Methodologic Considerations to Guide Clinician Interpretation and Assessment of Network Meta-Analyses in Psoriasis

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Key Takeaways

- **The abundance and variable quality of published NMAs investigating treatments for psoriasis can make it challenging for clinicians to draw meaningful conclusions to inform clinical practice.**
- **Many published NMAs differ according to included trials, outcomes assessed, and methods applied, making comparisons between NMAs difficult.**
- **Clinicians should critically assess each NMA according to several key parameters, including trial eligibility criteria, baseline risk adjustments, interpretation of point estimates alongside estimates of uncertainty, short- and long-term comparisons across trials, and inclusion of safety outcomes.**
- **Even when appropriate methods are applied for NMAs, conclusions drawn from their results may have limited context, so it is important for clinicians who treat psoriasis to be informed by diverse sources of information.**

Background

- Understanding comparative evidence for available treatments within a disease space is critical to inform clinical decision making. Randomized controlled trials (RCTs) are the gold standard for evaluating the comparative efficacy of two treatments; however, they can be expensive and time consuming and are often unfeasible.
- Indirect treatment comparisons (ITCs) are a commonly used alternatives to assess comparative efficacy of two or more treatments in the absence of head-to-head trials. The optimal ITC method ultimately depends on the type of data available, the comparability of the included studies, and the number of treatments being assessed.
- Each ITC method has its own strengths and limitations, so it is essential to critically assess their attributes and limitations when considering using ITC studies to inform clinical decision making. One increasingly popular method, network meta-analysis (NMA), is the focus of this review.

Objectives

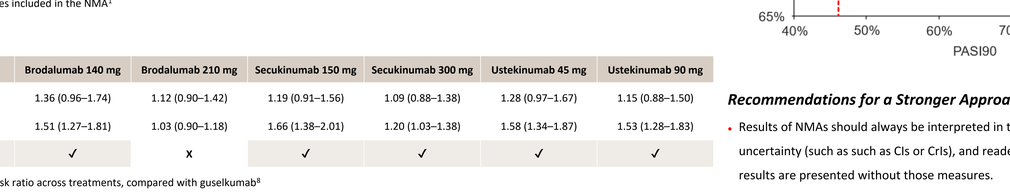
To assist clinicians who treat psoriasis with the evaluation and interpretation of NMAs, so that this type of evidence can be properly leveraged for decision making in clinical practice.

Overview of Network Meta-Analyses

- NMAs use statistical methods to combine results from two or more studies with similar designs (**Figure 1**).
- NMAs compare treatments using direct and indirect evidence within a network of RCTs.
- They should be informed by a systematic literature review to ensure inclusion of all relevant data from published studies.
- Analyses must meet the **three key statistical assumptions** of an NMA:

1. **Transitivity**: There are no systematic differences in characteristics being statistically compared between trials.
2. **Consistency**: The actual treatment effects observed for comparators roughly align with the estimated indirect treatment effects for those same comparators.
3. **Homogeneity**: Components such as patient population, inclusion criteria, time to follow up, and treatment experience are reasonably similar between trials.

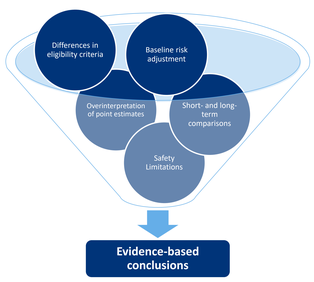
Figure 1: Steps for conducting an NMA



NMAs in Psoriasis

- Psoriasis is a complex, chronic, and prevalent inflammatory skin condition. Recent advances have introduced numerous new treatment options; however, the abundance of data on currently available agents has been an obstacle for some clinicians, as they face the challenge of analyzing conflicting comparative evidence. Consequently, it may be difficult to discern whether discrepancies between therapeutics may arise from true differences in treatment effects, or from biased or misleading comparative analyses.
- Key elements of ITCs of treatments for psoriasis, such as prior treatment experience, outcomes measured, timepoints analyzed, and methodologies used, differ between published NMAs, resulting in discrepancies in conclusions.
- It is critical that all NMAs either only include studies with highly similar designs or carefully select appropriate analyses that can account for heterogeneity between trials and reduce bias in estimated outcomes.
- There are five key topics to focus on when evaluating an NMA for sources of bias: differences in eligibility criteria, baseline risk adjustment, overinterpretation of point estimates, short- and long-term comparisons, and safety limitations (**Figure 2**).

Figure 2: Summary of key topics to consider when evaluating and interpreting NMAs



1. *Differences in Eligibility Criteria*

- Substantial, unmanaged differences in the eligibility criteria of included studies can bias the NMA and produce misleading results. A well-conducted analysis will involve careful review of eligibility criteria for all included trials.
- For example, one NMA of psoriasis treatments compared 50 studies, but did not assess or account for any heterogeneity in eligibility criteria across them (**Table 1**).[1]

Recommendations for a Stronger Approach

- An assessment of cross-trial heterogeneity must be performed. If heterogeneity between studies is identified, steps should be taken to mitigate its impact.
- Depending on the type and extent of the heterogeneity, the following strategies can help to accommodate and minimize bias:
  - Use of a random effects rather than a fixed effect model
  - Excluding trials with particularly different designs or eligibility criteria
  - Conducting sensitivity analyses
  - Performing baseline risk adjustment(s)

	NCT01241591[2]	AMAGINE-1[3]	IXORA-S[4]	UltIMMa 1&2[5]	VOYAGE 1[6]&2[7]
Therapies	Tofacitinib, etanercept, placebo	Brodalumab, placebo	Ixekizumab, ustekinumab, placebo	Risankizumab, ustekinumab, placebo	Guselkumab, adalimumab, placebo
Disease duration	≥12 months	≥6 months	≥6 months	≥6 months	≥6 months
Baseline PASI cut-off	≥12	≥12	≥10	≥12	≥12
≥1 CST failure or intolerance	Required	Not Required	Required	Not required	Not required

Table 1: Key differences in eligibility criteria across select studies included in the NMA[1]

2. *Baseline Risk Adjustment*

- Differences in baseline risk may impact outcomes at the study level and can bias the results of an NMA.
- While other ITC methods that leverage individual patient data can better account for differences in baseline characteristics than NMAs, it remains important to address residual heterogeneity as much as possible.
- For example, a 2018 NMA that investigated the impact of adjusting for differences in placebo response between trials demonstrated that adjusted NMAs led to different conclusions compared to unadjusted NMAs (**Table 2**).[8]

Recommendations for a Stronger Approach

- Assessment of variation in placebo response across trials can help to detect heterogeneity in baseline risk.
- Cross-trial heterogeneity often manifests as differences in placebo response, so baseline risk adjustment should be conducted to account for placebo response.
- Adjusting for placebo response can reduce unexplained variation between studies and improve reliability of results.

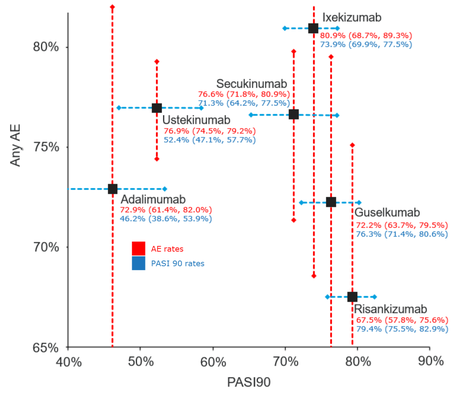
Comparison with Guselkumab	Infliximab	Brodalumab 140 mg	Brodalumab 210 mg	Secukinumab 150 mg	Secukinumab 300 mg	Ustekinumab 45 mg	Ustekinumab 90 mg
Initial Risk Ratio (CrI)	1.24 (0.80–1.50)	1.36 (0.96–1.74)	1.12 (0.90–1.42)	1.19 (0.91–1.56)	1.09 (0.88–1.38)	1.28 (0.97–1.67)	1.15 (0.88–1.50)
Adjusted Risk Ratio (CrI)	1.30 (1.08–1.56)	1.51 (1.27–1.81)	1.03 (0.90–1.18)	1.66 (1.38–2.01)	1.20 (1.03–1.38)	1.58 (1.34–1.87)	1.53 (1.28–1.83)
Change in interpretation?	✓	✓	X	✓	✓	✓	✓

Table 2: Impact of adjusting for placebo response on PASI 90 risk ratio across treatments, compared with guselkumab[8]
Note: A risk ratio >1.0 indicates a result favoring GUS. Non-overlap of the credible interval with 1.0 indicates statistical significance.

3. *Overinterpretation of Point Estimates*

- Some studies do not report estimates of uncertainty, such as confidence intervals (CI) or credible intervals (CrI), which can result in overinterpretation of point estimates. Conclusions derived from point estimates alone are not informed by the full context of the analysis.
- An NMA published in 2021 featured a bivariate plot that overstated differences between treatments, suggesting superior safety and efficacy for risankizumab compared to other included treatments.[9] However, if CrIs are added, the uncertainty in the data becomes clear (**Figure 3**).

Figure 3: Bivariate plot from a published NMA[9] with added credible intervals for AEs and PASI90[10].



Recommendations for a Stronger Approach

- Results of NMAs should always be interpreted in the context of measures of uncertainty (such as such as CIs or CrIs), and readers should be cautious when results are presented without those measures.

4. *Short- and Long-term Comparisons*

- Sometimes, when long-term data are limited, short-term outcomes are used to extrapolate results for long-term outcomes. This requires making assumptions about the continuation of short-term trends to predict long-term results.
- However, extrapolating short-term results is often inappropriate, as short-term relative efficacy is not necessarily predictive of long-term outcomes.

Recommendations for a Stronger Approach

- It is important to consider the timepoints at which outcomes are assessed when drawing conclusions about the results of an analysis.
- Methodological differences are sometimes observed between analyses of short- and long-term outcomes within the psoriasis literature. However, these differences may be based on factors such as availability of data rather than heterogeneity or study design and therefore may not be the most appropriate methods.

5. *Safety Limitations*

- The classification of adverse events (AEs) can be subjective and can also vary between regions, leading to differences in how serious AEs and non-serious AEs are categorized across studies.
- The absence of a clear causal relationship between the intervention and observed AEs makes the conclusions drawn from safety NMAs inappropriate.

Recommendation for a Stronger Approach

- While incorporating safety outcomes may give the impression of a more rigorous analysis, the certainty of these results is overstated when one therapy is both safer and more efficacious than others, while there is no evidence to support this assertion.
- Readers should be critical of any conclusions of safety outcomes drawn from NMAs due to these significant limitations.

PRESENTED AT: ISPOR 2025. **ABBREVIATIONS:** AE, adverse event; CI, confidence interval; CrI, credible interval; CST, conventional systemic therapy; ITC, indirect treatment comparison; mg, milligrams; NMA, network meta-analysis; PASI, Psoriasis Area and Severity Index; PICOS, population, intervention, comparator, outcomes, and study design; RCT, randomized controlled trial. **REFERENCES: 1**. Mrowietz U, Warren RB, Leonardi CL, et al. Network meta-analysis of biologic treatments for psoriasis using absolute Psoriasis Area and Severity Index values ≤1, 2, 3 or 5 derived from a statistical conversion method. J Eur Acad Dermatol Venereol. 2021;35(5):1161-75. **2**. Bachelez H, Van De Kerkhof PC, Strohal R, Kubanov A, Valenzuela F, Lee JH, Yakusevich V, Chimenti S, Papacharalambous J, Proulx J, Gupta P. Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomized non-inferiority trial. The Lancet. 2015 Aug 8;386(9993):552-61. **3**. 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