A Causal Multistate Framework for Treatment Switching in Network Meta-Analyses of Time-to-Event Outcomes in Oncology

PT8

Shomoita Alam,[1] Nathaniel Dyrkton,[1] Jay JH Park[1,2]

[1]*Core Clinical Sciences Inc., Vancouver, Canada*
[2]*Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada*

Contact Information:
shomoita@coreclinicalsciences.com

core clinical sciences

Background and Objectives

- Treatment switching is common in oncology. Control arm patients cross to active therapy at progression. This inflates the observed control arm survival, compressing the apparent treatment benefit of the active drug.
- When switching rates differ across trials, this inflation is differential across the common comparator arm. Standard indirect NMA comparisons inherit this differential contamination, potentially biasing or even reversing treatment rankings.
- Empirical review confirmed, while the *Treatment Policy* estimand retains switching effects, the *Hypothetical* estimand, i.e., the effect had no switching occurred, is not directly observable and rarely reported.
- **Objective:** To develop and validate a parametric multi-state g-computation framework that recovers unbiased Hypothetical estimands across a star-shaped NMA network with individual patient data (IPD) and aggregate data (AgD).

Methods

- We fit a four-state semi-Markov illness-death model with parametric Weibull transitions to each trial. Switching is modeled as an explicit state transition, distinguishing control arm crossover patients from those randomized to active treatment.

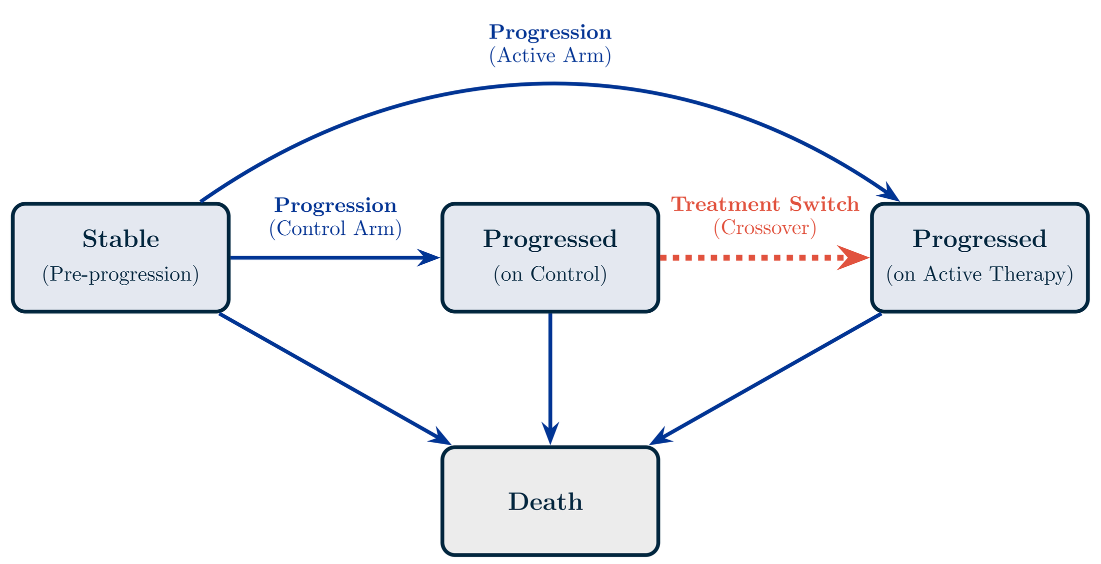

Figure 1: Four-state illness-death model with treatment switching.

- The hypothetical estimand is recovered by disabling the switching transition in the fitted model and applying parametric g-computation.
- A joint likelihood is optimized across all trials simultaneously. IPD trials contribute exact per-patient transition likelihoods. AgD trials, including those where patient-level data are reconstructed from digitized Kaplan-Meier curves, contribute a marginalized likelihood integrating over the published covariate prevalence. Shared control arm parameters are informed by all trials in the network.
- Indirect estimates are derived by differencing the hypothetical restricted mean survival time (RMST) contrasts from each direct trial. Confidence intervals are obtained via the delta method.

Simulation Design

We evaluated the method in a star-shaped network with a common control arm (A) connected to two active treatments through separate trials.

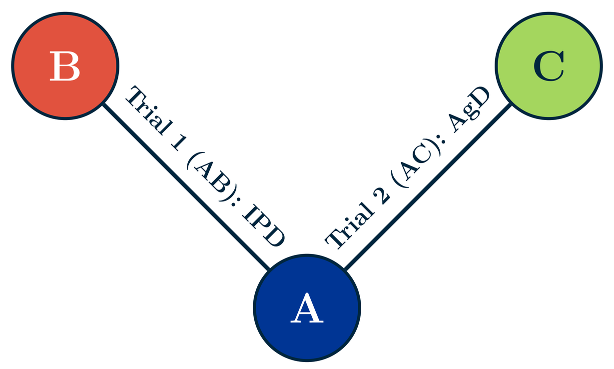

Figure 2: Network geometry of simulated trials. The shared node (Treatment A) enables the indirect comparison of B vs. C.

- **Trial AB:** Drug B vs Control (IPD), ∼50% switching in control arm.
- **Trial AC:** Drug C vs Control (Aggregate data), ∼75% switching in control arm.
- **True effects:** Drug C superior to Drug B. It is obscured by differential switching under the policy estimand.
- **Design:** *N* = 400 per trial (200 per arm); binary effect-modifying covariate with asymmetric prevalence (40% vs 60%) across trials.
- **Performance:** 500 Monte Carlo replicates; bias, RMSE, and 95% CI coverage evaluated against a Monte Carlo approximation of the truth (*N* = 10^6 draws).

Results

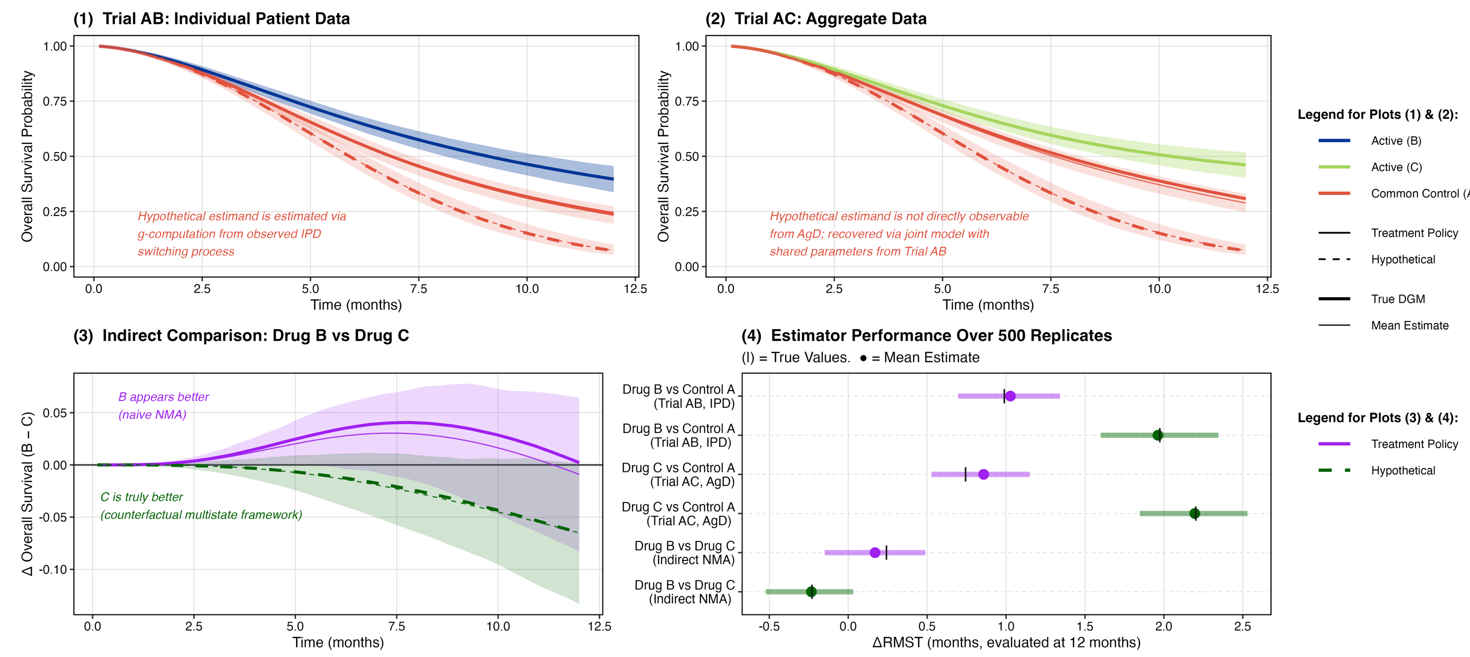

Figure 3: Simulation study results. (1) Trial AB (IPD), (2) Trial AC (AgD), (3) Indirect B vs C comparison, (4) Estimator performance.

Contrast	Estimand	Bias (months)	Coverage
Drug B vs Common Control A	Treatment Policy	+0.036	94.6%
	Hypothetical	−0.014	92.4%
Drug C vs Common Control A	Treatment Policy	+0.112	93.8%
	Hypothetical	−0.008	95.5%
Drug B vs Drug C	Treatment Policy	−0.076	95.5%
	Hypothetical	**−0.006**	**96.4%**

Table 1: Estimator performance across estimands. Bias is measured in months as the difference between the estimated and the true △RMST evaluated at 1 year. The highlighted row represents the primary indirect causal contrast of interest.

- Switching masks the true treatment benefit: Drug B's advantage over control appears to be only +1 month (policy) when it is truly +2 months (hypothetical). For Drug C, the distortion is greater; a true advantage of +2.2 months is compressed to just +0.7 months (23 days) by heavier switching.
- Standard NMA concludes Drug B is superior to Drug C by approximately 7 days (policy △RMST = +0.24 months). The counterfactual multi-state framework reverses this. Drug C is truly superior by 7 days (hypothetical △RMST = -0.23 months).
- All hypothetical estimands recovered with near-zero bias and delta method coverage between 92–96% across 500 replicates.

Conclusions

- Differential switching across trials biases indirect NMA comparisons. In this example, it is reversing the treatment ranking entirely, with direct implications for HTA decisions.
- The proposed method recovers the hypothetical estimand with near-zero bias across all direct and indirect contrasts, using only aggregate covariate data where IPD is unavailable.

Limitations & Future Work

Results hold under correct Weibull specification; misspecification scenarios, bootstrap inference, and formal identifiability conditions are under investigation.

References

1. Campbell et al., *RSM*, 2025 (10.1017/rsm.2025.21); **2.** Jansen et al., *Stat Med*, 2023 (10.1002/sim.9810); **3.** Phillippo et al., *arXiv*, 2024 (2401.12640); **4.** Young et al., *Stat Med*, 2020 (10.1002/sim.8471); **5.** Latimer et al., *SMMR*, 2019 (10.1177/0962280220912524); **6.** Metcalfe et al., *RSM*, 2026 (10.1017/rsm.2026.10076).