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A Stepwise Approach for Assessing the Feasibility of Population-Adjusted Indirect Treatment Comparisons

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INTRODUCTION

- In the absence of direct head-to-head randomized evidence, indirect treatment comparisons (ITCs) are often conducted to estimate the relative effectiveness, tolerability, and safety of competing pharmacological, or nonpharmacological, medical interventions as part of healthcare technology assessments and appraisals.
- ITCs are often conducted with reported aggregate data (AgD) from published outcomes of randomized controlled trials (RCTs) and use a common comparator to compute relative effects.[1,2]
- It is assumed the included evidence is sufficiently similar, with the key assumption being that treatment effect-modifying (TEM) covariates are balanced across studies.
- In the event of an imbalance of TEMs between studies of interest, population-adjusted ITCs (PA-ITCs) are undertaken to 'adjust' for these observed differences and reduce bias in the relative estimates. These methods require individual patient data (IPD) from at least one of the studies included in the comparisons.
- Although guidance exists for conducting PA-ITCs, a formal process for assessing the feasibility of such analyses, to the best of our knowledge, is yet to be established.

OBJECTIVES

- The objective of this study is to provide a practical stepwise process for assessing the feasibility of performing valid and appropriate PA-ITCs to synthesize direct, indirect, and unconnected evidence for competing medical interventions.

METHODS

- For the applicability of this process, we consider matching-adjusted indirect comparison (MAIC), simulated treatment comparison (STC), and multi-level network meta-regression (ML-NMR).
- All methods are intended to 'adjust' for the imbalance in TEMs observed across studies. Understanding how to identify potential TEMs is integral to the research question and forms a key component of the feasibility process.
- The outlined PA-ITC techniques are described in detail across current literature[3,4] and guidance on MAIC and STC is provided as part of the National Institute for Health and Care Excellence's TSD series.[5]
- For understanding, a brief description of each method is included in Table 1. The applicability of each method is also provided in the third column, as this is important to the decision-making process when assessing the feasibility of conducting a PA-ITC.
- Figure 1a to 1c provides example networks of evidence that are relevant to the feasibility process. Firstly, 1a represents a simple two-study network with a common comparator where anchored indirect comparisons can therefore be performed. 1b represents a simple two-study network without a common comparator, where only unanchored indirect comparisons can be made. Finally, 1c demonstrates a network with 6 treatments where comparisons via network meta-analysis would be suitable to combine evidence.

Table 1. Summary and application of relevant PA-ITC techniques

PA-ITC Method	Description	Application
MAIC	Patients from the IPD trial are assigned weights such that their weighted mean baseline characteristics match those from the reported characteristics of the AgD study. All TEMs are adjusted in anchored analyses; all TEMs and prognostic variables are adjusted for in unanchored analyses.	Anchored and unanchored comparisons - designed in nature for a 2-study approach
STC	A regression-based approach that predicts the outcome in the population of the comparator trial. All effect modifiers in imbalance are adjusted for. Prognostic covariates should be added to the regression for unanchored analyses; otherwise, these can be omitted if they do not improve model fit in anchored analyses.	Anchored and unanchored comparisons - designed in nature for a 2-study approach
ML-NMR	An extension of the standard NMA framework; however, incorporates IPD and AgD data and can be employed in an extensive connected network of evidence with many studies included, such as that of Figure 1c. Unlike MAIC and STC, ML-NMR cannot be used in the presence of an unconnected network (Figure 1b). Effectively, ML-NMR integrates an individual-level model over the covariate distribution in each AgD study in the network.	Anchored comparisons only. Applicable to both a two study network and an extensive network of evidence

Abbreviations: MAIC, matching-adjusted indirect comparison; ML-NMR, multi-level network meta-regression; PA-ITC: population-adjusted indirect treatment comparison; STC, simulated treatment comparison

Figure 1. Network examples

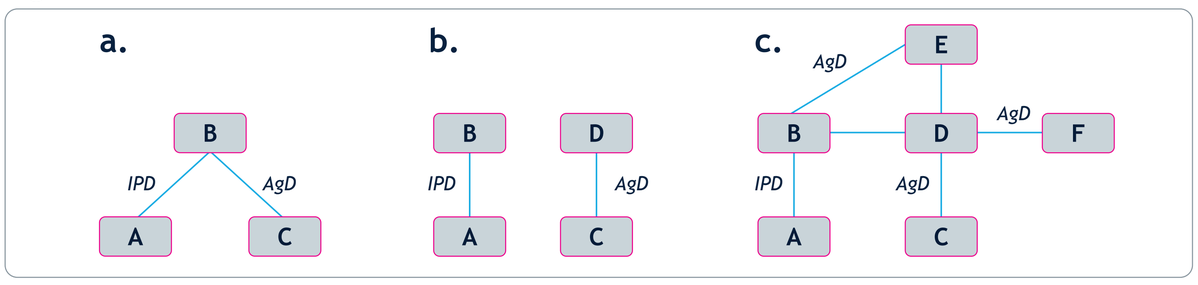


Figure 1a. A two-study anchored indirect comparison where IPD is available in the AB study and AgD available in the CB study, where B represents the common comparator. Figure 1b) An unanchored indirect comparison between two studies without the presence of a common comparator and IPD is available in the AB study and AgD in the CD study. Figure 1c. An example of an extended network of evidence with six treatments that include direct and indirect evidence; IPD is only available in the AB study and AgD in the remaining studies.

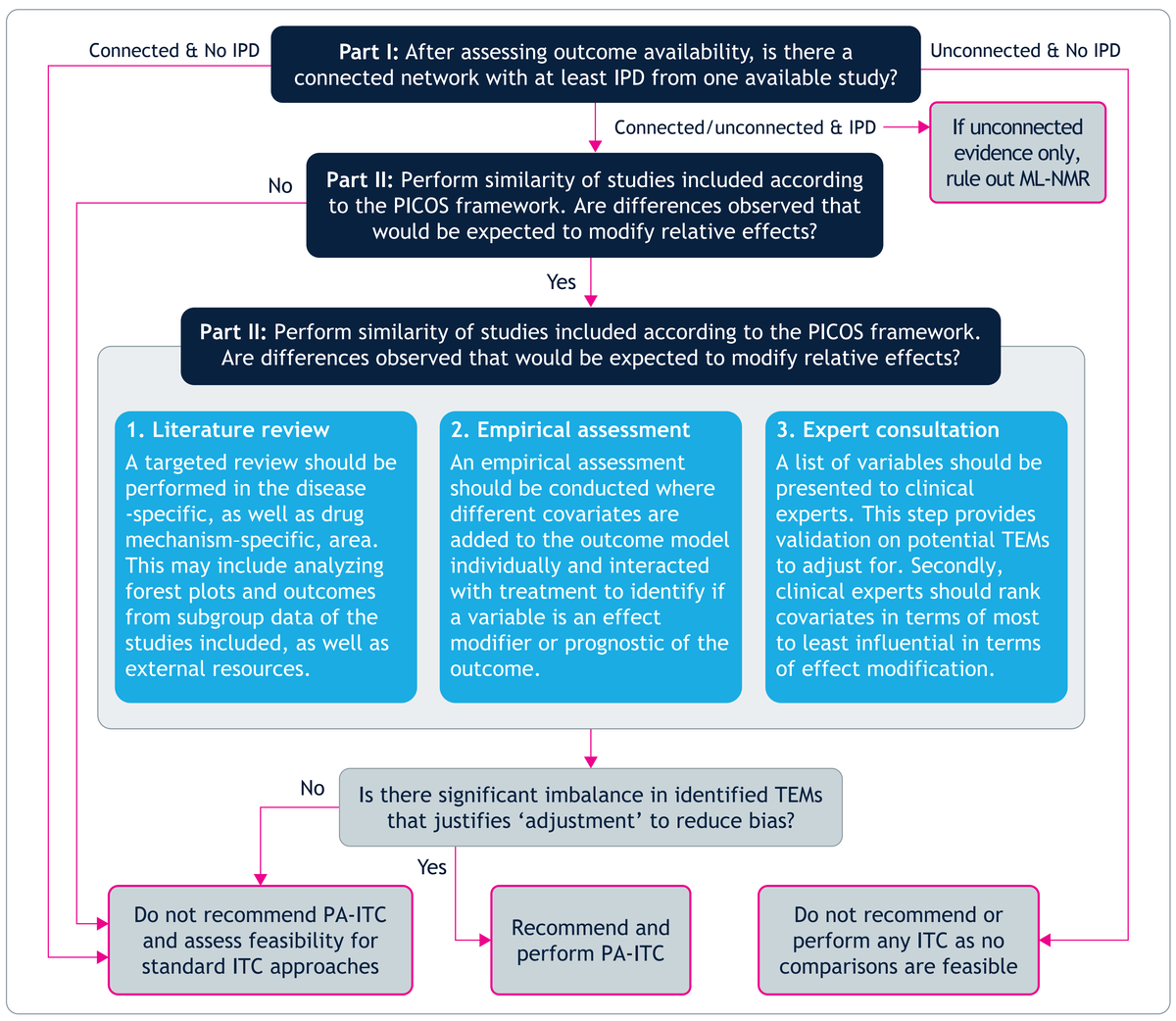
- The stepwise process is intended to be enacted as part of the ITC protocol or statistical analysis plan.
- Initial steps consider the evidence base in terms of the **outcomes** and available **network of evidence** (Figure 2, Part I). The second step involves an investigation into the clinical and study characteristics in terms of the **population, intervention, comparator, outcome** and **study design** (PICOS) framework (Figure 2, Part II). The third step involves a deeper investigation into the differences in patient characteristics that may modify the **treatment effect** (Figure 2, Part III). Finally, the analyst will decide whether these observed differences warrant the application of population-adjusted methods.

RESULTS

Assessing the feasibility of a PA-ITC

- The stepwise process outlined in Figure 2 should be applied to assess whether an ITC would be feasible by means of population-adjusted techniques, to indirectly compare competing treatments.

Figure 2. Process for assessing the feasibility of conducting valid PA-ITCs



Abbreviations: IPD, individual patient data; ITC, indirect treatment comparison; ML-NMR, multi-level network meta-regression; PA-ITC, population-adjusted indirect treatment comparison; PICOS, population, intervention, comparator, outcome, study design; TEM, treatment-effect modifier

Outcomes of the stepwise process

- Once the researcher has followed these steps, an educated decision can be made as to whether there is significant imbalance in the carefully selected TEMs to require a PA-ITC.
- Although there is some discussion on the method (MAIC, STC, or ML-NMR) that may be most preferable in terms of bias reduction,[6] not all methods are applicable to every scenario. For example, in unanchored comparisons, which carry their own risks in terms of stronger assumptions, ML-NMR cannot be implemented and therefore the researcher can rule this method out early in the stepwise process.
- The stepwise process is therefore created to guide the user in determining if a PA-ITC should be enacted given the data availability and considerations, especially in terms of TEMs, as outlined in the above figure. Once this is determined, the analyst should be able to make an informed decision on the methodology to employ for the specific research question. The decision may include performing two approaches—for example, MAIC and STC—with one as a scenario/sensitivity analysis. However, the researcher may determine that population-adjusted techniques should be abandoned in favor of standard ITC techniques or decide no valid indirect comparisons can be mad

CONCLUSIONS

- While extensive guidance exists on the steps for conducting PA-ITCs, a comprehensive guide for assessing the feasibility for conducting such analyses is yet to be developed.
- The stepwise process developed in this study outlines the necessary steps to assess the feasibility of conducting PA-ITCs.
- The process will help the analyst understand both the data requirements and clinical considerations that are required when synthesizing and indirectly comparing treatment effects from RCTs, observational studies, and single-arm trials.
- Future research should apply this feasibility framework to a case study and assess the relevance and performance of each technique.

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