Surrogate outcome validation within the new EU HTA guidance framework - Practical considerations from an industry perspective based on experience from German HTA

HTA307

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SURROGATES IN THE GUIDANCE ON OUTCOMES FOR JOINT CLINIAL ASSESSMENTS (JCA)

- Patient-centred outcomes are outcomes that directly measure mortality, morbidity and outcomes related to patients' feelings, beliefs, preferences, needs and functions
- A surrogate outcome is an outcome that is intended to replace an outcome of interest in situations in which direct measurement of a patient-centred effect is not feasible or practical
- Surrogate outcomes include biomarkers, e.g., levels of cholesterol, haemoglobin A1C (HbA1C) or antibody titre after vaccination and intermediate outcomes, e.g., objective response rate or progression-free survival in oncology
- The JCA is an assessment, and JCA reports shall not contain any value judgement. This means that technology appraisal remains fully in the competency of Member States (MS).
- In the past acceptance of surrogate outcomes varied greatly across HTA agencies (Ciani et al. 2021). The JCA guidance specifies that for surrogates the clinical relevance and fit to the JCA need to be considered by MS.
- This means that differences in the appraisal of surrogates among Member States may persist also with EU HTA.
- The health technology developer (HTD) is requested to a) explain for which patient-centred outcome of interest a surrogate is applied and b) to validate the surrogate. For validation three levels of evidence are defined for consideration in the appraisal by Member States (see Table 1).

Table 1. Levels of evidence for surrogacy (based on HTA CG (2024)

Level of evidence	Evidence needs	Comment
Level 3 Only evidence of biological plausibility	Pathophysiological studies and/or an understanding of the disease process	Lowest level of evidence
Level 2 Association between surrogate outcome and final patient-centred outcome	Interventional, epidemiological or observational studies	Not restricted to disease stage or interventions
Level 1 • Evidence demonstrating that treatment effects on the surrogate outcome correspond to effects on the patient-centred outcome • Establishment of correlation between effects on the surrogate outcome and the patient-centred outcome in the respective disease stage and sufficiently restricted to the interventions investigated [a]	Meta-analysis of several randomised controlled trials (RCT)	• Level 1 evidence typically not needed for regulatory submissions • Number of relevant RCT available at HTA dossier submission typically limited • No methodological details provided in the JCA guidance document. However, the guidance refers to Molenberghs et al. 2010 who describe several approaches including an individual patient-level data based hierarchical two-level meta-analytic approach for Level 1 validation

[a] A correlation of at least 0.85 is described as "high" and can be used as a criterion for validation of surrogate outcomes. The concept of the surrogate threshold effect (STE) is helpful for decision-making because it represents the minimum effect regarding the surrogate outcome that is required to conclude that there is also high certainty of an effect on the patient-centred outcome

PRACTICAL CONSIDERATIONS BASED ON EXPERIENCE FROM GERMAN HTA

- Methodological requirements for surrogate validation in the guidance on outcomes for JCA (Level 1 evidence) are comparable to the existing IQWiG requirements described in General Methods (IQWiG 2023)
- Whereas some few surrogates are accepted within German HTA, **all previous formal attempts by a HTD to provide sufficient evidence to validate and apply additional surrogate endpoints have failed.** This was either due to methodological concerns raised by IQWiG or the association between surrogate and patient-relevant endpoint was deemed to be not strong enough.
- Examples include the validation of disease-free survival as surrogate for overall survival in adjuvant breast cancer (IQWiG 2018, IQWiG 2020) and the validation of progression-free survival as surrogate for overall survival in metastatic breast cancer (IQWiG 2017a, IQWiG 2017b).

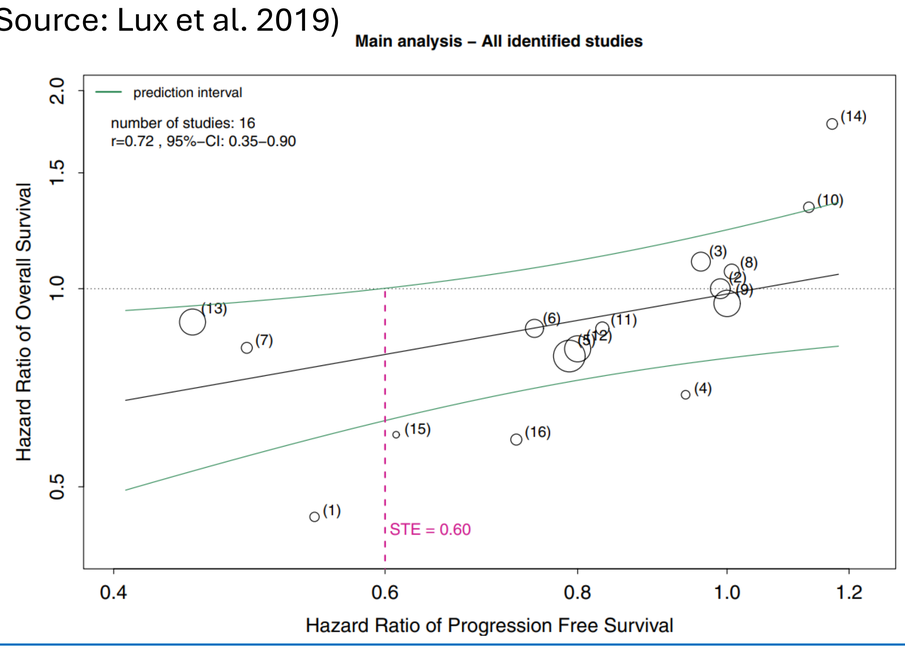
Table 2. Practical considerations relevant for JCA based on experience from HTA Germany

Topic	Learnings
Study pool relevant for JCA Level 1 validation	• A systematic literature review is essential to identify studies for surrogate endpoint validation • As studies need to be restricted to the disease stage and interventions investigated, the number of relevant studies is typically limited • In situations where a therapy of the same class and in the same indication has been on the market for already a longer time, a sufficient study pool might be available for surrogate endpoint evaluation. An example is the case of the antibody drug conjugate trastuzumab emtansine where study data from previous trastuzumab studies could be incorporated in the surrogate endpoint validation study (IQWiG 2020).
Analysis based on aggregate data (AGD) only versus usage of AGD+IPD	• Correlation-based meta-analytic methods are applicable both on individual patient data (IPD) level and on aggregated data level. From a methodological standpoint analyses based on IPD are preferable (Burzykowski et al. 2005). • Getting access to company-external IPD can be very effortful and requires extensive planning. • In situations where IPD are available from some but not all studies in the study pool, the correlation between the surrogate and the patient-centric outcome at the individual patient-data level might be shown for the available IPD studies. The correlation between effects on the surrogate and effects on the patient-centric outcome at a study level might be shown based on all aggregated data in a meta-regression.
Presentation of results	• Sensitivity analysis should be included (e.g., related to study selection) • Estimates of correlation and STE are relevant to provide, and graphical summaries are useful for interpretation (see Figure 1)

RECOMMENDATIONS AND CONCLUSIONS

- When planning for a clinical study program, it is important to consider the acceptability of outcomes and take advantage of the opportunity for early HTA consultations (Joint Scientific Consultation (JSC) or national HTA advice).
- If there is still a need to include surrogate outcomes in a JCA dossier, the corresponding surrogate endpoint validation requires thorough planning. It is recommended to conduct a feasibility study in which the availability of a sufficiently large study pool is determined.
- Analyses based on IPD are in general preferable from a methodological standpoint. However, these are effortful and require extensive planning and a large time budget (especially in case of inclusion of company-external IPD which might require involving a trusted third party).
- As technology appraisal remains fully in the competency of Member States, differences between countries in the acceptance of surrogate outcomes and related validation requirements may persist also with EU HTA.

Figure 1. Illustrative example for presentation of STE results
(Source: Lux et al. 2019)



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Further details around surrogate endpoint validation within German HTA can be found in the German Benefit Assessment White Paper (QR code)

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