Bucher Versus Bayesian NMA Approaches for Indirect Treatment Comparisons

What Do HTA Agencies Want?

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When considering potential reimbursement of a new treatment, health technology assessment (HTA) bodies worldwide need to evaluate how the product's clinical effects compare with already available treatment options for the indication in question. One obvious source of such evidence is the randomized controlled trials (RCTs) conducted to obtain regulatory approval since these will have explored whether the new product offers superiority, equivalence, or non-inferiority compared to a standard of care or placebo. However, these studies alone are unlikely to provide enough information, given that it is usually impractical to compare the new treatment with all the available active comparators in RCTs, particularly where there is a rapidly changing treatment landscape populated by multiple competitor interventions. Consequently, it is common for there to be an absence of any direct comparisons between a new treatment and one or more relevant comparators. For this reason, indirect treatment comparison (ITC) is a standard approach manufacturers rely on for their HTA reimbursement submissions. Of various approaches for comparing treatments indirectly, two are most commonly used in the HTA setting: an adjusted indirect treatment comparison method first proposed by Bucher et al.[1] and the mixed treatment comparison (MTC) of interventions combining direct and indirect evidence within a Bayesian framework proposed by Lu and Ades.[2] There have been several extensions to the Bayesian NMA (network meta-analysis) methods proposed by Lu and others, especially around evaluating consistency between the direct and indirect evidence.[3-4] Here we consider the Bucher ITC and Bayesian NMA techniques, some common misconceptions surrounding their use, and how they are regarded by various HTA bodies worldwide.

About Bucher ITC

Bucher and colleagues developed a method to compare treatments indirectly by preserving the randomization of the originally assigned patient groups. This approach contrasts with the unadjusted indirect comparisons or


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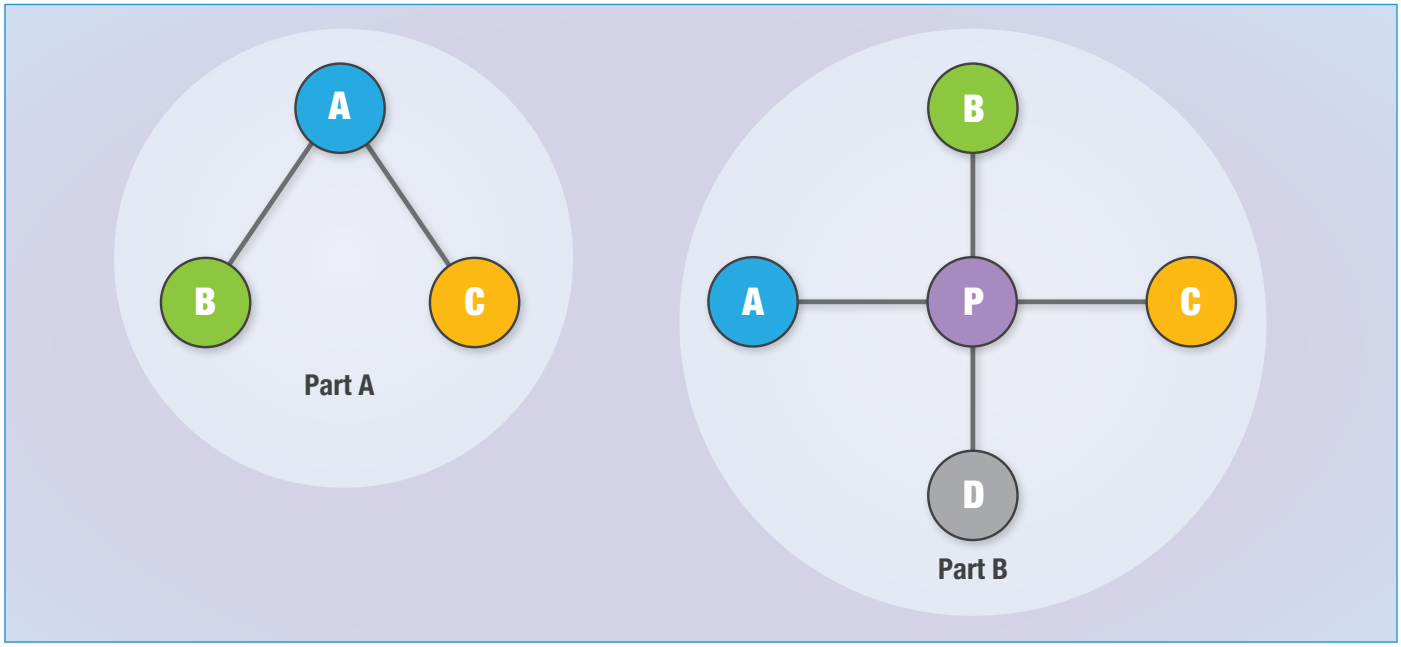
Figure 1.

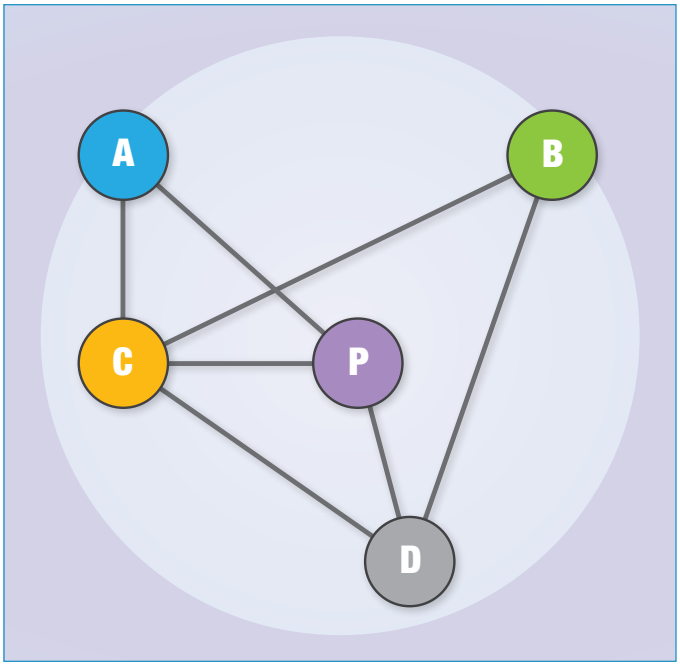


naïve comparisons of treatments, in which randomization between the treatment groups cannot be preserved.[1] Bucher analysis can be used in a simple indirect comparison to compare outcomes (either binary or continuous) between treatment B and treatment C (as in Part A of Figure 1) or across a star-shaped network of treatments, where several different interventions are compared to common comparator P (as in Part B of Figure 1). It assumes that the trials included in the ITC are similar with regards to the study population, study design, outcome measurements, and the distribution of treatment effect-modifiers (i.e., study and patient characteristics that have an independent influence on treatment outcome). However, this approach is unsuitable for performing indirect treatment comparisons within more complex networks of treatments with multi-arm trials, for which the Bayesian NMA methods are widely used instead.

About Bayesian NMA

The NMA method proposed by Lu and Ades, also commonly known as Bayesian NMA, differs from a standard meta-analysis. Specifically, it extends the concept of standard pairwise meta-analysis to conducting multiple pairwise comparisons across the interventions studied to yield the relative treatment effects. This approach combines both the direct and the indirect evidence for the interventions being compared.[2] It can be applied to networks with multi-arm trials and complex networks with closed loops, such as that shown in Figure 2. In addition to the continuous and binary outcomes, this approach can also be used to analyze counts and survival outcomes in trials. Similar to the Bucher ITC approach, the Bayesian NMA approach also has assumptions such as homogeneity, transitivity (similarity), and additionally, consistency, another key assumption of any NMA. Homogeneity occurs when the relative treatment effects of two interventions compared directly are similar across the trials including such a comparison in a network, and this can be tested using a statistic such as I^2. Similarity or transitivity looks at all the comparisons involved in the network to see if the trials included in the network are similar enough to be combined into a network. Similarity assumption requires that the distribution of the treatment effect-modifiers be similar across the studies included in the NMA, and this assumption can only be evaluated qualitatively not quantitatively. Consistency assumption of an NMA requires that when direct and indirect evidence are available for a pairwise comparison, the direct and indirect estimates should be similar statistically, and this assumption can be evaluated quantitatively using various methods.

Figure 2.



Common Misconceptions about the Methods

Although both Bucher ITC and Bayesian NMA are widely used, the following misconceptions are often expressed about both how they can and cannot be applied and the information they yield.

Bucher analyses can be used only when there is a single study per treatment comparison. The Bucher method is suitable, or even ideal, in such situations. However, it can also be used when multiple studies are available for one or more comparisons. If so, estimates from multiple studies for a treatment contrast are pooled into one estimate using classical (pairwise) meta-analysis approach before computing Bucher indirect estimate for a different treatment contrast.

Bucher ITC and Bayesian NMA are different statistical approaches, and so the results they provide will inevitably be different. In reality, where the treatment comparisons involve simple networks with two pairwise comparisons or a star-shaped network with a single common comparator, Bucher ITC and Bayesian NMA are likely to provide similar, if not identical, results. However, with more complex networks involving closed loops and multi-arm RCTs, the Bucher methodology cannot be applied, as it assumes independence between pairwise comparisons – something not found in multi-arm studies. The Bucher method has been formally compared to other ITC methods to evaluate whether both approaches produce mutually consistent results when used to conduct a given treatment comparison. For example, O'Regan and colleagues have compared Bayesian NMA and Bucher's method across a range of network types and concluded that in most cases, the two methods produced similar results, especially where all studies share a same comparator.[5] Also, Glenny et al. have compared Bucher's method with meta-regression, logistic regression, and mixed models from sample data of 15 trials, and concluded that, except for mixed models, other models provided comparable effect estimates and confidence intervals.[6]

What Do HTA Bodies Think?

The Bayesian NMA method can handle more complex networks with more than two treatment arms per trial, and can also incorporate meta-regression with study level covariates, analysis that is not possible with Bucher's method. Although Bayesian NMA offers these distinct advantages in the context of HTA submissions, both Bucher's and Bayesian methods are widely recognized as having a place by HTA bodies. However, there is some geographical variation across these organizations in how the two techniques are regarded.

IQWiG

Germany's Institute for Quality and Efficiency in Health Care (IQWiG) has made recommendations regarding the acceptability and use of indirect treatment comparisons. Specifically, it advises that ITC should only be considered when the analysis is targeted towards the overall research question rather than individual outcomes. Under these circumstances, IQWiG considers Bucher's adjusted ITC and Bayesian NMA methods to be appropriate for indirect comparisons in health economic evaluations.[7]

EUnetHTA

The European Network for Health Technology Assessment (EUnetHTA) also recognizes the use of both Bucher's method and Bayesian NMA for submissions. However, it notes that when the evidence supports the use of either method, Bucher's method offers the most in terms of transparency and ease of application. By contrast, EUnetHTA considers that the complexity of the Bayesian NMA models renders them less advantageous than Bucher's ITC.[8]

CADTH

The Canadian Agency for Drugs and Technologies in Health (CADTH) has reviewed the ITC methods in detail and recognizes the use of both Bucher's method and the Bayesian NMA. In doing so, it argues that the Bucher is appealing because it is designed to be applied with minimal information to the common ITC involving a simple star design. CADTH also considers the complexity of Bayesian NMA as a limitation to its use in comparing treatments indirectly.[9]

PBAC

Australia's Pharmaceutical Benefits Advisory Committee (PBAC) also acknowledges that Bucher's method is a widely accepted approach to ITC and suggests that more complex methods such as NMA may be presented as an appendix in the submissions.[10]

HAS

France's Haute Autorité de Santé (HAS) states that in the absence of any known differences between adjusted ITC methods and Bayesian NMA, it is difficult to recommend any approach. Therefore, HAS accepts the use of both Bucher's and Bayesian NMA, although it observes that the Bayesian NMA is the most useful method as it is flexible.[11]

Although HTA agencies differ subtly in their recommendations about using Bucher methods or Bayesian NMA, they all well understand from their wide experience that it is generally unwise to find statistically significant differences between active treatments in such analyses. Unlike the direct comparisons in clinical trials, an indirect comparison does not have to show statistical significance to be relevant or useful. Indirect comparisons (whether Bucher or Bayesian) inevitably have wider (95%) confidence/credible intervals than any given direct comparison included, and relative effects in comparisons between active treatments are generally expected to be smaller than those in comparisons between an active treatment and either no treatment or placebo.

Conclusion

Indirect treatment comparisons using Bucher's method or Bayesian NMA are generally accepted by HTA bodies for submissions to assess new technologies for potential reimbursement. Both approaches have key strengths and limitations, and these may determine whether one or the other is more appropriate to use in a given situation. However, in situations where both approaches can be applied, they can be used interchangeably, with the reasonable expectation of generating similar results. ■

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Acknowledgments

The authors thank Kyle Fahrbach, PhD, Principal Statistician, and Binod Neupane, PhD, Statistician, of Evidera's Meta Research team for their excellent support in the quality review of this article.

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