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Performance of Matching Adjusted Indirect Comparisons (MAIC) for Single-Arm Trials: A Simulation Study

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OBJECTIVE

- Assess the sensitivity of MAIC for unanchored single-arm trials with time-to-event outcomes to excluding prognostic factors and effect modifiers.
- Characterize the performance of variance estimation approaches for MAIC.

CONCLUSION

- Exclusion of a single prognostic factor or effect modifier introduces substantial bias to the MAIC estimator.
  - Bias increases with magnitude of prognostic strength and effect modification.
  - Users of unanchored MAIC are advised to include all potential variables into the weighting scheme.
- Robust variance estimator is conservative, resulting in adequate confidence interval coverage.
  - Both the naïve and bootstrap estimator consistently underestimated true variance.
  - Robust (sandwich) estimator inflated standard errors across scenarios.

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METHODS

MAIC Process

- MAIC is a method for conducting population adjustment between patient-level trial data and aggregate summary data.
- Population adjustment is done via weighting, where weights are computed to balance patient characteristics of interest across trials.
- The patient characteristics that are selected have significant implications for the reliability of the resulting estimates.

Simulation Structure

- Artificial patients were generated by drawing random values across 9 patient characteristics: 4 continuous and 5 dichotomous.
- Five factors chosen as fixed-strength prognostic characteristics. Additional effect modifier and prognostic factor of varying strength were selected.

Simulation Structure

- Artificial patients randomized to individual-patient trial vs. summary trial using a propensity model to induce imbalance in patient characteristics.
- Survival outcomes were generated from a proportional hazards model with conditional treatment effect and the patient characteristics determining risk.
- We evaluated 5 different weighting schemes on each scenario:
  - MAIC including all factors
  - Including only prognostic factors
  - Excluding the prognostic factor of varying strength
  - Excluding the effect modifier
  - Excluding both the prognostic factor and effect modifier.
- We evaluated bias, mean-squared error, and the accuracy of variance estimation approaches.

BACKGROUND

Need to characterize performance

- For unanchored trials with time-to-event outcomes, MAIC is an increasingly popular method to compare treatment effects across trials.
- In the absence of comparator arms, MAIC relies on the assumption that all prognostic factors or effect modifiers are included in the matching scheme.
  - This assumption is often unrealistic, creating a need to assess how sensitive MAIC is to excluding factors.
- Including non-prognostic factors reduces precision of the estimator.
  - Need to characterize this effect and weigh the risk-benefit of including non-prognostic factors versus excluding prognostic factors.

Emphasis on the correct estimand

- Prior simulation studies for unanchored MAIC have assessed performance relative to the conditional, rather than marginal, treatment effect.
- We remedy this by fixing the marginal log hazards ratio across scenarios.
  - For each scenario, we select the conditional treatment effect which induces a log hazards ratio of –0.5.

SCENARIOS

Factor	Values
Sample Size	Moderate, high (n = 400, 800 for both trials)
Population Imbalance	Low, moderate, high (ESS Reduction: 10%, 30%, 60%)
Prognostic Factor (PF) Strength	Low, moderate, high (Log-HR: 0.25, 0.5, 1.0)
Effect Modification (EM)	None, low, moderate (Log-HR: 0, 0.25, 0.5)
Covariate Correlation	None, moderate (Continuous factors only: r = 0, 0.4)

- All possible combinations of scenarios were assessed.

Key Takeaways

Trade-Off Considerations

- Across all scenarios, we observed that the gain in precision from removing non-prognostic factors was minimal (median 2% greater efficiency).
- It is advised that users of MAIC should include all available patient characteristics in their weighting scheme.
  - Bias from inadvertently dropping a prognostic factor outweighs benefits.

Detailed Results

Summary of Bias Results

- Removing even a single factor introduces significant bias.
  - Bias ranged between 6-7% for weak factors with virtually no imbalance between trials to over 25% with strong factors and high imbalance.
- The resulting bias due to excluding an effect modifier or prognostic factor was determined by the prognostic strength.
  - Contrary to perceived notions, excluding effect modifiers was not more impactful at the same magnitude of association.
- Correlation between covariates constrains the weighting algorithm, introducing bias at high levels of imbalance.
- The bias resulting from excluding both an EM and PF was roughly the sum of excluding both individually.

Summary of Variance Results

- No variance estimator consistently yielded correct standard error estimation or confidence interval coverage.
- The robust (sandwich) variance estimator tended to overestimate standard errors (median 8% inflation), resulting in conservative confidence intervals.