Characterizing the Impact of the Shared-Effect Modification Assumption on Population-Adjusted Indirect Comparisons.

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Introduction

BACKGROUND

- Population adjustment indirect comparison (PAIC) are used to support comparative efficacy of treatments for use in health technology assessments (HTAs).
- Typically, during preparation for an HTA, analysts have access to the individual patient data (IPD) for one clinical trial received from the sponsoring company and the aggregate data (AgD) for the comparators retrieved from the literature.
- PAIC methodology is used to adjust the IPD data such that the distribution of treatment effect modifying variables reflect those as reported in the AgD data.
- The result provides a relatively unbiased relative treatment effect (RTE) estimation of the outcome in the AgD population. However, during HTA discussions the population under focus is not on the AgD population, but the pivotal trial (IPD) population.
- The shared effect modification (SEM) assumption mitigates this technicality and if valid allows for the RTE to be projected into any target population. However, this assumption often goes unmentioned in HTA.

OBJECTIVES

- This simulation study demonstrates the mathematical consequences of erroneously assuming SEM.

Methods

- Patient-level data were simulated (n=1000) for two hypothetical clinical study populations (i.e., IPD; AgD) using the ‘wakefield’ package in R.
- Effect modification of the baseline characteristic genomic risk (high-risk [HR], low-risk [LR]) was set to present in the IPD and absent in the AgD.
- The distribution of the between-study genomic HR was set as significantly different values, 50% (IPD) and 30% (AgD).
- Equivalent PAIC models were applied to each dataset providing indirect treatment comparison (ITC) results, which were interpreted in the context of the IPD and AgD populations assuming SEM.

Table 1. Distribution of risk and relative treatment effects

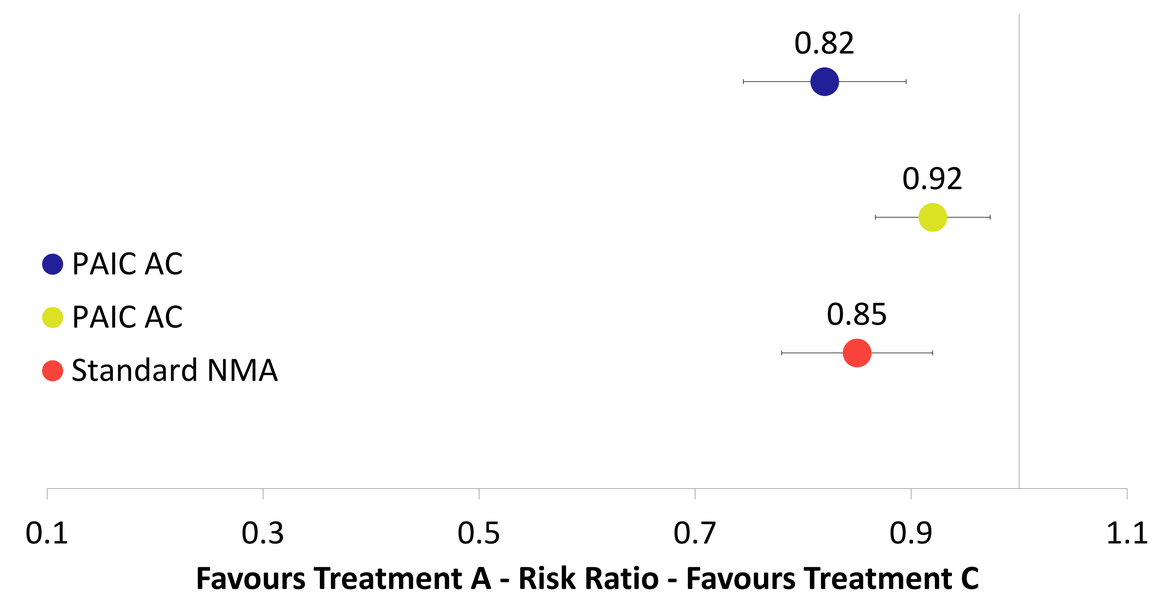
	Pivotal AB trial (IPD)		BC trial (AgD)	
Category	**Relative Tx Effect (RTE)**	**Distribution of genomic risk (%)**	**Relative Tx Effect (RTE)**	**Distribution of genomic risk (%)**
ITT	0.60	-	0.70	-
High risk	0.50	50%	0.90	30%
Low risk	0.70	**50%**	0.50	**70%**

Results

RESULTS

- The RTE in the IPD was 0.60 (intention-to-treat [ITT]), 0.50 (HR) and 0.70 (LR) and 0.70 (ITT), 0.90 (HR) and 0.50 (LR) in the AgD.
- After adjustment, the estimated RTE for an ITC of IPD vs AgD was 0.82 ($p<0.05$) when interpreted in the AgD population context and 0.92 ($p<0.05$) in the IPD population context. The estimated RTE from the standard network meta-analysis (NMA) was 0.85 ($p<0.05$).
- The RTE of A vs C is worse for A when interpreted in the AgD population compared to the IPD population, as there are more low risk patients in the AgD population in which A is less effective. Contrarily, the RTE of B vs C will be worse for C in the IPD population, as there are less low risk patients in the IPD population in which A is more effective. Therefore, the comparison A vs C is dependent on the population.
- Typically, one applies the AC RTE estimated in the AgD population to the IPD population in health economic models which necessitates the SEM assumption. This would underestimate the true RTE of A vs C substantially in the IPD population, which is the population of interest.

Figure 1. Population adjustment indirect comparison result



DISCUSSION

Violation of the SEM assumption led to an incorrect and more optimistic generalization of the RTE in the IPD population than if the opposite sponsor had conducted the analysis.

To allow relative treatment effects to be projected into any target population, the SEM assumption is required.

- Assumes the effect modifiers of the index treatment applies to all included treatments.
- A change in treatment effect cause by each effect modifier is the same for all included treatments.
- Not technically required to conduct PAIC but limits the generalizability of the interpretation to the aggregate population.

The premise of PAIC methodology is that the treatment effect depends on the population. It is therefore not sufficient to use PAIC to generate an ‘‘unbiased’’ comparison in just any population; they are only useful for decision making if they can produce a fair comparison in the target population for the decision.

Depending on which sponsor performs the matching (i.e., which trial has the IPD), the conclusions will differ. Loss of precision may impact the confidence in decision-making. A balance needs to be struck between eliminating bias and loss of precision by over adjusting through the unnecessary reduction of sample size.

This research demonstrates that SEM is critical for interpretation of the results in the IPD population.

Table 2. Relative treatment effects

Target population	Trial AB RTE	Trial BC RTE	PAIC AC RTE
Trial BC	**0.58**	0.70	**0.82**
Trial AB	0.6	**0.65**	**0.92**
Standard NMA			0.85

Conclusions

- PAIC methods are at risk of creating bias due to incorrect generalization of the relative treatment effect in the IPD population of the sponsor.
- The clinical plausibility of shared effect modification should be assessed by comparing subgroup analyses of the AgD and the IPD trials.
- In case of potential violations, discussion can be held with clinicians’ to better understand potential bias of specific effect modifiers.

References

1. Phillippo, D., Ades, T., Dias, S., Palmer, S., Abrams, K. R., & Welton, N. (2016). NICE DSU technical support document 18: methods for population-adjusted indirect comparisons in submissions to NICE.
2. Tyler Rinker, Josh O'Brien, Ananda Mahto, Matthew Sigal, Jonathan Carroll, Scott Westenberger (2020). Wakefield: Generate Random Data Sets. Version 0.3.6.

Abbreviations: AgD, aggregate data; HR, high risk; HTA, health technology assessment; IPD, individual patient data; ITC, indirect treatment comparison; ITT, intention-to-treat; LR, low risk; NMA, network meta-analysis; PAIC, population adjusted indirect comparison; RTE, relative treatment effect; SEM, shared effect modification.

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