How an Early Network Meta-Analysis Can Inform Clinical Trial Design and Help with Health Technology Assessment Submissions

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KEY POINTS . . .

A clinical trial designed without considering the existing evidence can make it difficult to demonstrate the full clinical value of a new treatment.

Performing a network meta-analysis (NMA) early in the drug development process is important to understand the evidence landscape.

Understanding the evidence landscape is critical to ensure that the phase 3 trial fits into the right evidence network to support a health technology assessment submission.

When considering a new technology for reimbursement, private and national payers prefer evidence from head-to-head randomized controlled trials (RCTs) comparing the new technology to the current established practice or standard of care in the patient population for which the new technology is indicated. The trial should examine outcomes that have an impact on benefits relevant to the patient, such as mortality, morbidity, safety, and quality of life. In the absence of head-to-head RCTs meeting these requirements, payers often expect to see a network meta-analysis (NMA) to demonstrate the clinical value of the new technology. NMAs, however, are not a panacea and cannot overcome the absence of good clinical evidence. In some health technology assessment (HTA) submissions to the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK), NMAs were not undertaken because the manufacturer's clinical trial design made it impossible to include the drug in an evidence network with other treatments [1]. This problem could be avoided by performing an NMA early in the drug development process. An early NMA can inform phase III trial designs by identifying relevant patient subpopulations, comparators, outcomes, and timepoints for data collection, and ensure that the phase III trial will connect to other studies in the network.

Network Meta-Analysis

NMA is based on evidence from multiple RCTs that include both direct and indirect comparisons of treatments of interest. A direct comparison is a trial that compares two or more treatments of interest directly. An indirect comparison is based on multiple trials that each compare a treatment of interest to a common comparator. The validity of both types of comparisons is based on an "exchangeability assumption"; that is, they assume that the true effects of each treatment relative to a given comparator are "exchangeable or comparable across trials," even trials that did not examine a given treatment. Heterogeneity among trials (differences in patient population, interventions, outcome definitions, timepoints for data collection, and so on) and a large number of "links" in a network required to join two comparators of interest can limit the validity of this assumption.

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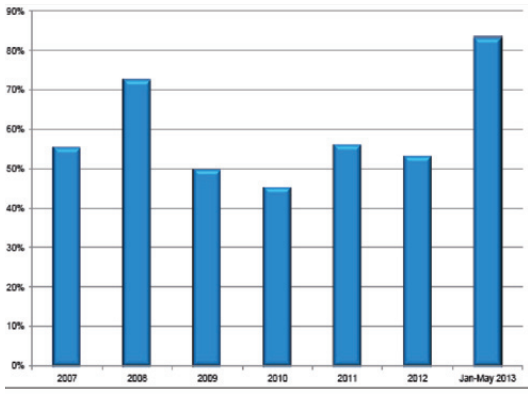
Performing an NMA early in the drug approval process can guide clinical trial design by providing information about both the competitive landscape and the evidence landscape. The information gathered can help ensure that the design of the clinical trial is optimal to provide strong support for an HTA submission. Many of the NMAs cited in submissions to NICE in recent years have been critiqued to some extent (Fig. 1). An early NMA can prevent such issues, providing insight into populations and subpopulations, time-points, and outcomes where evidence for the comparator of interest exists.

Examples

Figure 2 shows an example where a manufacturer ran a trial comparing their product (D) to an established, traditional treatment (C). In the past 10 years, however, very few other studies had used treatment C as a comparator, and no studies compared it with any of the active treatments of interest (E, F, G, H, I, J, K, L, and M, N, O, P). Most trials were placebo-controlled. In order to use this evidence network for a statistical comparison of the client's product with a comparator of interest, a minimum of three links, or trials, had to be included. Even though the product outperformed the standard of care in the

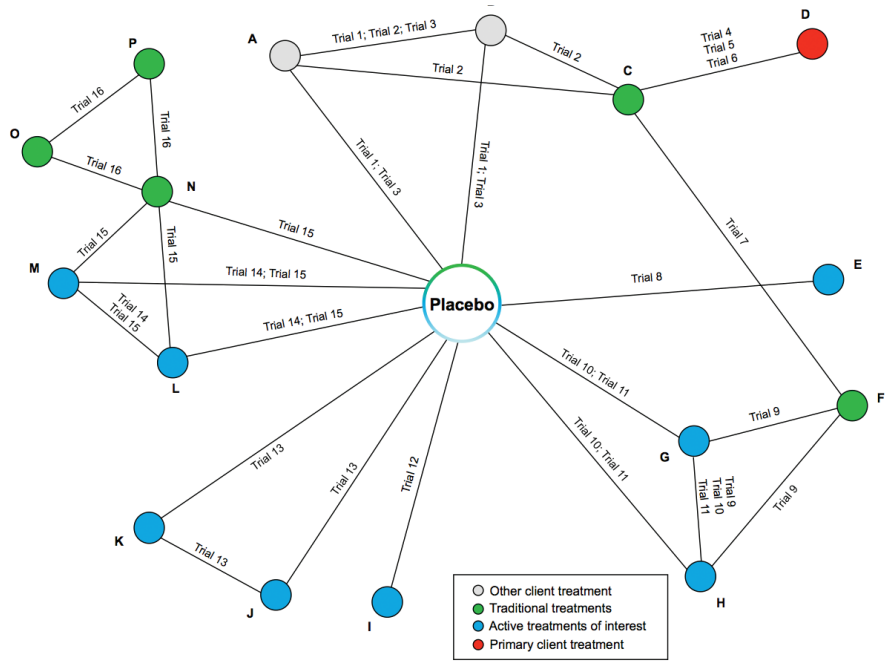
Figure 1. Percentage of NMAs Cited in Submissions to NICE that were Critiqued [1].



Along with other considerations, the population and comparators should be taken into account when designing a clinical trial. An NMA can help with the definition of the target patient population for the phase III trial or identify a situation in which evidence for different treatment combinations is in separate evidence networks. The next two examples illustrate each of these issues.

Figure 3 shows an example for which there were two populations of interest. In the figure, the client's trials are Trial 3 and Trial 4. The

Figure 2. Remote Connection to Competitor Treatments and Placebo.



manufacturer's trial, when the data were analyzed based on the evidence network, a statistically significant advantage was not found for the client's product. Because of the uncertainties introduced by the "distance" between trials in the network, the credible intervals resulting from the NMA were very wide and were of limited use in supporting HTA submissions. If the manufacturer had considered the available evidence network before designing the clinical trial, it might have chosen to compare its drug to placebo or to a different comparator.

patient population in Trial 3 was previously treated patients; Trial 4 was performed in treatment-naïve patients.

In Trial 4, the product was compared to placebo, although no placebo-controlled clinical trial had ever been published. The intent was to compare the product to treatments A and C in the treatment-naïve population. Unfortunately, the only trial providing a network link between the competitive treatments of interest (A and C) and the product (D) was Trial 3, performed in a population of previously treated patients. To perform an NMA in this situation would require assuming that relative rates for the outcome were identical in the previously treated and untreated patient populations—highly unlikely, and unlikely to be accepted by clinicians or payers. Thus, no NMA was possible for the treatment-naïve population. If an early NMA had been performed, the situation would have been clear and the client could have elected to use the same comparator (B) that was used in Trial 3, linking the network for both treated and untreated patients.

An example of separate evidence networks is shown in Figure 4. In this trial, the manufacturer added its product (E) to a key dual therapy comparator (F+G). As shown in Figure 4, however, the majority of the comparator treatments of interest were in another network, with no links available to the manufacturer's trial. Also, most of the therapies in both networks were single-drug or two-drug regimens. Demonstrating cost-effectiveness is likely to be more difficult with the three-drug regimen tested in the manufacturer's trial. A subsequent trial, shown as a dotted red line in Figure 4, was run with a two-drug regimen and connected to the network containing the key comparator treatments. If the manufacturer had performed an NMA prior to designing the initial trial, it might have chosen to run the subsequent trial (comparing E+G to B+G) first, and then been able to present a more convincing clinical and economic story in support of its new drug.

The Perspective from NICE

NICE is an independent government body that is dedicated to identifying the most effective ways to prevent, diagnose, and treat disease and to ensure quality and value for money for the UK National Health Service (NHS). When conducting technology appraisals for new healthcare technologies, NICE compares the clinical and cost-effectiveness of the proposed technology to the current established practice in the NHS. The preferred evidence is a head-to-head RCT; an NMA is acceptable, where appropriate, for comparisons where no head-to-head RCT is available. Methodology decisions made in the NMA are expected to be described in detail. The NICE technology appraisal committee expects to see systematic identification of studies, justification for the inclusion and exclusion of selected studies, analysis of the heterogeneity between studies, and sensitivity analyses >

exploring the impact of including or excluding potentially heterogeneous studies. A discussion of how the NMA results are used in the economic analyses presented in support of the product is also expected. Companies should consider these issues before embarking on pivotal trials to identify evidence that is already available and to design their trial program to facilitate links with this evidence. Companies should also consider comparators that may become available at a later date, and think about how their study designs may affect an NMA at the time of a future technology appraisal. As shown in Figure 1, the fraction of NMAs cited in submissions to NICE that have been critiqued has recently increased. Common issues include: inadequate search for studies; missing key studies; lack of transparency about how study inclusion and exclusion decisions were made; choices of population, comparators, and outcomes; inadequate or poor reporting; and errors in statistical analysis. While an early NMA cannot solve all of these problems, the earlier in the process that investigators are aware of issues with the evidence database, the less likely the submission is to be incomplete. This is true even if the early NMA does not or cannot change the population, outcomes, or comparators in any phase III trials conducted.

An early NMA can also help identify relevant outcomes, and ensure that outcome, definitions are matched to other available evidence. Timing is also important for outcomes as they should be measured at the same timepoints to be truly comparable.

In summary, early consideration of an NMA can help with population, comparator, and outcome selection and planning. The available evidence will always be imperfect, so analyze what is available, present the limitations, and justify the choices made. An NMA is not required with the HTA submission, but the NICE committee expects to see the choices made in the clinical trial design clearly explained and supported. The following example describes a situation where a manufacturer used an early NMA to understand how the available evidence for an NMA from an HTA perspective would fit with regulatory requirements (in this example, specifying an expected endpoint).

In this example, a manufacturer performed an NMA before phase III, to get a sense of

Figure 3. Disconnected Network Due to Different Trial Populations.

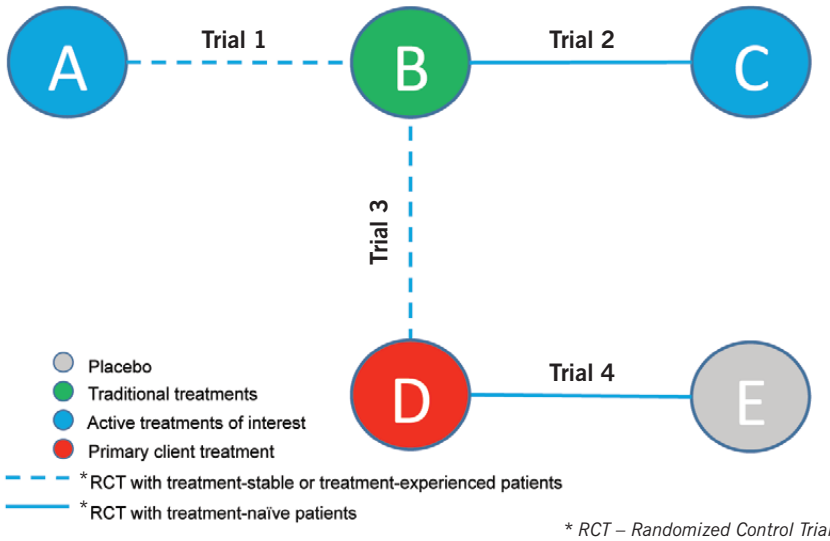


Figure 4: Disconnected Networks Due to Different Comparator Treatments.

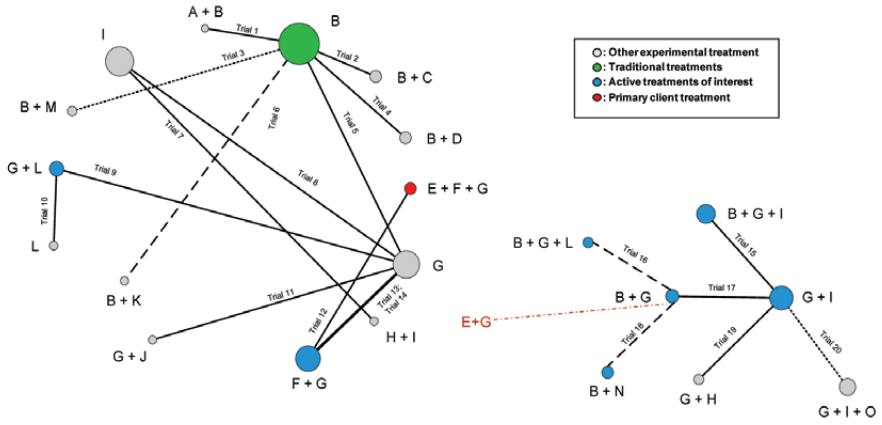
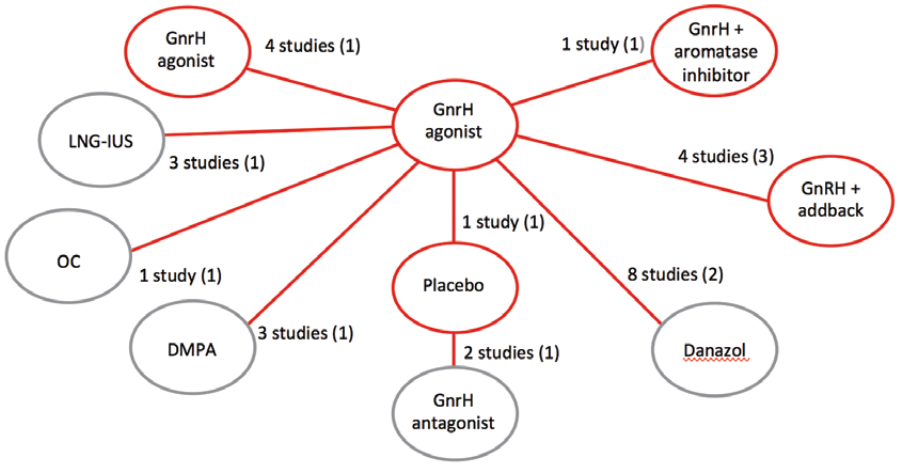


Figure 5. Network of RCTs in Endometriosis.



the competitive landscape and understand the available evidence. The result of the literature review of RCTs in endometriosis is the extensive network of 27 clinical trials shown in Figure 5 [2]. Most of the trials used the Modified Biberoglu and Behrman scale to report symptoms. The United States Food and Drug Administration (USFDA) recommends, however, that endometriosis symptoms be measured by the daily pain level reported by the patient. None of the 27 RCTs reported this measure. The drug manufacturer can use the results of this early NMA to ensure that the expectations of both regulatory bodies and payers are met.

Conclusion

In the first three examples discussed, a non-optimal trial design made it difficult to demonstrate the full clinical value of a new treatment. If an NMA had been performed before designing the phase III trials, different decisions might have been made that would have allowed the manufacturer to better demonstrate the clinical and economic value of the new product.

Performing an NMA early in the clinical trial design process can help determine the optimal population, subpopulations, comparators, and outcomes to investigate. The information developed can also help the manufacturer explain and justify the design choices made for the clinical trial in support of an HTA submission.

References

[1] Martin A, Rizzo M, Iheanacho I. Faulty connections: Can criticisms of network meta-analysis in NICE submissions be avoided? Poster presented at ISPOR 16th Annual European Congress. November 2013, Dublin, Ireland.
[2] van Nooten FE, Novak A, Langham J. Feasibility of a Network Meta-Analysis in Endometriosis. ISPOR 17th Annual European Congress 8-12 November 2014, Amsterdam, The Netherlands. ■

Additional information:
The preceding article was based on the workshop, "How an Early Network Meta-Analysis Helps Inform Clinical Trial Design and Technology Appraisal (TA) Submissions?," presented at the ISPOR 19th Annual International Meeting, Montreal, QC, Canada, June 2, 2014.

To view the presentation, go to: http://www.ispor.org/Event/ReleasedPresentations/2014Amsterdam#workshoppresentations