Anchors Away: Navigating Unanchored Indirect Comparisons with Multilevel Unanchored Meta-regression

MSR28

Conor Chandler,[1] K. Jack Ishak[2]

[1]Thermo Fisher Scientific, Waltham, MA, USA; [2]Thermo Fisher Scientific, Montreal, Canada

Background

- Imbalances in clinically relevant baseline characteristics (i.e., treatment effect modifiers and/or prognostic factors [PFs]) across study populations may lead to biased results in unadjusted indirect comparisons (e.g., network meta-analysis).
- Multilevel network meta-regression (ML-NMR)[1] enhances network meta-analysis by statistically adjusting for effect modification (EM) in connected networks.
  - ML-NMR is the most flexible anchored population-adjusted indirect comparison (PAIC) method, as it enables transporting effect estimates to any target population of interest and is capable of comparing any number of treatments.
- Existing PAIC methods for disconnected networks (i.e., unanchored matching-adjusted indirect comparison [MAIC] and simulated treatment comparison [STC]), however, are limited to pairwise comparisons and cannot transport estimates beyond the comparator population.

Objectives

- **To address this gap, we introduce multilevel unanchored meta-regression (ML-UMR)—a novel extension of ML-NMR for unanchored comparisons—and assess its performance via simulation.**

Methods

ML-UMR: A Novel Extension of ML-NMR

- We introduced two types of Bayesian ML-UMR models (**Figure 1**) and motivated the application with simulated examples of pairwise PAICs for treatment A (index) vs. B (comparator). Here, patient-level data (PLD) are available for A, while only aggregate-level data (ALD) are reported for B.
  1. The first type of ML-UMR model, invoking the shared PF assumption (SPFA), implied there is treatment effect homogeneity at the individual level (i.e., no EM) for A vs. B.
     a. Fitted using PLD for A and ALD for the overall population for B.
  2. The second type of ML-UMR model, relaxing SPFA, allowed for potential treatment effect heterogeneity at the individual level (i.e., EM) for A vs. B.
     a. Fitted using PLD for A and ALD for non-overlapping subgroups that partition the overall population for B (e.g., four subgroups formed by the interactions between PFs X_1 and X_2 in simulated examples).
- The general formulas for an ML-UMR indirectly comparing A vs. B are presented in **Figure 1**, which extend straightforwardly to analyses involving additional treatments and/or multiple studies per treatment.

Figure 1. ML-UMR Model Comparing A vs. B

	ML-UMR Type 1 (Invoking SPFA)	ML-UMR Type 2 (Relaxing SPFA)
Individual-level component	$y_{i(A)} \sim \pi_{Ind}(\theta_{i(A)})$ $g(\theta_{i(A)}) = \alpha_{(A)} + \boldsymbol{x}_{i(A)}^T \boldsymbol{\beta}_{PF}$	$y_{i(A)} \sim \pi_{Ind}(\theta_{i(A)})$ $g(\theta_{i(A)}) = \alpha_{(A)} + \boldsymbol{x}_{i(A)}^T \boldsymbol{\beta}_{(A)PF}$
Aggregate-level component	$y_{\bullet(B)} \sim \pi_{Agg}(\theta_{\bullet(B)})$ $\theta_{\bullet(B)} = \int g^{-1}\left(\alpha_{(B)} + \boldsymbol{x}_{(B)}^T \boldsymbol{\beta}_{PF}\right) f(\boldsymbol{x}_{(B)}) dx$ $\theta_{\bullet(B)} \approx \sum_{j=1}^{n_{(B)}} g^{-1}\left(\alpha_{(B)} + \boldsymbol{x}_{j(B)}^T \boldsymbol{\beta}_{PF}\right) * \left(\frac{1}{n_{(B)}}\right)$	$y_{\bullet(B)z} \sim \pi_{Agg}(\theta_{\bullet(B)z})$ $\theta_{\bullet(B)z} = \int g^{-1}\left(\alpha_{(B)} + \boldsymbol{x}_{(B)z}^T \boldsymbol{\beta}_{(B)PF}\right) f(\boldsymbol{x}_{(B)z}) dx$ $\theta_{\bullet(B)z} \approx \sum_{j=1}^{n_{(B)z}} g^{-1}\left(\alpha_{(B)} + \boldsymbol{x}_{j(B)z}^T \boldsymbol{\beta}_{(B)PF}\right) * \left(\frac{1}{n_{(B)z}}\right)$

Abbreviations: ML-UMR = multilevel unanchored meta-regression; SPFA = shared prognostic factor assumption
Where π_{Ind} and π_{Agg} are individual- and aggregate-level distributions (e.g., Bernoulli and Binomial in simulations), θ represents the mean outcome, $\boldsymbol{x}$ is a vector of PFs, $\boldsymbol{\beta}_{PF}$ is a vector of regression coefficients for PFs, α is the baseline outcome for treatments A and B, i is the number of individuals in the index study (A), z is an indicator for the mutually exclusive subgroups (for each possible combination of PFs) for B. Note the individual-level and aggregate-level components of ML-UMR presented here are for a simple pairwise PAIC of A vs. B. These formulas can be extended and written more generally to handle three or more treatments and multiple studies per treatment.

Simulation Study

- Our simulation study indirectly compared binary outcomes for A vs. B from two single-arm studies.
- Population imbalance was induced across studies by generating correlated PFs with different means, and outcomes were simulated: 1) assuming PFs have the same effect on outcomes for A and B (i.e., SPFA), which implies no EM; and 2) relaxing SPFA, thereby inducing weak to strong EM.
- Bayesian ML-UMR models were fitted using OpenBUGS (3 chains, 2,000 total iterations per chain, 1,000 burn-in period) to assess the absolute and relative bias and coverage of 95% credible intervals (CrIs) of predicted marginal log odds ratios (LORs) in the comparator and index populations.
- The two types of ML-UMR models were evaluated under three scenarios: 1) shared PFs for A and B (i.e., no EM); 2) weak violation of SPFA (i.e., weak EM); and 3) strong violation of SPFA (i.e., strong EM).
- **Table 1** summarizes the assumptions and simulation settings settings for this study.

Table 1. Assumptions for Simulation Study

Parameter	Assumption
Monte Carlo replications	500
Sample sizes	Equal samples of n=1,000 for each trial
PFs	Two binary variables (X_1, X_2) with moderate correlation (0.5) Index: $X_1 = X_2 = 0.3$ Comparator: $X_1 = X_2 = 0.7$
Prognostic strength of X_1*	Scenarios 1-3: $\beta_{1,A} = \beta_{1,B} = -1$
Prognostic strength of X_2*	Scenario 1: $\beta_{2,A} = \beta_{2,B} = -2$ Scenario 2: $\beta_{2,A} = -2,\ \beta_{2,B} = -1.75$ Scenario 3: $\beta_{2,A} = -2,\ \beta_{2,B} = -1$
Baseline outcome*	$\alpha_A = 1; \alpha_B = 0.25$

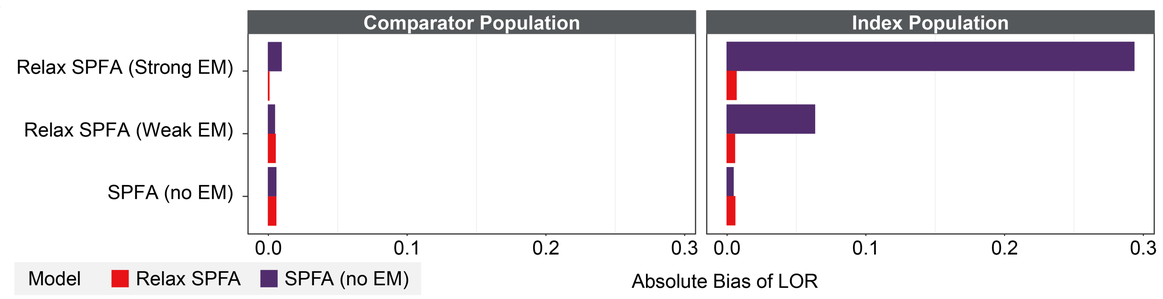
Abbreviation: PF = prognostic factor
*Modeled on the logit scale

Results

Simulation Study

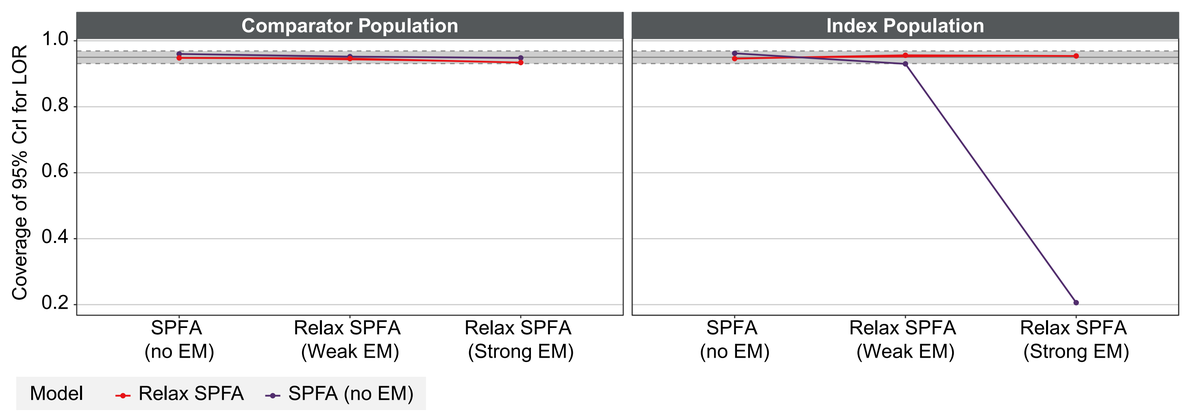
- ML-UMR models invoking SPFA accurately predicted LORs for A vs. B in the comparator population regardless of the true EM strength (|bias|<0.009 [<6.4%] and 94.8%–96.0% coverage) (**Figure 2** and **Figure 3**).
- The predicted LORs for A vs. B in the index population were unbiased in the absence of EM and relatively robust to weak EM (bias=-0.06 [-11%]; coverage=93%); a high degree of bias (-0.29 [-67%]) was observed, however, when EM was strong.
- Relaxing SPFA in the ML-UMR model resulted in accurate LORs in both the index and comparator populations across all scenarios: bias<0.007 [<1.5%] and 93.4%–95.6% coverage.

Figure 2. Absolute Bias of LOR



Abbreviations: EM = effect modification; LOR = log odds ratio; SPFA = shared prognostic factor assumption
The absolute bias represents the difference between the average prediction of the ML-UMR model and the true treatment effect (ignoring the direction of error), where values closer to 0 indicate that the average model predictions more closely reflect reality and large values indicate a systematic error with model predictions (i.e., over or under prediction of the true effect). Note, the predicted effect in the index is biased when SPFA is incorrectly assumed in the model, but the estimate in the comparator population has negligible bias. This is because the regression coefficients for PFs are more heavily influenced by the PLD for A, and do not generalize for B outside of the comparator population.

Figure 3. Coverage of 95% CrIs for LOR



Abbreviations: CrI = credible interval; EM = effect modification; LOR = log odds ratio; SPFA = shared prognostic factor assumption
Empirical coverage probabilities of estimated 95% CrIs for LORs. Estimates within the shaded region did not significantly differ from the nominal confidence level of 95%. Note, the assumed samples sizes were large in the simulation study (n=1,000 for each arm) and other simplifying assumptions were imposed, which may contribute to the observed coverage probabilities.

Conclusions

- **This study demonstrates that the ML-NMR framework can be extended for unanchored indirect comparisons.**
- **In the pairwise unanchored setting, the SPFA is the fundamental assumption for transporting effect estimates from the comparator population to a different target population, such as the index.**
  - **This is analogous to the shared effect modifier assumption (SEMA) in anchored PAICs. SPFA is a stronger assumption than SEMA, and thus it may be more difficult to achieve transportability in unanchored analyses.**
  - **The SPFA may be relaxed by leveraging comparator data for appropriate subgroups and/or multiple comparator studies[2] or clinical expert opinion. Stratified analyses could also be explored. Further research is required in this area.**
  - **Obtaining the data necessary to relax SPFA will be challenging in practice, as the reporting of comparator data is often limited.**
- **ML-UMR effectively simplifies to unanchored STC if two treatments are being compared in the comparator population.**
  - **Consistent with the findings of Ren et al.,[3] effect estimates in the comparator population were unbiased if all PFs were included in the model, regardless if the SPFA is violated.**
- **Unlike MAIC and STC, ML-UMR allows transporting relative effect estimates to any target population under certain assumptions (e.g., the SPFA may be required if sufficient data are not reported for comparators), can compare any number of treatments, and can synthesize multiple studies per treatment, but it remains subject to strong limitations inherent to unanchored comparisons.**

References

1. Phillippo DM, et al. *J R Stat Soc Ser A Stat Soc*. 2020 Jun;183(3):1189-1210. **2.** Phillippo, DM. PhD thesis, University of Bristol. 2019.
3. Ren S, et al. *Res Synth Methods*. 2024 Jul;15(4):657-670.

Disclosures

All authors are employees of PPD™ Evidera™ Health Economics & Market Access, Thermo Fisher Scientific. This poster was funded by Thermo Fisher Scientific.

Acknowledgments

Editorial and graphic design support were provided by Sean Smith and Shani Berger of Thermo Fisher Scientific.