FRIENDS of CANCER RESEARCH

Application of External Control Arms in Oncology Drug Development

Project Overview and Preliminary Findings

Background

External control arms (ECAs) derived from real-world data (RWD) and historical clinical trials can support evidence generation in oncology, particularly in settings where randomized trials are challenging or where existing standards of care are limited. ECAs offer the potential to contextualize single-arm trials, support regulatory decision-making, and accelerate development in rare or high unmet need settings.

However, variability in data capture, eligibility operationalization, and analytic methods raises important questions about reproducibility, interpretability, and whether ECAs can generate consistent evidence to inform regulatory decision-making. In particular, differences across data sources and methodological approaches may influence both cohort construction and outcome estimation, highlighting the need for alignment on best practices.

ECA Pilot Project Overview & Goals

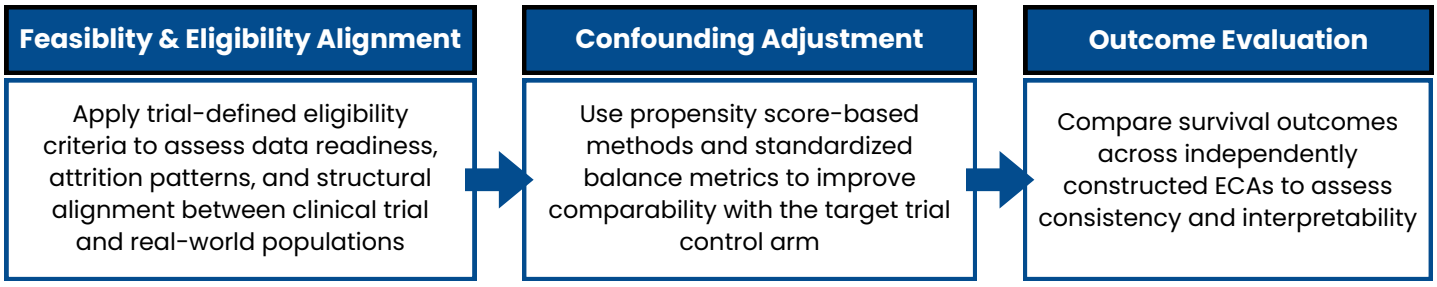
Friends of Cancer Research conducted a multi-partner pilot to evaluate whether independently constructed ECAs can approximate a common target trial control arm (i.e., the control arm of the RESOLVE study in metastatic pancreatic ductal adenocarcinoma) under a shared statistical analysis plan (SAP).

The pilot assessed:

- Feasibility of operationalizing trial eligibility criteria across heterogeneous external data sources
- Impact of matching and weighting strategies on baseline comparability to the target trial
- Alignment of ECA-derived survival outcomes with the target trial control arm

Findings from this pilot aim to inform best practices and define key data, methodological, and reporting considerations to support use of ECAs in regulatory and clinical contexts.

Project Approach



Project Analyses

Primary Analysis

- Compare overall survival between each ECA and the target trial control arm by estimating hazard ratios and visually comparing Kaplan–Meier survival curves

Secondary and Exploratory Analyses

- Assess baseline covariate balance pre- and post-adjustment
- Evaluate cohort attrition driven by eligibility criteria

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Key Findings

- Independent construction of ECAs across heterogeneous data sources is feasible under a common SAP with consistent overall approaches and dataset-specific implementation choices across partners.
- Trial eligibility criteria substantially shape cohort composition and highlight challenges in aligning clinical trial populations and RWD sources.
- Despite data variability, independently constructed ECAs can achieve baseline comparability to the target trial population using appropriate adjustment methods.
- Availability and balance of baseline prognostic variables within a data source are closely tied to the degree of alignment between ECAs and the target trial, particularly for overall survival, reinforcing the importance of fit-for-purpose data to mitigate residual confounding.
- Variability in outcome estimates (i.e., hazard ratios and confidence intervals) underscores the influence of methodological choices and underlying data differences.
- Credible use of ECAs requires transparent documentation of data capture, eligibility implementation, and analytic choices.

Implications & Future Directions

- The pilot advances a structured, evidence-based framework for evaluating the reproducibility and fitness-for-use of ECAs and informs alignment on methodological rigor, transparency, and reporting expectations.
- This work helps clarify the conditions under which ECAs may support regulatory and clinical decision-making, while highlighting key limitations related to variability and uncertainty.
- Future efforts will extend these analyses to additional endpoints, sensitivity analyses, and use cases to further assess the impact of ECAs on trial interpretation and regulatory conclusions.

Project Data Partners

AbbVie
American Society of Clinical Oncology (ASCO)
ConcertAI
Flatiron Health
Guardian Research Network
iOMEDICO
IQVIA
Medidata
Ontada
Pancreatic Cancer Action Network (PanCAN)
Tempus AI
Verana Health (COTA)

Thank you to our working group collaborators for their active participation and valuable contributions, which informed the development of the project and preliminary findings.