**Session - Bias in indirect treatment comparisons and evolving methodology: implications for health technology assessment and beyond**

*Katrin Kupas, BMS*

The centralized European Joint Clinical Assessment (JCA) is kicking off in January 2025, which will inform reimbursement and pricing decisions in the Health Technology Assessment (HTA) process for the 27 EU member states. This process requires comparative evidence versus the national standard of care(s) within one submission dossier. Given the probable lack of direct evidence against every unique comparator forming the national standard of care, rigorous and scientifically sound Indirect Treatment Comparisons (ITCs) will play an integral role in the JCA process. Those ITCs will provide value evidence in support of assessing innovative treatments and will shape patient access to these treatments across Europe.

This session will give an overview of the EU HTA JCA scoping procedure, and the methodological and reporting requirements for ITCs. Then there will be a deep dive into statistical methodologies to adjust for measured and unmeasured confounding in ITCs. The case studies presented will showcase the application of these methodologies. The session will conclude with a panel discussion of the presenters, providing attendees with a unique  opportunity to engage with experts in the field and gain valuable insights into the latest developments in ITC methodology and their application in the impending EU HTA regulation.

**Presentation 1 - Meeting Evidence Requirements in the EU HTA Landscape: PICOs and ITCs**

*Dave Gelb, MSD*

This presentation provides an overview of the practical application and relevance of the PICO (Population, Intervention, Comparator, Outcome) concept in the context of Indirect Treatment Comparisons (ITCs) for Health Technology Assessment (HTA) purposes. The imminent implementation of the centralized European HTA Joint Clinical Assessment (JCA) process, influencing reimbursement and pricing decisions across the EU, necessitates statisticians to meet the evidence requirements in this diverse landscape. Understanding the methodological requirements, statistical considerations, and practical implications of ITCs is crucial for successful navigation of the upcoming JCA process and aligning with evolving HTA needs in the EU.

The session begins by reviewing the EU HTA JCA scoping procedure, highlighting the importance of providing comparative evidence that satisfies the demands of all 27 EU Member states. Rigorous and scientifically sound ITCs play a significant role in situations where direct evidence against each unique comparator is limited.

An overview of the EU HTA methodological guidelines for conducting robust ITCs is presented, focusing on key considerations and requirements. Additionally, the session delves into the acceptance and utilization of ITC evidence by several key agencies during recent HTA appraisals.

Recommendations on the use of innovative statistical methods to address confounding and bias in ITCs, as well as key elements to include in ITC reporting, are summarized. These insights equip statisticians with the necessary knowledge and tools to perform reliable ITC assessments and make informed decisions, ensuring alignment with the evolving evidentiary requirements for both EU and national-level HTA.

**Presentation 2 - Methodologies to adjust for measured confounding in ITC: an overview of population adjustment approaches**

*David Philippo, University of Bristol*

Network meta-analysis (NMA) and indirect comparisons combine aggregate data (AgD) from multiple studies on treatments of interest, assuming that any effect modifiers are balanced across study populations. Population adjustment methods such as matching-adjusted indirect comparison (MAIC), simulated treatment comparison (STC), and multilevel network meta-regression (ML-NMR) aim to relax this assumption, and are becoming increasingly prevalent in HTA. These methods use available individual patient data (IPD) to adjust for differences in effect modifiers between studies in a connected network, and are also used to incorporate single-arm studies or disconnected networks under much stronger assumptions.

We give an overview of population adjustment approaches, and their properties and assumptions. ML-NMR extends the standard NMA framework to coherently incorporate IPD and AgD studies whilst avoiding aggregation bias, and has several advantages over MAIC and STC. It can analyse networks of any number of trials and treatments, and in larger networks allows key assumptions to be assessed. Crucially, ML-NMR can provide comparisons in any target population for decision making. We illustrate with an example and compare results between the different approaches. A user-friendly R package multinma is available for performing ML-NMR analyses.

**Presentation 3 - Methodologies to adjust for unmeasured confounding in ITC**

*Kate Ren, University of Sheffield*

Population-adjusted indirect comparison methods such as matching-adjusted indirect comparisons (MAIC) and simulated treatment comparisons (STC) are useful tools to correct trial population differences when estimating treatment effects from single-arm trials. However, unanchored MAIC and STC assume that all effect modifiers and prognostic factors are accounted for, which is largely considered impossible to meet. We therefore developed a sensitivity analysis approach to formally quantify the impact of unmeasured confounding in indirect treatment comparisons, with an aim to address the limitation of the current population adjustment methods where certain prognostic factor and/or effect modifiers are not reported in the comparator trial.

**Presentation 4 - Case Study**

*Nicolas Scheuer, Roche*

Use of real-world (RW) external controls play a critical role in informing relative effects when randomised comparators are infeasible or, more broadly, not available for a given decision problem. However, due to the potential for systematic bias related to the non-randomised trial-RW comparison, Health Technology Assessment (HTA) agencies have been reluctant to consider them at face value in their reimbursement decisions. Here, the impact of such decisions on patient access will be illustrated with a Roche use case within a trial-RW external control setting using Quantitative Bias Analysis (QBA) methods for bias assessment.

**Methods**:

Trial-RW effects were obtained using propensity score weighting with the Flatiron Health database. QBA was then used to estimate the strength of unmeasured confounding, deviation from missing-at-random assumptions, and poorer RWD performance, needed to nullify any survival benefit.

**Findings**:

Significantly longer median survival were seen for the intervention compared to their real-world comparators. QBA showed that results for the trial-RW comparisons were robust to data missingness, residual confounding and potential poorer outcomes in RW data. However, decision-makers remained cautious with trial-RW informed relative effects to make coverage decisions.

**Interpretation**:

These findings suggest that QBA can be a useful tool to characterise uncertainty for decision-making, but much work is needed to showcase its strength to HTA bodies. The availability of real-world evidence frameworks globally offer a suitable platform for it.