Multi-Level Network Meta-Regression (ML-NMR) vs Matching-Adjusted Indirect Comparison (MAIC): A Comparative Analysis via Simulations to Illustrate the Importance of Population Adjustment

Chopard-Lallier C[1], Bertin N[2], Le Nouveau P[3], Gauthier A[4]

[1]Amaris Consulting, Toronto, ON, Canada, [2]Amaris Consulting, London, United Kingdom, [3]Amaris Consulting, Nantes, France, [4]Amaris Consulting, Barcelona, Spain

Abstract No. #146661
MSR164

INTRODUCTION

- **Matching-Adjusted Indirect Comparison (MAIC)**[1] is a commonly used population adjustment method to assess the relative treatment effect of two treatments in heterogeneous trials. However, MAIC has known limitations, including the limited validity of estimates to the comparator's population, due to the reweighting process based on treatment effect modifiers (TEMs) distribution from the aggregated data (AgD).
- The **Multi-level Network Meta-Regression (ML-NMR)** approach, introduced by Phillippo in 2019[2], is the most methodologically robust population-adjusted indirect comparison as endorsed in the recent Health Technology Assessment Coordination Group Guidelines for Quantitative Evidence Synthesis[3].

OBJECTIVES

- To illustrate through simulations the **importance of the population used for the adjustment** and how ML-NMR overcomes this known MAIC limitation.

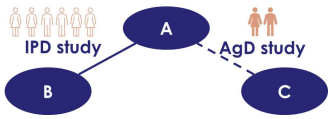
METHODS

Data simulation

A **time-to-event outcome** following a Weibull model and three covariates from two 1:1 randomised controlled trials, respectively assessing drugs A vs B and A vs C, were **simulated once** using the *simsurv*[4] R package. The **covariates act as prognostic factors and TEMs**, with same TEM effects per treatment classes, with B and C being active treatments, and A placebo. *Figure 1* illustrates the network of evidence.

- The **true values of hazard ratios** (HRs) were computed using the Weibull model used for simulation.
- Available set of data was restricted to **individual patient data** (IPD) for AB trial and **AgD** for AC, i.e., baseline characteristics, C vs A HR [95% confidence interval (CI)] from Cox model, and Kaplan-Meier curves.

Figure 1. Network of evidence



Matching-Adjusted Indirect Comparison

A **MAIC** was computed **weighting AB trial** on patient characteristics from AC trial. Proportional hazard assumption was tested and a weighted Cox model estimated the B vs A HR [95% CI] in AB weighted trial. A Bucher comparison[5] was then used to estimate B vs C.

Multi-Level Network Meta-Regression

A **ML-NMR** using IPD from AB and AgD from AC was computed **adjusting for the three covariates** and assuming shared TEMs across treatment classes. Parameters were estimated from a Markov Chain Monte Carlo algorithm with non-informative priors, Weibull likelihood, and using 2,000 iterations through the *multinma*[6] R package.

RESULTS

- To conduct the MAIC, **AB was weighted based on AC** patient characteristics. An **effective sample size** (ESS) of 88.75 was identified, representing 44.4% of the original sample size. This ESS can be interpreted as the sample size if this was a de-novo trial with the same statistical power. Thus, smaller the ESS, greater the variability in weights and instability in the estimate. No patient had a high weight (*Table 1*) and AB weighted trial was similar to AC population characteristics distribution (*Table 2*).

Table 1. AB weights distribution

	Min	Q1	Median	Q3	Max
Weights	0.05	0.34	0.55	1.13	6.97

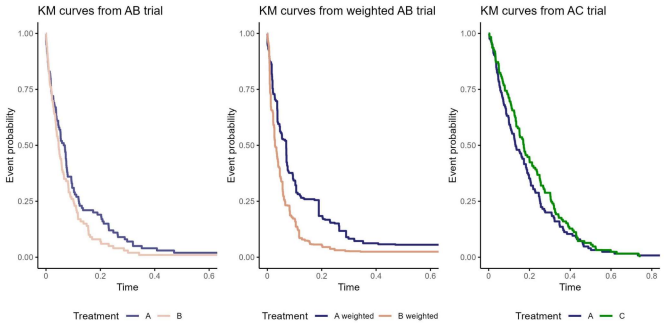
Table 2. Baseline characteristics across trials

Trial	Sample size / ESS	X1, mean (sd)	X2, mean (sd)	X3, proportion
Overall baseline characteristics				
Trial AB	200	0.97 (0.51)	2.62 (1.11)	19%
Trial AC	250	1.16 (0.47)	2.49 (1.15)	55%
Baseline characteristics of AB after MAIC weighting process				
Trial AB weighted	88.75	1.16 (0.47)	2.49 (1.15)	55%

RESULTS

- For both MAIC and ML-NMR, **proportional hazards assumption (PHA) was tested and not rejected** for the different Kaplan-Meier curves. The weighted B vs A HR [95% CI] was then computed. *Figure 2* illustrates the different Kaplan-Meier curves.

Figure 2. Kaplan-Meier curves



- The ML-NMR is based on an **IPD regression**. A **numerical integration** step was required to average the individual level model over the covariates distribution and then form the aggregate-level model. IPD **correlation matrix** and **IPD variables distributions** were used.
- True estimates from simulation along with the MAIC and ML-NMR HRs are summarised in *Table 3* **according to the population of interest**. MAIC was found to be limited in adjusting for heterogeneity, providing one estimate per comparison, only valid for the AgD population. In contrast, ML-NMR estimates treatment effects for both AB and AC populations.

Table 3. HR [95% CrI/CI] from true Weibull model, MAIC, and ML-NMR

Model	Comparison	Population AB	Population AC
True	B vs A	1.34	1.57
	C vs A	0.66	0.78
	B vs C	2.01	2.01
MAIC	B vs A	-	1.61 [1.01, 2.56]
	C vs A	-	0.85 [0.67, 1.09]
	B vs C	-	1.89 [1.12, 3.21]
ML-NMR	B vs A	1.28 [0.96, 1.72]	1.65 [1.10, 2.48]
	C vs A	0.61 [0.39, 0.90]	0.79 [0.58, 1.03]
	B vs C	2.08 [1.30, 3.57]	2.08 [1.30, 3.57]

: MAE < 10%, : MAE ≥ 10 %

- HRs obtained through the **ML-NMR were closer** to the true values compared to the MAIC based on mean absolute error (MAE). ML-NMR generates estimates for **any target populations**, based on baseline characteristics and survival hazard, while MAIC is limited to the AgD population.
- ML-NMR also provides **estimates of the impact of covariates** on HRs within active treatment class. These estimates aligned with the true values *(Table 4)*, offering a comprehensive **overview of TEMs impacts**.

Table 4. TEMs impact estimates in true Weibull model and ML-NMR

Covariate	True	ML-NMR
X1	0.20	0.17 [-0.33, 0.67]
X2	-0.10	-0.35 [-0.60, -0.10]
X3	0.30	0.46 [-0.20, 1.15]

- This study is an illustrative case, based on one simulated dataset and would need additional scenarios for findings to be generalized.

CONCLUSIONS

The relative treatment effect estimates obtained through the MAIC or ML-NMR are **specific to the population characteristics** in terms of TEMs. While the MAIC can compute estimates for the comparator's population only, the **ML-NMR can compute estimates applicable to different target populations**, making it a more flexible and potentially less biased method for indirect comparisons.

REFERENCES AND ABBREVIATIONS

References: [1]Signorovitch et al. (2012). Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. Value Health J Int Soc Pharmacoeconomics Outcomes Res. 2012;15(6):940-7. [2]Phillippo DM (2019) Calibration of treatment effects in network meta-analysis using individual patient data. PhD Thesis, University of Bristol. [3]Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons. Adopted on 8 March 2024 by the HTA CG pursuant to Article 3(7), point (d), of Regulation (EU) 2021/2282 on Health Technology Assessment. [4]Brilleman SL et al. (2020). "Simulating Survival Data Using the simsurv R Package." Journal of Statistical Software, 97(3), 1–27. doi:10.18637/jss.v097.i03. [5]Bucher HC et al. (1997). The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. juin 1997;50(6):683-91. [6]Phillippo DM (2024). multinma: Bayesian Network Meta-Analysis of Individual and Aggregate Data. doi:10.5281/zenodo.3904454, R package version 0.7.2.

Abbreviations: AgD: aggregated data; CI: confidence interval; CrI: credible interval; ESS: effective sample size; HR: hazard ratio; IPD: individual patient data; ITC: indirect treatment comparison; MAE: mean absolute error; MAIC: matching-adjusted indirect comparison; ML-NMR: multi-level network meta-regression; sd: standard deviation; TEM: treatment effect modifier

DISCLOSURES

Chopard-Lallier C., Le Nouveau P. and Gauthier A. are employees of Amaris Consulting. Bertin N. was an employee of Amaris Consulting at the time of preparation of the work of this poster. He is no longer affiliated with Amaris Consulting.

Presented at: ISPOR Europe 2024: 17-20 November 2024; Barcelona, Spain