

# INDIRECT TREATMENT COMPARISON: A PROPOSED DECISION ALGORITHM TO DEFINE THE BEST APPROACH

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## Background

- Indirect treatment comparisons (ITC) are used to synthesize evidence obtained from all available clinical trials conducted in the target population of interest and assessing the treatments identified as relevant to the study question or decision problem.<sup>1</sup>

## Objective

- To develop a user-friendly decision algorithm to help define the best approach when conducting a feasibility assessment of an ITC.

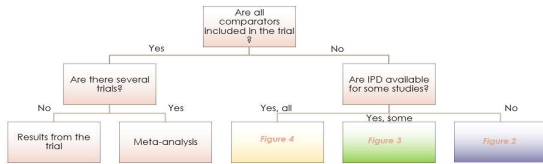
## Methods

- Recommendations from the National Institute for Health and Care Excellence (NICE), including the Technical Support Documents (TSDs) related to ITCs and comparative effectiveness were reviewed and used to develop the decision algorithm.

## Results

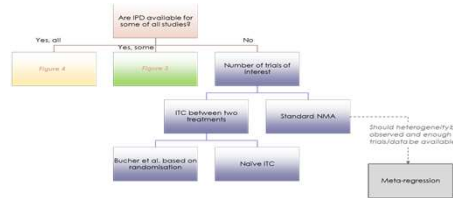
- Decision nodes rely on simple assessments including
  - network connectivity
  - access to patient level data
  - presence or extent of heterogeneity in the evidence
- Approaches considered include standard network meta-analysis, population-adjusted ITCs, propensity score approaches or multi-level network meta-regression
- The first step consists of verifying if there is a need for an ITC (Figure 1). If an ITC is needed, the availabilities of Individual Patient Data (IPD) is assessed.

Figure 1. First step : verifying if an ITC is needed



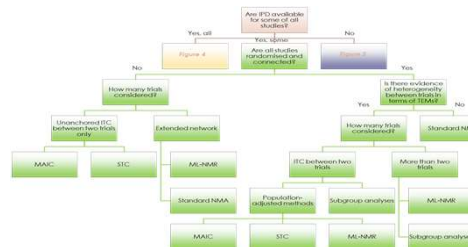
- If none of the trials have the IPD available three choices are considered, depending on the shape of the network: if the two treatments of interest have been compared to a common comparator, an ITC based on the relative treatment effect (Bucher method) or a naïve ITC (Figure 2) is considered.
- Naïve ITC compares treatments from separate trials as if they were from the same randomized trial. It is therefore subject to bias and avoided if possible.<sup>2</sup>
- The Bucher ITC preserves the randomization of the originally assigned patient groups. The method assesses the difference between the treatments and their common comparator by evaluating the magnitude of the treatment effect across studies.<sup>2</sup> It assumes that the trials are similar in terms of study population and design, outcome measurements and distribution of treatment effect-modifiers.<sup>2</sup> This approach is always preferred over the naïve comparison.
- If the network of evidence combines direct and indirect evidence, an NMA, which also preserves randomization, is considered. If there is "explained" heterogeneity between studies, a network meta-regression may be considered.

Figure 2. Path to follow if no IPD is available



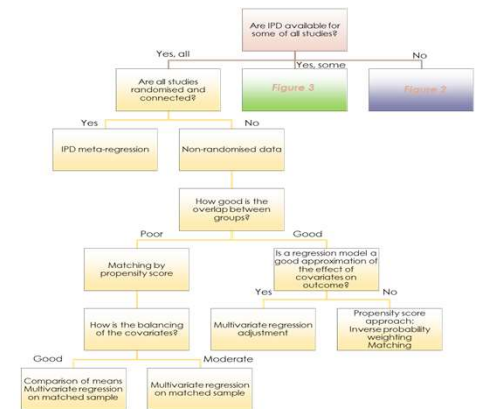
- If IPDs are available for some of the trials, five types of analyses are considered (Figure 3): matching adjusted indirect comparisons (MAIC), simulated treatment comparisons (STC), multilevel network meta-regression (ML-NMR), standard NMA and/or subgroup analyses.
- If the evidence network is disconnected, or the studies are subject to an important level of heterogeneity that cannot be adjusted for by a meta-regression, a MAIC, STC or ML-NMR might be considered.
- Both the MAIC and STC are population-adjusted indirect comparisons where the outcomes for the intervention are adjusted for the characteristics of the population enrolled in the comparator's trial.<sup>3</sup>
  - The MAIC uses balancing weights to reweight patients in the index trial to match the distribution of patients' characteristics of the comparator's trial.
  - The STC uses predictive equations (e.g. generalized linear models) to estimate the relationship between the outcome and baseline characteristics. Attention needs to be paid if the link function is not the identity as joint covariate distribution needs to be accounted for to obtain unbiased estimates.
- From a practical perspective, the STC is more suitable when there is an interest in multiple comparators for few outcomes, whereas the MAIC is preferred when there are multiple outcomes and few comparators in the analysis.<sup>4</sup>
- The ML-NMR is similar to the STC in concept; however, this method goes a step further by integrating, when available, all individual patient data from multiple trials at the same time.<sup>5</sup> Given the fact that the method accounts for joint distributions of covariates, it overcomes the issue faced with the STC. In addition, unlike the STC and MAIC methods, the ML-NMR is applicable to treatment networks of any size which facilitate the use of all available information.<sup>5</sup>

Figure 3. Path to follow if IPD are available for some trials



- If all selected trials have the IPD available five options are possible (Figure 4):
  - If all the studies are randomized and connected, then an IPD meta-regression can be conducted.
  - If the data are not randomized, then propensity score approaches (using inverse probability weighting matching) and/or multivariate regressions can be considered.

Figure 4. Path to follow if IPD are available for all trials



## Conclusion

- This proposed decision algorithm provides a synthesis of current NICE TSD guidelines to help standardize the selection of methods used for conducting indirect treatment comparisons.
- Given the ongoing research, the algorithm may evolve, in particular with regards to the conditions under which the MAIC, STC and ML-NMR should be preferred.

## References

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