research and private payers have also begun to evaluate EC study evidence for payment purposes.

In Europe, the situation is more diverse. While the EMA has expressed cautious optimism in the use of RWD for decision-making, providing recommendations on registry-based trials and engaging in RWD partnerships, national HTA agencies differ greatly in their receptivity: Nordic nations, such as Sweden and Finland, have comparatively high adoption rates due to robust registry systems and a culture of integrated digital health systems. In contrast, the UK, Germany and France continue to prioritize RCT-based data for coverage choices.[6]

In the Asia-Pacific region, regulatory and HTA adoption are still developing. Japan's Pharmaceuticals and Medical Devices Agency (PMDA) published its "Points to Consider for Externally Controlled Trials" in 2025 — a significant step that formalizes PMDA's engagement with EC methodology. The guidance acknowledges EC studies as a legitimate design option in oncology and rare disease where RCTs are not feasible, and outlines expectations around data quality, population matching, and statistical rigor. Japan's well-developed cancer registry infrastructure, including hospital-based registries linked to the Japan Clinical Oncology Group (JCOG) network, positions the country to operationalize EC studies more broadly in the near term. Combined with Japan's active participation in ICH E17 multi-regional trial frameworks, this regulatory signal suggests PMDA is moving toward a more permissive stance than its historical conservatism would suggest. General adoption in non-oncology indications, however, remains limited.[7] China and South Korea are relatively reserved in their acceptance of EC study usage for decision-making.[8,9]

However, both countries are making significant investments in their digital health infrastructure, which may lead to more acceptance and usage in the short to medium term. Similarly, infrastructure is an issue in Latin America and Africa where RWE usage is limited due to poor data ecosystems and other restrictions.

Overall, the landscape is characterized by a combination of fragmentation and promising developments: Harmonization measures, such as those by the GetReal initiative, the Joint Clinical Assessment (JCA) framework, and transnational data-sharing platforms, represent moves toward more universal delivery, but the level of EC study integration into decision-making is largely influenced by local stakeholder attitudes, digital preparedness, and therapeutic urgency.[10, 11]

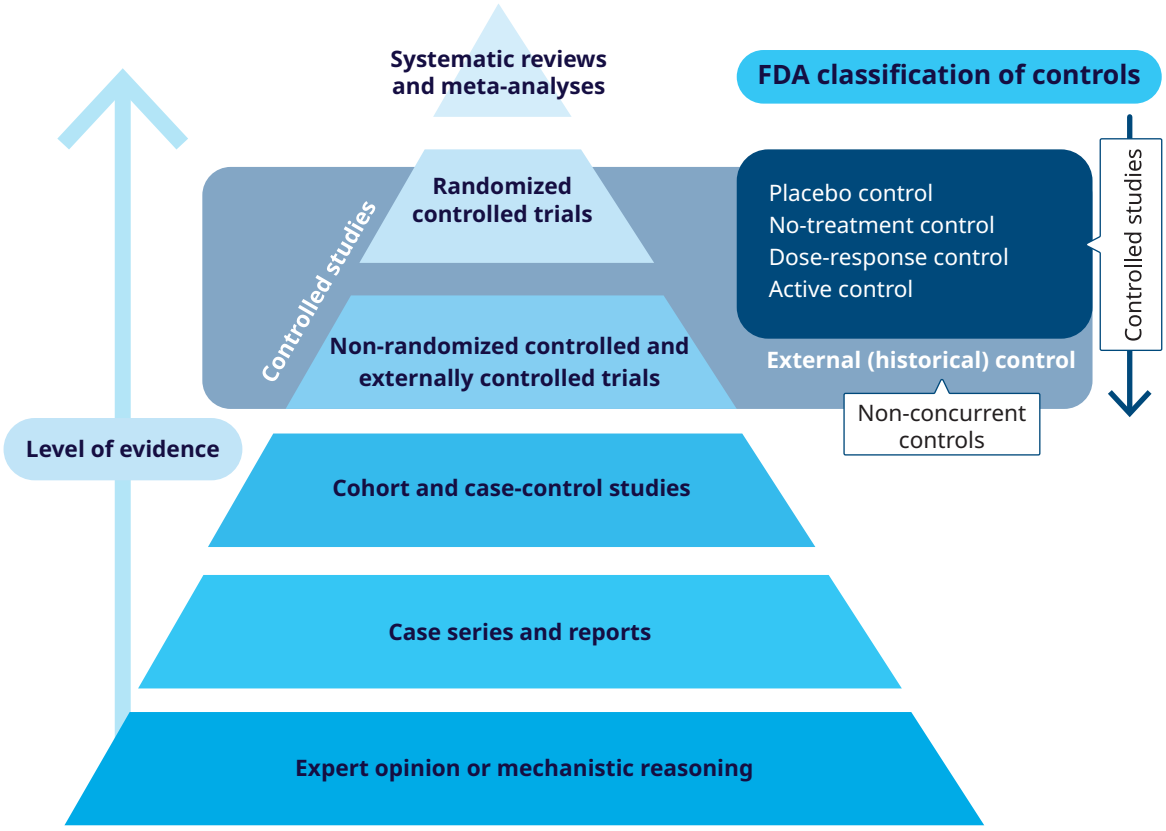
The anatomy of external comparators

EC studies and the hierarchy of evidence

For Biotech and Pharma , the practical importance of the evidence hierarchy is that regulators and HTA bodies use it — implicitly or explicitly — to calibrate the level of scrutiny applied to a submission. Where an RCT is not feasible, the question is not whether the evidence package will be at the apex, but how far up the hierarchy it can credibly sit. An EC study is the mechanism by which a SAT-based programme moves from low-grade observational evidence toward the level of rigour regulators expect for an approval decision.

The evidence pyramid is a well-established tool used to illustrate the varying strengths of evidence that different types of clinical studies provide (Figure 1). Meta-analyses of RCTs occupy the apex, reflecting the rigorous design and superior capacity of RCTs to limit bias. In contrast, SATs can be useful in specific scenarios, although they generally yield weaker evidence due to the missing internal control arm. However, incorporating an EC can increase the evidentiary strength of a traditional SAT, effectively elevating its position within the hierarchy. They constitute a new layer of evidence generation in the classical evidence hierarchy.

Figure 1: Hierarchy of evidence



When planning a study, stakeholders should thoughtfully assess the need to reach a particular level of the evidence hierarchy to choose the most suitable study design for regulatory considerations.

Fit-for-purpose data — the foundation of an EC study

Selecting and qualifying the right data source is one of the most consequential decisions sponsors make in an EC programme — and one of the most common reasons EC studies fail at regulatory or HTA review. Sponsors face a recurring tension: the most accessible datasets are rarely the most fit-for-purpose, and the most fit-for-purpose datasets often require investment in curation, linkage, or chart abstraction long before the SAT reads out. Getting this decision right early is what separates an EC study that supports a submission from one that becomes a liability inside it. The reliability of an EC study is closely tied to how accurate, complete, and relevant its data sources are. Regulators describe "fit-for-purpose" data that have sufficient quality and relevance for the intended regulatory use.[14, 12, 13] This ensures the data is suitable for regulatory decisions without necessarily requiring data to be close to perfect as it is expected for RCT data.

EC datasets can be drawn from a range of real-world data sources, such as chart reviews, EHRs, patient registries, and the recent increase of digital health tools. Each source comes with specific benefits and drawbacks, but also may be combined, linked or enriched to meet evidentiary standards. For instance, EHRs can provide comprehensive clinical details but may sometimes be incomplete; registries typically use standardized formats but may not be widely applicable; Patient-Generated Health Data (PGHD) from apps, fitness trackers and wearable devices can improve patient focus but often need additional validation before being used for regulatory purposes. These newer tools can capture information such as daily routines, medication use, symptoms, and physiological measurements. Although these technologies are promising for EC studies, regulatory experience is still developing.

Table 2 shows the 'data continuum', which spans from highly structured clinical trial data to more informal patient-reported information.

Table 2 Comparison of EC data source types that could be used to collect data to create an EC study

DATA SOURCE TYPE	RELEVANCE	CLINICAL DEPTH	STAKEHOLDER FAMILIARITY	TIME TO SOURCE	COST TO SOURCE
Literature	Utilizing results from previously published studies. Limited ability to match the trial population and data requirements.	Low-Medium	Low (Regulators) High (HTA Bodies)	Short	Low
Administrative databases	Utilizing databases established for tasks such as claims. Data collection is limited to scope of the primary task and therefore likely lacking clinical depth required for an EC study.	Low	Low	Medium	Medium
Patient registries	Partnering with existing patient registries can provide access to suitable patient cohorts and clinical data. May not be able to alter data capture strategy to suit EC requirements.	Medium-High	Low	Medium	Medium
Electronic medical records	Collecting data from digital patient records that are in "research ready" format. Often provides good clinical data and the opportunity to be enhanced to meet EC study requirements	Medium-High	Medium	Medium-Long	Medium
Retrospective chart review	Abstraction of data from existing patient records into a case report form to create a new database. Enables often access to rich clinical data.	High	Medium	Medium-Long	Medium-High
Prospective chart review	Abstraction of data from patient records over time in a prospective fashion. Provides contemporary and rich clinically rich data but limited to the timeframe of the data collection period.	High	Medium-High	Long	High
Historic RCT Data	Use of historic RCT data to provide an EC for a current parent trial. Data can be sufficiently rich but challenges exist around population matching and data access.	Medium-High	Medium	Medium	Medium

Note: Information in the table is provided on a relative scale and based on the authors' experience, individual cases may vary.

Using individual patient-level data — the substance of an EC study

EC studies must be distinguished from other study types like Indirect Treatment Comparisons (ITCs), Network Meta-Analyses (NMA), Matching-Adjusted Indirect Comparisons (MAIC), and Simulated Treatment Comparisons (STC). Each of these techniques seeks to determine comparative efficacy in the setting of no randomization.[14]

- **ITC/NMA** integrates data from one or multiple trials using aggregated data only.
- **MAIC** reweighs patient-level data from a SAT to match mean baseline characteristics from published external data but still uses only aggregated data for the comparator.
- **STC** uses no real comparator data; instead, outcomes are simulated by statistical models calibrated to available trial-level summaries. This method stands and falls with the accuracy of the underlying model, and is particularly vulnerable to model misspecification in heterogeneous populations. Critically, STC has faced notable resistance at HTA bodies: the Gemeinsamer Bundesausschuss (G-BA) in Germany and National Institute for Health and Care Excellence (NICE) in England have both questioned the validity of STC-derived estimates in recent appraisals, citing concerns

about the reliability of the simulation assumptions when individual patient-level data from the comparator arm is unavailable. EC studies, by contrast, sidestep this limitation entirely through direct access to patient-level records.

EC studies, on the other hand, use individual patient-level data, which allows best bias control using causal inference methods.[15]

ADVANTAGES OF EC STUDIES:

- Patient-level data offers more granularity, superior bias control, and clinical realism.
- An ITC/NMA/MAIC/STC needs to take available data, while an EC study constitutes a new effort with an opportunity to customize data collection.
- EC studies are particularly suited when comparator data from the literature are not or only scarcely available.
- EC studies allow long-term follow-up.

LIMITATIONS OF EC STUDIES RELATIVE TO TRADITIONAL ITCS:

- Lack of randomization demands well-designed studies and rigorous statistical methodology to avoid residual confounding and bias.
- Unmeasured confounding, measurement accuracy, and missing data are potential challenges which may limit the level of generated evidence.
- Regulatory skepticism is significant where data provenance, transparency, and data quality / validation are lacking.

To address these challenges, EC studies must incorporate best-in-class models for causal inference, missing data handling, endpoint validation, and sensitivity analyses addressing the potential for unmeasured confounding. Also, regulatory authorities expect early engagement and case-by-case EC study justification.

Adoption, trends, and case studies

Drivers of change

There is an increasing demand to foster customized evidence generation for rare diseases and niche populations because patients affected by these conditions often cannot wait for the lengthy timelines of traditional randomized trials. Examples like gene therapies and biomarker-targeting medicines have offered new paradigms for personalized therapy and require suitable evidence frameworks to ensure fast approval and coverage.[16]

Digital health data and the widespread use of big data have profoundly improved the data environment. Researchers now have unparalleled access to EHRs, insurance claims, mobile health applications, wearables (e.g., Fitbit), and linked devices, allowing them to develop credible data from a variety of external data sources. This increase in data availability, along with enhanced analytics, is changing the way clinical evidence is created and assessed.[17,18]

Spotlight case studies

For sponsors building an EC strategy, the value of these case studies lies less in the regulatory outcomes themselves than in what they reveal about successful design choices — the data sources used, how comparator cohorts were matched, how endpoint alignment was justified, and how each programme engaged regulators early. The examples below are not just precedents; they are templates of the design decisions that get an EC study accepted. Numerous case studies demonstrate how EC studies have been successfully incorporated into regulatory and HTA processes. These examples cover a wide range of therapeutic areas, demonstrating the flexibility of EC study applications.

- The FDA's rapid approval of *blinatumomab* (BLINCYTO®) for relapsed or refractory acute lympho¬blastic leukemia is among the most often cited cases. The pivotal study employed anSAT design, which results were compared to an EC based on a previous clinical trial and registry data.[19] This approach enabled rapid access to a novel therapy for a highly aggressive and rare malignancy where RCTs were ethically and logistically challenging.

- Similarly, *tisagenlecleucel* (KYMRIAH®), a CAR-T cell treatment, was authorized for pediatric B-cell acute lymphoblastic leukemia employing an EC study for contextualization. Results from a SAT were compared to matched historical populations from disease registries. The FDA accepted these comparisons as supporting data, noting significant effectiveness signals[1] and the absence of alternative treatments.[20]

- In the EU, the EMA assessed *patisiran* for hereditary transthyretin-mediated amyloidosis using registry-based data as an EC 40.[21] The Swedish HTA body TLV (Tandvårds-och läkemedelsförmånsverket; The Dental and Pharmaceutical Benefits Agency) conducted an examination using real-world registry data to assist cost-effectiveness modeling. The effective integration of EC data was credited to Sweden's robust longitudinal datasets and rigorous data quality requirements.[22]

These cases show that with adequate scientific explanation and data quality assurance EC studies can play an important role in getting treatments to market, especially in high-need, low-prevalence contexts. Future EC study use cases will most certainly come with improved techniques, clearer advice, and more coordination among data custodians, regulators, and payers.

[1]In late 2025 and early 2026, FDA leadership, including the Commissioner and the Director of CBER, outlined a new framework establishing RCTs as the preferred standard for new CAR-T approvals. They explicitly noted that while earlier approvals were based on single-group trials, future initial approvals will generally require **superiority** over a standard-of-care control group in an RCT. See Association for the Advancements of Blood & Biotherapies.

Global regulatory and HTA ecosystem

The policy landscape

For sponsors targeting multi-region launches, regulatory heterogeneity is no longer a downstream concern to be solved at submission, but an upstream design constraint. An EC study that satisfies the FDA may not satisfy the EMA, and neither may satisfy G-BA, HAS, or the EU JCA. Sponsors who design once and adapt later routinely encounter HTA rejection or pricing concessions that wipe out the time-to-market advantage the EC study was meant to deliver.

The strategic question is therefore not which jurisdiction sets the bar, but how to design an EC study whose evidence package clears the highest bar that matters for the product's commercial geography. While EC studies are increasingly recognized for their early clinical development potential regarding internal decision-making, their regulatory and HTA acceptance varies widely across jurisdictions.[3] These differences stem from a mix of cultural, technical, and policy factors—including the maturity of digital health ecosystems, regulatory frameworks for RWE, and national attitudes toward observational data.

Table 3 summarizes how major regions evaluate EC studies for regulatory approval and HTA decisions. It highlights disparities in infrastructure readiness, RWD acceptance, and integration into clinical and reimbursement decision-making: The United States leads in EC study design adoption, with the FDA having issued formal guidance on EC studies and RWE in general, promoting pragmatic regulatory frameworks.[4] These have enabled earlier access to innovative therapies in oncology and rare diseases, where EC studies have supported accelerated approvals. However, HTA acceptance in the U.S. remains fragmented and payer-dependent, with evidentiary standards varying across insurers.

In the European Union, EC study design adoption is more heterogeneous. EMA supports RWD in specific contexts, including registry-based studies, as outlined in recent guidance.[12,13,23] National HTA bodies, however, diverge sharply in their acceptance. Countries like Sweden and Finland integrate EC study data due to strong registries, while Germany and France remain RCT-focused. The United Kingdom has shown renewed interest in alternative evidence generation following Brexit, with Medicines and Healthcare products Regulatory (MHRA) Agency and National Institute for Health and Care Excellence (NICE) being increasingly open to real-world comparators, especially in cancer and infectious diseases.[25]

In Asia, progress is heterogeneous. Japan and China are investing in digital health and piloting EC study-based evaluations, especially in oncology.[26,27,28,29] South Korea has adopted a cautious but supportive stance.[29] Meanwhile, Brazil, India, and other emerging economies face challenges due to limited infrastructure, fragmented data systems, and constrained HTA capacity.[30]

Collectively, these trends reveal a patchwork policy landscape for EC study integration. Harmonization efforts such as the JCA initiative and the GetReal Institute aim to standardize evaluation criteria and promote data-sharing frameworks. Still, continued investment in regulatory engagement, methodological consensus and data quality is needed.

Table 3: Global Landscape for Regulatory and HTA Acceptance of EC studies

REGION/ COUNTRY	REGULATORY BODY	HTA BODY	RWD ACCEPTANCE	HTA ECA ACCEPTANCE	INFRASTRUCTURE READINESS	EXAMPLE USE CASES
USA	FDA	CMS[2]/Payers	High (formal guidance)	Limited (payer-dependent)	High	Oncology, rare disease
EU (EMA-wide)	EMA[3]	HTAR[4]/ Joint Clinical Assessment Framework	Medium (cautious)	Low–medium (varies)	Medium–high (Nordics strong)	Rare disease, oncology
UK	MHRA[5]	NICE	Medium (post-Brexit interest)	Increasing cautiously	High	Oncology, COVID-19
Germany	BfArM[6]/PEI[7]	G-BA[8]/IQWiG[9]	Low–moderate	Very limited (prefers RCTs)	Moderate	Rarely accepted
France	ANSM[10]	HAS[11]	Low	Very limited	Moderate	Rarely accepted
Japan	PMDA[12]	Chuikyo[13]	Emerging	Low	Moderate	Oncology pilots
China	NMPA[14]	NHSA[15]	Growing (policy-driven)	Emerging	Rapidly improving	Post-market monitoring
South Korea	MFDS[16]	HIRA[17]	Medium	Cautiously supportive	Moderate	Cancer, rare diseases

[2]Centers for Medicare & Medicaid Services evaluates the clinical and cost effectiveness of medical technologies to inform coverage decision for Medicare beneficiaries.

European Medicines Agency (EMA) is the decentralised EU agency responsible for the scientific evaluation, supervision, and safety monitoring of medicines across the EU.

Health Technology Assessment Regulation (HTAR, Regulation EU 2021/2282) establishes a framework for Joint Clinical Assessments (JCAs) across EU member states, coordinated by the Health Technology Assessment Coordination Group (HTACG). It came into full effect for oncology and advanced therapy medicinal products in January 2025, with broader therapeutic area coverage phased in thereafter.

[5]MHRA is the regulator of medicines, medical devices, and blood components in the UK.

[6]Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices) is the federal higher authority which licenses, monitors safety, and assesses risks of drugs and medical devices.

[7]Paul-Ehrlich-Institut is the federal agency for research and regulation of vaccines and biomedicines.

[8]Gemeinsamer Bundesausschuss (Federal Joint Committee) makes binding regulations in lieu of legal decisions, discussions, and health reforms.

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) is Germany's independent scientific institute that assesses the benefits and harms, quality, and cost-effectiveness of medical interventions, producing evidence reports for the G-BA.

[10]Agence Nationale de Sécurité du Médicament et des Produits de Santé is the responsible for safety of health products and increase access to innovative therapeutics.

Haute Autorité de santé (HAS) sets clinical guidelines, accredits hospitals, certifies physicians, and evaluates drugs, devices, and procedures for reimbursement in France.

[12]The Pharmaceuticals and Medical Devices Agency (PMDA) is Japan's regulatory body responsible for the review and approval of pharmaceuticals, medical devices, and regenerative medicine products, as well as post-marketing safety surveillance.

[13]Chūyō Shakai Hoken Iinkai (Central Social Insurance Medical Council) is an advisory body to Japan's Ministry of Health, Labour and Welfare (MHLW) responsible for approving new drugs, revising medical service fees, and setting reimbursement prices for drugs and medical devices.

[14]National Medical Products Administration is the regulatory body to ensure the registration and regulation, and safety of medicines and medical devices, and cosmetics.

[15]National Healthcare Security Administration is the primary healthcare insurance regulator in China.

Evolution of guidance

The development of regulatory and HTA recommendations on EC studies indicates a growing, albeit cautious interest across worldwide jurisdictions. Over the last decade, health authorities have moved away from perceiving EC studies as experimental tools and toward acknowledging their potential importance in well-justified use cases. This transition has been driven by the demand for evidence in rare illnesses, cancer, and fast access routes, as well as the advancements in RWD infrastructures and analytic methodologies.

The FDA in the United States has been at the forefront of this trend. Since the publication of the 2017 framework on Real-World Evidence, the FDA has produced specifically tailored EC study draft advice in 2023, outlining the parameters under which EC studies may be admissible in regulatory submissions.[4] These include the availability of high-quality data, well-defined comparator populations, and the application of suitable statistical methods. Oncology and rare diseases remain the principal areas of regulatory approval, with numerous oncology medicines already authorized using EC studies.

The EMA has taken a more cautious approach but is steadily increasing its involvement through initiatives like the EMA registry-based research guideline (2021) and funding the GetReal Institute.[12] These measures promote scientific rigor in RWD usage and early collaboration with regulators. National HTA agencies in Europe (e.g., NICE in the UK, TLV in Sweden) have also begun to issue condition-specific recommendations on the acceptability of EC studies, particularly in the setting of SATs.[25, 32]

The EMA 2025 Draft Concept Paper on External Controls represents the most significant regulatory development in the European Union. It explicitly signals the development of an EMA Reflection Paper on the use of external controls for evidence generation. This transition marks a definitive move from perceiving external comparators as experimental observational tools toward a harmonized, scientifically sound and rigorous framework for regulatory decision-making.

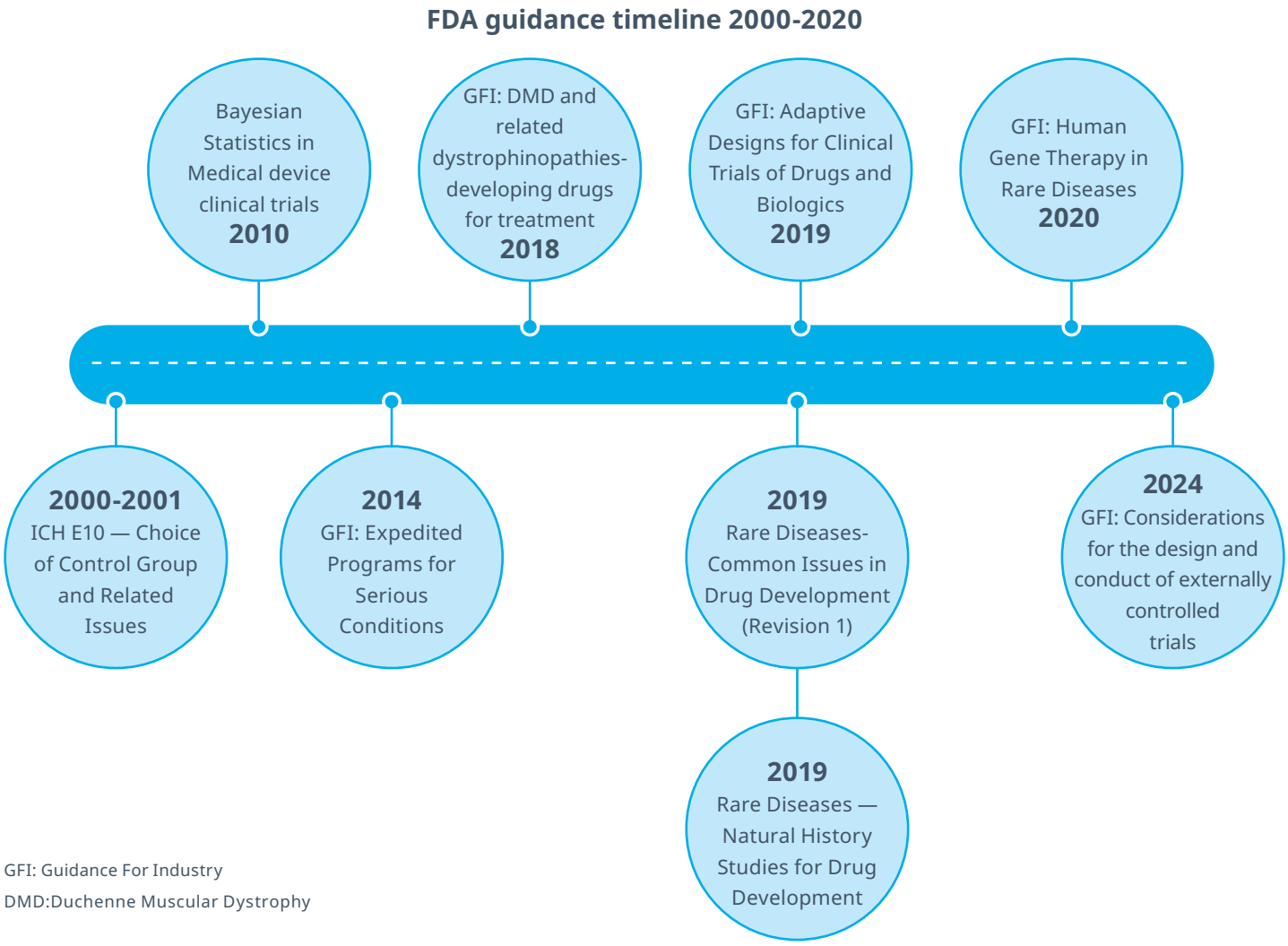
In the UK, the MHRA EC study draft guideline from 2025 "lays out general principles and points to consider for sponsors", which is a positive step towards EC studies, indicating principal agreement that EC studies can be suitable for evidence generation under the right conditions.[30]

Across the Asia-Pacific region, Japan's PMDA has started pilot projects to investigate EC study design usage in oncology, while China's NMPA has implemented rules to encourage post-market RWE research (Du & Han). South Korea's MFDS has shown cautious support for EC studies when solid data infrastructure is available.[33]

Despite the pace, worldwide advice remains scattered. Differences in data standards, data privacy and governance frameworks — notably the EU's General Data Protection Regulation (GDPR), which imposes strict constraints on cross-border patient data transfer and secondary use of health records, versus the United States' Health Insurance Portability and Accountability Act (HIPAA), which operates under a different consent and de-identification model — alongside variation in institutional preparedness, impede harmonization. These regulatory asymmetries have direct operational consequences for EC studies that draw on multi-national data sources. International initiatives, such as the EU's JCA and collaborative frameworks like the GetReal Institute, seek to overcome these gaps by providing standardized techniques and precompetitive data-sharing mechanisms.

[16]Ministry of Food and Drug Safety is South Korea's primary agency responsible for safety, efficacy, and quality assurance of food, pharmaceuticals, medical devices, and cosmetics.
[17]Health Insurance Review & Assessment Services is responsible for reviewing medical claims and assessing the quality of healthcare.

Figure 2: Development of Global EC Study Guidance (2020-2025) (Image adapted from Jahanshahi et al. 2021 and FDA, 2023)



GFI: Guidance For Industry
DMD:Duchenne Muscular Dystrophy

Barriers, breakthroughs, and unresolved issues

Potential concerns

Most sponsor anxieties about EC studies cluster around a single question: will the regulator or HTA body accept the comparator? The concerns set out below are real, and they are also predictable. Each can be anticipated and mitigated at study design rather than addressed reactively in review, but only if sponsors plan for them as defendable design choices rather than as residual risks. Despite their potential, EC studies come with challenges, mainly due to constituting a non-randomized study design, as opposed RCTs.

One potential risk is unmeasured confounding, which should be made subject to sensitivity analyses using Quantitative Bias Analysis (QBA). Further, regulatory bodies expect high-quality datasets, but not all Real-World Data (RWD) sources are fit-for-purpose. Data quality issues as indicated by missing data, potential measurement error and misclassification must be handled by appropriate data validation steps (like blinded adjudication of outcome data), by rigorous statistical methodology, and, if necessary, by rejecting potential data source candidates due to being unsuitable.

EC Study use case differentiation

The value and appropriateness of EC studies are heavily context dependent. Large-scale RCTs for rare illnesses or ultra-rare subpopulations, such as genetic variants or pediatric malignancies, are sometimes impractical or unethical, while EC studies may offer in these circumstances a helpful alternative design for bridging evidence gaps and expediting patient access. In contrast, EC studies are less typical in common therapeutic areas with well-established treatment standards. In these situations, regulators and HTA authorities frequently seek greater justifications for deviating from the RCT design. Therefore, the strategic deployment of EC studies should be customized to specific use cases: orphan illnesses or early-phase drug development. However, their usage in standard clinical indications is confined to rare situations or additional roles.

Future strategies and innovation pathways

Emerging methodologies

Each of the methodological advances discussed below maps to a specific operational problem the drug developing industry faces today: AI-assisted extraction addresses the cost and timeline of chart abstraction in indications where structured data is sparse; federated analysis addresses the impossibility of pooling rare-disease data across borders without violating GDPR or local consent frameworks; digital twins offer a route to early-development decision support where no comparator cohort yet exists. None of these is a replacement for rigorous EC design — they are tools that, used appropriately, reduce specific friction points in the EC programme.

Data science innovations are reshaping the way EC studies are designed and evaluated AI models are increasingly being used to identify patient comparators, extract data elements from real-world datasets, and address confounding factors that may influence results. FDA guidance recognizes the potential of AI for rapid, scalable, and sophisticated data processing, particularly for unstructured health records. These solutions have special potential for high-dimensional EHR or claims data.

However, protocols employing AI must specify model assumptions, provide pre-specified validation metrics, and demonstrate that AI-assisted extraction does not introduce systematic bias into the comparator cohort. The EMA has similarly signalled caution, noting that AI-derived data elements require the same level of traceability and auditability as manually abstracted data. Regulatory reviewers are increasingly requesting detailed documentation of AI model training data, performance benchmarks, and error rates before accepting AI-assisted data in registrational submission.[34]

Likewise, the statistical science is moving ahead at a heightened pace, and new publications presenting customized methodological solutions for EC studies are being published every year.[35,36,37,38,39,1, 40, 41,42] Relevant topics include the best use of multiple imputation, causal inference methods, and index date selections.

Federated statistical models are another frontier now available to be applied for EC studies. These models promote multi-institutional collaboration without the need to exchange sensitive data by allowing model-building across decentralized datasets while maintaining patient privacy.[43] This is especially useful for rare diseases, where no single location has sufficient patient volume, and no data can be shared across locations.

Digital twins use statistical or machine models trained on RWD to generate patient-specific representations of

actual individual patients. They are being explored for treatment pathway simulation, prognostic enrichment, trial design optimization and predictive modeling.[44,45] When calibrated with sufficient observational, biomarker and/or clinical data, digital twins have the potential to enable simulation or prediction of patient outcomes. Some digital twins may be defined at a single time point, while others are maintained through ongoing or periodic alignment with the patient's evolving clinical data.[46]

These models work best with well-characterized diseases, as the prediction is not allowed to have any bias (e.g., due to unknown prognostic factors or unknown disease heterogeneity), so the application for rare diseases may be limited. Foundation models, trained on large and diverse healthcare datasets, are improving the possibility for scaling and reuse across more indications. However, regulatory acceptance of digital twins techniques has been broadly established, and the best positioned use case is as an exploratory or complimentary approach rather than replacing more traditional statistical, causal, or mechanistic methods.

Early EC study planning

The single largest determinant of whether an EC study supports or undermines submission is when planning starts. Sponsors who begin EC design once the SAT is enrolled have already lost the optionality to align data sources, endpoint definitions, and index dates with the comparator cohort that will eventually appear next to their pivotal data. The cost of late planning is rarely measured in study budget but in lost months at HTA review and in pricing concessions when payers question the comparison. Proactive planning of EC studies during the clinical development lifecycle is crucial. The EC study value improves significantly when it is included early in the clinical development plan or as a contingency to support faster approval paths. This necessitates coordination among sponsors, statisticians, and regulatory bodies.

Planning involves identifying relevant data sources, establishing consistency in endpoint definitions, and pre-defining analytic procedures. Early involvement with regulators, such as through pre-IND (Investigational New Drug) meetings or scientific advice protocols can help to mitigate downstream difficulties.

Best strategies include proactively curating registry or real-world cohorts alongside single-arm trials and using outcome criteria that align with those in the experimental arm. Sponsors should consider how regulators and HTA authorities may evaluate evidence derived from non-randomized comparisons.

Global harmonization efforts

As EC methodology evolves in sophistication, the demand for standardized frameworks increases, as heterogeneous standards for targeted RWD quality, analysis, and reporting present impediments to global contributions. Harmonization efforts lead to reduced fragmentation and increase the consistency and reliability of externally regulated evidence.

The GetReal Institute in Europe, for example, encourages transparent RWE standards and cross-stakeholder collaboration, and the JCA project aims to improve efficiency in health technology evaluations among EU member states. International consortia such as the Innovative Medicines Initiative (IMI) and the International Council for Harmonization (ICH) are looking at unified definitions and risk assessment systems.

Progress is gradual but encouraging. Initiatives to build standard data models, such as OMOP and Sentinel, have increased data interoperability. HTA agencies are increasingly engaging in conversations with regulators to harmonize evidential standards.

The next stage is to infuse global RWD standards into regulatory science, ensuring that EC studies are not only acceptable in isolated states but also consistently recognized across borders. Achieving this ambition will need ongoing investment in global harmonization efforts.

Actionable insights for innovators

Principles for EC study design and execution

Due to their design, EC studies have inherent challenges such as the need for causal inference methods addressing the non-randomized setting. Because missing randomization is the biggest critique of such studies, it is necessary that EC studies are carefully designed and analyzed in the most rigorous methodological standards. Another aspect is the use of RWD, which is not the same quality as data from a trial. Hence, risks around using RWD should be clearly described in the protocol and mitigated as much as possible, for example, by using independent and blinded adjudication of important clinical events.

In every case, available guidelines must be followed to gain the trust of doctors, regulators, and HTA authorities. Also, early and consistent interaction with regulators and HTA authorities strengthens trust. Pre-IND meetings, scientific advice consultations, and parallel advice programs are essential. Sponsors and service providers can also consider forming collaborations with data custodians to ensure longitudinal consistency and context-rich RWD.

Finally, EC studies are not isolated. They must be developed with an ecosystem in mind, incorporating adequate digital health data, registries, claims data, wearable or other sensor data. Interdisciplinary collaboration among doctors, biostatisticians, informaticists, and patient advocates helps to improve quality, technical validity and public confidence.

Summary and key takeaways

Key findings

EC studies have transitioned from an experimental design option to a recognized regulatory and HTA evidence pathway. Across the FDA, EMA, MHRA, and PMDA, formal guidance published between 2023 and 2025 reflects growing institutional consensus on when and how EC studies are acceptable. The EU Joint Clinical Assessment framework has introduced a new cross-border evidentiary standard that is already shaping how sponsors design comparative evidence strategies.

Individual patient-level data remains the defining advantage of EC studies over aggregate-data methods. EC studies using IPD-based causal inference approaches consistently outperform ITC, NMA, MAIC, and STC comparisons in regulatory acceptability, particularly in rare disease and oncology contexts where HTA bodies have shown increasing skepticism toward model-based comparisons without IPD.

Methodological progress is accelerating. Publications addressing causal inference methods, missing data handling, index date selection, and quantitative bias analysis have expanded the toolkit available to EC study designers. OMOP harmonization, federated learning, and AI-assisted data extraction are reducing operational barriers — but each carries regulatory validation requirements that sponsors must plan for explicitly.

EC study design principles at a glance

- **Start early**. EC study planning should begin at IND stage, not after SAT enrolment closes. Early data source identification and regulatory alignment are the single greatest determinants of downstream study success.
- **Engage regulators proactively**. Pre-IND meetings, EMA scientific advice, and MHRA Early Access to Medicines Scheme interactions are not optional — they are the mechanism by which EC study design assumptions are stress-tested before they are committed to protocol.

- **Fit-for-purpose data first**. The comparator cohort is only as strong as the data that defines it. Prioritise sources with clinical depth, longitudinal follow-up, and documented data quality over sources that are merely accessible. Chart review remains the gold standard for data richness; registry data offers scale.
- **Match on what matters**. Population matching must address the prognostic factors most likely to confound the treatment effect estimate. Work backwards from the known confounders in your indication — do not rely on propensity scores alone when important covariates are unmeasured.
- **Document everything**. Regulators and HTA bodies are increasingly requesting full transparency on data provenance, adjudication processes, sensitivity analyses, and QBA results. Treat the EC study protocol with the same documentation rigour as the parent SAT protocol.
- **Plan for HTA as well as regulatory**. Regulatory approval is necessary but not sufficient. G-BA, NICE, HAS, and the EU JCA all apply different and sometimes stricter methodological standards than the FDA or EMA. The EC study that secures approval may still fail at reimbursement if its design did not anticipate HTA evidentiary expectations.

Putting EC studies into action

The promise of EC studies can only be realized through proactive and coordinated leadership across the drug development ecosystem. Drug developers, particularly in oncology and rare disease, should take the initiative to propose EC study strategies early in clinical development. Regulatory agencies, in turn, should accelerate efforts to finalize guidance and establish consistent review criteria across divisions and regions.

There is a clear need for collaboration between key stakeholders including regulatory and HTA bodies, researchers, and drug development companies. In order to succeed, life science companies who propose EC strategies will progress from a specialized to a more general and standardized approach through collaborative work. Now is the moment to act — to develop infrastructure, establish consensus guidelines, and aim for EC studies being implemented in the most ethical, transparent, and efficient ways possible.

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