Poster #MSR32

Harnessing the Value of External Control Arms Beyond the Oncology and Rare Disease Settings

Olga Volodina,1 Riley Geason,2 Evie Merinopoulou3
1Cytel, Inc., Toronto, ON, Canada; 2 Cytel, Inc., Waltham, MA; 3Cytel, Inc., London, UK

Background

- External control arms (ECAs) derived from real-world data (RWD) are increasingly being used to generate comparative evidence when a randomized controlled trial (RCT) is not ethical or feasible, or to increase power when sample size is limited.
- ECAs can be applied to a single-arm trial as an independent control group or to augment an already existing RCT control arm.
- To date, most ECAs have been used in regulatory submissions in oncology and rare diseases.
- Broader use of ECAs could be to support early stopping decisions during drug development, health technology assessment submissions or engagement with healthcare providers when evidence against comparators not included in trials is needed.
- However, the use of ECAs outside the oncology/rare indications is limited.

Objective

This literature review was conducted to describe the existing use of ECAs in non-oncology prevalent disease settings and to illustrate the potential applications and summarized learnings of using external data in clinical development and post-marketing.

Methods

Search Strategy

- This targeted review utilized an OVID and web-based search to identify review papers and case studies of non-oncology and non-rare disease ECAs:
  - **Comprehensive search via OVID MEDLINE** (conducted on September 18, 2024).
  - **ISPOR database search** (key words: “external control arm”).
  - **Desktop search** (first 5 pages; keywords: “external control arm real world evidence”).
- Real-world, observational studies and hybrid RCT/RWD studies were included. Literature review articles and methodological overviews were also included.
- Two-stage approach was adopted for **OVID** search. Articles were excluded at title and abstract screening if there was no mention of ECA use. At the full-text screening phase, studies were excluded due to study design, non-English language, topic, or focused on rare disease/oncology.

Data Extraction

- The following data was extracted from relevant articles: study details (title, authors, year of publication, etc.), study design (study design, country/region, therapeutic area, details of ECA methods, etc.), patient characteristics (population sampled), outcomes (planned use of ECA, ECA impact, main study finding, limitations, etc.).

Results

Of the 98 articles identified via OVID search, 4 articles identified via the ISPOR database, and 4 articles identified via desktop search, 8 were selected for extraction (shown in **Table 1**).

Table 1. Use of ECAs Outside the Oncology and Rare Disease Setting

Study details	Therapeutic area / Indication	Details of ECA methodology	Purpose of ECA	ECA Learnings
Exploring the feasibility of using real-world data from a large clincal data research network to simulate clinical trials of Alzheimers disease Chen Z, et al. [2021] (1)	Neurodegenerative diseases	RWD: One Florida Clinical Research Consortium Trial data: NCT00478205 (Phase III clinical trial in Alzheimer’s disease) Approach: 1. a one-arm simulation for a standard-of-care external control 2. a two-arm simulation with matched patients for comparative effectiveness analysis.	Demonstration study (i.e. illustrating methods/applicability of ECAs)	This study successfully demonstrated the feasibility of trial simulation using RWD, particularly for simulating external standard of care control arms. • The one-arm simulation yielded estimates comparable to the original trial's control arm. • However, the two-arm simulation faced challenges as the outcome measures diverged significantly from the original trial despite effective randomization through propensity score matching (PSM).
Utilization of anonymization techniques to create an external control arm for clinical trial data Mehtala J, et al. [2023] (2)	Cardiovascular diseases	RWD: Finnish healthcare data sources Trial data: control arm of the PACIFIC-AF trial Approach: The research aimed to evaluate the effectiveness of anonymized real-world data in creating an external control arm compared to pseudonymized data.	Demonstration study (i.e. illustrating methods/applicability of ECAs)	• This case study highlighted the complexities of using anonymized data to create an ECA in clinical trials, where regulatory requirements and data harmonization already pose significant challenges. • Anonymization can introduce uncertainty that may hinder certain analyses, so it is recommended to utilize pseudonymized data for improved usability.
Case study of semaglutide and cardiovascular outcomes: An application of the Causal Roadmap to a hybrid design for augmenting an RCT control arm with real-world data Dang LE, et al. [2023] (3)	Diabetes mellitus	To evaluate tradeoffs between traditional RCTs and a hybrid study using RWD controls through simulation, three potential study designs were constructed. • Design 1 is based on the non-inferiority trial to demonstrate safety of oral semaglutide. • Design 2 is a hypothetical scenario in which only a superiority RCT is conducted. • Design 3 is a hybrid RCT-RWD study.	Demonstration study (i.e. illustrating methods/applicability of ECAs)	The case study illustrates how simulations can help sponsors quantify design trade-offs, revealing that: • Design 3, using unbiased external data, offers similar confidence interval coverage but reduces patient time without a GLP1-RA compared to Design 1. • However, when simulated bias is introduced, Design 3 may lead to increased patient time without treatment, emphasizing the importance of evaluating the potential for bias before adopting this design.
Development of an External Control Arm Using Electronic Health Record-Based Real-World Data to Evaluate the Efficacy of COVID-19 Treatment Jeon JY, et al. [2023] (4)	COVID-19	To evaluate the feasibility of using these RWD-based ECAs as control arms in clinical trials for COVID-19 treatment development, ECAs were created for the ACTT-1, ACTT-2, and ACTT-3 trials using the KNIDCC COVID-19 cohort dataset.	Demonstration study (i.e. illustrating methods/applicability of ECAs)	• The study found no significant difference in recovery time compared to control arms from prior randomized clinical trials (ACTT-1, ACTT-2, ACTT-3). • This study shows that using ECA with EHR data from COVID-19 patients could effectively substitute for the control arm in an RCT.
Real-world evidence to support regulatory submissions: A landscape review and assessment of use cases Alipour-Haris G, et al. [2023] (5)	Infectious diseases	The current study was a multi-center, open-labeled, superiority study involving HBsAg-positive/HBsAg-negative liver transplant patients. • Active treatment group: patients enrolled to receive the described dosing regimen of HepaGam B starting during transplant and continuing over the course of a year • ECA: a retrospective untreated control group of historical patients with data gathered by chart review.	Regulatory use: label expansion	• Results from this study are presented in the HepaGam B treatment label and supported the first license of a biologic product to prevent hepatitis B reinfection in liver transplant patients. • **This study represents the application of an ECA composed of RWD to support a regulatory label expansion.**
Relapse Rates With Paliperidone Palmitate in Adult Patients With Schizophrenia: Results for the 6-Month Formulation From an Open-label Extension Study Compared to Real-World Data for the 1-Month and 3-Month Formulations Turkoz I, et al. [2024] (6)	Neurodegenerative diseases	RWD: IBM Multistate Medicaid Database (MDCD) were used to create ECAs for the PP1M and PP3M cohorts. Trial data: NCT04072575 (single-arm phase 3 OLE study). Approach: The current Phase 4 study aims to enhance the interpretation of clinical findings by utilizing RWD and conducting comparative analyses to support clinical decision-making.	Demonstration study (i.e. illustrating methods/applicability of ECAs)	• Well-matched ECAs for PP3M and PP1M were created using real-world data from an administrative claims database to evaluate outcomes against the PP6M cohort from a single-arm, Phase 3 OLE study. • Treatment with PP6M significantly delayed time-to-relapse and resulted in lower relapse rates and risk compared to the real-world PP3M and PP1M cohorts. • Results from this study further endorse PP6M as an effective maintenance therapy with the longest dosing interval for managing schizophrenia.
Applying propensity methods to the United States transplant registry for external real-world evidence control arms for 5-year survival in the BENEFIT study Klein A, et al. [2024] (7)	Transplantation	The BENEFIT study enrollment criteria were applied to the OPTN registry population of transplant recipients resulting in the formation of two analysis: • Analysis group 1 consisted of recipients on TAC-based immunosuppression, serving as a relevant historical control • Analysis group 2 included CSA-based immunosuppression recipients from non-BENEFIT centers, ensuring no overlap with the original BENEFIT study control arm	Demonstration study (i.e. illustrating methods/applicability of ECAs)	• This study demonstrated that external registry data can effectively serve as an additional control source to estimate drug treatment effects on long-term outcomes beyond those in the original BENEFIT study. • It also confirmed the external validity of transplant recipients from the same period and highlighted that propensity methods resulted in better-balanced cohorts.
Review article: Externally derived control arms—An opportunity for clinical trials in inflammatory bowel disease? Sailish Honap, Laurent Peyrin-Biroulet [2023] (8)	Gastrointestinal diseases	**Example use case from review:** An external placebo control group was synthesized using two methods that incorporated comparable patient populations from pivotal trials of tofacitinib, ustekinumab, and upadacitinib: • The first method utilized historical placebo data from a meta-analysis, ensuring similarity in patient characteristics through a Bayesian approach. • The second employed 1:1 propensity score matching with individual-level data from the upadacitinib trials to create a balanced placebo group using a greedy nearest-neighbor algorithm.	Clinical development	• The encouraging safety and efficacy results of ravagalimab from this study provide further justification for its development as a potential treatment for UC.

Conclusions

- ECAs could save resources while maintaining high evidentiary standards.
- This review showed that ECAs have a potential for a wide array of applicability beyond oncology and rare diseases.
- Additionally, this research demonstrated that application of ECAs outside the rare disease and oncology therapeutic areas is still in its infancy, with most studies being simulations conducted within the past year.
- **Further research and education are needed to address limitations and expand its use in decision-making to effectively leverage the benefit of ECAs.**

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Disclosures

- Olga Volodina, Evie Merinopoulou, and Riley Geason are full time employees of Cytel Inc. that conducted this review. The contributors have no other conflict of interest to declare.