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**Name of Journal:** *World Journal of Methodology*

**Manuscript NO:** 72513

**Manuscript Type:** MINIREVIEWS

**Network meta-analyses: methodological prerequisites and clinical usefulness. A mini review**

Clinical relevance of NMAs

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**Author contributions:** Prof Venu Karthavapu and Konstantinos Tsikopoulos were involved in the conceptualization of the study. Mr. Tsikopoulos and Mr. Sidiropoulos conducted the literature research and extracted relevant information. Mr. Konstantinos Tsikopoulos and Mr. Dimitrios Kitridis assessed the quality of the included studies. Mr. Savvas Ilias Christofilos and Mr. Panagiotis Stoikos were involved in the generation of tables and the writing of the paper. Professor Venu Kavarthapu supervised and revised the paper accordingly. Throughout the study, Mr. Savvas Ilias Christofilos was an intern of Professor Maniatis's group at University College London. All authors have read and approved the final manuscript.

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**Received:** October 19, 2021

**Revised:**

**Accepted:**

**Published online:**

## **Abstract**

It is an undeniable fact that systematic reviews play a crucial role in informing clinical practice; however, conventional head-to-head meta-analyses do have limitations. In particular, studies can only be compared in a pair-wise fashion, and conclusions can only be drawn in the light of direct evidence. In contrast, network meta-analyses can not only compare multiple interventions but also utilize indirect evidence which increases their precision. On top of that, they can also rank competing interventions. In this mini-review, we have aimed to elaborate on the principles and techniques governing network meta-analyses to achieve a methodologically sound synthesis, thus enabling safe conclusions to be drawn in clinical practice. We have emphasized the prerequisites of a well-conducted Network Meta-Analysis (NMA), the value of selecting appropriate outcomes according to guidelines for transparent reporting, and the clarity achieved *via* sophisticated graphical tools. What is more, we have addressed the importance of incorporating the level of evidence into the results and interpreting the findings according to validated appraisal systems (i.e., the Grade of Recommendations, Assessment, Development, and Evaluation system - GRADE). Lastly, we have addressed the possibility of planning future research *via* NMAs. Thus, we can conclude that NMAs could be of great value to clinical practice.

**Key Words:** Network meta-analysis; quality of evidence; evidence-based medicine; systematic reviews

Christofilos SI, Tsikopoulos K, Tsikopoulos A, Kitridis D, Sidiropoulos K, Stoikos PN, Kavarthapu V. Network meta-analyses: methodological prerequisites and clinical usefulness. A mini review. *World J Methodol* 2022; In press

**Core Tip:** Systematic reviews with or without meta-analyses provide the highest quality of evidence, thus lying on the top of evidence based medicine hierarchy. However, pair-wise meta-analyses present the inherent limitation of exclusively

comparing direct evidence only. By contrast, Network Meta-Analyses (NMAs) also consider indirect evidence, thereby offering additional useful information. Conducting a NMA, however, has certain requirements such as assuming that transitivity across the included studies exists. What is more, maintaining sufficient statistical power in the analyses is crucial. In addition, performing head-to-head statistical comparisons prior to setting up networks of interventions is a prerequisite for a methodologically sound NMA, and selecting not only positive but also negative outcomes is required. Lastly, implementing quality appraisal systems to grade the level of evidence is highly recommended. Should all the above criteria are fulfilled, then accurate clinical conclusions can be drawn from a NMA.

## **INTRODUCTION**

### **Introduction**

Due to the plethora of different interventions for various clinical entities such as injection therapies for plantar fasciopathy<sup>[1]</sup> identifying the most efficient and safe treatment is among the prime interests of a researcher<sup>[2-4]</sup>. In the case of conventional meta-analyses, only two interventions can be compared at a time, and only those evaluated in head-to-head trials<sup>[5-7]</sup>. What is more, intervention effect estimates can only be calculated from direct evidence<sup>[2]</sup>. In contrast to pair-wise meta-analyses, network meta-analyses (NMA) enable not only simultaneous direct comparisons of multiple interventions but also indirect comparisons provided a common comparator is shared between interventions<sup>[2]</sup>. This is even possible in the case of two interventions that have never been directly compared<sup>[2]</sup>. In addition, interventions may also be ranked by means of the surface under the cumulative ranking (SUCRA) curves, thus allowing for judgements as to which treatment presents the highest probability of being the most effective<sup>[2]</sup>. It is underlined that identifying more than one highly efficacious treatments in a NMA is a common phenomenon given the subtle differences in treatment rankings of the modalities lying on the top of ranking probabilities tables. Overall, incorporating the results from network meta-analyses into clinical

practice guidelines could help clinicians to select the best available medication and/or intervention for a particular condition with the aim to improve healthcare.

### **Prerequisites for a well-conducted NMA - The assumption of transitivity and heterogeneity**

For a systematic review of randomized evidence to qualify for a network meta-analysis, the assumption of transitivity must be fulfilled. To elaborate further, transitivity implies that it is possible to conclude hypothetical comparisons through a common comparator<sup>[6]</sup>. However, this is only possible in the absence of systematic differences between studies<sup>[8]</sup> with some degree of heterogeneity being permitted<sup>[6]</sup>. To illustrate, heterogeneity is defined as a form of inter-study discrepancy due to differences that cause deviations in the observed effects other than sampling error<sup>[9]</sup>. However, when the discrepancy between studies exceeds that explained by clinical diversity, effects sizes cannot be safely estimated based on direct and indirect evidence and the distribution of effect modifiers needs to be examined<sup>[6]</sup>.

### **Prerequisites for a well-conducted NMA- Statistical power**

It is worthy of note that the statistical power of a network of interventions should be sufficient to enable safe clinical conclusions to be drawn. To be more specific, the ratio between the number of included papers relative to the number of the competing interventions should be satisfactory. On top of that, the sample size per intervention arm as depicted by the size of the nodes in a network meta-analysis plot should also be robust enough (Figure 1). Lastly, prospective registration with systems such as the grade of recommendations, assessment, development, and evaluation system (GRADE) is valuable in assessing the heterogeneity and additional characteristics such as publication bias, indirectness, imprecision, the study limitations, and inconsistency<sup>[5]</sup>.

**Figure 1. A Network-Meta-Analysis plot example**

### **Conducting pair-wise meta-analysis prior to NMA**

Of additional note, for a given dataset, researchers must conduct not only NMA but also traditional pair-wise meta-analysis. To be more precise, one can take advantage of early exploration of the results of conventional pair-wise meta-analyses before setting up networks of intervention. Authors should then proceed with network meta-analysis to take advantage of indirect evidence synthesis in order for them to supplement their study results.

### **Prerequisites for a well-conducted NMA- Selecting appropriate outcomes**

In determining primary and secondary outcomes, considering not only positive but also negative ones is crucial. Outcomes of primary interest should be prioritized over outcomes of secondary clinical importance to ensure that the findings will be clinically relevant. For instance, laboratory tests are not routinely considered as primary endpoints as they tend to not directly inform decisions. However, they may play an explanatory and/or adjuvant role in explaining the intervention outcome<sup>[10]</sup>.

### **Following guidelines for transparent reporting**

The PRISMA guidelines represent a checklist of 27 items that may be used when reporting a systematic review of health interventions with or without meta-analysis<sup>[11]</sup>. Hutton *et al*, in 2015, has expanded the original list by including 5 additional items that apply to network meta-analyses. Firstly, the geometry and summary of the intervention networks have been incorporated in the methods, including a diagrammatic representation and brief description. What is more, the findings of inconsistency assessment can be included in addition to the presentation of the networks' structure<sup>[12]</sup>.

It should be noted that prospective registration (eg with PROSPERO database) of all NMAs is encouraged. By doing so, transparency is promoted and bias is prevented by avoided unintended duplicate reviews<sup>[13]</sup>. It is also highlighted that adherence to a pre-existing protocol plays a crucial role in preventing selective outcome

reporting<sup>[10,14,15]</sup>. In other words, registration of a systematic review in advance of study commencement precludes data manipulation and/or unethical reporting. Last but not least, prospective registration may enable researchers to assess whether the topic they intend to investigate has already been addressed by earlier authors, thus avoiding unnecessary research repetition.

### **Sophisticated graphical tools in NMA - Do we need them?**

Despite NMAs gaining popularity, a lot of criticism exists given their complex methodology discouraging clinicians from getting involved in this type of research<sup>[16]</sup>. This is due to the increased level of statistical and computational knowledge required. To tackle this issue, introducing graphical tools into the manuscript results in significant increase in clarity and reproducibility<sup>[16]</sup>.

What is more, competing interventions can be ranked from the best to the least effective *via* the use of surface under the cumulative ranking (SUCRA) curves<sup>[2]</sup>. On the other hand, league tables enable a structured presentation of the results of each pair of comparison with its corresponding 95% confidence intervals.

### **Figure 2. A league-table example**

### **Publication bias in NMA and its impact on clinical estimates**

It has been evidenced that detection of publication bias (that is reporting positive more often than negative results) in NMA is not uncommon. Inevitably, introducing this kind of bias in meta-analysis threatens the validity of the results of the study as an “overly rosy picture” may be painted. To elaborate further, the evaluation of small study effects acts as a proxy for the assessment of publication bias. For the above assessment, a sophisticated statistical tool namely a comparison-adjusted funnel plot can be implemented. Apart from funnel plots, researchers can also employ Egger’s test to statistically evaluate the presence of small-study effects<sup>[16-18]</sup>.



### **Quality appraisal systems and transition to clinical practice**

The GRADE system features 6 components<sup>[5]</sup>, that is study limitations, heterogeneity, inconsistency, indirectness, imprecision, and publication bias<sup>[5,19]</sup>. The quality of evidence may be high, moderate, low, or very low. As a rule of thumb, randomized trials yield high-quality evidence, whereas observational studies more often than not offer low quality of evidence with the the risk of bias potentially affecting this judgement<sup>[20]</sup>.

Potential <sup>1</sup>limitations of randomized trials include failure to conceal allocation, failure to blind, loss to follow-up, and failure to appropriately consider the intention<sup>[20]</sup>. <sup>1</sup>Guyatt *et al*, in 2011, also mentioned terminating a study early for apparent benefit, and selective reporting of outcomes according to the results<sup>[20]</sup>. The indirectness may be due to patients deviating from those of interest, when the treatments have not been compared in head-to-head trials, and when there are different outcomes from those being expected from the study <sup>[21]</sup>. Furthermore, the contributions of biological and social factors to the magnitude of effect in the outcomes represents indirectness<sup>[21]</sup>. On the other hand, inconsistency is defined as a disagreement between direct and indirect evidence in NMA<sup>[19]</sup>. In addition, Salanti *et al*, have suggested the adoption of a quantitative approach to assess the risk of bias<sup>[19]</sup>.

### **Investigating clinical diversity in NMA**

It is an undeniable fact that a great many confounding factors can be encountered in a broad systematic review of randomized trials. Thus, conducting sensitivity analysis to delineate the impact of clinical heterogeneity factors is strongly recommended. For instance, the effect of low-quality trials, variation in intervention characteristics as well as differences due to variable outcome measurement tools needs to be considered in those secondary analyses. From a technical point of view, the researcher needs to improve the trial(s) with the above characteristics from the analysis, repeat the statistical tests and subsequently compare the new results with the findings of the primary analysis<sup>[22]</sup>.

### **Planning future research with NMA- Is it possible?**

Directing the design of future studies based on NMA results appears to be of significant importance as mismanagement of resources can be overcome<sup>[23-25]</sup>. For a researcher to provide an estimate of whether the results of a subsequent trial are likely to change in the future, an interval plot should be considered. By visually inspecting an interval plot, an investigator can enable predictions on the efficacy of a particular intervention in a future trial<sup>[16,26,27]</sup>.

### **Improving interpretation of NMA findings**

To improve interpretability and clarity of the results of an NMA, researchers are encouraged to back-transform their data in a manner that interpretation of their results is improved. For instance, when it comes to Patient-Reported Outcome Measures (PROMS), investigators can back-transform Standard Mean Differences (SMDs) to Mean Differences (MDs) and subsequently assess their findings against the established minimal clinically important difference (MCID) for a particular questionnaire<sup>[28]</sup>.

### **CONCLUSION**

Overall, NMAs play a crucial role in the decision-making process. As long as common methodological mistakes are avoided, researchers can produce reliable and accurate clinical conclusions.

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