



INTERNATIONAL BIOMETRIC SOCIETY

Importance of Results from Indirect Comparisons

Joint Statement from IQWiG, GMDS and IBS-DR

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On 23rd September 2011, version 4.0 of the General Methods of the Institute for Quality and Efficiency in Health Care (IQWiG) was published (IQWiG, 2011). The Act on the Reform of the Market for Medicinal Products (AMNOG) had come into force in January 2011 (Deutscher Bundestag, 2010). Besides the implementation of the new requirements posed by AMNOG concerning the early benefit assessment of drugs, the new version of the General Methods contains, amongst other things, a new section on indirect comparisons. Similar to the Methods Guide of the National Institute for Health and Clinical Excellence (NICE) in England, the IQWiG methods paper also shows a strong preference for the use of direct comparisons from randomized controlled trials as a basis for proof of benefit (NICE, 2008; IQWiG, 2011). On the other hand, both institutes mention the possibility of applying methods for indirect comparisons if no direct head-to-head trials are available. For acceptance of the decisions made by the Federal Joint Committee (G-BA) on the basis of IQWiG reports, it appears to be desirable to achieve a scientific consensus regarding the importance of results from indirect comparisons within the framework of benefit assessments.

“Methods for indirect comparisons” mean procedures for simple indirect comparisons of 2 interventions as well as procedures combining direct and indirect evidence. The latter are referred to as mixed treatment comparison (MTC) meta-analysis, multiple treatment meta-analysis (MTM) or network meta-analysis. Schöttger et al. (2009) and Wells et al. (2009) give an overview of currently available methods for indirect comparisons.

There is a general scientific consensus that it is inappropriate to apply non-adjusted indirect comparisons (i.e. the naïve use of individual study arms from different studies for a comparison of interventions applied in these study arms without consideration of randomization) (Gartlehner & Moore, 2008; Higgins et al., 2008; Schöttger et al., 2009; Song et al., 2009). Therefore such an approach is rejected by both NICE and IQWiG (NICE, 2008; IQWiG, 2011). Consideration is only given to methods for adjusted indirect comparisons where randomization of the analysed studies is maintained.

In the next section it is explained why, on the one hand, the application of methods for adjusted indirect comparisons in benefit assessments is necessary and helpful, while on the other, at present the corresponding results generally represent an evidence basis from which conclusions on benefit can be derived only with a lower certainty of results.

The results of adjusted indirect comparisons are only valid if, besides the assumptions of common meta-analyses, the similarity assumption as well as – in the case of combination of direct and indirect evidence – the consistency assumption are also satisfied (Song et al., 2009). In this context similarity means the comparability of the analysed studies regarding possible effect modifiers across all interventions, and consistency means the comparability of effect estimations from direct and indirect evidence (Song et al., 2009).

While the analysis of the similarity assumption – if conducted at all – is done by subjective evaluation of the study characteristics (if necessary, supplemented by subgroup analysis or meta-regression) (Song et al., 2009), the development of statistical methods for the analysis of the consistency assumption is still ongoing. However, many methodological questions still remain to be answered. A current overview of the present developments is provided by Dias et al. (2011). The problems and the technical implementation of existing methods for the consistency analysis are described in the technical support document of Dias et al. (2011). However, the question as to when reliable conclusions can in practice be drawn from results of indirect comparisons is not explicitly answered. In a current review Song et al. (2011) describe that significant differences between results from indirect and direct comparisons occur more frequently than previously assumed. Due to the high risk of biased results and the numerous unresolved methodological problems, in general no certain proof of benefit of a medical intervention can currently be inferred from results of indirect comparisons. The gold standard for the inference of proof of benefit is generally still the synthesis of direct evidence from studies with sufficient certainty of results. This requires adequate study designs, adequate inclusion and exclusion criteria regarding study populations (including the question as to what extent the study population covers the target population), adequate comparative therapies, correct data analyses as well as correct presentations of results (Heres et al., 2006; Bero et al., 2007).

However, this high evidence standard is not maintainable or necessary in all situations. Examples in which methods for adjusted indirect comparisons can play a valuable role are health economic evaluations (IQWiG, 2009), as well as the early benefit assessment of drugs (Deutscher Bundestag, 2010). In a health economic evaluation the costs are usually determined by modelling, i.e. the evidence level is per se lower than in the case of pure benefit assessments. Furthermore it is often necessary to perform simultaneous analyses of multiple interventions, which is only feasible in a reasonable way with network meta-analyses. Hence, in this field methods for adjusted indirect comparisons are reasonable and necessary, but only deliver conclusions with a lower certainty of results.

In the early benefit assessment of drugs the appropriate comparative therapies determined by the G-BA can differ from the control arms of the approval studies, so that especially regarding newly approved interventions no direct comparative studies are available. In order to nevertheless enable benefit assessments, in such a case adjusted indirect comparisons are essential.

But as long as there is still no methodological investigation of the question as to when and under what conditions indirect comparisons allow reliable conclusions, only conclusions with a lower certainty of results are generally possible.

The GMDS (German Society for Medical Informatics, Biometry and Epidemiology), the German Region of the International Biometric Society, and IQWiG agree that currently a reliable derivation of proof of benefit in terms of a high certainty of results can usually only be generated from direct evidence. In various situations the application of methods for adjusted indirect comparisons is often helpful, necessary or even essential (e.g. if direct comparisons are lacking), but currently only provides conclusions with a lower certainty of results. Methods for adjusted indirect comparisons, including methods for the analysis of the consistency assumption, are important research fields which should be appropriately promoted in order to provide approaches to solve the still existing methodological problems.

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