Evidence Synthesis for HTA

Squaring the Circle: Bridging Innovation with Application

Duration-90 mins

Indirect treatment comparisons- *Is there a gap in the market*?

In Health Technology Assessment (HTA) direct evidence informing comparative efficacy of all treatments of interest is often lacking and therefore indirect treatment comparisons (ITCs) and network meta-analyses (NMAs) are used. These methods assume that the study populations are similar in terms of effect modifiers. When this assumption does not hold population adjustment methods simulated treatment comparisons (STCs) and matching adjusted indirect comparisons (MAICs) are commonly employed, but Multilevel network meta-regression (ML-NMR), a method which leverages aggregate data and individual patient data (IPD) to estimate the relative efficacy of a network of treatments given the covariate distribution of a user-specified target population, has recently been introduced. The method accounts for treatment effect modification and estimates effects in any population of interest to HTA decision-makers. In terms of methodology, ML-NMR has clear benefits over NMAs, MAICs and STCs, but from a policy and industry perspective there are challenges that could limit wide-spread adoption of ML-NMR. The introduction of ML-NMR also comes at a time where industry is being pressured to rethink their approach to evidence generation for ITCs. Moreover, there is often a lack of consideration during the early stages of drug development regarding the necessary ITCs at the HTA step that could be critical for successful market access. This oversight can lead to missed opportunities for adapting pivotal trial designs—such as adapting eligibility criteria to include relevant populations, including additional stratification factors, and ensuring adequate sample sizes for some subpopulations—or at the very least, for collecting all needed information to support ITCs in the clinical request form (CRF). This challenge is further exacerbated in the context of the Joint Clinical Assessment (JCA) in the EU, where multiple ITCs may be requested within a condensed timeframe for a single indication, underscoring the critical need for timely planning and swift execution.

The aim of this panel is to discuss the friction between the need for successful adoption of novel methods such as ML-NMR and the need to improve early integration of ITC consideration to accommodate the JCA guidelines. Several topics will be addressed; What does ML-NMR entail as a method and what assumptions are made when performing it? What challenges do we face in adopting novel methods and how can stakeholders be convinced to accept them? Should we perhaps focus on improving the evidence generated by prioritizing ITCs in the early phases of clinical trial design, instead of addressing evidence limitations after collection through complex ITC methods? To conclude, most importantly, how can we combine all these insights to ensure that the best evidence is produced, within the short timeframes set, to improve HTA decision-making.

Prior to diving into these complex methods and challenges, we will provide a concise introduction to commonly used ITC methods and the JCA guidelines. Furthermore, to set the scene, results from a review of ITCs recently submitted to NICE will be presented discussing methods used, and criticism from the evidence review groups.

Multilevel network meta-regression- *the method*

This session will give an introduction to ML-NMR from a methodological point of view. ITCs may be biased when there are differences between studies in treatment effect modifiers (TEMs) - factors that interact with treatment effects. ML-NMR can be used to adjust for population differences between study populations when there is IPD for at least one trial. ML-NMR specifies an individual level model for studies with IPD, and integrates over this to form the likelihood for studies with aggregate-level data, and includes as special cases IPD NMA and standard NMA with aggregate data. We will compare ML-NMR with other population adjustment ITC methods that are commonly used in HTA: MAIC and STC. MAIC and

STC are only available for simple indirect comparisons with IPD for one trial and aggregate data for another, whereas ML-NMR can be used for broader evidence networks with multiple trials and treatments. MAIC and STC can only produce estimates in the aggregate study population, whereas ML-NMR can produce estimates in any specified target population with some overlap with the IPD studies. On the other hand MAIC and STC can be used for unanchored indirect comparisons whereas ML-NMR cannot currently be used for disconnected networks. We will end with a discussion of recent methodological advances and remaining methodological challenges to be addressed for ML-NMR to be used routinely in HTA.

Multilevel network meta-regression- ***the new golden standard for industry?***

In this presentation we will discuss how ML-NMR is increasingly used in the pharmaceutical industry to analyze outcomes such as overall survival and progression-free survival from a network of evidence.

The focus will be on the challenges that must be addressed for ML-NMR in order to gain wider acceptance: The complexity of modeling a ML-NMR requires significant statistical expertise, posing barriers for clinicians and policymakers. ML-NMR does not have the same level of transparency as other methods because of restrictions placed on the availability of IPD. Additionally, the computational demands of ML-NMR are substantial, often resulting in slow processing times. The reliance on high quality data, choice of covariates and model specification within ML-NMR further complicates its implementation. Therefore, convincing reviewers of HTA submissions to accept the results from a ML-NMR may be difficult. Regulatory acceptance remains a challenge, as clear guidelines for using ML-NMR are still evolving. Collaborative efforts among researchers, industry representatives, and regulatory bodies are essential to establish standardized protocols and promote best practices.

If these challenges can be overcome, ML-NMR may be a powerful tool for ITC, enhance the drug development process and improve therapeutic decision-making for all stakeholders involved.

Adaptive integration and software engineering to drive planning and execution of ITCs for EU HTA- ***The early bird gets the worm***

The Joint Clinical Assessment (JCA) under the EU Health Technology Assessment (HTA) Regulation requires manufacturers to submit comprehensive evidence dossiers to address diverse HTA questions from 27 member states. This will typically involve performing Indirect Treatment Comparisons (ITCs) to provide evidence versus comparators not included in head-to-head trials. To meet the short timelines and potentially large volume of ITCs needed for the JCA, statisticians and data scientists will have to demonstrate operational excellence at the time of submission. Additionally, they will need to facilitate early internal decision-making about which potential future HTA questions could be addressed with ITCs, in order to inform trial designs and strategic evidence planning. Finally, it may be necessary to revisit these elements throughout the development process, as evidence accumulates and HTA scenarios evolve.

This talk will explore holistic quantitative scenario planning for ITCs from the early stages of clinical development. We will discuss applying ideas from clinical trial simulation at an aggregate data level to integrate internal and external information and expectations about treatments and comparators. In combination with an optimized production engine, this framework could seamlessly support both early quantitative decision input through to final analysis and reporting at the time of dossier submission. Implementing such a framework requires a multidisciplinary effort that blends strategic planning, communication, and advanced statistical software engineering skills. We will touch on the potential role of opensource collaborations, and how statisticians and data scientists can lead this adaptive integration of ITC considerations into clinical development and decision-making.

Better methods or better planning? - ***Improving HTA decision-making***

According to Guernsey McPearson, a nom de plume of Stephen Senn, a ‘Meta-analyst’ is ‘One who thinks that if manure is piled high enough it will smell like roses’ and a ‘Medical Statistician’ is ‘One who won't accept that Columbus discovered America because he said he was looking for India in the trial Plan”. In this presentation we will consider whether ML-NMR is indeed a fragrant and useful methodology and might lead to the discovery of new continents. Or whether it might simply lead to larger compost heaps.

We will consider the assumptions typically required to employ ML-NMR in practice compared to commonly used alternatives. Furthermore, the interaction between the scoping of a decision problem and the analytic challenges of data synthesis will be discussed. Although more sophisticated and extensive analysis might be helpful, sometimes better planning and improving the precision of a question is easier. This is an especially pertinent consideration in light of the EU’s Joint Clinical Assessment initiative. Bearing in mind Harry Truman’s plea for a ‘one handed economist’, hopefully we can arrive at some final observations.

Panel discussion- 20 minutes