Simulated Treatment Comparisons Using Jackknife Pseudo Values for Population-Adjusted Marginal Effect Estimation

[MSR186]

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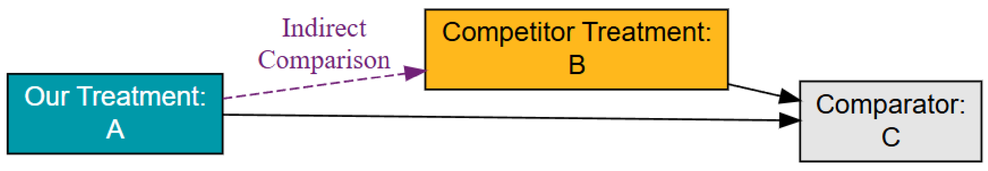
Why did we perform this research?

Setting:

An anchored cross-trial ITC, with IPD available for our trial of treatment A vs C but only aggregate data available for a competitor's trial of treatment B vs C.



Rationale:

Existing population adjustment methods have limitations.

- MAIC: Targets marginal effects but can be inefficient or infeasible when covariate overlap is limited.
- STC (conventional): Applicable under poor overlap but targets conditional effects, which for non-linear outcome models differ from marginal effects due to non-collapsibility.
- Recent STC extensions: Target marginal effects but require the full joint covariate distribution and/or simulation of patient-level data, adding computational complexity.

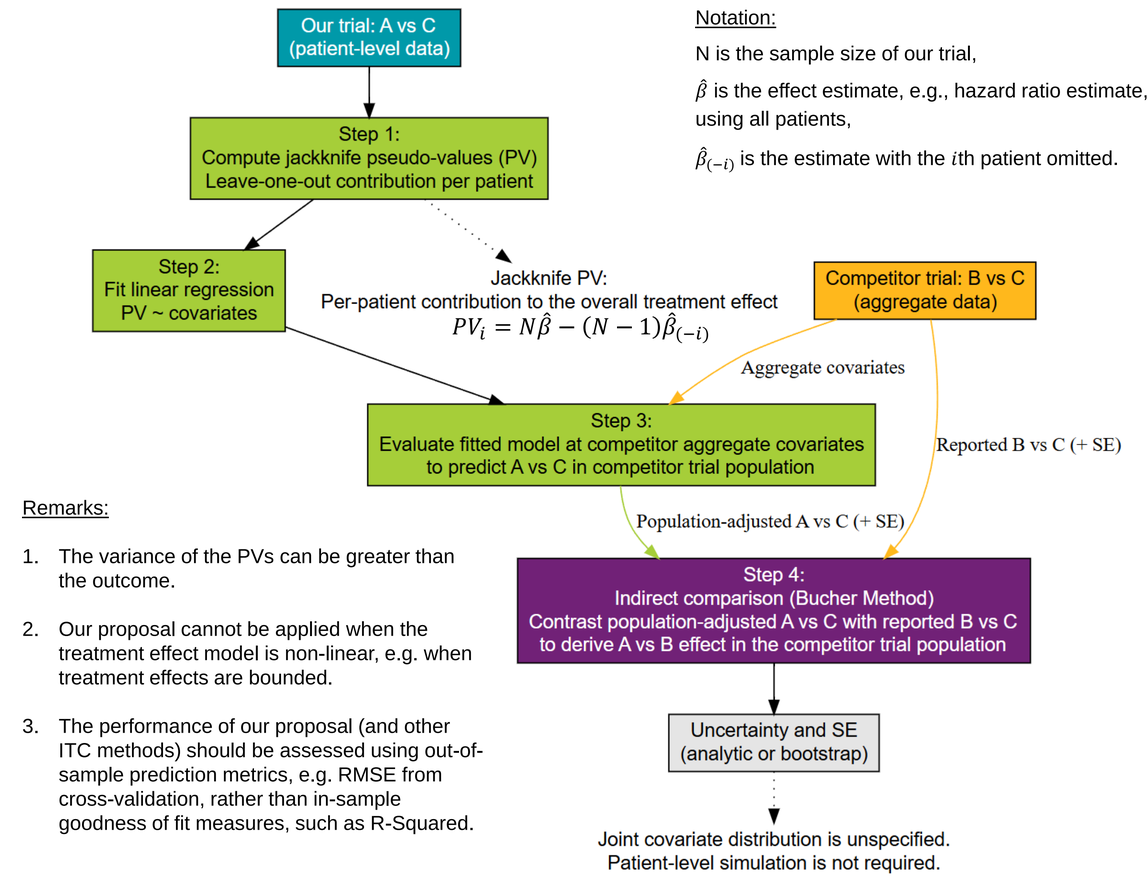
Aim:

Develop a practical ITC method to estimate marginal treatment effects for non-linear outcome models without specifying the full joint covariate distribution.

How did we perform this research?

Proposed approach:

Applicable when the treatment effect model is linear on the predictor scale (commonly assumed for log OR and log HR in meta-regression). Our proposal is to apply STC to jackknife pseudo values of the marginal treatment effect on that scale.



Notation:

N is the sample size of our trial,

$\hat{\beta}$ is the effect estimate, e.g., hazard ratio estimate, using all patients,

$\hat{\beta}_{(-i)}$ is the estimate with the ith patient omitted.

Remarks:

1. The variance of the PVs can be greater than the outcome.
2. Our proposal cannot be applied when the treatment effect model is non-linear, e.g. when treatment effects are bounded.
3. The performance of our proposal (and other ITC methods) should be assessed using out-of-sample prediction metrics, e.g. RMSE from cross-validation, rather than in-sample goodness of fit measures, such as R-Squared.

Performance was contrasted with standard MAIC and STC approaches in simulation settings with continuous, binary and time-to-event outcomes.

What did we find?

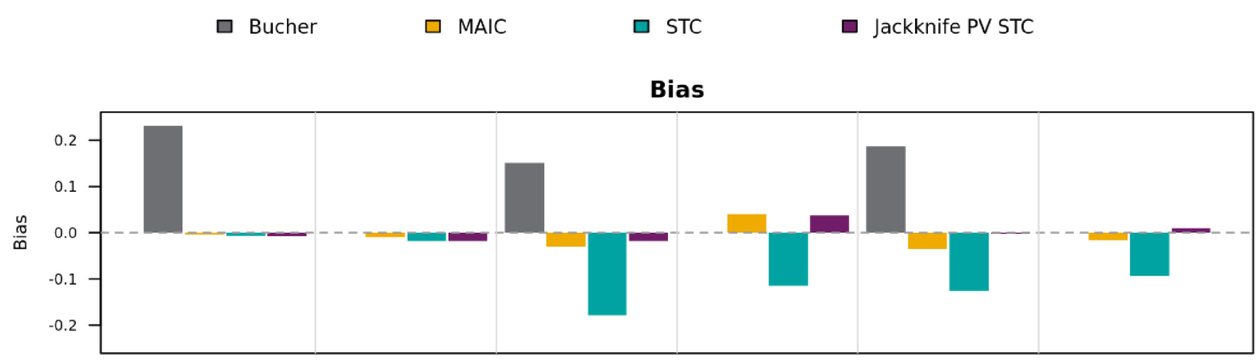
Simulation setup

- Two anchored RCTs (A vs C; B vs C); 500 patients per trial.
- Covariates (cross-trial imbalance):
  - Our trial (A vs C):

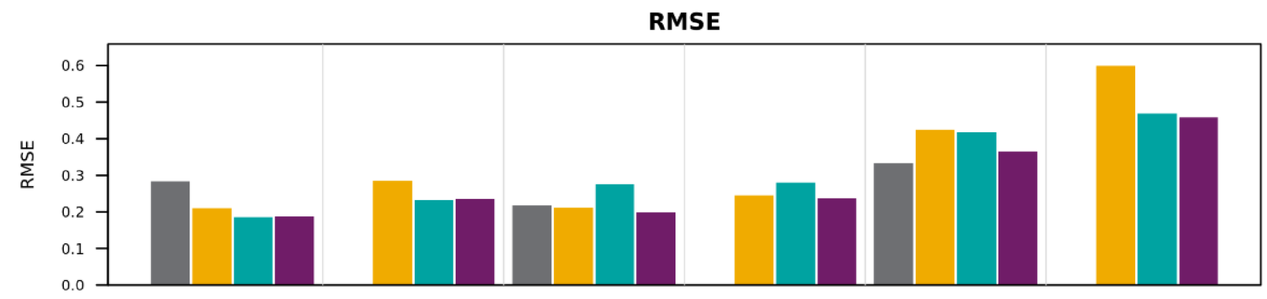
    $X_1 \sim N(0,1)$; $X_2 \sim N(1,1)$; $X_3 \sim$ Bernoulli(0.5)
  - Competitor (B vs C):

    $X_1 \sim N(1,1)$; $X_2 \sim N(2,1)$; $X_3 \sim$ Bernoulli(0.7)
- Outcomes:
  - Continuous: normal distribution with linear mean model
  - Binary: logistic mean model
  - Time-to-event: exponential distribution with log-linear hazard model; right-censored at 1.5 years
- Effect size of A vs B in competitor trial population:
  - Linear settings: MD -0.855 (continuous), log HR -0.659 (time to event), log OR -0.6724 (binary)
- Simulations: 1,000 per outcome scenario.
- Robustness to model misspecification with population adjustment on:
  - Untransformed effect modifiers: X_1 and X_3
  - Transformed effect modifiers (X_1 . X_2), and (X_1 + 2 X_3)

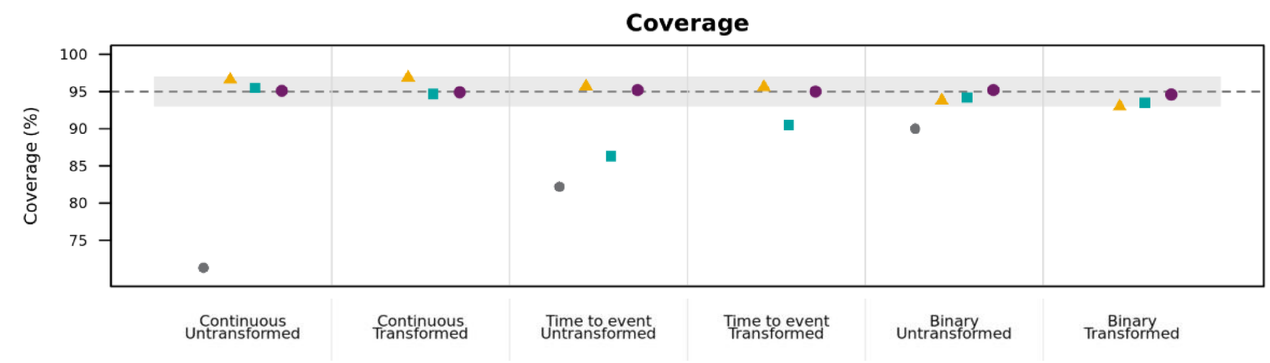
Findings were similar at n=200 (results not shown).



Bias: Jackknife PV STC reduced bias vs conventional STC for non-linear outcome models by targeting marginal effects (addressing non-collapsibility). It showed the least bias under model misspecification.



Accuracy: RMSE for Jackknife PV STC was lower or comparable to MAIC and conventional STC for binary and time-to-event outcomes, and similar to STC for continuous outcomes. The (unadjusted) Bucher method sometimes had lower RMSE but remained biased.



Coverage: Under Jackknife PV STC, the 95% CI coverage was close to nominal based on the analytical variance, with some reduction under model misspecification (e.g., transformed modifiers in binary settings).

How might this impact current clinical practice?

- Jackknife PV STC estimates marginal treatment effects without the need to specify the full joint covariate distribution or conduct complex modelling.
- The implementation is straightforward and practical, using standard regression software.
- The proposed method resulted in lower bias and improved accuracy compared with conventional MAIC and STC methods.
- Jackknife PV STC can serve as complementary to alternative population adjustment methods, strengthening confidence in comparative effectiveness evaluations.

Abbreviations

HR: Hazard ratio; **IPD**: Individual patient data; **ITC**: Indirect treatment comparison; **MAIC**: Matching Adjusted Indirect Comparison; **MD**: Mean difference; **OR**: Odds ratio; **PV**: Pseudo value; **RMSE**: Root mean squared error; **SE**: Standard error; **STC**: Simulated Treatment Comparison

References

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