Ranking of Treatments in Multi-Level Network Meta-Regression (ML–NMR): Incorporating Minimally Important Differences

MSR234

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Objective

To incorporate minimally important differences (MIDs) into treatment ranking for multi-level network meta-regression (ML–NMR), avoiding unwarranted prioritisation of statistically different but clinically comparable treatments.

Background

- In NMA and its population-adjusted extension, ML–NMR, the magnitude of relative treatment effects is typically ignored in the calculation of ranking metrics, such as probability best and surface under the cumulative ranking curves (SUCRAs). This leads to treatment rankings that may not reflect clinically meaningful differences and may therefore mislead decision-making.
- Minimally important differences represent the smallest value in a given outcome that is considered by patients or clinicians to represent a meaningful difference between treatments. In general, MID-adjusted ranking metrics can support interpretation when a shifted null hypothesis, that is, a point of no effect other than zero, is useful or required, as in certain cases under EU Joint Clinical Assessment (JCA) indirect treatment comparison guidance.
- Previous work by the authors has developed the theory and an associated R package for incorporating MID in treatment ranking for Bayesian NMA; until now, the R package did not incorporate MID in ranking metrics when conducting ML–NMR.[1]

Methods

- We extended the R package mid.rank.nma (an extension of multinma) to apply the MID-based treatment ranking methodology developed for Bayesian NMA by Curteis et al. (2025) to ML–NMR.[2]
- As a proof-of-concept example, we applied mid.rank.nma to an ML–NMR in plaque psoriasis. Specifically, IXORA-S (a head-to-head trial comparing ixekizumab and ustekinumab) demonstrated superiority of ixekizumab Q2W over ustekinumab based on a non-inferiority margin of -12.6% of difference in risk of PASI 90 assuming a 43% response rate for ustekinumab.[3]
- We applied the same margin (converted to the odds ratio [OR] scale; comparator-vs-treatment OR =1.66) to generate IXORA-S population-specific MID-adjusted ranking metrics via ML–NMR.
- The ML–NMR comprised 7 treatments across 9 studies in achieving Psoriasis Area and Severity Index (PASI) 90, adjusting for duration of psoriasis, previous systemic therapy, body surface area affected, body weight, and presence of psoriatic arthritis.
- A sensitivity analysis assessed the impact of varying the MID on the OR scale, on mean SUCRA values.

Results

- The network plot is shown in **Figure 1**.
- Even accounting for an MID of -12.6% of difference in risk of PASI 90, ixekizumab Q2W retained a 100% probability of being best or equal best.
- With no MID, ixekizumab Q4W, secukinumab 300 mg, secukinumab 150 mg and ustekinumab had distinct median ranks 2 through 5 respectively (**Table 1**), indicating statistical non-equivalence. With MID adjustment, ixekizumab Q4W and secukinumab 300mg (equal median rank 2.5), and secukinumab 150 mg and ustekinumab (equal median rank 4.5), were tied (**Table 1**), suggesting clinically comparable efficacy. Median ranks were preserved across projected trial populations.
- Varying the MID around the primary value (OR=1.66) revealed sensitivity of mean SUCRA value to MID magnitude (**Figure 2**).

Conclusion

The R package mid.rank.nma now supports MID-adjusted ranking metrics for ML–NMR, facilitating MID-adjusted treatment ranking metrics to inform decision making in a population-adjusted context. Rank estimates were sensitive to the value of MID, highlighting the importance of justifying selection of MID value, and the relevance of sensitivity analyses. MID-adjusted ranking avoids the influence of unwarranted distinct ranks on clinical decision-making, and as such supports best practice interpretation when a shifted null hypothesis is relevant.

FIGURE 1

Plaque psoriasis ML–NMR: network plot

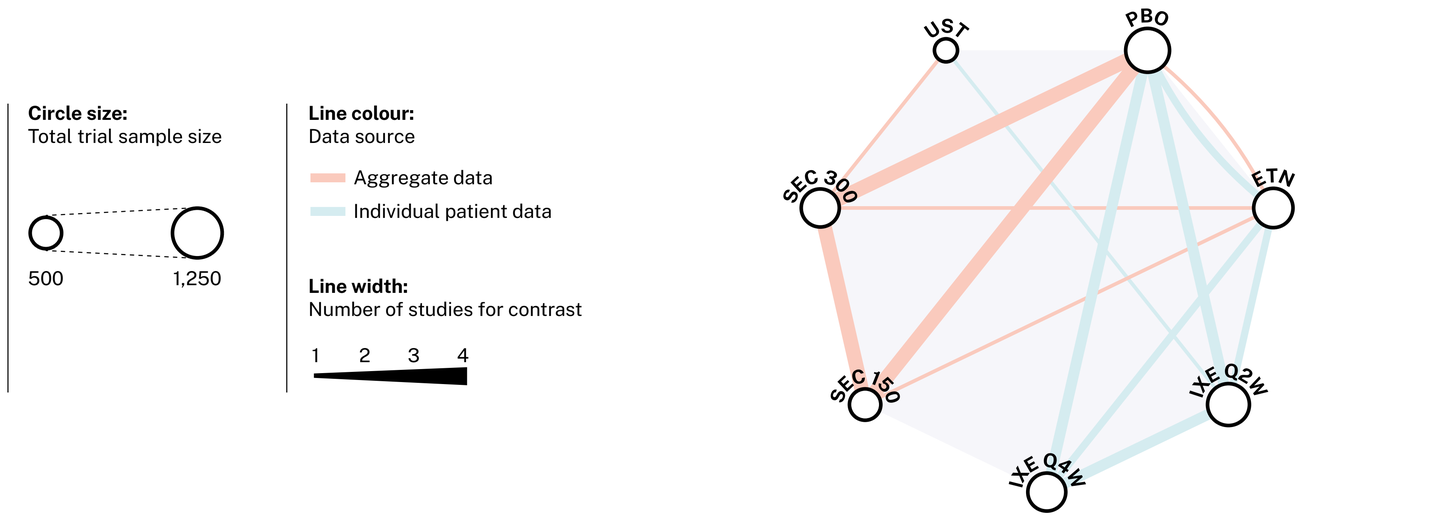


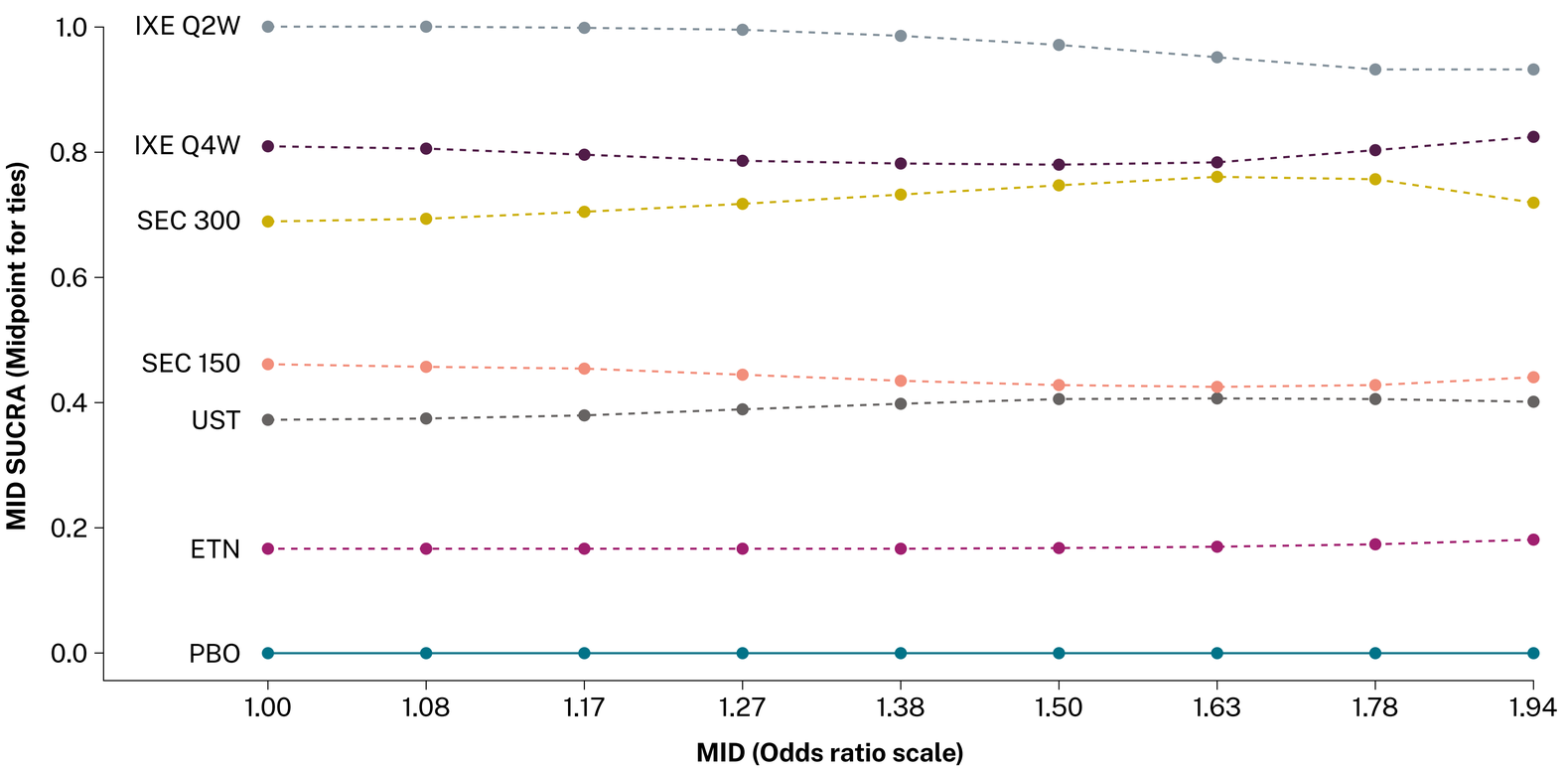
TABLE 1

Plaque psoriasis NMA ranking metrics: with and without MID adjustment

	Median Rank (no MID)	MID-Median Rank	SUCRA (no MID)	MID-SUCRA	P Best (no MID)	MID-P Best	MID-P Best or Equal Best
Ixekizumab Q2W	1	1	1.00	0.95	1.00	0.64	1.00
Ixekizumab Q4W	2	2.5	0.81	0.79	0.00	0.00	0.34
Secukinumab 300 mg	3	2.5	0.69	0.76	0.00	0.00	0.30
Secukinumab 150 mg	4	4.5	0.46	0.43	0.00	0.00	0.00
Ustekinumab	5	4.5	0.37	0.41	0.00	0.00	0.00
Etanercept	6	6	0.17	0.17	0.00	0.00	0.00
Placebo	7	7	0.00	0.00	0.00	0.00	0.00

FIGURE 2

Sensitivity analysis: variation in mean SUCRA value associated with magnitude of MID value



Abbreviations: AgD: aggregate data; **ETN:** Etanercept; **IPD:** individual patient data; **IXE:** ixekizumab; **JCA:** Joint clinical assessment; **MID:** Minimally important difference; **ML–NMR:** Multi-level network meta-regression; **NMA:** Network meta-analysis; **OR:** odds ratio; **P:** probability; **PASI:** Psoriasis area and severity index; **PBO:** Placebo; **Q2W:** Once every two weeks; **Q4W:** Once every four weeks; **QXW:** dosed X times per week; **SEC:** secukinumab; **SUCRA:** Surface under the cumulative ranking curve; **UST:** ustekinumab.

References: [1]Phillippo DM. Multinma: a comprehensive R package for Bayesian network meta-analysis with aggregate data, individual patient data, or a mixture of both, In Society for Research Synthesis Methodology Annual Meeting 2024, 2024; [2]Curteis T, Wigle A, Michaels CJ, et al. Ranking of treatments in network meta-analysis: incorporating minimally important differences. BMC medical research methodology 2025;25:67; [3]Reich K, Pinter A, Lacour J, et al. Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a phase III study. British Journal of Dermatology 2017;177:1014-1023.

Acknowledgements: The authors thank Hannah Barallon and Louis Nassé, Costello Medical, for graphic design assistance. We also thank Alex Porteous for his review and editorial assistance in the preparation of this poster.

Presented at ISPOR Europe 2026 | Vienna, Austria | 8–11 November

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