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Indirect treatment comparisons in health technology assessment submissions: a review and critique of best practice

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BACKGROUND & METHODS

- In the absence of direct evidence, indirect treatment comparisons (ITCs) are often used to assess the comparative effectiveness of novel treatments.
- ITC methods commonly employed include network meta-analyses (NMAs), matching-adjusted indirect comparisons (MAICs), simulated treatment comparisons (STCs), and multi-level network meta-regression (ML-NMR) (**Table 1**).
- Despite methodological differences, all methods rely on the assumption of exchangeability. That is, treatment effects estimated in one study can be generalized across other studies because they are sufficiently similar. [1]
- Exchangeability is assessed by determining similarity across trials in baseline characteristics, outcomes and study design, by assessing homogeneity and by examining consistency of direct and indirect evidence in a network. [1]
- Potential violations of the assumptions underlying an ITC can lead to biased results. Accordingly, guidelines offer recommendations to support method selection in various circumstances. For instance, when heterogeneity concerns are present, PAICs can be used, random-effects models can be fitted, and baseline risk adjustment can be employed. [1-4]
- Despite established best-practice guidelines aiming to reduce the risk of biased results, it is not clear whether ITCs used in National Institute for Health and Clinical Excellence (NICE) submissions are complying with these guidelines.

OBJECTIVE: To inform future health technology assessment (HTA) submissions by examining the present use of ITC methods within NICE technology appraisals (TAs), identifying gaps in adherence to guidelines, and gathering critique regarding the limitations of analyses used.

- A targeted review of the NICE website was performed to identify TAs published in the 3-year interval before study initiation (April 2022-March 2025). Terminated TAs were excluded and all TAs reporting NMAs, MAICs, STCs, and ML-NMRs were included.
- Data on the ITC methodology used and relevant critique of submissions was extracted.

Table 1. Advantages and disadvantages in ITC methods.

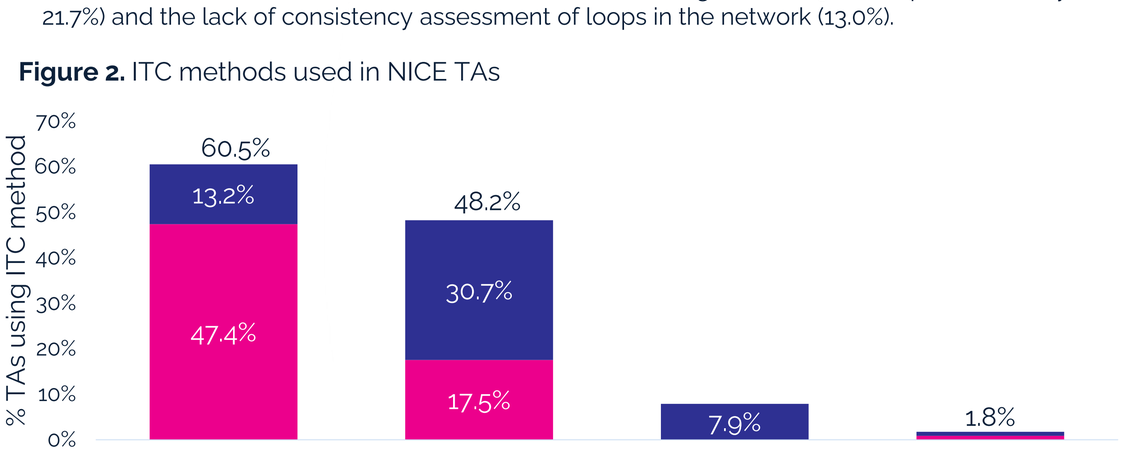
Method	Advantages	Disadvantages
NMA	• Standard well-known approach • Allows for a comparison including more than two treatments and trials	• No population adjustment, imbalance of TEMs may bias results • Target population not clearly specified • Requires a connected network of evidence
MAIC/STC	• Population adjusted for imbalances in TEMs (and PVs) • Can be used for unconnected networks of evidence • Target population clearly specified	• Limited to pairwise comparisons • If TEMs/PVs are missing this may result in biased results • Target population must be that of the comparator trial with AgD
ML-NMR	• Population adjusted for imbalances in TEMs • Allows for a comparison including more than two treatments and trials • Can include IPD from multiple trials • Target population can be specified	• Assumes the same correlation structure observed among the IPD covariates for the AgD studies • Novel method, not yet frequently submitted to HTA agencies • Requires connected network of evidence

Abbreviations: AgD: aggregate-level data, HTA: health technology assessment, ITC: indirect treatment comparisons, IPD: individual patient-level data, MAIC: matching adjusted indirect comparison, ML-NMR: multilevel network meta-regression, NMA: network meta-analysis, PV: prognostic variable, TEMs: treatment effect modifier.

RESULTS

- Of the 256 TAs identified, 112 met the inclusion criteria (**Figure 1**).
- More than half of included TAs (N=75, 67.5%) used one of the ITC methods of interest, whereas the remaining 37 (32.5%) employed more than one of the ITC methods of interest (**Figure 2**).

Figure 1. Flowchart of the inclusion and exclusion of NICE TAs.



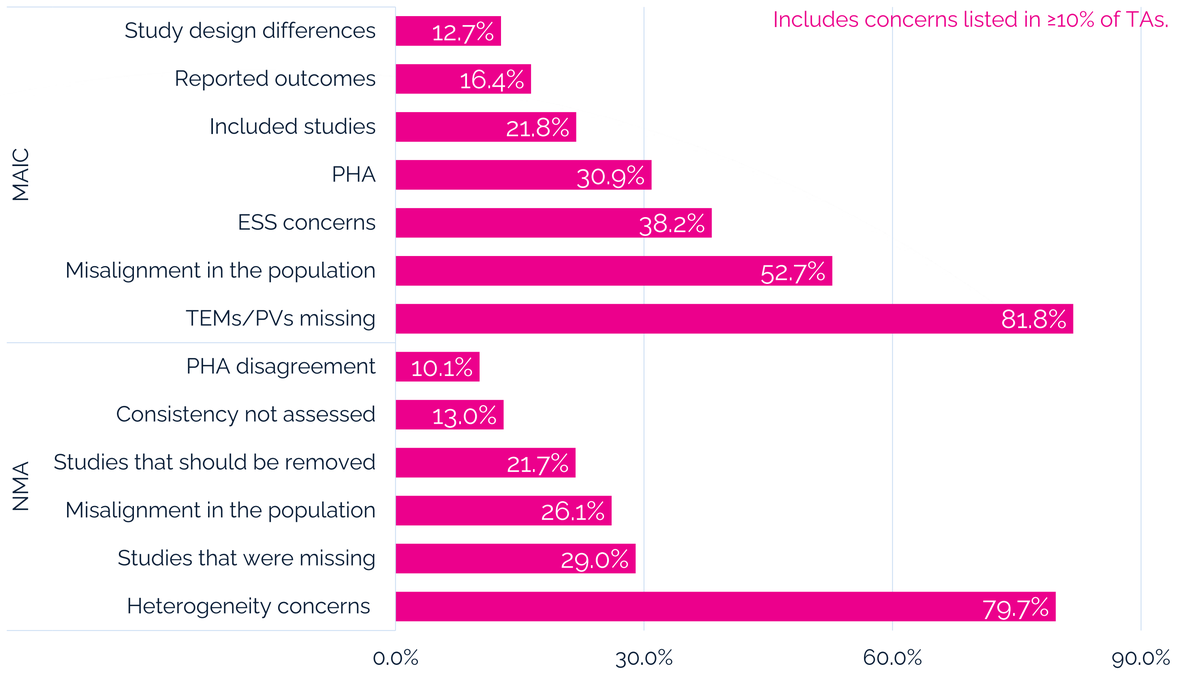
Abbreviations: ITC: indirect treatment comparisons, IPD: individual patient-level data, MAIC: matching adjusted indirect comparison, ML-NMR: multilevel network meta-regression, NMA: network meta-analysis, TA: technology appraisal

- NMAs and MAICs were the most frequently adopted ITC methods, used in 60.5% and 48.2% of TAs, respectively. In almost half of the TAs (47.4%) multiple ITC methods were used to assess robustness of results and STCs (7.9%) and ML-NMRs (1.8%) were solely included as sensitivity analyses.
- The most common concerns were heterogeneity in patient characteristics in NMAs (79.7%) and missing TEMs and PVs in MAICs (81.8%) (**Figure 3**).
- Misalignment between the population for which evidence was provided and the target population of interest was a recurring issue in both MAICs (52.7%) and NMAs (26.1%).
- For MAICs, additional concerns related to small effective sample sizes (ESS) (38.2%), and the violation of the proportional hazard assumption (PHA) (30.9%).
- For NMAs, concerns related to the included studies (missing studies 29.0%, request for study removal 21.7%) and the lack of consistency assessment of loops in the network (13.0%).

Figure 2. ITC methods used in NICE TAs

Abbreviations: ITC: indirect treatment comparisons, MAIC: matching adjusted indirect comparison, ML-NMR: multilevel network meta-regression, NMA: network meta-analysis, STC: simulated treatment comparison, TA: technology appraisal

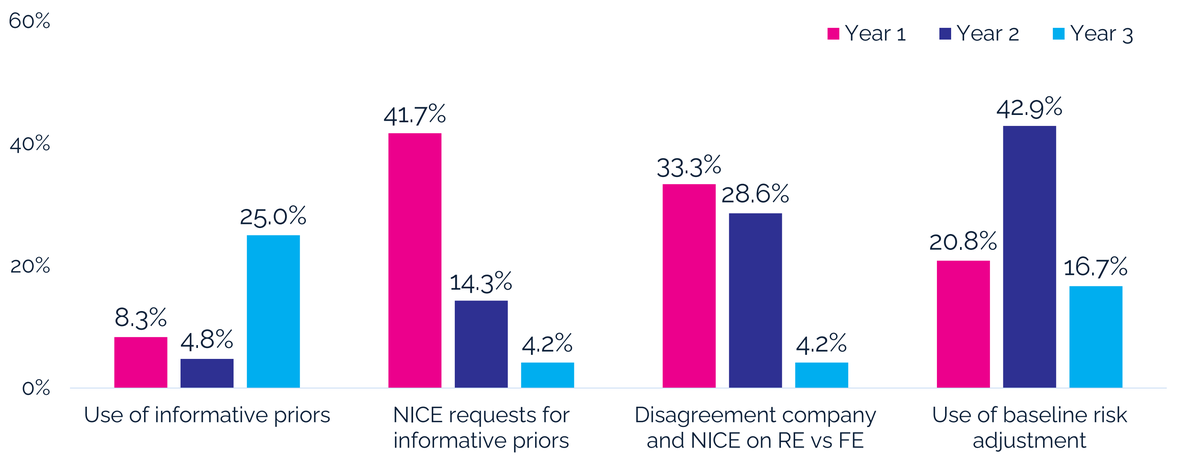
Figure 3. Concerns in performed ITC analyses in NICE TAs



Abbreviations: ESS: effective sample size, ITC: indirect treatment comparisons, MAIC: matching adjusted indirect comparison, NMA: network meta-analysis, PHA: proportional hazard assumption, PV: prognostic variable, TA: technology appraisal, TEMs: treatment effect modifier.

- In 21.7% of NMAs, companies favored fixed-effects (FE) models while the ERG preferred random-effects (RE) or vice versa. However, this percentage varied considerably across the three years (year 1: 33.3%, year 2: 28.6%, year 3: 4.2%). Baseline risk adjustment was used in 26.1% of NMAs (**Figure 4**).
- Furthermore, the use of informative priors increased in RE models for Bayesian NMAs (year 1: 8.3%, year 2: 4.8%, year 3: 25.0%) and consequently ERG requests to add them declined (year 1: 41.7%, year 2: 14.3%, year 3: 4.2%).

Figure 4. Concerns on performed (Bayesian) NMAs



Abbreviations: FE: fixed effect, RE: random effects.

CONCLUSIONS

- Overall, limitations expressed by NICE for analyses in TAs related to the risk of heterogeneity, the use of fixed effect models and the studies included in NMAs, as well as missing TEMs and PVs and small effective sample sizes in MAICs. Furthermore, for both methods, the misalignment between the population of interest and the population for which evidence was presented was a common concern.
- Simultaneously, improved adherence to NICE guidelines was observed across the three-year interval with an increased use of RE models and informative priors.
- To reduce the impact of limitations in future submissions, methods should be carefully selected and possibly include the use of ML-NMRs, RE models, and flexible models when the PHAs is violated. These more complex methods could be encouraged by increasing their accessibility through publications (e.g., on informative priors by Turner et al) and software packages (e.g., *multinma*).

REFERENCES 1. Directorate-General for Health and Food Safety, Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons; 2024; **2**. Dias S, Welton NJ, Sutton AJ, Ades AE. A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. London: National Institute for Health and Care Excellence (NICE); 2014.; **3**. Dias S, Sutton AJ, Welton NJ, Ades AE. Heterogeneity: subgroups, meta-regression, bias and bias-adjustment. NICE DSU Technical Support Document 3. National Institute for Health and Clinical Excellence (NICE). 2012 Apr;27905717.: **4**. Phillippo, D., Ades, T., Dias, S., Palmer, S., Abrams, K. R., & Welton, N. NICE DSU technical support document 18: methods for population-adjusted indirect comparisons in submissions to NICE; 2016 **ACKNOWLEDGMENTS:** We would like to thank Dr Elisabeth Fenwick, Chief Scientific Officer, OPEN Health HEOR & Market Access, for her review.

Presented at: ISPOR Europe, 9-12 November 2025, Glasgow, Scotland

Sponsored by OPEN Health's Scientific Office