Collaborative Population-adjusted Indirect Comparison with Multiple Single-arm Data Sources

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Background

In biomedical studies and policy research, multiple treatments or policies are often available for the same condition. While randomized control trials (RCTs) are the gold standard for comparing treatments, head-to-head RCTs for all available treatments are often impractical. Some single-arm trials allocate treatment to all patients without a control group, especially in studies of rare diseases[1].

When head-to-head trials are lacking, indirect comparisons using data from different studies provide valuable evidence for evaluating treatment effects. Methods such as matching-adjusted indirect comparison (MAIC)[2], simulated treatment comparison (STC)[3], and multilevel network meta-regression (ML-NMR)[4] have been developed for this purpose. MAIC and STC, which use weighting and regression adjustments respectively, are popular for comparing treatments across two studies.

In the unanchored scenario involving the comparison of treatments from two treatments without a common comparator, one study provides individual patient data (IPD) for treatment A, while another study provides aggregate data (AgD) for treatment B. MAIC or STC can only be used for a population-adjusted indirect comparison of the effect of B vs. A in the AgD population. Opposite conclusions may arise if MAICs or STCs were conducted with the IPD and AgD populations switched, as the results reflect average treatment effects (ATEs) for different target populations with varying covariate distributions. This discrepancy motivates the consideration of comparing the two treatments in a combined population consisting of both the IPD and AgD populations. Furthermore, the estimation of the ATEs between two treatments in any another target population combing different data sources is of interest. Unfortunately, MAIC and STC approaches are not applicable for these objectives.

ML-NMR is a general framework to incorporate both individual and aggregate data from a connected network formed by any number of studies and treatments[4]. It allows the treatment comparison in a larger treatment network and produce estimates in any target population. However, it relies on strict assumptions on data distribution.

STC and ML-NMR leads to biased results in the case of model misspecification. For MAIC, limited number of summary statistics may cause inadequate balance, leading to a lack of accuracy in statistical inference. Recently, there are many studies propose the doubly-robust estimation in data integration and transfer learning, which combines the advantages of both weighting and regression[5,6].

Methods

In this study, we propose a novel collaborative population-adjusted indirect comparison method of estimating the ATEs of any two treatments in the combined population consisting of arbitrary number of populations for single-arm studies in the collaborative framework. It allows for flexibility in the specification of the target population, which can be the underlying population of a given data source, or

multiple data sources, or the overall population combining all data sources.

We develop doubly robust and locally efficient estimators leveraging these multiple single-arm data sources. These estimators accommodate flexible working models, and are consistent and asymptotically normal even with flexible machine learning methods for nuisance parameter estimation. To balance covariates, we use the calibration weighting (CW) approach. A procedure to implement the statistical inference in this collaborative framework is proposed, where only aggregated data from separated data sources are required to communicate. The whole procedure involves three shots and is lossless.

Results

The simulation results demonstrate that the proposed estimators have very small bias if either the set of outcome models or the set of propensity score models is correct. However, if both sets of working models are incorrect, the estimators may be biased. The coverage probability approximates the nominal level of 0.95 as long as either set of working models is correct. These findings confirm the robustness of our proposed estimators compared to calibration weighting and outcome regression estimators. Additionally, the estimators and their variance estimators obtained using aggregated data from multiple single-arm data sources is very close to those obtained by directly using pooled data, indicating that our algorithm is lossless.

Conclusion

To estimate the ATEs of any two treatments in a target population using data from multiple single-arm studies, we propose a novel collaborative population-adjusted indirect comparison method. Our estimators are doubly robust and locally efficient. The procedure requires only aggregated data from separate sources and involves three communication rounds. Simulation and real data analyses confirm that the results are lossless. This approach is particularly useful for indirectly comparing different drugs, especially for rare diseases, and addresses concerns about sharing individual-level data.

References

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