Revisiting Conflicts in Population-Adjusted Indirect Comparisons: A Duality Perspective

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Background

- Each pharmaceutical company utilizes its own individual patient data (IPD) derived from clinical trials to perform indirect treatment comparisons. By applying population adjustment methods—such as Matching-Adjusted Indirect Comparison (MAIC) or Simulated Treatment Comparison (STC)—each company reweights or models its trial population to more closely resemble the patient characteristics of a competitor's clinical trial population. This adjustment aims to improve the comparability of treatment outcomes across studies in the absence of direct head-to-head trials.

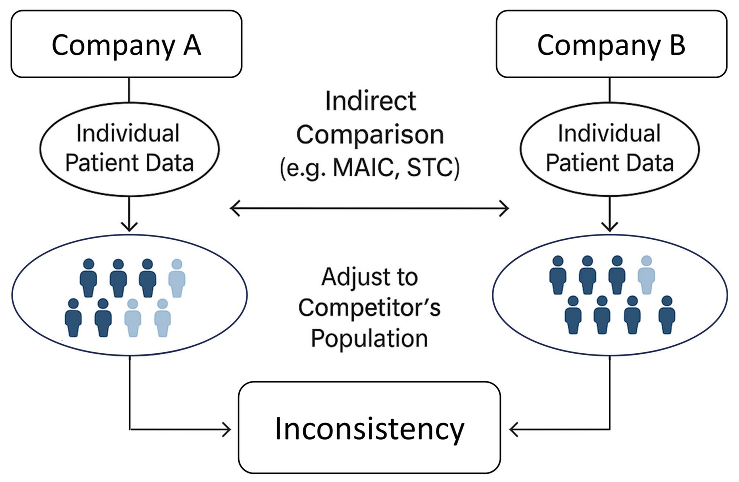

Fig 1. Sponsor-Specific Population Adjustment in Indirect Treatment Comparisons

- However, since each company conducts the analysis independently using its own data and assumptions, the inconsistent resulting estimates have raised concerns about methodological biases.

Objective

This study aims to introduce a duality perspective to analyze and resolve the conflicts arising from differences in target patient population in cross-trial treatment effect comparisons using population-adjusted indirect comparison methods.

Methods

- This study introduces the duality perspective in order to address the reciprocal use of competitor's trial data as target population.
- This study applies the duality theory from the field of operations research to provide a mathematical framework for addressing the challenge of selecting an appropriate target population in indirect treatment comparisons.
- The Kullback-Leibler (KL) Divergence, Jensen-Shannon (JS) Divergence, and entropy concepts and applications are also introduced from information theory.

Perspective I : Duality theory

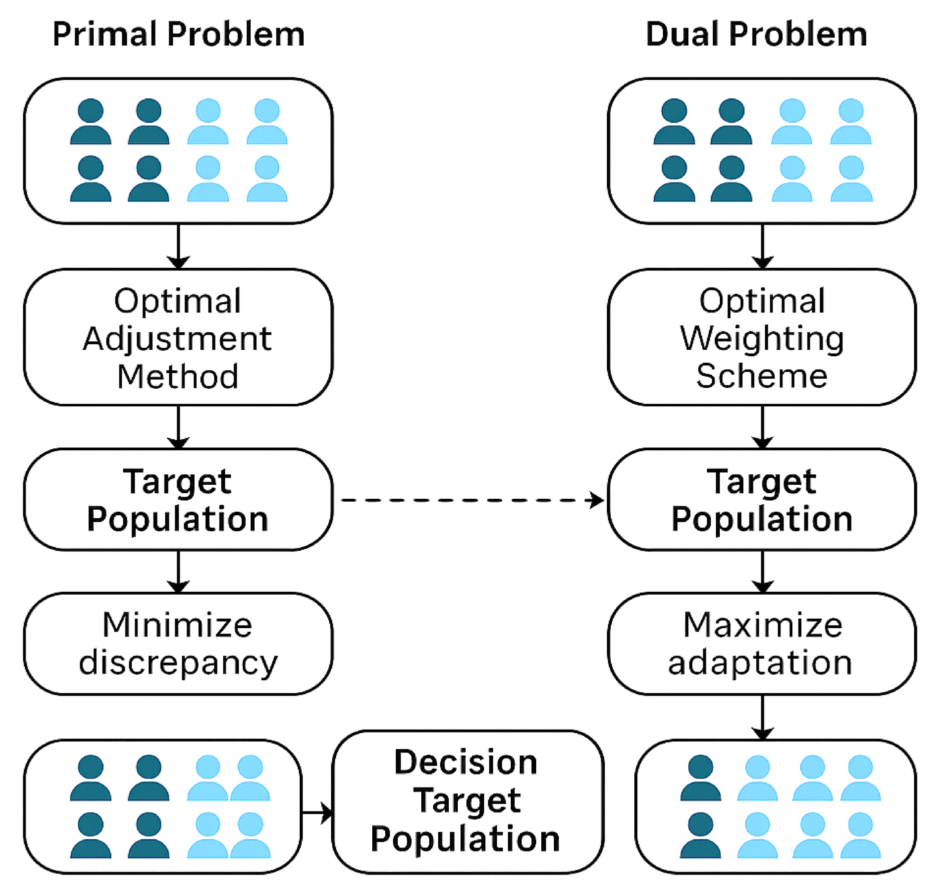

Fig 2. Primal and Dual Optimization in Target Population Alignment

➢ **Conventional Perspective**

Given a target population z_B from the perspective of A, find optimal weights to best match z_B:

$$\underset{w_A}{argmin} \parallel w_A^T z_A - z_B \parallel^2 \qquad w_A = w_A(X_A) \qquad w_{Ai} \geq 0$$

➢ **Primal Problem**

We consider the problem of identifying an optimal target covariate profile z that best represents a reference population:

$$\underset{w_A, w_B}{argmin}\left(\parallel w_A^T z_A - z \parallel^2 + \parallel w_B^T z_B - z \parallel^2\right)$$

➢ **Dual Problem**

To facilitate analysis, we reformulate the inner minimization over weights as a dual optimization problem:

$$\underset{z}{argmin}\left(\left(\frac{w_A}{\parallel w_A \parallel} - 1_z\right)^2 + \left(\frac{w_B}{\parallel w_B \parallel} - 1_z\right)^2\right)$$

* The optimal solution z^* represents a balanced "decision target population" that is simultaneously compatible with the covariate structures of both study.
* The derived w_A, w_B reweight each population toward this target.

- In the primal problem, the objective is to determine an optimal adjustment method—such as the reweighting techniques in MAIC—that minimizes the differences between the characteristics of the study population (from the intervention trial) and those of a predefined target population (from the comparator trial).
- The corresponding dual problem seeks to identify a common target population, aiming to maximize the degree to which the reweighted samples from both studies approximate the common target.

Perspective II : KL Divergence-related

KL Divergence

- The concept of KL divergence, denoted by $D_{KL}(p(x)||q(x))$, originated in probability theory and information theory. It is a non-symmetric measure of the difference between two probability distributions $p(x)$ and $q(x)$. In the scenario of population-adjusted indirect comparisons such as MAIC, we would code samples from $p(x)$ (the distribution of the intervention trial) using a code based on $q(x)$ (the distribution of the comparator trial), using the concept of KL divergence, which is defined as following discrete version: $D_{KL}(p(x)||q(x)) = \sum_{x \in X} p(x) ln \frac{p(x)}{q(x)}$
- $D_{KL}(p(x)||q(x))$ is a non-negative measure and equals 0 if and only if $p(x)$=$q(x)$.
- In a reciprocal way, coding samples from $q(x)$ (the distribution of the comparator trial) using a code based on $p(x)$ (the distribution of the intervention trial) : $D_{KL}(q(x)||p(x)) = \sum_{x \in X} q(x) ln \frac{q(x)}{p(x)}$, $\quad D_{KL}(p(x)||q(x)) \neq D_{KL}(q(x)||p(x))$
- Using $D_{KL}(p(x)||q(x))$ or its reversal formulation it is possible to measure the efficiency loss when using distribution $q(x)$ to compress (with matching algorithm in practice) data from the distribution of $p(x)$, which may be related to the information loss involved in effective sample size (ESS).

JS Divergence

- Jensen-Shannon Divergence (JS Divergence) was further introduced as a symmetrized and smoothed version of the KL divergence:
- The symmetry of JS Divergence indicated the importance of the formulation of a common distribution, $M(x)$, and its divergence with MAIC definition of target population. JS Divergence is bounded by ln(2) or 1 (using the base 2 logarithm).

$$D_{JS}(q(x)||p(x)) = \frac{1}{2}(D_{KL}(p(x)||M(x)) + \frac{1}{2}(D_{KL}(q(x)||M(x)), \qquad M(x) = \frac{1}{2}(p(x) + q(x))$$

Perspective II (Cont.)

- Note that when using $q(x)$ to code or compress $p(x)$, from the perspective of information theory, the approximated model adds excess entropy, but this is outweighed by the model's small size. In general, the size of a compressed data set is:

$$N_q + [D_{KL}(p(x)||q(x) + H(X)]N_p$$

Where
* p(x) is the probability mass function of the information source (intervention trial)
* q(x), information from comparator trial, is the approximation of P(x)
* H(X) is the information entropy of the source (intervention trial)
* DKL(p(x)||q(x)) is the KL divergence
* Np is the size of p(x) to encode
* Nq is the number of bits used to store q(x)

- The above equation about size of compressed data set may be related to the ESS again.

Implication

The use of aggregate data from the comparator trial in population-adjusted indirect comparisons may introduce inconsistencies in outcomes, not due to methodological limitations, but as a consequence of the reciprocal mismatch between study populations. In the absence of a pre-defined common target population to facilitate cross-trial comparability, the introduction of duality and KL divergence-related theories presents a promising conceptual development that may contribute to resolve conflicts in target population alignment across trials.

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