IQWiG methods 8.0 – Draft version

May 2025

methodological changes (compared to version 7.0)

1. Combined endpoints with weighted components possible
2. Indirect comparisons
3. Bayesian meta-analysis for cases with 3 and 4 studies
4. Next steps: Pharmaceutical companies aligned on comments to Baysian meta-analysis

Combined endpoints

new (draft version 8.0):

Finally, combined endpoints can also be considered, where the individual components are weighted according to their relevance (e.g., win-ratio approach).

indirect comparisons – no relevant changes

old (version 7.0):

However, there are still numerous unresolved methodological issues, so it is currently advisable to refrain from the routine application of these methods in the context of benefit assessment.

new (draft version 8.0):

However, indirect comparisons require stronger assumptions than direct comparisons, so results from indirect comparisons generally have a lower certainty of results than those from direct comparisons.

As in pairwise meta-analyses, a random effects model should also be chosen by default in network meta-analyses.

In case of 3 or 4 studies: bayesian meta-analysis

new (draft version 8.0):

Depending on the number of studies, the following standard procedure should be chosen for conducting meta-analyses unless there are clear reasons against it:

2 studies:

Use a fixed effects model, applying the inverse variance method for continuous data or the Mantel-Haenszel method for binary data.

3 to 4 studies:

Use a random effects model, specifically for effect sizes such as SMD, odds ratio, relative risk, and hazard ratio, utilizing a Bayesian meta-analysis with non-informative prior distributions for the treatment effect and informative prior distributions for the heterogeneity parameter τ according to Lilienthal et al. Additionally, there should be a comparison with a qualitative summary of the study results using the concept of concordant effects. For other effect sizes, it should be determined on a project-specific basis whether to apply the Knapp-Hartung method, a qualitative summary of the study results, or another procedure.

In case of 3 or 4 studies: bayesian meta-analysis

5 studies and more:

Use a random effects model, specifically using the Knapp-Hartung method. Initially, pooled effects will be calculated according to the Knapp-Hartung method – with and without ad-hoc variance adjustment – as well as the Paule-Mandel method for estimating the heterogeneity parameter τ, and pooled effects according to the DerSimonian-Laird method will be calculated. It will be checked whether the confidence interval according to Knapp-Hartung (without ad-hoc variance adjustment) is narrower than that according to DerSimonian-Laird. In this case, the effect estimate according to Knapp-Hartung with ad-hoc variance adjustment will be used; otherwise, it will be used without ad-hoc variance adjustment. Then it will be checked whether this effect estimate is informative. An estimate will be considered informative if the confidence interval (of the overall effect) is contained within the union of the confidence intervals of the individual studies. In this case, this effect estimate (according to Knapp-Hartung) will be used for the final assessment. Otherwise, a joint effect estimate will be regarded as not meaningful, and a qualitative summary of the study results will be provided using the concept of concordant effects.

Bayesian meta-analysis – Choose of Prior

IQWiG refers to the (own) publication from Lilienthal et al [1] in which they suggest priors for the heterogeneity τ

On the basis of Figure 7 we suggest the use of

1. HN(0.1) for the effect measures RR and HR
2. HN(0.2) for the effect measure OR
3. HN(0.3) for the effect measure SMD

as prior distributions for future Bayesian random-effects meta-analyses. We used approximately the 95% quantiles of the scale parameters' posteriors, and rounded these to the nearest value with a single decimal place. This also

Priors have been choosen very conservative based on all IQWiG Metaanalyses up to Dec 2021. This dataset includes also non-pharmacological studies as well as studies where they tested heterogeneity to assess heterogeneity for network meta-analysis. Both tend to more heterogeneity compared to HTA assessments.

Database has not been shared.

1) Lilienthal J, Sturtz S, Schurmann C et al. Bayesian random-effects meta-analysis with empirical heterogeneity priors for application in health technology assessment with very few studies. Res Synth Methods 2024; 15(2): 275-287.

Bayesian meta-analysis – Critical points to consider / comment on

- A lot of studies do not reflect situation in HTA assessments
- According to other publications (Turner at al) endpoint categories show substancial differences in heterogeneity (e.g. OS low heterogeneity, PROs higher heterogeneity → this isn‘t considered by IQWiG)
- Prior for τ is choosen based on 95% CI – even this is very conservative given that the underlying datasets already tends to overestimate heterogeneity

We assume that the aim of IQWiG to be able to quantify the added benefit more often with a Bayesian meta-analysis isn‘t realitistic for HTA assessments. Moreover we assume that we face power loss and therefore lower grades of additional benefit or loss of potential additional benefit.

What we ask for:

- Grant access to the database
- Update database regularly
- Let‘s talk about it

Bayesian meta-analysis – Open questions we will raise

Some Questions are open and should be discussed with IQWiG, academia & pharmaceutical industry

- How to conduct subgroup analysis?
- How would the Prior look like if it is choosen by endpoint category?
- How would the Prior look like if it is based on HTA assessments only?