Early Network Meta-Analyses (NMAs): Filling a Need in Clinical Trial Designs and HTA Submissions

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Stakeholder demands for evidence on new health treatments and technologies are increasing, and these demands are progressively more complex. As a result, companies must think about evidence requirements for reimbursement decisions, as well as regulatory approval, earlier in the development process. One crucial piece of evidence that private and national payers expect to see when evaluating a new treatment within a given patient population is results from comparative studies, ideally from head-to-head randomized controlled trials (RCTs) comparing the new treatment with the current standard of care. In the absence of head-to-head RCTs meeting these requirements, payers (such as the National Institute for Health and Care Excellence [NICE]), often expect to see a network meta-analysis (NMA) that collates and combines results across studies to evaluate the clinical value of the new technology. However, NMAs are not a panacea and cannot overcome the absence of good clinical evidence. In some health technology assessment (HTA) submissions to NICE, NMAs were either not feasible or criticized to some extent because the manufacturer's clinical trial design made it impossible to compare the drug with current standard of care in an evidence network.[1] One solution to this problem is to perform an NMA earlier in the drug development process. An early NMA can inform Phase 3 trial designs by identifying relevant patient subpopulations, comparators, outcomes, and timepoints for data collection, and ensuring that the Phase 3 trial will connect to other studies in the network.

Network Meta-Analysis

An NMA is based on evidence from multiple RCTs of the treatment of interest, including both direct comparisons (trials that directly compare two or more treatments of interest) and indirect comparisons (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. It is important to note that the validity of this assumption can be limited due to heterogeneity among trials (e.g., differences in patient population, interventions, outcome definitions, timepoints for data collection, etc.), and the risk of a violation increases when a large number of "links" in a network is required to connect two comparators of interest.

For the drug evaluation process, an early NMA can fill an important need by providing information about both the competitive landscape and the evidence landscape of the treatment. This information can then be used to help ensure the design of the clinical trial for the new treatment is optimal to provide strong support for an HTA submission. Specifically, an NMA can help with the definition of the target patient population for the

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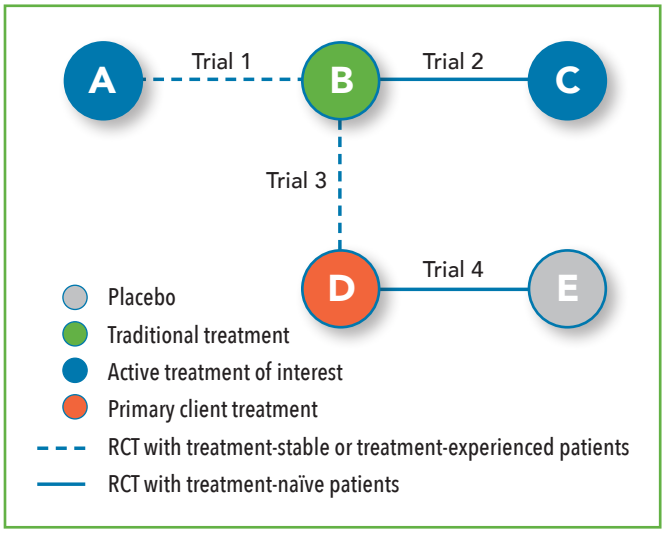
Figure 1: Disconnected Network Due to Different Trial Populations



Phase 3 trial and identify a situation in which evidence for different treatment combinations are in separate evidence networks.

Figure 1 shows an example where there were two populations of interest. In the Figure, the client's trials are Trial 3 and Trial 4. The patient population in Trial 3 was previously treated patients; Trial 4 was performed on 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 (D) 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) in Trial 4 that they had used in Trial 3, linking the network for both treated and untreated patients.

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. Once again, the preferred evidence is a head-to-head RCT. When no head-to-head RCT is available, an NMA is acceptable, if appropriate, for comparisons, along with a detailed description of the methodology used. 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. Additionally, NICE also requires details on how the NMA results are used in the economic analyses presented in support of the product, in addition to the reference case analysis. Before undertaking any pivotal trials, companies should plan accordingly to identify evidence that is already available, ensuring that the trial program design facilitates links with the available evidence. Comparators that may become available at a later date should also be considered, as well as how their study designs may affect an NMA at the time of a future technology appraisal.

As shown in Figure 2, there has been a recent increase in the proportion of criticized NMAs cited in submissions to NICE. Common issues include: inadequate searches 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. Having knowledge of these issues with the evidence base earlier in the process would allow investigators the opportunity to address these challenges and plan for a more complete submission. For example, an early NMA may facilitate the identification of relevant outcomes and provide the knowledge to

Figure 2: Percentage of NMAs Cited in Submissions to NICE that were Criticized[1]

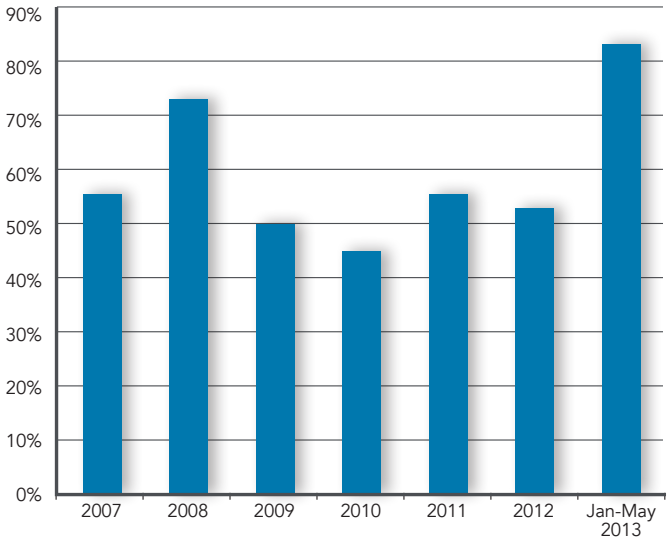
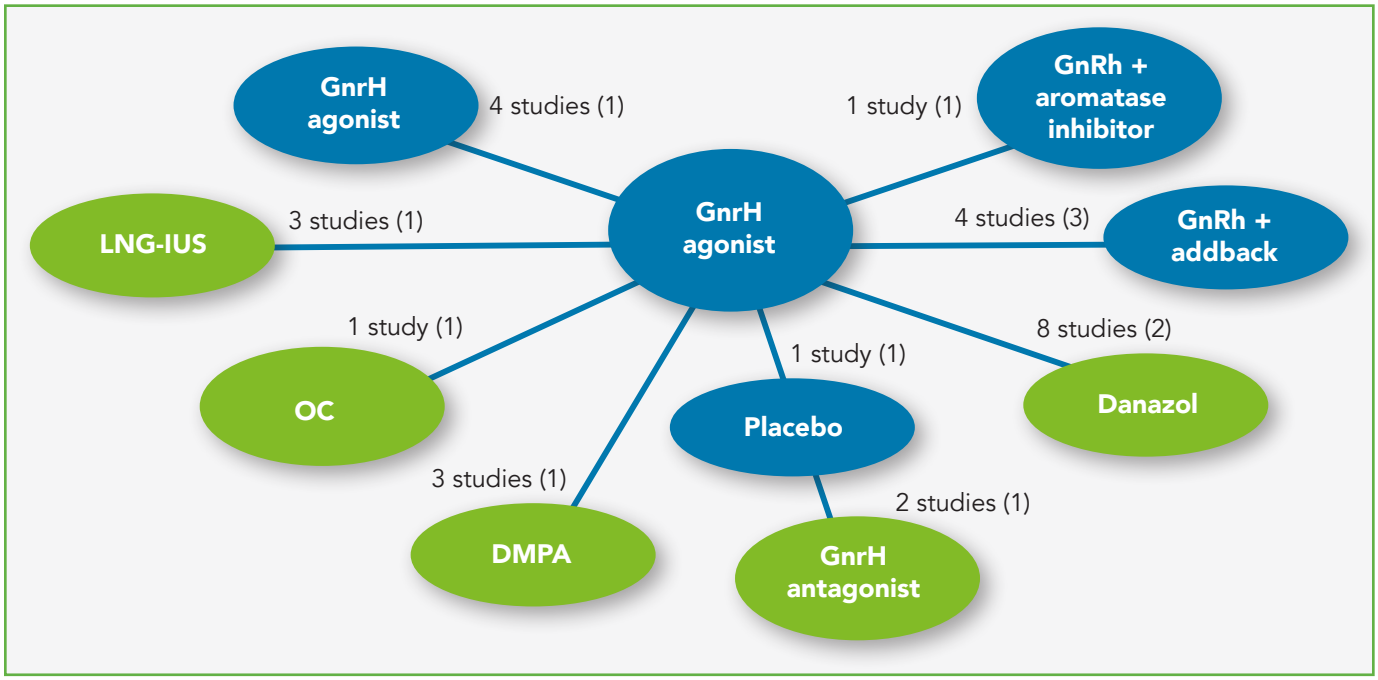


Figure 3: Network of RCTs in Endometriosis



ensure that outcome definitions are matched to other available evidence, and that the outcomes are measured at the same timepoints to be truly comparable. Even if, ultimately, an early NMA does not or cannot change the population, outcomes, or comparators in any Phase 3 trials conducted, companies are still further along by knowing where they stand earlier in the process.

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). The manufacturer performed an NMA before Phase 3 to get a sense of 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 3.[2] Most of the trials used the Modified Biberoglu and Behrman scale to report symptoms. However, the U.S. Food and Drug Administration (FDA) recommends that symptoms of endometriosis be measured by the daily pain level reported by the patient – a measure that none of the 27 RCTs reported. The drug manufacturer could use the results of this early NMA to ensure that the expectations of both regulatory bodies and payers are met.

Conclusion

When head-to-head RCTs are not available for the treatment under consideration, early NMAs can potentially fill a need when planning for HTA submissions. In many cases, a non-optimal trial design can make it difficult to demonstrate the full clinical value of a new treatment. An NMA performed before designing a Phase 3 trial, or earlier if conditional reimbursement is sought, may provide improved insight and direction for manufacturers to better demonstrate the clinical and economic value of a new product. Performing an NMA early in the clinical trial design process can not only help determine the optimal population, subpopulations, comparators, and outcomes to investigate, but the resulting information can also help the manufacturer explain and justify the design choices made for the clinical trial in support of an HTA submission.

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