Paper RE06

The Curious Case of External Controlled Arms (ECAs): Practical Solutions for External and RWD Integration

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ABSTRACT

The use of External Control Arms (ECA) in clinical trials is increasing, particularly for rare diseases where typical Randomized Controlled Trials (RCTs) may be difficult. Recent FDA guidance emphasizes both the potential and challenges of ECAs, emphasizing data reliability, bias mitigation, adherence to CDISC SDTM and ADaM, statistical approaches such as propensity score matching, and regulatory communication. Additionally, CDISC and PHUSE have released guidance on integrating Real-World Data (RWD) into CDISC datasets.

Here, we will summarize key insights from these documents regarding the use of RWD for ECAs and showcase two case studies on integrating ECA data into CDISC-compliant datasets:

(1) constructing an ECA using natural history studies and past RCTs and

(2) leveraging publicly available RWD and RCT sources, such as the Critical‑path Alzheimer's Disease database.

We will discuss data integration, conformance challenges, and regulatory engagement, offering lessons for future rare disease studies.

INTRODUCTION

RCTs are the cornerstone of clinical evidence. Yet there are settings where recruiting a concurrent control group is infeasible, unethical, or would unduly delay access to promising therapies. In rare diseases, small populations and heterogeneous natural histories hinder adequate randomization. In life-threatening conditions, balance may be limited, and placebo exposure may raise ethical concerns. In such contexts, carefully constructed ECAs based on historical clinical studies, natural history cohorts, registries, or other RWD can supplement or, in select cases, partially replace internal controls. When rigorously designed, ECAs can improve interpretability, enable earlier decision-making, and reflect broader, more representative patient populations - potentially increasing the external validity of findings. This paper offers practical guidance for statisticians and statistical programmers tasked with translating heterogeneous external sources into review-ready evidence.

REGULATORY PERSPECTIVE AND BACKGROUND

Regulatory bodies recognize the growing role of RWD and its importance to conclusively analyze the data in assessing treatment effectiveness and safety. They require that endpoints be consistently defined, analytic strategies be prespecified, confounding and bias be mitigated, and data lineage be transparent. CDISC SDTM and ADaM compliance are essential for traceability and reproducibility. Review artifacts such as define.xml and reviewer guides must clearly document assumptions. ECAs are not considered shortcuts to regulatory approval; their credibility depends on data quality, alignment of clinical concepts, and robust analytic plans.

CONSTRUCTING ECAs FROM RWD

Figure 1: Challenges in incorporating ECAs

Developing a credible ECA requires careful harmonizing across different data dimensions such as eligibility criteria, baseline definitions and dates, and visit schedules. Endpoint definitions also need to be standardized across sources, including event logic, censoring rules, and handling of intercurrent events. In parallel, data completeness and quality should be evaluated systematically, with transparent documentation of imputation strategies and adjudication rules. Consistent use of terminology - such as aligned MedDRA versions, standardized units, and controlled dictionary terms - is essential to minimize sources of variability.

Statistical adjustment plays a central role in addressing confounding and other systematic differences between cohorts. Common approaches include propensity score matching or weighting, prognostic scores, or doubly robust estimators. The adequacy of

these adjustments must be evaluated using diagnostic tools, including standardized mean differences and assessments of covariate overlap, to confirm acceptable balance. When follow-up durations differ across data sources, additional methods, such as inverse probability weighting, landmark analyses, or time-aligned analytic frameworks, may be required. Sensitivity analyses are also critical to assess the robustness of results to alternative modeling assumptions and analytic choices.

For regulatory submission, heterogeneous data sources must be mapped to CDISC standards, with raw data transformed into SDTM domains and analysis-ready ADaM datasets derived accordingly. Throughout this process, traceability must be maintained through detailed specifications, derivation macros, and comprehensive documentation, including define.xml. Finally, reproducible programming practices, such as version-controlled code and cross-environment portability are essential to support transparency, auditability and overall submission readiness.

ILLUSTRATIVE CASE STUDIES

Case 1 required the integration of two external real-world evidence (RWE) cohorts with a randomized Phase III pivotal trial to enhance assessment of long-term treatment impact. The RWE datasets, derived from multicenter natural history studies in two regions, provided broader longitudinal follow-up and additional patient representation, helping to fill gaps in the trial's population coverage. Key baseline covariates - including functional score, genetic subtype, age, sex and age at symptom onset - were harmonized across sources and incorporated into propensity score matching to ensure comparability between treated and untreated groups.

Multiple analytical and technical challenges emerged during data integration. The RWE sources included missing, partial, and non-SDTM-formatted data, requiring careful transformation to align with ADaM and CDISC standards. Non-traditional structures led to expected Pinnacle 21 findings, such as absent DM or EX domains, consistent with regulatory expectations for certain RWE submissions. Long model runtimes, sometimes exceeding several hours per figure, added operational complexity.

Submission activities were further constrained by confidentiality protections, as one RWE dataset remained blinded, necessitating secure execution of programs on a third-party system. Close collaboration with the sponsor and rapid iteration were essential to address evolving regulatory queries and maintain documentation accuracy.

Case 2 assesses the effectiveness of hydromethylthionine mesylate (HMTM) monotherapy in Alzheimer's disease by benchmarking a pivotal Phase III randomized, double-blind trial against external controls drawn from the Critical Path for Alzheimer's Disease (CPAD) database using propensity score matching. The pivotal study applied CDISC SDTM/ADaM standards and included a long-term open-label extension. A

minimal “inactive” dose added to placebo to mimic physiological effects introduced potential residual symptomatic activity, complicating isolation of disease-modifying effects in the absence of a fully inert control arm.

CPAD provided pooled RCT data in SDTM structure. Key covariates for matching included education, genotype, baseline Mini-Mental State Examination (MMSE), and other clinically relevant factors. Access, harmonization and integration posed notable challenges: restricted, single-use data access limiting reproducibility; heterogeneity in source trials; complex variable interpretation; and alignment of inclusion/exclusion criteria requiring algorithms and manual medical review. Outcome harmonization was constrained by missingness, differing instruments/versions, and visit window disparities. An ADaM-like analysis dataset was derived, though no sponsor-level CDISC package existed.

We outline a standards-aligned, metadata-aware approach to external control construction, emphasizing transparent specification, clinical oversight, and auditability. Lessons learned highlight early endpoint mapping, rigorous covariate selection, and governance to mitigate bias and support regulatory dialogue alongside Phase III readouts.

ANALYTICAL, TECHNICAL AND SUBMISSION CHALLENGES

Figure 2: Analytical, Technical and Submission Challenges

Data harmonization poses several challenges, including reconciliation in naming conventions, variable formats, timing, and endpoint inconsistencies. RWD sources often lack direct mappings to CDISC domains, requiring careful data lineage documentation. In addition, substantial computational demands came up from resampling procedures and complex modeling, which were mitigated through algorithmic optimization and parallel processing.

Operational challenges included privacy constraints that required analyses to be conducted within secure third-party environments, thereby necessitating portable and reproductible workflows. Furthermore, accelerated regulatory review cycles underscored the need for rigorous version control and fully regenerable tables and figures. Heterogeneity across data sources introduced additional risks of bias, reinforcing the importance of prespecified alignment strategies and comprehensive documentation.

BEST PRACTICES AND KEY TAKEAWAYS

- Ensure full traceability through rigorous and transparent documentation
  - Describe key assumptions, data limitations, and transformation steps.
  - Maintain alignment between define.xml, reviewer's guide, and the analysis.
- Harmonize terminology and coding (e.g., MedDRA versions, lab units, controlled terms) across datasets and over time to support consistency and interpretability.
- Proactively plan sensitivity analyses to address variability and uncertainty in external data and report robust assessments alongside primary results.
- Anticipate regulatory review by preparing clear, evidence-based justifications for mapping decisions, inclusion/exclusion criteria, and analytical assumptions.
- Adress non-standard data formats and missing information systematically using prespecified, auditable rules rather than ad-hoc solutions introduced late in the analysis process.
- Align external data and trial data to CDISC standards early to minimize downstream rework and improve reviewability.

CONCLUSION

ECAs can meaningfully enhance the feasibility and interpretability of clinical evidence when RCTs are constrained. Achieving credible inferences requires disciplined cohort alignment, principled confounding control, and meticulous standards-based data engineering. Operational realities from privacy-preserving execution to rapid regulatory interactions further underscore the need for reproducible programming and end-to-end traceability. With transparent design and comprehensive documentation, ECAs derived from high-quality RWD can support robust decision-making and efficient regulatory review.

REFERENCE AND FURTHER READING

- External Control Arms: A Powerful Tool for Oncology and Rare Disease Research.
  - https://cytel.com/perspectives/external-control-arms-a-powerful-tool-for-oncology-and-rare-disease-research/
- The Role of External Data in Oncology Drug Development.
  - https://cytel.com/perspectives/the-role-of-external-data-in-oncology-drug-development/
- External Control Arms in Drug Development: Methodological and Regulatory Considerations
  - https://cytel.com/perspectives/external-control-arms-in-drug-development-methodological-and-regulatory-considerations/

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