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An extended simulated treatment comparison approach accounting for unobserved confounding in indirect comparisons for single-arm trials

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Background

Population-adjusted indirect comparison methods such as matching-adjusted indirect comparison (MAIC) and simulated treatment comparison (STC) are useful tools to correct trial population differences when estimating treatment effects from single-arm trials. However, unanchored MAIC and STC without a common comparator assume that all prognostic factors (PFs) and effect modifiers (EMs) are accounted for, which is largely considered impossible to meet.

Aim

To address the limitation of the current population adjustment methods where certain prognostic factors and/or effect modifiers are not reported in the comparator trial.

Methods

STC is a form of outcome regression approach, where a regression model is fitted to the individual patient-level data from the company's trial. The fitted model is then used to predict the outcomes that would have been observed in the comparator trial with only aggregate data available. We developed an extended STC (ESTC) approach which take into account of unobserved confounding in the indirect treatment comparison.

Table 1: Comparison between standard STC and ESTC: assuming individual patient-level data (IPD) for treatment A (Study A) and aggregate data (AgD) for treatment B (Study B)

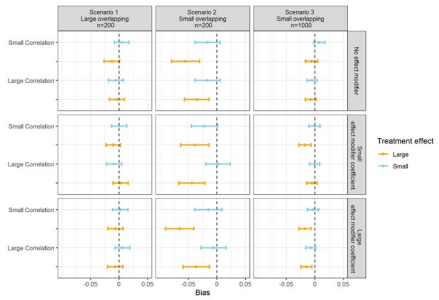
		Standard STC	Extended STC
Regression model	Covariates	Observed PFs and EMs only	Both observed and unobserved/unmeasured PFs and EMs
	Data	IPD for Study A and AgD for the Study B	IPD for Study A and AgD for the Study B; Assume AgD for unobserved/unmeasured covariates for Study B
Prediction	Continuous outcome	Plug in mean of covariates	Plug in mean of covariates
	Other types of outcome	Simulate covariates for other types of outcomes	Simulate covariates for other types of outcomes using Copula; G-estimation
Obtain treatment effect		Assume all PFs and EMs are adjusted for in the analysis	Sensitivity analysis for the impact of unobserved/unmeasured PFs and EMs

Simulation

Setting: binary outcome, two binary covariates

ESTC provides an asymptotically unbiased estimate for the treatment effect from unanchored indirect treatment comparison when the outcome is binary.

Figure 1: Simulation results



Discussion

The ESTC approach formally quantifies the bias associated with unobserved/unmeasured confounding, and provides a quantitative assessment of the impact of this bias. The ESTC approach increases the robustness of the treatment indirect comparison approach for single-arm trials.

Case study

Re-analyse the data from a randomised Phase III trial of panitumumab with infusional fluorouracil, leucovorin and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer (the PRIME study: NCT00364013).

- Obtain anonymous patient-level data for the PRIME study from the Project Data Sphere® platform
- Drop the FOLFOX4 arm and treat the data in the panitumumab with FOLFOX4 arm as a single-arm trial
- Obtain summary statistics for the FOLFOX4 arm from an external source (Cunningham et al. 2009)
- Apply ESTC method for objective response rate

Figure 2: Sensitivity analysis assuming the number of metastatic sites (U) is not reported in Cunningham et al. (2009).

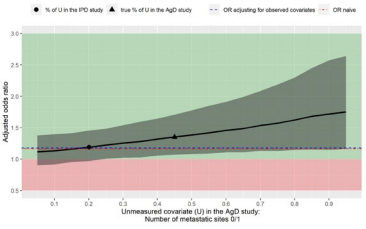
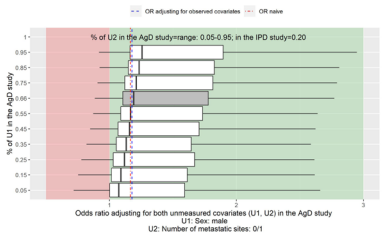


Figure 3: Sensitivity analysis assuming sex (U1) and number of metastatic sites (U2) are not reported in Cunningham et al. (2009).



The estimated odds ratios suggest that panitumumab + FOLFOX4 would always be more beneficial than FOLFOX4 alone regardless of the value for unobserved covariates.

Reference

The PRIME study: DOI: 10.1200/JCO.2009.27.4860
Cunningham et al. (2009): DOI: 10.1093/annonc/mdn638
Project Data Sphere® platform: https://www.projectdatasphere.org/

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