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# External Control Arms for Rare Disease Trials: Opportunities and Strategies

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Patients who suffer from rare medical conditions often face challenges in obtaining newly developed treatments due to the long and slow process of drug development. Traditional clinical trials, like randomized controlled trials, are considered the gold standard for drug development. However, they often require large patient pools and are not feasible for rare conditions. Single-arm studies, where all participants receive the new drug, offer a potential solution, but lack the robust evidence needed by regulatory and health technology assessment (HTA) agencies to make informed decisions.

As an alternative, evidence from studies using external control arms (ECAs) is increasingly being used by regulatory bodies and HTA agencies to guide their decision-making process when the preferred evidence standard is lacking.[1-4]

ECAs offer a unique way to evaluate the effectiveness of treatments without directly comparing them to a placebo group within the same study. By using existing data sources like patient registries or medical records to create a “synthetic control group” that closely matches the characteristics of patients receiving the new therapy, researchers can gain valuable insights into the benefits of the treatment.[1,5]

## Selection bias and confounding should be addressed to generate reliable evidence for regulatory and HTA submissions

With improvements in the quality and availability of medical data, ECAs hold significant promise in expediting the development and approval of treatments for rare diseases. However, conducting robust ECA studies presents its challenges, including the possibility of residual biases even with best efforts.[1,5,6]

**Abbreviations:** ECA, external control arm; EMA, European Medicines Agency; FDA, Food and Drug Administration; HTA, health technology assessment; G-BA, Federal Joint Committee; HAS, Haute Autorité de Santé; NICE, National Institute for Health and Care Excellence.

A recent study examining seven oncology submissions from 2014 to 2021 highlighted two main issues with ECAs across regulatory and HTA agencies: **selection bias** and **confounding factors**.[6] Selection bias arises when the data used for evaluation does not accurately represent real-world patients, while confounding factors are variables that can impact patient outcomes regardless of treatment.

This study considered the drugs blinatumomab (for two indications), avelumab, erdafitinib, entrectinib, trastuzumab deruxtecan, and idecabtagene vicleucel. It included evaluations from various regulatory agencies such as the FDA, EMA, and Health Canada, as well as HTA agencies like NICE, G-BA, HAS, pCODR, and PBAC.[6]

## A rigorous approach to data selection and study design is essential for overcoming methodological challenges

While ECAs offer a promising approach to developing treatments for rare diseases, they require careful planning and execution to ensure the validity and reliability of results meet the standards required for regulatory and HTA submissions.[1,5,6]

When choosing external controls from real-world data sources, it is important to ensure that the data are comparable to the trial participants in terms of key patient characteristics, disease severity, and management practices. It is also crucial to confirm that the data source accurately captures treatments and endpoints relevant to the study. Endpoint definitions may vary between the trial and real-world data sources, which can introduce bias. Additionally, careful study design and robust analytic approaches are necessary to address confounding factors. [1]

Figure 1 outlines essential steps to address challenges in ECA studies, emphasizing the importance of a rigorous approach to data selection and study design.[1,5,6] For pharmaceutical and biotech companies seeking support in this area, IMAC has a proven track record (refer to our case study for further details).

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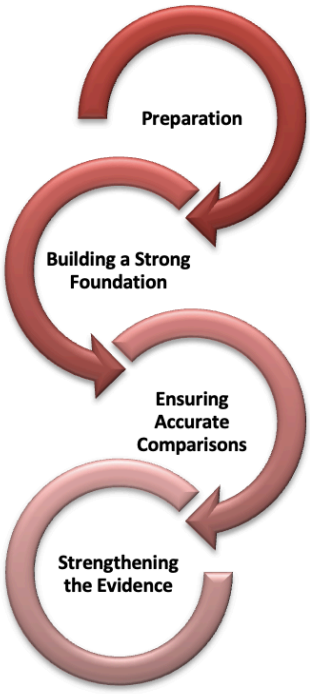


1. **Feasibility Assessment:** Evaluate data source suitability and comparability to the trial participants (Are the populations similar? Does the data capture key factors?)
2. **Patient Population:** Ensure the external control group accurately reflects the study population in terms of demographic, disease severity, etc.
3. **Bias and Limitations:** Address potential biases and limitations in the external data source (eg, availability of key demographic and prognostic characteristics, as well as exposure data for treatments of interest).
4. **Endpoint Alignment:** Align endpoint definitions and assessments (how outcomes are measured) between the study and external control groups.
5. **Robust Analysis:** Implement robust statistical methods to minimize bias such as immortal time biases and unmeasured confounding (e.g., propensity score matching).

*Figure 1 A breakdown of key steps to overcome challenges in ECA studies.*

## Conclusions

Even with careful design, ECA studies can be prone to biases. To ensure the validity and relevance of their findings, it is essential to complement ECA findings with evidence from studies that employ diverse analytical methods and incorporate data from multiple external control groups.[1] In addition, early collaboration with regulatory bodies through scientific advice is crucial when considering ECAs in clinical research for rare diseases.[1]

## How IMAC can help

IMAC's expert team of senior consultants including epidemiologists, real-world data scientists, and senior statisticians, is exceptionally positioned to assist you in navigating the utilization and integration of ECAs to support your reimbursement submissions. As a boutique firm of senior consultants, we are flexible and can develop multicentre, international ECAs as part of your team. Our capabilities include:

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1. Assessing whether an ECA is suitable for your study
2. Providing support for your product strategy
3. Prioritizing key selection criteria
4. Validating real-world outcomes
5. Identifying appropriate real-world data sources to meet study requirements
6. Developing and validating advanced ECA methodologies
7. Efficiently implementing and operationalizing ECAs, utilizing existing databases or facilitating data collection through chart review or prospective patient enrollment.
8. Running and analyzing the ECA, providing comparative data for your non-controlled clinical trial and facilitating HTA submissions internationally

## References

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