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Operationalizing Real-World Data for External Control Arms: An End-to-End Framework for Rare Disease and Oncology Trials

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ABSTRACT

Randomized controlled trials (RCTs) remain the reference standard for causal inference, yet in rare diseases and precision oncology, RCTs are frequently infeasible or ethically constrained. Real-world data (RWD), from electronic health records (EHRs), registries, claims, and linked assets, can be transformed into regulatory-grade real-world evidence (RWE) to construct external control arms (ECAs) that contextualize single-arm trials and accelerate access to therapies[1,2]. This paper presents an end-to-end framework to operationalize RWD-based ECAs, spanning target-trial emulation, bias identification and mitigation, data provenance and linkage, and CDISC-aligned SDTM and ADaM programming with reviewer-oriented traceability. We introduce a trust architecture that combines semantic harmonization with clinical-grade QC. This paper highlights recurring catch-22 constraints in rare disease[3] and oncology (ethical barriers to randomization, ultra-small populations, rapidly evolving standards of care) and show how fit-for-purpose RWD/RWE mitigates these constraints under evolving FDA/EMA/PMDA expectations. Case vignettes illustrate feasibility and guardrails for regulatory use.

INTRODUCTION

In rare disease and oncology, recruitment scarcity, urgency, and ethical concerns often undermine RCT feasibility. ECAs constructed from RWD can supply the necessary comparative context to single-arm programs, provided data and methods meet regulatory expectations for fitness-for-purpose, transparency, and causal interpretability[4]. This paper presents a practical operating model spanning data source selection, harmonization, bias control, standardized programming, and reviewer-ready documentation to traverse the trust gap between traditional trials and RWD-enabled submissions.

THE CATCH-22 OF RARE DISEASE AND ONCOLOGY TRIALS

Drug developers in these indications frequently face a methodological catch-22. It is a circular constraint where a program cannot proceed without randomized evidence that is impossible to generate.

Ethical Barriers to Randomization: In life-threatening conditions where no effective standard of care (SoC) exists, withholding a promising investigational therapy is often considered unethical.

Ultra-Small Populations: Rare diseases may have populations too small to power a traditional multi-arm RCT logistically.

Rapidly Shifting Standard of Care: By the time an RCT concludes, the control arm may be obsolete due to rapid clinical evolution.

Urgency for Access: Lengthy recruitment timelines can deny patients timely access to life-saving interventions.

Mitigation via RWD: ECAs break this deadlock by synthesizing a control arm from contemporaneous or historical real-world clinical settings, providing context for overall survival or progression without requiring randomization.

COMPARATIVE EVIDENCE LANDSCAPE

Comparative evidence can be generated through several approaches.

Anchored indirect treatment comparisons (ITCs) / Network meta-analysis (NMA): Comparisons through a shared comparator across trials; rely on transitivity/consistency.

Matching-Adjusted Indirect Comparison (MAIC): Reweights patient-level data to published baseline

summaries when no shared comparator exists.

Historical controls vs. ECAs: ECAs draw on contemporaneous or near-contemporaneous RWD and deploy design/analytic safeguards to mitigate bias relative to older historical cohorts.

While anchored methods remain strong where feasible, ECAs become pivotal when randomization is infeasible, offering structured non-randomized comparators with explicit causal design, alignment, and diagnostics[5,6].

A TRUST ARCHITECTURE FOR RWD-BASED ECAS

To bridge the trust gap, we propose four mutually reinforcing pillars

1) Semantic harmonization & endpoint fidelity: Map protocol concepts onto heterogeneous RWD (e.g., LOT, ECOG, RECIST-like progression proxies) with explicit, validated algorithms.

2) Automated clinical-grade QC: Scale completeness, plausibility, and longitudinal continuity checks with audit trails linked to source refresh cycles.

3) Principled causal inference via target-trial emulation: Make explicit the hypothetical RCT (eligibility, time-zero, endpoints, follow-up, contrast), then emulate it in RWD to reduce design-induced biases (immortal time, selection, temporal drift).

4) CDISC-aligned statistical programming & traceability: SDTM where feasible; otherwise a justified direct-to-ADaM approach with exemplary ADRG/cSDRG traceability and reviewer aids.

DESIGNING AN ECA WITH TARGET-TRIAL EMULATION

Target-trial emulation clarifies key design elements. These include time-zero with synchronized indexing, eligibility alignment, treatment strategies, endpoints and censoring, and confounders or effect modifiers. Confounding control typically uses propensity score matching, stratification, inverse probability of treatment weighting (IPTW), and doubly robust estimators[7,8]. Diagnostics should include standardized mean differences (SMDs), overlap plots, and effective sample size (ESS) under weighting.

5.1 Biases to Anticipate and Address

• Measured confounding → prespecify covariates; matching/IPTW; report balance and ESS.

• Unmeasured confounding → enrich data via linkage; quantitative bias analysis (QBA), negative controls.

• Selection bias → mirror trial I/E, ascertainment windows; attrition diagrams; IPCW.

• Temporal bias → favor contemporaneous cohorts; stratify by calendar time.

• Immortal time bias → define synchronized index; avoid exposure definitions that guarantee survival time.

• Exposure/outcome misclassification → validate algorithms; prioritize high specificity for RR; conduct QBA.

• Missing data/informative censoring → MAR/MNAR strategies, pattern-mixture/selection models; tipping-point analyses.

• Positivity (overlap) → restrict to common support; weight truncation; report ESS.

• Specification dependence → prespecify model families; multiverse analyses.

DATA SOURCES, PROVENANCE, AND LINKAGE

Robust ECAs begin with fit-for-purpose data. This includes sufficiently granular exposures, outcomes, covariates, and follow-up. It also requires well-documented lineage such as extraction windows and refresh cycles, plus privacy-preserving linkages across EHR, claims, registries, and labs to maximize completeness. Programs should quantify linkage quality using overlap, discordance, and error rates.

They should also document deduplication and adjudication strategies so reviewers can replicate cohort formation and endpoint derivation.

PROGRAMMING & STANDARDS: SDTM, ADAM, AND REVIEWER TRACEABILITY

Real-world data rarely conforms to clinical trial structures. Practical implications include harmonizing local lab units and terminologies such as LOINC, inferring exposure from medication and procedure signals, and preserving provenance. When SDTM mapping would require heavy inference or reduce analytic line of sight, a direct-to-ADaM approach can be justified. This should be paired with an exceptionally robust ADRG and early regulatory alignment. Reviewer packages should include cSDRG and ADRG, data-flow diagrams, cohort attrition summaries, balance and overlap diagnostics, and prespecified sensitivity analyses.

7.1 SAS Macro Sketches for Direct-to-ADaM (Appendix)

Example A — Algorithmic Line-of-Therapy (LOT) Derivation from Pharmacy Claims

```
/* %Derive_LOT: Infer treatment episodes from RWD pharmacy fills */
%macro Derive_LOT(indata=, outdata=, subject_id=, fill_date=, days_sup=, max_gap=28);
  proc sort data=&indata; by &subject_id &fill_date; run;

  data &outdata;
    set &indata; by &subject_id;
    retain LOT_Number Rx_End_Date; format Rx_End_Date yymmdd10.;
    if first.&subject_id then do;
      LOT_Number = 1; Rx_End_Date = &fill_date + &days_sup;
    end;
    else do;
      Gap_Days = &fill_date - Rx_End_Date;
      if Gap_Days > &max_gap then LOT_Number + 1;
      Rx_End_Date = max(Rx_End_Date, &fill_date) + &days_sup;
    end;
    /* map to ADaM analysis variables */
    PARAMCD="LOT"; AVAL=LOT_Number; ADT=&fill_date;
  run;
%mend;
```

Example B — Dynamic Lab Harmonization to Canonical Units

```
/* %Harmonize_Labs: Normalize local lab names/units to ADaM parameters/units */
%macro Harmonize_Labs(indata=, ref_mapping=, raw_test_var=, raw_unit_var=, raw_result_var=);
  proc sql;
    create table mapped_labs as
```

```
    select a.*,
           b.Standard_PARAMCD as PARAMCD,
           b.Standard_PARAM   as PARAM,
           b.Conversion_Factor,
           b.Standard_Unit    as AVALU
    from &indata a
    left join &ref_mapping b
      on upcase(a.&raw_test_var) = upcase(b.Local_Test_Name)
     and upcase(a.&raw_unit_var) = upcase(b.Local_Unit);
  quit;

  data final_adlb;
    set mapped_labs;
    if Conversion_Factor ne . then AVAL = &raw_result_var * Conversion_Factor;
    else AVAL = &raw_result_var;
    if missing(PARAMCD) then DTYPE = "UNMAPPED RWD";
  run;
%mend;
```

GLOBAL REGULATORY LANDSCAPE AND CASE PRECEDENTS

Health authorities are increasingly aligned on the value of real-world data (RWD). However, expectations still vary by region.

FDA (United States)[9,10]: The July 2024 EHR and claims guidance highlights the importance of data relevance, robust linkage approaches, and strong QA/QC. A major 2025 policy shift may allow de-identified datasets without identifiable patient-level data for specific submissions.

EMA (European Union)[11,12]: The 2025 Reflection Paper outlines methodological standards for non-interventional studies (NIS) and requires transparency via the HMA-EMA RWD catalogues.

PMDA (Japan)[13]: The 2025 "Points to consider" clarifies the use of RWD as external comparators for single-arm studies.

Landmark precedents that illustrate regulatory acceptance

Several approvals and label changes show how high-quality RWD can strengthen the evidence package when randomized trials are infeasible or incomplete[14].

Fosdenopterin (Nulibry) for MoCD Type A (2021): Approval relied on survival outcomes compared with a genotype-matched natural history cohort from a registry[15]. This is a strong example of when well-constructed external comparators can support substantial evidence.

Palbociclib (IBRANCE) for male breast cancer (2019 label expansion): Real-world evidence from EHR and claims data complemented existing clinical trial results in an ultra-rare subgroup where large randomized trials were not practical[16].

Tacrolimus (Prograf): Observational registry data supported confirmatory evidence generation and helped strengthen the overall benefit–risk narrative during the transition from accelerated pathways to

broader regulatory confidence.

PRACTICAL OPERATING MODEL

1. **Upfront planning:** Establish a concept-centric integration layer, implement terminology governance, and run pilot sprints to validate mappings and data flows.
2. **Standardization & QC:** Define canonical laboratory units and conversions, and implement automated normalization with an auditable trail.
3. **SDTM/ADaM strategy:** Prototype TS/TV/TE early and justify any deviations. When SDTM is impractical, consider a direct-to-ADaM approach, supported by strong ADRG traceability and end-to-end lineage. Align early with regulators.
4. **Reviewer documentation:** Provide cSDRG/ADRG, data lineage, cohort attrition summaries, programming flowcharts, sensitivity analyses, and explicit causal assumptions.

DISCUSSION & FUTURE DIRECTIONS

Hybrid evidence architectures that combine small randomized cohorts with external control arms (ECAs) can strengthen the overall evidence package for regulators and HTA bodies. The field is converging on target-trial emulation as a common framework for non-randomized causal inference; teams should invest in tooling and transparent reporting aligned with evolving guidance. Persistent barriers include heterogeneity in data quality and analytic methods, as well as limited HTA acceptance[17]. These challenges can be addressed through fit-for-purpose source selection, standardized diagnostics, and quantitative bias analysis.

CONCLUSION

When operationalized within a rigorous trust architecture, fit-for-purpose data, target-trial emulation, principled bias control, and CDISC-aligned traceability enable RWD-based ECAs to ethically and efficiently mitigate the catch-22 constraints common in rare disease and oncology development. Sponsors should leverage evolving FDA/EMA/PMDA guidance and data-source catalogues to select credible sources, pre-register methods, and document assumptions, thereby accelerating access to therapies while maintaining evidentiary standards.

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DISCLAIMER

This paper is intended solely for informational purposes and should not be interpreted as professional advice or guidance. The views and opinions expressed are those of the author and do not necessarily represent the views or policies of AstraZeneca.

AI ASSISTANCE DISCLOSURE

Microsoft Copilot was used for non-substantive editorial assistance (grammar, sentence refinement, and clarity). The author reviewed and approved the final wording. All interpretations, conclusions, and any remaining errors are the author's responsibility.

APPENDIX A: Supplemental Table 1. Bias Mitigation Checklist (Design → Analysis → Sensitivity)

Bias Category	Primary Mitigation Strategy	Programming & Traceability	Sensitivity / Robustness Check
Measured Confounding	Target Trial Emulation: Align I/E and synchronize "Time Zero".	ADRG: Document PS model variables and SMDs < 0.1.	Negative Control Outcomes: Test associations where none should exist.
Immortal Time Bias	Defined Indexing: Avoid definitions requiring future survival.	Analysis Flag: Create BASE_ELIG_FL in ADaM for Index Date status.	Re indexing: Vary the index date (e.g., diagnosis vs. treatment).
Selection Bias	Mirroring: Apply exact trial I/E criteria to the RWD cohort.	Attrition Diagram: Provide step by step patient counts in the cSDRG.	Tipping Point Analysis: Assess impact of unobserved selection.

Bias Category	Primary Mitigation Strategy	Programming & Traceability	Sensitivity / Robustness Check
Unmeasured Confounding	Data Enrichment: Link EHR to claims/registries to fill gaps.	Lineage Map: Document "Source to Analysis" flow for linked variables.	QBA: Model the impact of missing confounders.
Misclassification	Validated Phenotypes: Use "Proxy" algorithms for endpoints.	Validation Metric: Report Sensitivity/Specificity of the algorithm.	Multiverse Analysis: Run model using multiple outcome definitions.
Temporal Bias	Contemporaneous Control: Prioritize RWD from the same era as the trial.	Era Stratification: Include "Calendar Year" as a covariate or strata.	Placebo Benchmarking: Compare RWD control to historical RCT arms.

APPENDIX B: Supplemental Table 2. Key Challenges in Mapping RWD to SDTM and Corresponding Mitigation Strategies

Challenge	Description	Mitigation Strategies
Lumped RWD Source	Meds, labs, and events in a single wide table.	Staged parsing workflow; rule based domain classification.
Domain Ambiguity	Inconsistent types (AE vs. MH).	Protocol aligned decision trees; pre defined exposure rules.
Missing Ref Dates	Lack of RFSTDTC or baseline windows.	Hierarchical index date derivation (Start > Enrollment > Diagnosis).
Terminology Gaps	ICD/SNOMED vs. CDISC CT.	Standardized mapping dictionaries (ATC to WHO DD).
P21 Failures	Required variables or CT mismatches.	Iterative validation cycles; clear traceability in the ADRG.

CONTACT INFORMATION

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