Advancing Evidence Generation with External Control Arms: FDA, EMA, and HTA Perspectives

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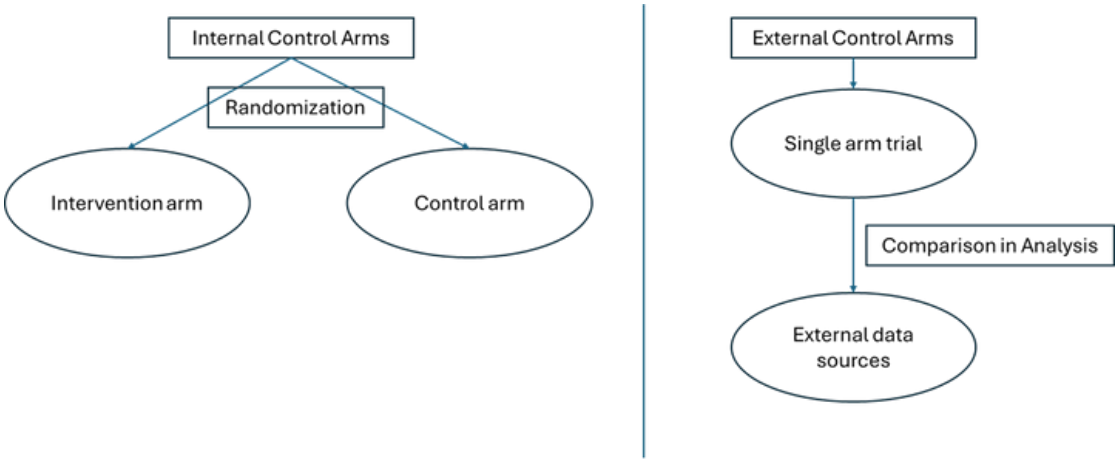
Introduction

Randomized controlled trials rely on assigning patients to intervention and control groups through randomization, which creates balanced comparison groups and minimizes bias (Figure 1). Yet in many therapeutic areas this design is difficult to carry out, either because eligible patients are scarce, withholding treatment is unethical, or the pace of clinical innovation makes traditional trials impractical. External control arms have emerged as an alternative in these situations. Rather than drawing comparators from within the same randomized study, ECAs use patients identified from outside sources such as historical trials, registries, or electronic health records. These external comparators help fill the evidentiary gap when only single arm data are available, enriching understanding of treatment effects when a conventional control group cannot be established.[1]

As challenges to running standard RCTs have become more common, ECAs have gained traction in regulatory and health technology assessment (HTA) settings.[2] Both regulators and HTA bodies are increasingly open to incorporating real world evidence alongside traditional trial data, especially in fields like rare diseases and oncology where patient populations are small and unmet needs are substantial.[3] In these contexts, ECAs offer a practical and ethically acceptable way to generate comparative evidence, supporting decisions in environments where traditional randomization is not feasible.

This document provides a brief overview of potential limitations and challenges with ECA, as well as mitigation strategies. We also consider the regulatory and HTA perspective regarding these designs.

Figure 1: Comparison between internal and external control arms



Importance

ECAs facilitate drug development by providing comparator groups when traditional randomized control arms are not feasible or ethical. They help address recruitment challenges, particularly in therapeutic areas where eligible patient populations are small, diseases are rare or rapidly progressive or where withholding potentially beneficial treatment would be unethical. By enabling comparative assessment without the need for concurrent randomization, ECAs can accelerate clinical development timelines and expedite patient access to promising therapies.[4,5]

ECAs also provide valuable contextual evidence for interpreting outcomes from single-arm studies, which are often used in early-phase trials or in areas with high unmet medical need. Such evidence supports regulatory and HTA submissions by allowing comparative evaluation of efficacy and safety against relevant real-world benchmarks. In particular, ECAs have demonstrated value in oncology and rare disease research, where traditional trial designs may be infeasible due to limited patient availability or evolving treatment standards.[3]

Importantly, ECAs leverage data derived from sources such as electronic health records, registries, and historical clinical trials. This approach maximizes the use of existing relevant patient data, potentially reducing study costs, improving operational efficiency, and expanding the evidence base to include more representative patient populations.[6]

Limitations & Mitigation Strategies

Risk of Bias and Confounding

Unlike RCTs, ECAs lack random allocation, increasing the potential for selection bias, confounding, and imbalance in baseline characteristics between treatment and control groups.[4,7] This can be mitigated by applying strict eligibility alignment to ensure the ECA population closely mirrors the trial population, implementing robust statistical methods such as propensity score matching, inverse probability of treatment weighting, or multivariable regression adjustment. Sensitivity analyses, negative control outcomes, and quantitative bias analyses can further test the robustness of findings. Additionally, transparent reporting of data quality, variable completeness, and methodological assumptions helps regulators and HTA bodies assess the credibility of the ECA. While residual confounding may still persist, these approaches collectively strengthen the validity of ECA-based comparisons.[4]

Temporal Mismatch with Trial

Differences in timing between the clinical trial and the external data source can lead to inconsistencies in standard of care and clinical practice. As treatments, diagnostics, and management approaches evolve over time, ECAs derived from earlier periods may not accurately reflect contemporaneous care. This can be solved by restricting data to time periods closely aligned with the trial, apply anchoring methods to synchronize index dates, and run sensitivity analyses to test the impact of temporal differences.

Differences in Protocol

ECA patients are not managed under a trial protocol, therefore their follow-up schedules and outcome assessments may differ from those in the investigational study. Non-standardized measurement frequency, inconsistent endpoint definitions, and variable assessment practices reduce comparability. Additionally, clinical decision-making in routine practice introduces variability in treatment exposure, dose adjustments, switching patterns, and monitoring frequency, which can bias comparisons. Finally, trial inclusion and exclusion criteria may not be fully reproducible in external datasets, particularly when baseline diagnostic tests, laboratory values, or performance status are missing.[8]

These limitations can be addressed by carefully selecting high-quality, fit-for-purpose data sources. Use datasets with detailed treatment exposure and apply robust treatment episode construction and exposure alignment methods. Scenario analyses reflecting different treatment pathways can help evaluate variability. Eligibility alignment and the use of validated proxy measures allow assessment of incomplete trial criteria. Endpoints should be harmonized through strict operational definitions, and datasets with structured follow-up should be prioritized, with algorithms implemented to replicate trial visit windows. Sensitivity analyses, including landmark analyses, can further mitigate the impact of variable observation intensity.[9]

Regulatory

FDA

The use of external controls is most common in orphan disease settings where it can be difficult to accrue patients, especially for a RCT. There are some notable examples of the use of external controls in oncology drug development for FDA submissions:[3]

Blincyto® (Blinatumomab):

- Blinatumomab is approved for treatment of adults with Philadelphia chromosome-negative acute lymphoblastic leukemia. Regulatory submission incorporated a phase II single-arm trial supplemented with an ECA. The ECA, constructed from a historical database of 1,139 patients from EU and US study sites, aimed to provide a comparative assessment of complete remission and overall survival between patients receiving blinatumomab in the experimental arm and those receiving standard of care in the external arm.
- The FDA granted breakthrough therapy designation and accelerated approval in December 2014.

Bavencio® (Avelumab):

- Avelumab is approved for the treatment of metastatic Merkel Cell carcinoma (mMCC).
- The submission included a single-arm study and an ECA using retrospective chart review and registry data to characterize the natural history of mMCC to contextualize the risk/benefit profile of avelumab.
- The FDA considered the ECA as supportive evidence, but the regulatory approval was based primarily on data from the single-arm trial alone.

Regulatory

EMA

Our team conducted reviews of EMA submissions and example cases from that review are summarized below:[10]

Ebvallo®:

- Ebvallo is used for the treatment of Epstein-Barr virus positive post-transplant lymphoproliferative disease. An external comparison using historical controls was conducted between Study ATA129-EBV-302 and the pivotal Study RS002 (2010–2018 cohort). After matching propensity score, tabelecleucel showed a notable overall survival benefit versus standard of care (unadjusted HR = 0.46; adjusted HR ≈ 0.34). Although subject to the inherent limitations of historical comparisons, the findings were considered supportive for contextualizing efficacy.
- The EMA found the evidence supportive for the safety and efficacy data.

Enhertu®:

- Enhertu is used in the treatment of breast cancer. A metastatic breast cancer database – French multicenter registry was used.
- Comparisons with the historical cohort were limited by differences in ORR and PFS definitions and timing, incomplete patient-level data, and uncertainties in population comparability and follow-up, resulting in insufficient evidence to consider the cohort supportive.
- The EMA considered the data of exploratory nature and RWE was not considered supportive.

ECAs for HTA

HTA submissions often require head-to-head evidence to inform cost-effectiveness analyses and health economic models. ECAs can serve as a source of comparative data to populate model inputs such as survival outcomes, progression rates, and quality-of-life estimates when no suitable RCT comparators exist.

In therapeutic areas characterized by rapid innovation such as oncology, gene therapy, and rare diseases, waiting for long-term or large-scale RCTs can delay patient access and reimbursement decisions. ECAs can provide interim or bridging evidence to support early HTA submission and conditional funding agreements while confirmatory evidence is generated post-launch.

Despite their promise, HTA agencies remain cautious about ECAs due to concerns over confounding, data quality, possible selection bias, and methodological transparency. Acceptance varies by jurisdiction: for example NICE [11] and CDA-AMC [12] have each issued guidance acknowledging the potential role of RWE and ECAs but emphasize the need for clear documentation of data sources, analytic methods, and sensitivity analyses to demonstrate robustness. Consequently, ECAs are often viewed as complementary rather than substitutive evidence, most valuable when used alongside other comparative analyses or indirect treatment comparisons.

Conclusion

ECAs offer a practical solution for generating comparative evidence when randomized controlled trials are not feasible. By leveraging real-world data, ECAs can support regulatory and HTA decision-making, particularly in rare diseases and oncology. However, their value depends on the quality of data, methodological rigor, and transparency. When carefully designed and appropriately applied, ECAs can complement traditional evidence and enhance the relevance of clinical and economic evaluations.

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