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DEFINITION OF TIME-ZERO FOR TIME-TO-EVENT DATA IN EXTERNAL ARM STUDIES

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Workshop on the Use of External Controls for Evidence Generation in Regulatory Decision-Making
European Medicines Agency

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OBJECTIVES

Define time zero (T0) to emulate a target trial using external control arms (ECAs)

Identify and illustrate time-related biases (immortal time, time-lag, calendar time)

Apply design/analytic strategies

Plan diagnostics and sensitivity analyses to stress-test T0 choices

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What is Time-Zero?

- T0 = The index date when follow-up begins and individuals first become at risk for the outcome of interest
- In trials: randomization = T0
- In ECAs, T0 needs emulate the decision point that would have triggered randomization in the target trial

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Why It Matters

- The correct time zero in the ECA ensures comparability with the trial arm
- Determines risk sets
- Shapes observed outcomes
- The choice of T0 determines which patients enter the risk set and, therefore, what causal question the study actually answers
- Misaligned T0 → wrong risk sets → bias effect estimates (often overstated benefit)
- Correct T0 → comparability, exchangeability, valid estimand

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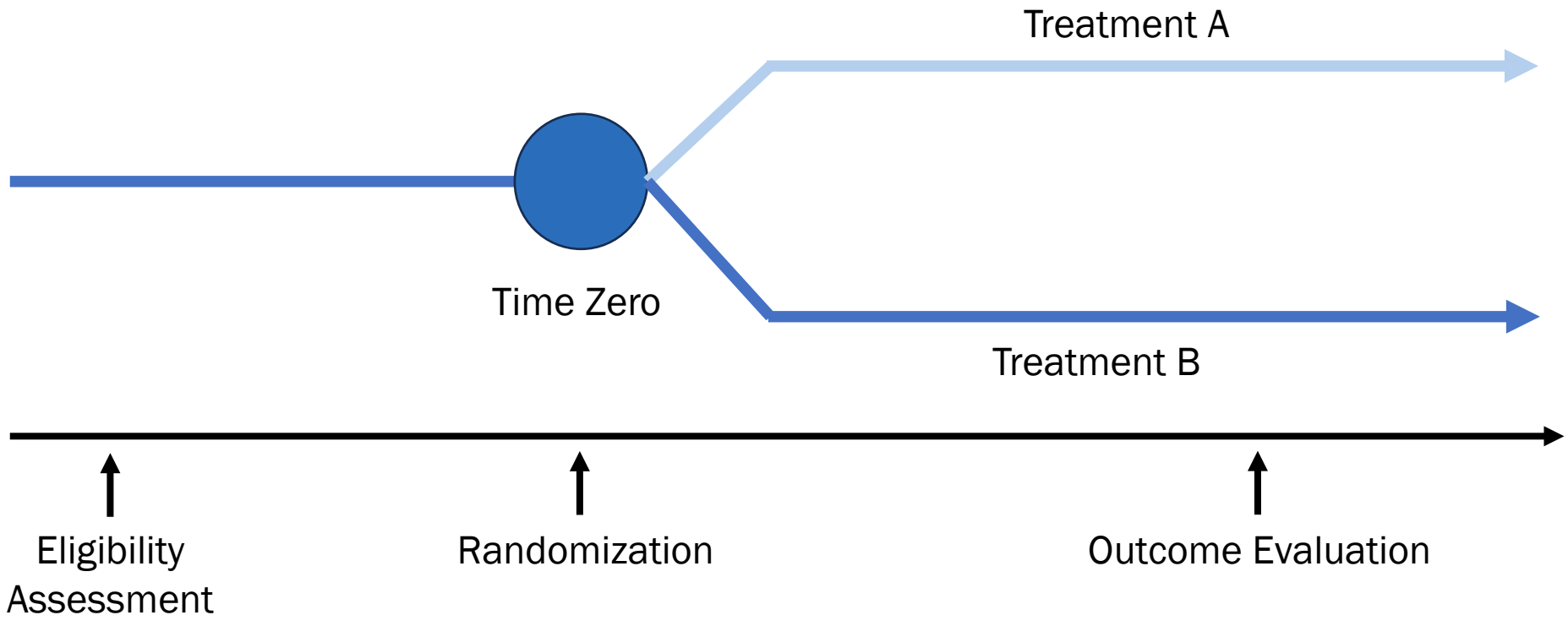
Trial vs. ECAs: Where T0 Comes From

Trial: T0 is fixed by randomization



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Trial vs. ECAs: Where T0 Comes From

Real-world data: multiple potential anchors for the ECA arm…

In ECAs, the anchor point must correspond to the hypothetical randomization time of the target trial

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Common Time-Zero Choices in ECAs

Option	Strength	Risk/Limitation
Treatment initiation	Clear anchor, avoids immortal time bias	Requires precise start dates
Diagnosis date	Captures broad population	May introduce immortal bias if pre-treatment time is included
First "eligibility" date	Earliest time when patients are eligible in dataset	May not match characteristics of patients in trial arm
Multiple eligibility points	Captures real-world sequencing of treatment where patients can become eligible at several lines of treatment	Risk of inconsistent alignment with trial arm across treatment lines

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Sources of Misalignment

- Trials: strict eligibility, fixed enrollment point
- Observational studies: varied patient journeys
- Misalignment leads to time-related biases that cannot be corrected post-hoc without explicitly redefining T0

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Illustrative Example: Blinatumomab in relapsed/refractory ALL

- Single-arm trial comparing 189 patients with relapsed or refractory acute lymphoblastic leukemia (R/R ALL) treated with blinatumomab [1]

- These patients were compared with 1112 external historical control patients

- HR: 0.54, 95% CI: 0.39-0.73 for all-cause mortality, adjusted by inverse probability weighting

[1] Gökbuget N, Kelsh M, Chia V, et al. Blinatumomab vs historical standard therapy of adult relapsed/refractory acute lymphoblastic leukemia. Blood Cancer J. 2016;6:e473.

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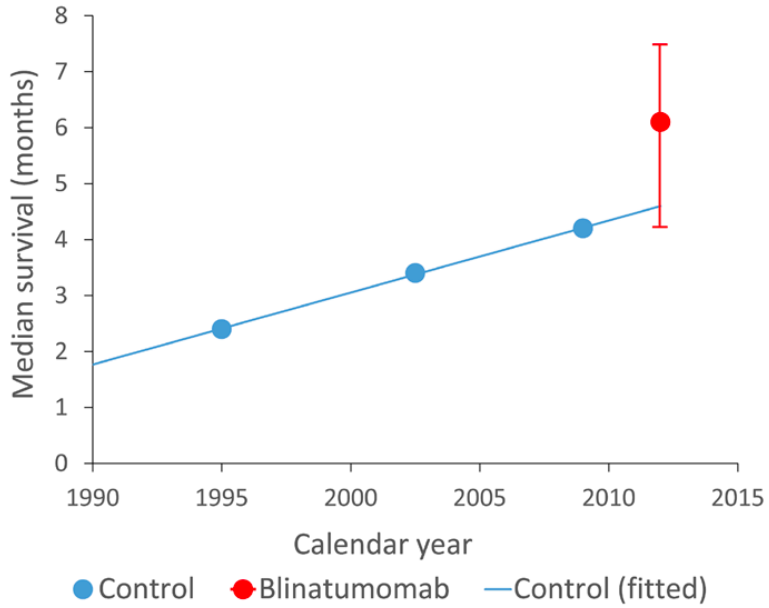
Two Time-Related Sources of Bias

1. Calendar time (non-concurrency)

   - Controls diagnosed from 1990 to 2013 versus blinatumomab from 2010 to 2014
   - Median survival in controls improved over time (≈2.4 → 4.2 months; projected ≈4.5 months in 2010–2014)
   - Failing to account for calendar time would make blinatumomab appear more effective than it truly is



Median survival in control patients improved steadily over time. If controls had been concurrent, the estimated HR would have been closer to 0.80

Suissa S. Single-arm Trials with Historical Controls: Study Designs to Avoid Time-related Biases. Epidemiology. 2021;32(1):94–100

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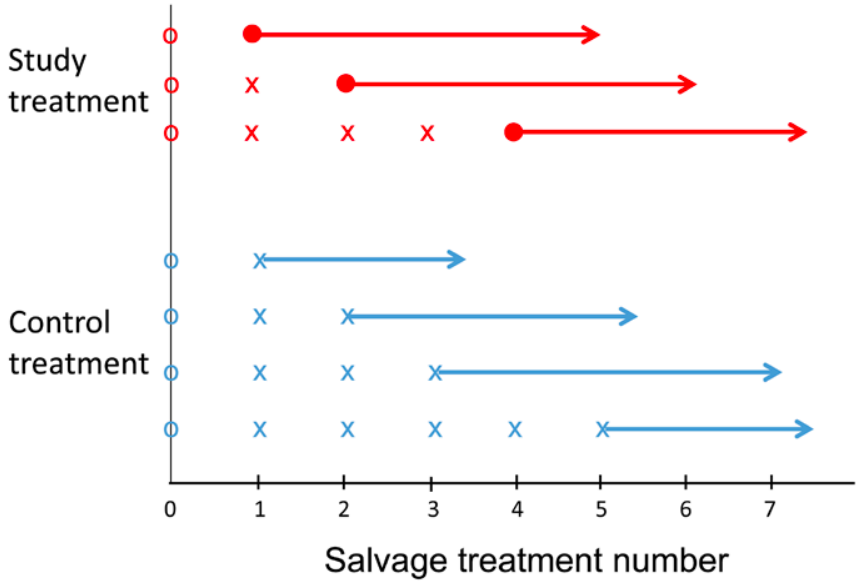
Two Time-Related Sources of Bias

2. Cohort entry timing (the choice of “time zero”)

- Defining cohort entry at the latest available salvage line ‘looks into the future’
- Patients must survive until that line to be included, a time closest to death, introducing selection bias
- Result: potential exaggeration of mortality in ECA arm



The three blinatumomab-treated patients (in red) and four control patients (in blue), by number of salvage treatments (x), with all four control patients entering the cohort at their latest salvage treatment. Solid arrow represents follow-up.

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Defining Time Zero and Time-to-Event Components for ECAs

Design Element	Specification / Purpose
Goal	Emulate the *target trial*[1] that would randomize patients at a defined disease stage or line of therapy
Eligibility	Identify patients eligible for treatment at line *k* (e.g., first relapse, third-line therapy), ensuring required pre-T_0 observation and washout
Time-Zero (T0)	Define as the start of line *k* treatment and corresponding to randomization in the target trial, so risk time begins consistently
Treatment Strategies	Compare trial therapy vs. standard of care at line k; specify treatment assignment rule and any grace period for initiation
Outcome & Time Origin	Time-to-event endpoint (e.g., overall or progression-free survival) measured from T0 until event or censoring
Follow-Up & Censoring	Follow-up starts at T0 and ends at event, next-line therapy, loss to follow-up, or cutoff; describe censoring and adjust via IPCW if informative
Estimand	Define target causal contrast (e.g., marginal hazard ratio or RMST difference from T_0) per ICH E9 (R1).
Analysis	Use time-conditional PS matching or weighting, calendar-time adjustment, competing-risk methods, and overlap diagnostics
Sensitivity Analyses	Test robustness to T0 definition (± grace period), concurrent-year restriction, censoring assumptions, and negative-control outcomes

[1] Hernán MA, Robins JM. *Causal Inference: What If.* Boca Raton: Chapman & Hall/CRC; 2020.

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Design & Analytic Approaches that Respect Time Zero

- Matched exposure-set design (prevalent new-user design)
  - For each treated patient at *line k*, match to ECA patients at line *k* using time-conditional propensity scores (covariates measured before or at line *k*)

- Full-cohort exposure-set analysis
  - Use all ECA patients at each *line k* with time-varying covariates or time-conditional PS (weights or adjustment)

- These approaches rely on information available up to T0, mirroring what would be known at randomization

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Diagnostics & Sensitivity Analyses

- **Covariate balance:** standardized mean differences ≤0.1 after match/weighting
- **Positivity (overlap):** verify overlap in propensity score distributions within each *line k*
- **Calendar time:** include year as a covariate; assess period-specific effects
- **Censoring diagnostics:** assess IPCW performance for transition to next line
- **Sensitivity:** vary T0 definitions (latest-line vs matched-line), restrict to concurrent years, alter grace periods, and test negative control outcome

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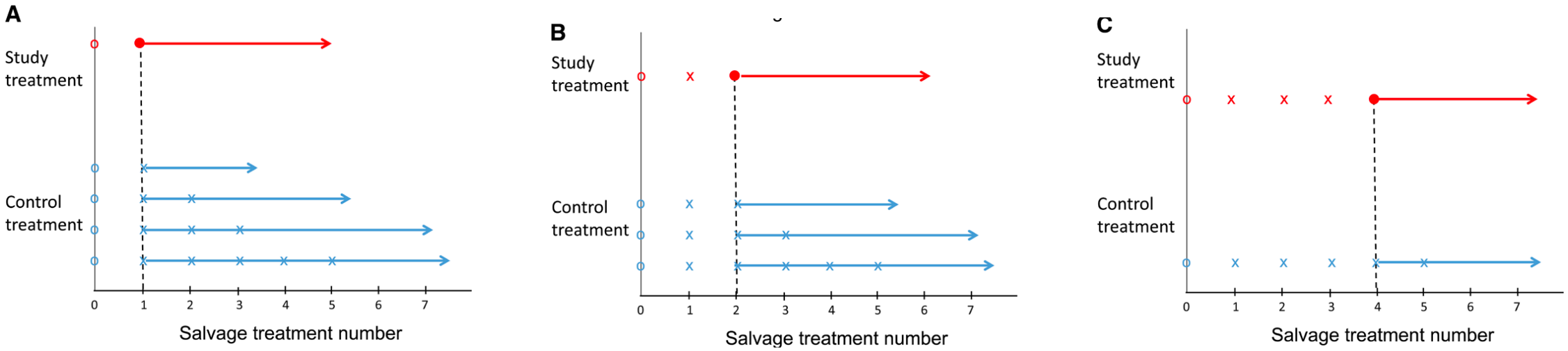
Prevalent New-User Design To Match Trial And ECA Patients



- Each treated patient at *line k* is matched to controls entering at the same *line k*; follow-up starts at T0=start of *line k*
- This approach ensures both groups are followed from a comparable disease stage and exposure point, preventing immortal-time bias

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Effect of Time-Zero Choice on Estimated Treatment Effect

Approach	Cohort Entry (T0) Definition	Adjusted HR	Interpretation
Latest-line comparator (biased)	ECA enters at last observed salvage line	0.56 (0.47–0.67)	Inflated benefit
Matched exposure-set (1:1)	ECA enters at matched salvage line k	1.04 (0.84–1.28)	Aligned
Full-cohort exposure-set	ECA enters at matched salvage line k	0.98 (0.83–1.15)	Aligned

Adapted from Suissa S. Single-arm Trials with Historical Controls: Study Designs to Avoid Time-related Biases. Epidemiology. 2021;32(1):94–100.

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Key Takeaway

- Time-zero is a design parameter
- Its correct specification is essential for causal validity
- Misspecification directly leads to biased treatment effect estimates

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References

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Hernán MA, Robins JM. *Causal Inference: What If.* Boca Raton: Chapman & Hall/CRC, 2020.

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Thank You!

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