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Indirect Treatment Comparisons: Current Practice and the Added Value of Multi-Level Network Meta-Regression

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BACKGROUND

- Indirect treatment comparisons (ITCs) are conducted when there is a lack of direct evidence to assess relative treatment effectiveness.
- Population-adjusted ITCs can be used to account for heterogeneity in patient characteristics that influence the treatment effect across trials.
- There are several methods available to account for heterogeneity in patient characteristics which vary in the number of treatments that can be compared, the effect they are estimating, and the population for which they estimate this effect (Table 1).
- Multi-level network meta-regression (ML-NMR) for binary outcomes has been available since 2020 and for time-to-event (TTE) outcomes since early 2024.[1,2]
- The potential benefits of ML-NMRs over matching adjusted indirect comparisons (MAIC) and simulated treatment comparisons (STCs) come from the possibility of comparing multiple treatments simultaneously and estimating population-average treatment effects for the population of interest.[2]
- Simulation studies have presented conflicting results as to the performance of population-adjusted ITCs, especially for MAICs and STCs.[3,4] Nevertheless, ML-NMR is recommended for anchored analyses and the use of STCs is recommended in unanchored analyses.[3,5]
- A review of NICE technology appraisals (TAs) between 2010 and 2018 assessed the use of population adjustment methods such as MAICS and STCs.[6] Results showed that most analyses were unanchored, as no common comparator was available, and that STCs were rarely used, as almost all analyses adopted MAICs.[6]

Table 1. Differences in population-adjusted indirect treatment comparison methods

	ML-NMR	MAIC	STC
Comparison	Multiple treatment effects	Single comparison	Single comparison
Treatment effect is estimated for	All trial populations included in the analysis	Population of aggregate data	Population of aggregate data
Treatment effect estimated	Population-average conditional treatment effect	Marginal treatment effect	Individual-level conditional treatment effect
Feasible with single-arm trials	✗	✓	✓

OBJECTIVES

- This poster assesses the current use of population adjustment methods in submissions to NICE and explores the potential of ML-NMR to displace the methods currently used for TTE outcomes.

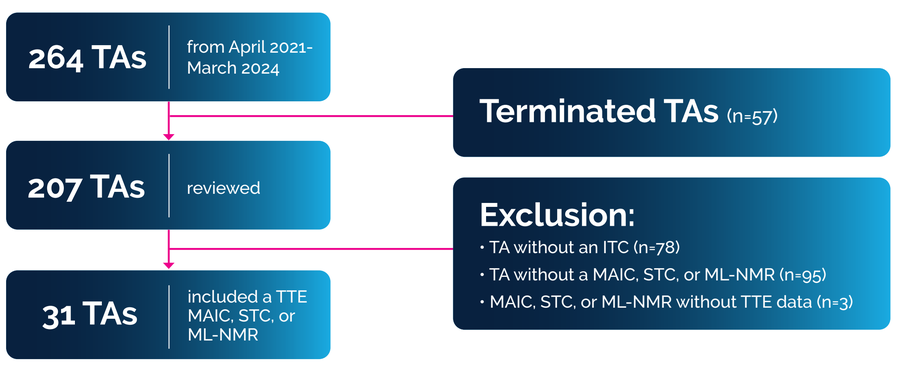
METHODS

- A targeted literature review was performed to identify TAs submitted to NICE between April 1, 2021- March 31, 2024. Terminated TAs were excluded.
- All TAs that reported results for TTE data were of interest.
- TAs reporting MAICs, STCs and/or ML-NMRs were included. TAs without population adjustment were excluded (i.e., NMAs).
- Information was extracted, from TAs, relating to the methodology used (MAIC/STC/ML-NMR, anchored/unanchored) along with the recommendations made by the evidence review groups (ERGs).

RESULTS

- Of the TAs published in the relevant timeframe, 31 met the inclusion criteria (Figure 1).

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



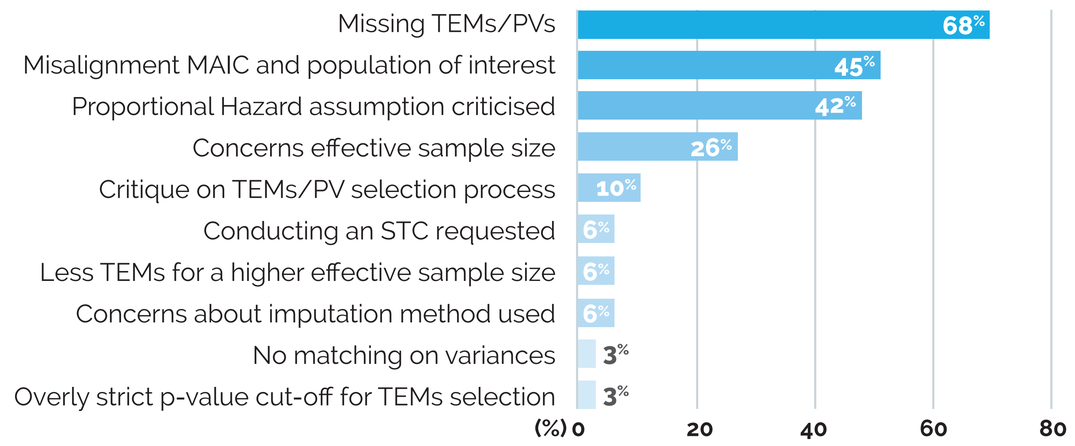
ITC= Indirect Treatment Comparison, MAIC= Matching Adjusted Indirect Comparison, STC= Simulated Treatment Comparison, TA = Technology Appraisal, TTE= Time-to-Event

- All 31 TAs, included in the final analysis, reported results for MAICs; STCs were sporadically used (N=3) and no ML-NMRs for TTE had been performed. One TA performed a MAIC as a sensitivity analysis alongside an NMA. The NMA was the final selected source of evidence, as the evidence for treatment effect modification was considered weak.
- Of the included TAs, 13% reported results for anchored analyses, 81% reported results for unanchored analyses and 6% included both anchored and unanchored analyses.

ERG Critique

- An overview of the points of criticism raised by the ERGs can be found in Figure 2. A concern repeatedly raised regarding MAICs, was the discrepancy between the population in which efficacy was assessed and the population of interest for decision makers (45% of TAs).
- The most frequently raised concern was around missing treatment effect modifiers (TEMs) (68% of TAs). Further, the TEM selection process was criticized (10% of TAs).
- Concerns about the validity of the proportional hazard assumption were also frequently discussed (42% of TAs).

Figure 2. ERG critique on MAICs and STCs



ERG= Evidence Review Group, MAIC= Matching Adjusted Indirect Comparison, PV= Prognostic Variable, STC= Simulated Treatment Comparison, TEM=Treatment Effect Modifier

ML-NMR

- ML-NMR would not have been possible for most TAs, as more than 80% reported results of unanchored analyses.
- Of these unanchored analyses, 23 included a single-arm trial, either for the intervention or the comparator. This limits the ability to create a connected network, required when conducting a ML-NMR.
- For the remaining four unanchored TAs, creating a connected network might be feasible as the intervention and comparator trials included multiple arms.

LIMITATIONS

- In this review of TAs, we only included analyses for TTE data; some of the findings are not generalizable to non-TTE outcomes. However, as only three TAs were excluded that reported MAICs only for non-TTE outcomes, the impact of this decision will likely be minimal.
- Moreover, this review focused on the possibility of using ML-NMRs instead of other population adjustment methods. We did not consider instances where NMAs could have been replaced with ML-NMRs.

CONCLUSIONS

- Most TAs reporting on population-adjusted ITCs included unanchored MAICs. STCs were rarely used, despite the absence of conclusive evidence that MAICs are preferred. This aligns with findings from TAs between 2010-2018, demonstrating this trend has not changed over the years despite recommendations for the use of STCs.[3,5,6]
- Missing TEMs/PVs in the analyses and misalignment of results with the population of interest were concerns most often raised by ERGs.
- ML-NMRs will not address all challenges faced when conducting ITCs. However, when it is feasible to perform them, they can ensure the estimation of effects in the population of interest to HTA decision makers; a concern frequently raised in previous TAs.
- However, it is important to note the widespread use of unanchored MAICs, which cannot be replaced with ML-NMRs.[7]

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ACKNOWLEDGEMENTS
We would like to thank Claire Ainsworth and Elisabeth Fenwick for their review of this poster

Presented at: ISPOR Europe 2024

Sponsored by OPEN Health's Scientific Office