Comparative effectiveness: Queries and clarifications

With thanks to Priti Jhingran, Craig Parzynski, and Alexandra Z Sosinsky

HEOR Theater Supplementary Information
May 2026

Why isn't comparative effectiveness always answered by a head to head trial?

While a head-to-head randomized controlled trial (RCT) is the gold standard for generating comparative efficacy data, RCTs are not always feasible, and multiple relevant comparators may exist which could make it unlikely that a trial will be conducted for every pairwise comparison of interest. In rare diseases, small patient populations can make it difficult to adequately power an RCT, and ethical considerations may preclude randomizing patients. Additionally, treatments may continue to come to market in a given therapeutic area, meaning a relevant comparator may not have existed when the pivotal trial was designed, and manufacturers of existing therapies may not be sufficiently incentivized to invest limited resources into a comparative trial. These gaps are why comparative effectiveness methods such as network meta-analyses (NMA), matching adjusted indirect comparators (MAIC), and external control arms (ECAs) are essential tools, enabling the generation of comparative effectiveness evidence using available data when head-to-head evidence from an RCT does not exist.

How do you decide between approaches like NMA, MAIC, or an external control arm?

The choice between these methods depends on several factors that include strategic needs, data availability, and methodological considerations. When considering ITCs, you should start with an evaluation of the treatment landscape and available evidence base from a systematic literature review. Once your evidence base is identified, you should assess the available evidence in the context of your strategic comparative evidence needs. When a connected network of sufficiently comparable randomized trials exists, NMAs are typically preferred because they maximize use of the evidence base while preserving the advantages of randomization across multiple treatments. When the evidence network is sparse or clinically heterogeneous across studies, MAICs become more appropriate because they explicitly address cross-trial differences that could bias indirect comparisons. External control arm studies are best suited for scenarios where the evidence base doesn't capture important treatment effect modifiers, or the evidence base is sparse and disconnected. Ultimately, the best approach is one that leverages the appropriate network of evidence and adheres to the methodological assumptions necessary to draw valid conclusions.

When should teams start thinking about comparative effectiveness strategy — and why is timing important?

HEOR, Medical, and Market Access teams should align on a comparative effectiveness strategy before Phase II/III trial designs are finalized, so the program generates evidence that supports reimbursement, access, and product differentiation. This includes choosing the comparators, endpoints, and patient populations most relevant to payers, Health Technology Assessment (HTA) agencies, and treatment decision-makers. Early planning is critical to answer a central question: why should this product be covered, reimbursed, or preferred over existing alternatives? If comparative evidence cannot be built into the Phase III program, teams should immediately develop a fit-for-purpose evidence generation plan to address expected gaps. Delayed planning increases the likelihood of evidence gaps that can weaken the value story, reduce leverage in pricing negotiations, and delay coverage decisions.

Want to find out more? Email our HEOR Theater presenters via solutions@genesisrg.com

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Don't miss our presentation!

HEOR THEATER, ISPOR 2026

Navigating Strategies for Comparative Effectiveness from Trials to Real-World Evidence

TUESDAY 19 MAY

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How do you choose the right approach and timing to **generate comparative effectiveness evidence**? How is your strategy shaped by limited head-to-head evidence, differences in study populations, or situations where fit-for-purpose real-world data may be available? What **practical and strategic considerations** should be taken into context in building this strategy?

HEOR Theater
3:15-3:45pm
Tuesday
19 May

This theater session examines **how to assess an evidence base and translate its strengths and gaps** into a comparative effectiveness approach that aligns with the decision context.

Framed by the pragmatic needs of regulatory/HTA bodies for comparative data, as well as commercial implications, the speakers will discuss how existing trial and real-world evidence can be used to **generate comparative effectiveness through indirect treatment comparisons (ITC),** such as network meta-analyses (NMA) and matching-adjusted indirect comparisons (MAIC), and external control arm (ECA) studies. The session will focus on **when each is most defensible**, what assumptions drive validity, and how tradeoffs in bias and feasibility shape evidence strategy. The discussion will also address considerations related to the scrutiny these approaches may face from regulators/HTA bodies.

Through examples, speakers will describe how **different evidence base scenarios lead to different methodological approaches** and how those choices may be justified as part of a broader evidence package for stakeholders. Attendees will gain insight into sizing up an evidence base and strategy for **selecting comparative effectiveness methods that are scientifically sound and decision relevant.**

Find out more about our approach to evidence, experience, and judgment.

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