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23 October 2025

Submission of comments on Draft Concept Paper on the Development of a Reflection Paper on the Use of External Controls for Evidence Generation in Regulatory Decision-Making

Name of organisation or individual*	General or Specific comment*	Line from* (line nr. or 0 for general comment)	Line to* (line nr. or 0 for general comment)2	Comment and rationale (to go to next line within the same cell use Alt + Enter)	Proposed changes / recommendation (if applicable - to be used if you want to propose specific text changes)	Outcome (To be completed by the Agency)
IQWiG	General	0	0	IQWiG appreciates the opportunity to provide comments on the Draft Concept Paper on the Development of a Reflection Paper on the Use of External Controls for Evidence Generation in Regulatory Decision-Making.		
IQWiG	Specific	25	28	We agree with the need for reflections on methodological reliability and operational aspects of external controls. Due to increasing numbers of single-arm trials in drug development programs we receive submissions to Health Technology Assessments using external controls. However, often basic methodological requirements for such comparisons are not met. Therefore, further clarification of appropriate methods for the use of external controls may be helpful.		
IQWiG	Specific	25	28	We would like to refer to Guidance documents by the EU HTA Coordination Group which includes reflections and recommendations on comparisons using external controls: Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons (https://health.ec.europa.eu/publications/methodological-guideline-quantitative-evidence-synthesis-direct-and-indirect-comparisons_en); Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons (https://health.ec.europa.eu/publications/practical-guideline-quantitative-evidence-synthesis-direct-and-indirect-comparisons_en)		
IQWiG	Specific	29	30	From our point of view, it is important to always specify the research questions for which an appropriate method should be used, which answers the research question and is feasible in the considered data situation.		
IQWiG	Specific	40	43	Systematic identification of confounding variables followed by sufficiently complete collection and adjustment for identified confounders are key to generate reliable results using external controls for causal effect estimation. For the systematic identification of confounders Pufulete et al. 2022 provide a framework (Pufulete M, Mahadevan K, Johnson TW et al. Confounders and co-interventions identified in non-randomized studies of interventions. J Clin Epidemiol 2022; 148: 115-123. https://doi.org/10.1016/j.jclinepi.2022.03.018).This approach has been applied in an example project in MS and has been shown to be feasible. [GA23-02] Systematische Confounderidentifikation in der Indikation schubförmig remittierende multiple Sklerose (RRMS)https://www.iqwig.de/projekte/ga23-02.html		
IQWiG	Specific	40	43	Un-anchored indirect comparisons to external controls are non-randomised comparisons for which the possibility of unmeasured confounding remains. Therefore, tests against a shifted null-hypotheses or quantiative bias assessment should be considered to account for remaining uncertainties.		
IQWiG	Specific	48	48	Reliable adjusting for confounding variables is only possible using individual patient level data. There should be a strong recommendation against using aggregated data for adjusting un-anchored indirect comparisons to external controls.		
IQWiG	Specific	93	94	We appreciate the information for the HTA Coordination Group and HTA bodies.		