Paper RE04

Outcome Blinding in External Control Arm Construction Using RWD: Challenges and Best Practices

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- ABSTRACT

External control arms (ECAs) are increasingly used to contextualize single-arm clinical trials using real-world data (RWD). A critical methodological principle in constructing ECAs is ensuring that cohort construction decisions are blinded to outcome data. Unlike prospective trials, where outcomes are naturally unknown at enrollment, RWD sources often contain both baseline characteristics and downstream outcomes at the time of extraction. The inappropriate use of outcome information during cohort selection or index-date assignment can introduce bias and undermine the credibility of comparative effectiveness estimates.

This paper discusses practical approaches to maintain outcome blinding in ECA studies, with a focus on cohort construction. Key considerations include staged programming workflows and controlled access to outcome data until the analysis-ready cohort is finalized. Emphasis is placed on clear documentation of assumptions and reproducible processes to ensure transparency. By adhering to outcome blinding principles, ECAs can achieve greater methodological robustness, align with regulatory expectations, and strengthen the use of RWD in clinical development.

- INTRODUCTION

The use of real-world data (RWD) to support regulatory and clinical decision-making has expanded rapidly in recent years. In settings where randomized controlled trials are infeasible or unethical, external control arms (ECAs) constructed from RWD have become an important approach to contextualize evidence from single-arm trials. Regulatory agencies have increasingly acknowledged the potential value of ECAs while emphasizing the need for robust, transparent, and reproducible methodology.

One of the most critical but often underappreciated challenges in ECA construction is outcome blinding. In traditional randomized trials, study design decisions are made without knowledge of future outcomes. In contrast, RWD sources such as electronic health records, claims databases, and registries often contain longitudinal patient histories in which outcomes are already observed at the time of cohort construction. Without appropriate safeguards, analysts may inadvertently use outcome information when defining cohorts, assigning index dates, performing propensity score methods, leading to biased estimates and reduced credibility.

This paper focuses on outcome blinding in the context of ECA cohort construction using RWD. We describe common challenges and risks, compare two practical implementation approaches used in our organization, and propose best practices that can be adopted to support robust and aligned with regulatory expectations of ECA studies.

- CHALLENGES OF OUTCOME BLINDING IN RWD-BASED ECA STUDIES

RWD differs fundamentally from clinical trial data in its structure, completeness, and temporal availability. These differences create several challenges for maintaining outcome blinding during ECA construction.

RWD typically captures complete longitudinal patient histories, including diagnoses, treatments, and outcomes, within a single data extract. As a result, analysts often have simultaneous access to baseline covariates and post-index outcomes. This coexistence makes it difficult to ensure that cohort-defining decisions are not influenced—consciously or unconsciously—by outcome information, particularly during feasibility assessments and data exploration.

- RISKS OF OUTCOME-INFORMED DECISIONS

Using outcome information when building a cohort can create different types of bias. For example, selection bias can occur if patients are included or excluded based on what is already known about their outcomes. Decisions that depend on outcomes—like choosing the starting point of a treatment or the order in which treatments are given—can make it hard to tell whether one factor causes another.

These biases threaten internal validity and raise concerns from regulatory and health technology assessment perspectives. FDA's draft guidance on externally controlled trials cautions that observing external control outcomes can drive data-dependent decisions and increase bias. FDA therefore recommends that key study design and analysis decisions be blinded to observed external control data (with limited feasibility exceptions). Consistent with this principle, outcome blinding/masking during ECA construction helps ensure cohort definitions and propensity score–based balancing specifications (e.g., IPTW or matching) are finalized without being influenced by observed outcome patterns.[i]

- ❖ What is IPTW and Matching Method?
  Inverse probability of treatment weighting (IPTW) and matching are commonly used propensity score–based methods to reduce confounding when comparing treatment groups in observational data. The propensity score summarizes each patient's probability of receiving the treatment given observed baseline covariates. In matching, treated patients are paired with control patients with similar propensity scores, creating a matched cohort in which baseline characteristics are more comparable across groups. In IPTW, each patient is weighted by the inverse of the probability of receiving the treatment they received, generating a pseudo-population in which the distribution of measured baseline covariates is balanced between groups.

By improving covariate balance, both approaches help mitigate selection bias and confounding due to measured variables, thereby supporting a less biased estimation of treatment effects.

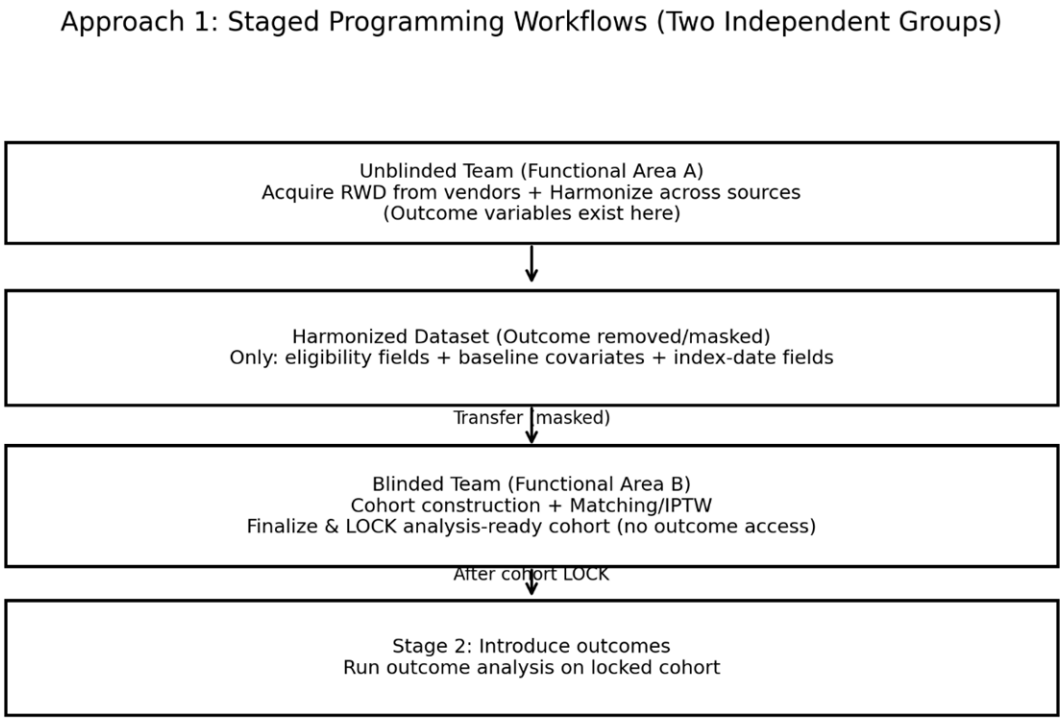
- BEST PRACTICES FOR MAINTAINING OUTCOME BLINDING

Several practical approaches can be implemented to preserve outcome blinding during ECA construction. Within our organization, two approaches have been implemented to prevent outcome-informed cohort construction bias.

1) STAGED PROGRAMMING WORKFLOWS

A staged programming approach separates cohort construction into discrete phases. In this approach, two independent groups from different functional areas are involved. An unblinded team is responsible for acquiring RWD from data vendors and harmonizing data across multiple sources. Once data harmonization is complete and qualified subjects are identified, only data elements required for eligibility criteria and baseline covariates are made available to a separate blinded team responsible for cohort construction. Outcome variables are explicitly excluded or masked at this stage.

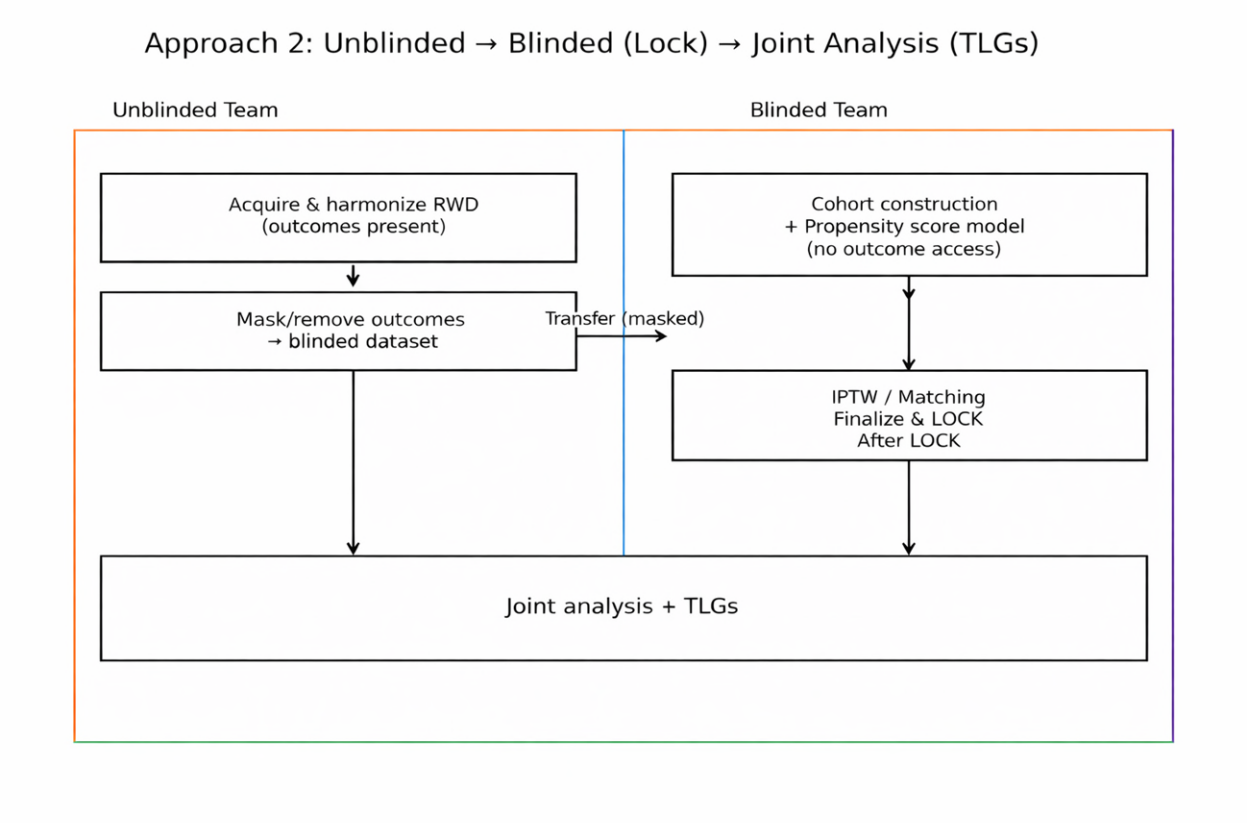
After the analysis-ready cohort is finalized and locked—such as when inverse probability of treatment weighting (IPTW) or matching datasets are created—a second stage introduces outcome data for analysis. This separation ensures that cohort definitions are finalized without knowledge of outcome distributions and closely mirrors the prospective nature of clinical trial conduct.



2) CONTROLLED ACCESS TO OUTCOME DATA WITHIN A SINGLE TEAM STRUCTURE

An alternative approach consolidates responsibilities within a single functional group while maintaining internal outcome blinding. In this model, team members, including statisticians and programmers, are divided into unblinded and blinded sub-teams.

The unblinded sub-team performs data acquisition and harmonization. Following harmonization, outcome variables and outcome-related fields are removed or masked from the datasets. These masked datasets are then transferred to a restricted-access environment for use by the blinded sub-team. The blinded team retains no access to outcome data until the analysis-ready cohort is constructed and finalized. Role-based access controls, data masking, and separate analytic environments are used to enforce this separation.



- COMPARISON OF THE TWO APPROACHES

Based on our experience, the single-team approach with controlled access to outcome data has proven more efficient and better suited to our current real-world evidence studies.

First, under the staged programming model, the blinded team cannot access baseline or inclusion/exclusion variables until the unblinded team completes full data processing and validation. In contrast, the controlled-access model allows partially harmonized (draft) baseline datasets to be shared with the blinded team in a timely manner. This enables early development and testing of cohort construction logic, including IPTW and matching datasets, and facilitates rapid feedback to the unblinded team while outcome-related processing continues in parallel.

Second, the controlled-access model provides greater flexibility in managing data quality and availability. During early planning stages, the unblinded team can assess data completeness from regular data transfers and identify gaps in critical variables. This enables targeted requests for customized data elements from vendors, which can substantially reduce missingness in key variables required for ECA construction.

Third, this approach allows more efficient resource utilization. Team members can alternate roles across multiple studies—for example, serving as unblinded team members on one study while acting as blinded team members on another. This flexibility reduces idle time and overall resource requirements. In contrast, the staged programming approach may create inefficiencies when one team must wait for another to complete data preparation.

- DOCUMENTATION AND TRANSPARENCY

Comprehensive documentation underpins all outcome blinding efforts. Study protocols and analysis plans should clearly pre-specify cohort definitions, inclusion/exclusion criteria, prognostic factors, index-date rules, and analytic methods. Any assumptions or deviations should be documented and justified.

Maintaining detailed programming specifications, decision logs, and data flow diagrams enhances transparency and facilitates regulatory review. Reproducible code, version control, and traceable outputs further strengthen confidence in the methodology.

- REGULATORY CONSIDERATIONS

Regulatory agencies have emphasized the importance of transparency, pre-specification, and bias mitigation in RWD-based studies. Outcome blinding aligns closely with these expectations by reinforcing trial emulation principles and reducing the potential for data-driven decisions.

Demonstrating robust outcome blinding practices can improve the acceptability of ECAs in regulatory submissions, particularly when ECAs are used to support efficacy or safety claims. Clear articulation of these practices in study protocols, analysis plans, and final reports is therefore essential.

- CONCLUSION

Outcome blinding is a foundational methodological principle in the construction of external control arms using real-world data. Given the inherent availability of outcomes in RWD sources, proactive safeguards are required to prevent bias and preserve credibility. Staged programming workflows, controlled access to outcome data, and thorough documentation collectively provide a practical framework for maintaining outcome blinding.

By adopting these best practices, study teams can enhance the methodological rigor of ECAs, align more closely with regulatory expectations, and strengthen confidence in RWD-based evidence to support clinical development and decision-making.

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[i] U.S. Food and Drug Administration. *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products: Guidance for Industry (Draft Guidance).* FDA; 2023. Available from: https://www.fda.gov/media/164960/download