THE ROLE OF SURROGATES FOR PATIENT-RELEVANT ENDPOINTS IN THE EARLY BENEFIT ASSESSMENT IN GERMANY

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BACKGROUND

The market authorization for a new drug can be granted even if the underlying clinical trials evaluated mainly surrogates rather than patient-relevant endpoints. A surrogate is a laboratory measurement or a physical sign used as a substitute for a patient-relevant endpoint that measures directly how a patient feels, functions or survives. In the German early benefit assessment however, only patient-relevant endpoints are accepted. If surrogates are used instead, they need to be validated, i.e. the correlation between the effects of the intervention on the surrogate and the corresponding patient-relevant endpoint needs to be demonstrated.

Surrogates

+ are physiological or biochemical markers that are usually not of direct relevance to the patient, but are determined in place of important clinical endpoints.
+ are biologically plausible and enable the prediction of the actual endpoint.
+ are often used in clinical trials because they allow changes to be detected earlier and quantified more easily.

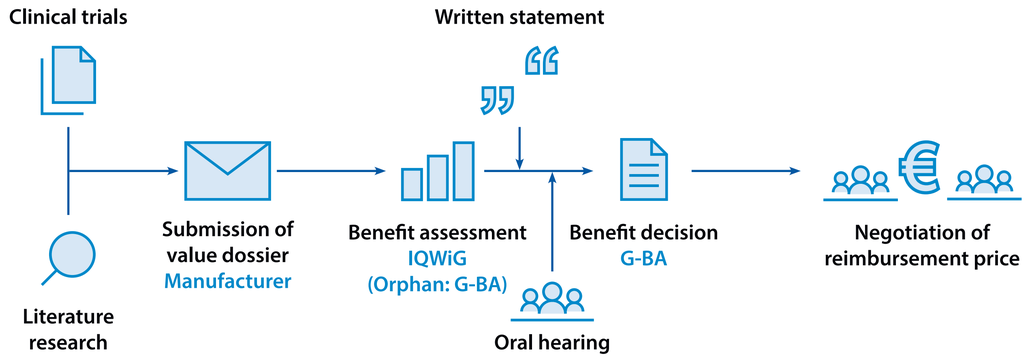

Figure 1: Early benefit assessment in Germany. IQWiG: Institute for Quality and Efficiency in Health Care. G-BA: Federal Joint Committee.

OBJECTIVE

We investigated the role of surrogate endpoints in the early benefit assessment by the Institute for Quality and Efficiency in Health Care (IQWiG) and the Federal Joint Committee (G-BA).

METHODS

Data source: All early benefit assessments since the Act on the Reform of the Market for Medicinal Products (AMNOG) in 2011 until September 2018 were evaluated.

Inclusion criteria: Surrogates were considered if they were defined as such in the manufacturers' value dossiers or during dossier assessment by IQWiG or G-BA.

Analysis: All identified surrogates were evaluated based on their justification by the manufacturer and their acceptance by the IQWiG and the G-BA.

RESULTS

+ Early benefit assessments analyzed: N = 331
+ Early benefit assessments including surrogates: n = 84 (25%)
+ Surrogates identified (multiple mentions possible): N = 363

Justification of surrogates in the manufacturers' value dossier

+ The majority of value dossiers did not contain an attempt of surrogate validation.

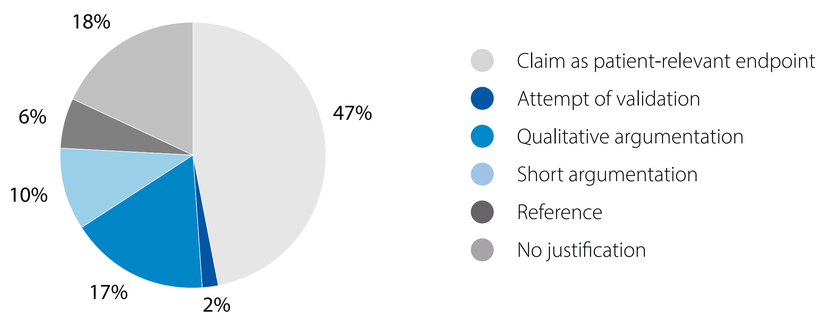

Figure 2: Distribution of surrogates among six categories of justification in the manufacturers' dossiers.

CONCLUSIONS

+ **Surrogates are rarely accepted in the German early benefit assessment.**
+ **The manufacturers' dossiers commonly base their claim for an additional benefit on surrogates, but only few manufacturers tried to validate them.**
+ **The use of surrogates is typically justified without statistical validation, or the surrogate is claimed to be a patient-relevant endpoint.**
+ **To increase the future acceptance of surrogates, more rigorous validation processes are necessary.**

RESULTS

Acceptance of surrogates in the benefit assessment

+ More than two thirds of surrogates were not accepted as valid. However, some surrogates were accepted although the value dossier did not contain a validation.

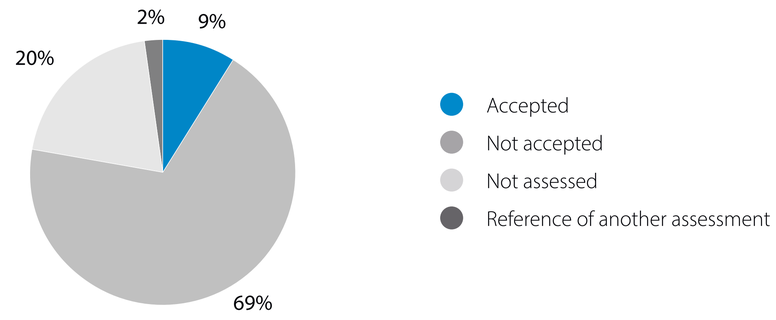

Figure 3: Distribution of surrogates among four categories of acceptance in the benefit assessment.

Acceptance of surrogates in the benefit decision

+ The acceptance of surrogates differed substantially between benefit assessment and decision. Example: Sustained virologic response (SVR) in chronic Hepatitis C (assessment Boceprevir 2012)
  - Assessment: valid surrogate for hepatocellular carcinoma
  - Decision: patient-relevant endpoint

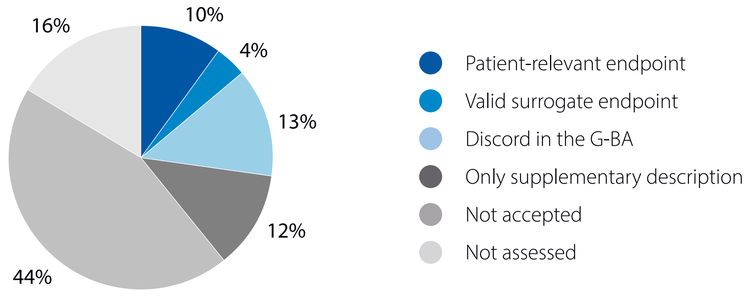

Figure 4: Distribution of surrogates among six categories of acceptance in the benefit decision.

+ Very few surrogates have been accepted as valid by the G-BA (Table 1).

Surrogate	Indication	Endpoint	Assessment
Virologic response	Human immunodeficiency virus infection	Occurrence of AIDS-defining diseases / death	Rilpivirin 2012
CD4 cell count	Human immunodeficiency virus infection	Occurrence of AIDS-defining diseases / death	Elvitegravir fixed combination 2013
Reduction of oral corticosteroids	Systemic lupus erythematosus	Prevention of glucocorticoid-induced side effects	Belimumab 2012
Reduction of oral corticosteroids	Asthma	Prevention of glucocorticoid-induced side effects	Mepolizumab 2016
HbA1c level	Type 1 diabetes	Microvascular complications	Insulin degludec 2015

Table 1: Surrogates that have been accepted by the G-BA in an early benefit assessment, their respective indication, the patient-relevant endpoint that was substituted, and the benefit assessment where the surrogate was first accepted.

+ Examples of surrogates which are commonly used in value dossiers but are not accepted by the G-BA:
  - Progression-free survival (PFS) in oncology as surrogate for overall survival
  - Forced vital capacity (FVC) in respiratory diseases as surrogate for respiratory distress
  - HbA1c level in type 2 diabetes as surrogate for hypoglycemia

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