Why Consider Using Multi-Level Network Meta-Regression (ML-NMR)? A Layman's Guide to the Approach and Its Benefits

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INTRODUCTION

- **Indirect treatment comparisons** (ITCs) are conducted to synthesize evidence from clinical trials involving multiple treatments. The most common method is the **Network Meta-Analysis** (NMA), based on **aggregate data** (AgD) under the assumption of **balanced treatment effect modifiers** (TEMs) across trials.
- In case of **heterogeneous distribution of TEMs**, **Matching-Adjusted Indirect Comparison** (MAIC) or **Simulated Treatment Comparison** (STC) are employed. However, these approaches provide only **head-to-head estimates** and cannot be applied within a larger network.
- The **Multi-Level Network Meta-Regression** (ML-NMR) was recently developed by Phillippo 2019[1] and aims to relax the hypothesis of homogeneity by **adjusting on covariates** using **individual patient data** (IPD) from at least one study, and AgD for the remaining studies in networks of any size.

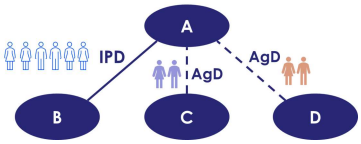
OBJECTIVES

- This work aims to provide a presentation of the recently suggested **Multi-Level Network Meta-Regression** method in layman's terms and to illustrate its benefits based on a simulated example in presence of heterogeneity.

METHODS

- A **time-to-event outcome** following a Weibull distribution and three covariates from three 1:1 randomised controlled trials, respectively assessing drugs A vs B, A vs C, and A vs D, were **simulated once** using *simsurv*[2] R package. The **covariates act as prognostic factors and TEMs**, with same TEM effects per treatment classes, with B, C, and D being active treatments, and A placebo. Data for AC and AD trials was restricted to AgD. *Figure 1* illustrates the network of evidence.

Figure 1. Network of evidence



- **Two scenarios** were generated: scenario 1 included trials with **homogeneous** covariates distribution, scenario 2 considered **heterogeneity** regarding TEMs.
- The *multinma*[3] R package was used to conduct ML-NMR on both scenarios through the following steps:

1 Leverage information from IPD trial

- Covariates **correlation** structure
- Definition of the **individual-level** regression model

2 Leverage information from AgD trial

- **Baseline characteristics** of each trial
- Digitization of **Kaplan-Meier curves**

3 Integrate over the AgD

- Generate **pseudo IPD** of the AgD trials based on AgD **covariates distribution** and **correlation structure** from IPD

4 Run the Bayesian model

- **Fixed- or random-effect(s)** models can be fitted depending on network geometry. Different parametric distributions can be assumed. The model uses Markov Chain Monte Carlo algorithm, 2,000 iterations and **adjustment on covariates.**

5 Estimate in the target population

- **Treatment effects are adjusted** to specific trial covariates distribution

- **True values** using the Weibull model and a fixed-effect **NMA** using AgD hazard ratios for both scenarios were computed to compare the approaches. ML-NMR was fitted based on these assumptions.

RESULTS

- The **covariates distributions** in scenarios 1 and 2 are presented in *Table 1*. Heterogeneity was induced in TEMs in scenario 2 through AB and AD trials in terms of X1 and X2 distributions.

Table 1. Covariates distributions in both scenarios

	Scenario 1 (homogeneity)			Scenario 2 (heterogeneity)		
Trial	Trial AB	Trial AC	Trial AD	Trial AB	Trial AC	Trial AD
X1, mean (sd)	0.89 (0.48)	1.15 (0.47)	0.97 (0.52)	**1.59 (0.48)**	1.15 (0.47)	**0.67 (0.52)**
X2, mean (sd)	2.50 (1.20)	2.58 (1.10)	2.13 (1.06)	2.54 (1.21)	2.58 (1.10)	2.13 (1.06)
X3, %	22 %	25%	20%	**44%**	25%	**12%**

Green/red: indicates an increase/decrease in the covariate between scenarios 1 and 2

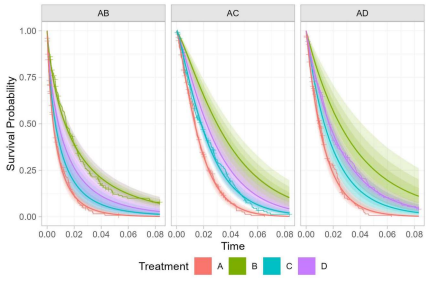
- Since scenario 1 was composed of homogeneous trials in terms of TEMs, HRs were expected to be similar across trials' populations. Both NMA and ML-NMR provided results close to true values and adjustment on target population was not essential.
- Scenario 2 presented heterogeneous populations and therefore true HRs were different across trials' populations. Results of the different approaches are summarised in *Table 2*. ML-NMR was adjusted for TEMs and provided **estimates per target population** whereas NMA provided only one global estimate per comparison.

Table 2. True values, NMA, and ML-NMR estimates in scenario 2

Comparison	Method	Trial AB	Trial AC	Trial AD
B vs A	**True**	**0.42**	**0.36**	**0.35**
	NMA		0.42 [0.34, 0.52]	
	ML-NMR	0.42 [0.34, 0.52]	0.37 [0.27, 0.51]	0.38 [0.23, 0.61]
C vs A	**True**	**0.77**	**0.66**	**0.63**
	NMA		0.67 [0.55, 0.82]	
	ML-NMR	0.78 [0.57, 1.05]	0.69 [0.56, 0.85]	0.70 [0.51, 0.94]
D vs A	**True**	**0.70**	**0.60**	**0.57**
	NMA		0.53 [0.42, 0.67]	
	ML-NMR	0.61 [0.36, 1.00]	0.54 [0.38, 0.75]	0.54 [0.43, 0.69]

- **ML-NMR** was found to be the **most accurate approach** in the context of TEMs heterogeneity where treatment effects are linked to patient characteristics distribution. ML-NMR computed **population-average results closer to true values** than NMA estimates which correspond to the initial trial's population. In particular, for the indirect link D vs A, the **NMA CrI does not include the true HR** value for the AB population.
- **Different estimates and predictions** can be computed through the ML-NMR using the covariates adjustment and baseline survival hazard such as median survival time or **predicted Kaplan-Meier curves** depicted in *Figure 2* for trials' populations included in the network or external target patients.

Figure 2. Predicted Kaplan-Meier curves in target populations



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

CONCLUSIONS

- This study offers a **simple overview of the ML-NMR**, advocating its integration in future HTA submissions and enhancing understandability for a non-statistical audience.
- ML-NMR enables **population-adjusted ITC** according to multiple factors at the network level, a significant advancement over previous methods that permitted population adjustments solely in a pairwise context (MAIC, STC) or according to a limited set of factors (NMR).

REFERENCES AND ABBREVIATIONS

References: [1]Phillippo DM (2019) Calibration of treatment effects in network meta-analysis using individual patient data. PhD Thesis, University of Bristol. Available from research-information.bristol.ac.uk
[2]Brilleman SL, Wolfe R, Moreno-Betancur M, Crowther MJ (2020). "Simulating Survival Data Using the simsurv R Package." Journal of Statistical Software, 97(3), 1–27. doi:10.18637/jss.v097.i03.
[3]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; HR: hazard ratio; IPD: individual patient data; ITC: indirect treatment comparison; MAIC: matching-adjusted indirect comparison; ML-NMR: multi-level network meta-regression; NMA: network meta-analysis; sd: standard deviation; NMR: network meta-regression; STC: simulated treatment comparison; 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.

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