POSTER
#PNS15

COVARIATE ADJUSTMENT IN INDIRECT TREATMENT COMPARISON (ITC): HOW TO BLEND THE USEFUL WITH THE AGREEABLE

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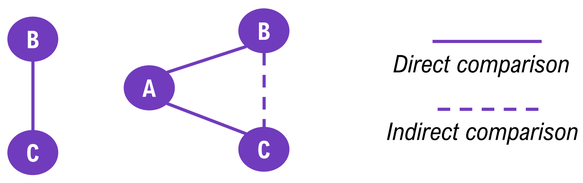
PURPLE SQUIRREL ECONOMICS

BACKGROUND

ITC Overview

- Quality health economics and outcomes research largely relies on robust clinical trial data. However, when no head-to-head clinical trials exist for the therapies or interventions of interest, the indirect treatment comparison (ITC) provides more accurate between-treatment estimates than when naïve (unadjusted) data are compared.
- Covariate-adjusted ITC (CA-ITC) is a comparison approach using trial-level covariates within an ITC adjustment that can be used to mediate the effect of between-trial differences.
- However, CA-ITC may be incorrectly applied and relied upon too often.

Figure 1: Direct and indirect treatment comparison



Traditional ITC vs. Covariate-adjusted ITC

Below presents the general equations for traditional (i.e., non-adjusted) and covariate-adjusted ITC. The difference is primarily reflected in the third line of the equation, where the covariate coefficient is introduced.

Traditional (non-adjusted) ITC

$$n_{jk} = \begin{cases} \mu_{jb} & \text{b} = \text{A, B, C,} \quad \text{if k} = \text{b} \\ \mu_{jb} + \delta_{jbk} & \text{k} = \text{B, C, D,} \quad \text{if k is 'after' b} \end{cases}$$

$$\delta_{jbk} \sim N(d_{bk}, \sigma^2) = N(d_{Ak} - d_{Ab}, \sigma^2)$$

$$d_{AA} = 0$$

Covariate-adjusted ITC

$$n_{jk} = \begin{cases} \mu_{jb} & \text{b} = \text{A, B, C,} \quad \text{if k} = \text{b} \\ \mu_{jb} + \delta_{jbk} & \text{k} = \text{B, C, D,} \quad \text{if k is 'after' b} \end{cases}$$

$$\delta_{jbk} \sim N\left(d_{bk} + \beta_{bk} X_j, \sigma^2\right) = N\left(d_{Ak} - d_{Ab} + (\beta_{Ak} - \beta_{Ab}) X_j, \sigma^2\right)$$

$$d_{AA} = 0, \qquad \beta_{AA} = 0$$

Legend:

n_{jk} : outcome for treatment k in study j

b : base treatment (anchor)

μ_j : outcome for treatment b in study j

δ_{jbk} : trial-specific effect of treatment k relative to treatment b, based on the random-effects distribution ($\delta_{jbk} \sim N(d_{bk}, \sigma^2)$)

d_{bk} : effect of treatment k relative to treatment b

d_{AA} : effect of treatment A relative to treatment A

β : covariate coefficient

Note that these equations are based on random-effects models and will be slightly different for fixed-effects models.

OBJECTIVES

This work aims to summarise the key considerations for utilising CA-ITC.
Particularly, it focuses on three main considerations:

1. Between-study transitivity **2. Data availability** **3. Covariate interaction assumptions**

CA-ITC CONSIDERATIONS

1. Between-study transitivity:

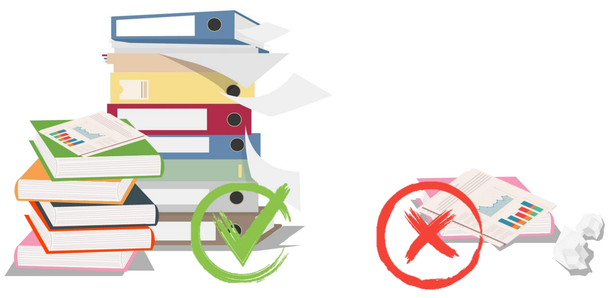
- Determining which studies to include in a network is the first decision to make and should be based on a transitivity assessment (Tremblay 2017).
- The transitivity assumption is satisfied when it is determined that the baseline characteristics between included studies are similar enough for comparison.

- While statistical methods may be used to help gauge the between-trial differences, it is usually a more qualitative clinical decision that determines which studies to include.
- It should be understood that covariate adjustment cannot fully correct for between-trial differences, so including widely differing studies will pose a risk of biased results, regardless of covariate adjustment.
- **<u>Takeaway</u>: CA-ITC is a valid and robust statistical approach only when the transitivity assumption is met but cannot control for all between-trial differences.**

2. Data availability:

- The variable(s) being adjusted for should be reported granularly and similarly in all included studies.

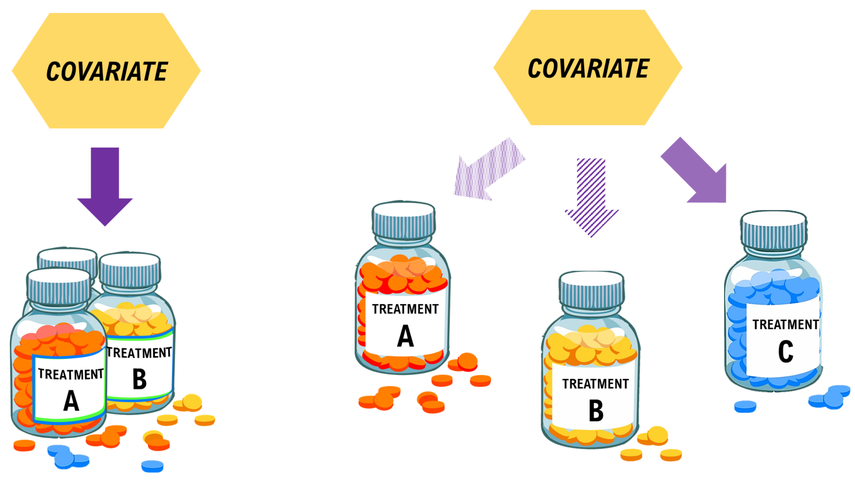
- Additionally, an adequate number of studies should be included to provide sufficient statistical power for the adjustment.



- Whether there are enough studies included in a network to perform the adjustment is still another subjective aspect of ITC. This consideration is further complicated based on whether a fixed- or random-effect ITC model is used (where, generally, more data is needed for random-effects models).
- **<u>Takeaway</u>: CA-ITC requires a enough studies and similar data granularity between studies.**

3. Covariate interaction assumptions:

- The final step is to determine whether the adjustment should assume the same covariate interaction across all treatments (i.e., should the CA-ITC produce a single result that accounts for the covariate), or if it should vary between treatments (i.e., should the CA-ITC produce stratified results for the covariate).



- The former approach will generally require less observations to obtain sufficient statistical power, but in some cases assuming the same interaction effects may not be appropriate (Donegan 2017).
- Model fit statistics can help inform which is the most appropriate interaction effect assumption to use. However, there are currently no objective guidelines on this, so, it is largely up to the individual researcher on how to employ covariate adjustment.
- **<u>Takeaway</u>: Researchers should decide what covariate interaction approach to use in the CA-ITC (varied between treatments vs equal interaction among treatments). The approach should be informed by model fit statistics and clinical understanding of the disease and covariate(s) assessed.**

- If sure conclusions for any of the three key decisions cannot be found, then covariate-adjusted ITC should be avoided.
- In the case where individual patient-level data are available, more robust statistical approaches can be used to help control for between-trial differences. For example, matching-adjusted indirect treatment comparison (MAIC) controls for patient differences by adjusting and reweighting individual patient data to match aggregate covariate values from the published comparator data.
- Results from MAIC have been published across numerous disease settings and it is becoming more standard practice in comparative research. When individual patient-level data are available, MAIC is almost always a more effective tool to control for differences in patient baseline characteristics compared with covariate-adjusted ITC.

FUTURE CONSIDEREATIONS

- Currently there are no published, centralized guidelines on assessing transitivity, though discussions in the literature generally advise to conceptually and epidemiologically assess trial differences between studies in a potential network (Salanti 2012 & Hutton 2015)
- While the comparison of ITC results with and without covariate adjustment can provide valuable information on which model provides the best "fit", there are currently no objective guidelines on how many studies are (and what sample size is) required to perform covariate adjustment.

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CONCLUSIONS

- **CA-ITC can be a powerful statistical tool in comparative research.**
- **However, if the key considerations cannot be satisfied, then CA-ITC should be avoided.**
- **While the theoretic CA-ITC requirements may seem clear, there is a significant deficiency in objective guidelines defining when its use is most appropriate, and when other comparison methods should be used (for example, unadjusted Bayesian ITC, matching-adjusted or simulated-trial comparisons when individual patient-level data are available).**

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