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Key Factors for the Consideration of Quality of Life Data in AMNOG Benefit Assessments

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Background

- According to the German Pharmaceuticals Market Reorganization Act (AMNOG), it is mandatory for pharmaceutical companies to submit a dossier for benefit assessment on the day of the launch of new pharmaceuticals.
- The AMNOG process is a two-step procedure. In a first step, the dossier is scientifically and methodologically assessed by the Institute for Quality and Efficacy in Health Care (IQWiG). In the case of orphan drugs this assessment is performed by G-BA. In a second step, a final resolution is made by G-BA who is the decision-making body and who is not bound in his decision to the recommendation of IQWiG.
- In recent years, the measurement of health-related quality of life (HrQoL) has become an important component of benefit assessments within the AMNOG process. According to the German Social Act Five, HrQoL represents a direct patient-relevant outcome in the benefit assessment of medicinal products. Consequently, G-BA is emphasizing the importance of HrQoL in decision making. In contrast, limitations regarding HrQoL data may be of negative impact on the outcome of the benefit assessment.

Objectives

- The aim of this study was to analyze the spectrum of HrQoL instruments and statistical methods used for HrQoL data analysis within submitted AMNOG dossiers. The analysis was based on dossiers on multiple myeloma, melanoma, and breast cancer drugs. Additionally, key factors for the acceptance by G-BA and/or IQWiG were examined.

Methods

- A database containing all AMNOG dossiers conclusively assessed by G-BA until the end of April 2019 was searched for multiple myeloma, melanoma, and breast cancer drugs. Relevant dossiers as well as the accompanying assessment reports of the IQWiG and G-BA decisions were screened regarding the HrQoL instruments, the applied statistical approaches, the methodological comments by G-BA and IQWiG, and the granted added benefit.

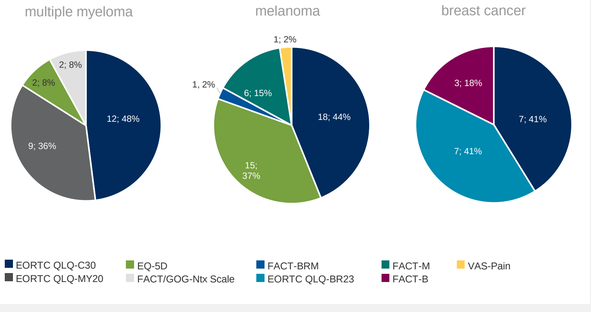
Results

- 42 dossiers (multiple myeloma n=11, melanoma n=21, breast cancer n=10) with 49 subpopulations (multiple myeloma n=13, melanoma n=24, breast cancer n=12) were identified.
- For 44 subpopulations, data on HrQoL was reported. For some subpopulations, multiple HrQoL instruments were available, resulting in a total of 83 HrQoL endpoints (HrQoL assessment based on one instrument was defined as an HrQoL endpoint).
- Overall nine different HrQoL instruments were applied (**Table 1**).

Table 1. Questionnaires used in AMNOG dossiers on multiple myeloma, melanoma, and breast cancer

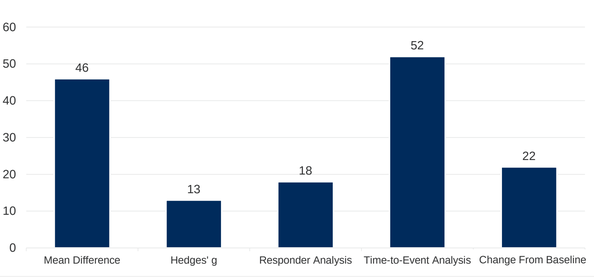
Generic or cancer-specific HrQoL instruments	Indication-specific HrQoL instruments
EORTC QLQ-C30 EQ-5D FACT/GOG-Ntx Scale VAS Pain	EORTC QLQ-MY20 (multiple myeloma) FACT-BRM (melanoma) FACT-M (melanoma) EORTC QLQ-BR23 (breast cancer) FACT-B (breast cancer)

Figure 1. Distribution of questionnaires in multiple myeloma, melanoma, and breast cancer



- The validated cancer-specific questionnaire EORTC QLQ-C30 was most prevalent throughout all indications (41%–48%), while the most prevalent indication specific HrQoL instruments were FACT-M in melanoma (15%), EORTC QLQ-MY20 in multiple myeloma (36%), and EORTC QLQ-BR23 in breast cancer (41%) (**Figure 1**).
- For most subpopulations (n=40) pharmaceutical manufacturers reported HrQoL based on one or more generic or cancer-specific HrQoL instruments. For 22 subpopulations, these data were additionally supported by one or two indication-specific questionnaires. Only in four subpopulations was data based exclusively on an indication-specific HrQoL instrument.

Figure 2: Data presentation by pharmaceutical manufacturers



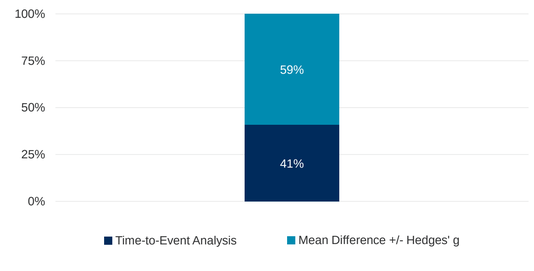
- On the 83 identified endpoints one or multiple analyses were performed to evaluate the outcome on HrQoL, resulting in a total of 151 HrQoL analyses. These analyses contained 52 time-to-event responder analyses, 46 analyses of the mean difference between treatment arms (30%; eg, mixed model for repeated measures [MMRM] analyses), 22 analyses of the change from baseline, and 18 responder analyses and 13 analyses of Hedges' g (**Figure 2**).

Table 2: Additional analyses on QoL data performed by IQWiG

Additional analyses performed by IQWiG	Number of benefit assessments
Yes	**10**
Hedges' g	4
MMRM	5
Responder Analysis	1
No	**73**

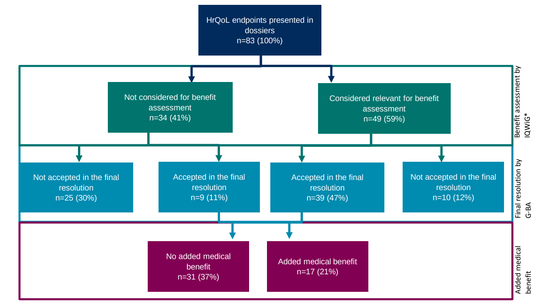
Results (cont.)

Figure 3: Data analyses used by IQWiG for benefit assessment



- For 10 out of 83 HrQoL endpoints, IQWiG performed its own analyses based on study data provided during benefit assessment (**Table 2**).
- In the end, 49 of the 83 HrQoL endpoints were considered relevant for benefit assessment by IQWiG. In 59% (n=29) of cases, the assessment was based on the mean difference between treatment arms (most often MMRM analyses; 24,5%) and in 41% (n=20) of the cases on time-to-event responder analyses based on validated minimal clinically important differences (MCID) (**Figure 3**).

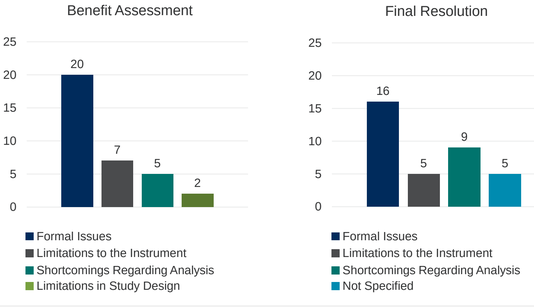
Figure 4. Frequency of QoL Data is used by IQWiG and G-BA for benefit assessment



*In the case of orphan drugs, benefit assessment is performed by G-BA.

- In the benefit assessment by IQWiG or G-BA, the first step of the AMNOG process, HrQoL data have been methodologically accepted for 49 of 83 HrQoL endpoints (59%), presented in a total of 30 subpopulations. In the second step, the final resolution G BA, HrQoL data have been accepted for 48 endpoints (58%), 9 of which have previously not been considered in benefit assessment. In 10 cases, the G-BA has not accepted the endpoint in the final resolution, although the endpoint has been considered as methodologically correct in the benefit assessment.
- For 17 of the 48 HrQoL endpoints that had been accepted by G-BA in the final resolution, an added medical benefit has been assigned, thereby covering all three indications (multiple myeloma, melanoma, and breast cancer) in a total of 11 subpopulations (**Figure 4**).

Figure 5. Reasons resulting in rejection of HrQoL data for benefit assessment



- The major reason for non-acceptance of HrQoL endpoints in benefit assessment and in the final resolution were formal issues (eg, inappropriate comparator) in either 59% or 46% of the cases. This was followed by limitations of the HrQoL instrument (21% vs 14%) or shortcomings regarding the analyses (15% vs 26%) (**Figure 5**).

Table 3: Key factors for the acceptance of HrQoL data by German health technology assessment authorities

Key factor	Requirements and recommendations
HrQoL instrument	▪ Use validated HrQoL instruments (eg, tested in the German healthcare context, standardized, internationally accepted) ▪ Apply indication-specific HrQoL instruments (preferred by G-BA) which are adapted to the patient population and the age group ▪ Combine the use of generic and indication-specific HrQoL instruments and consider G-BA recommendations for generic HrQoL instruments (eg, SF-36) ▪ Apply the full (not truncated) validated version of the HrQoL instrument covering all dimensions of HrQoL
Analysis	▪ Consider that, according to the G-BA requirements, response rate to the questionnaire should be ≥70% or <15% difference between the treatment groups ▪ Present prespecified measures according to statistical analysis plan ▪ Provide data on clinical relevance (demonstrated by exceeding a validated MCID) ▪ Provide reasonable explanations for missing values and/or appropriate imputation approaches

Conclusions

- Using validated HrQoL instruments is crucial for the acceptance of HrQoL data in AMNOG benefit assessments. Another key factor is the choice of an adequate statistical approach, such as time-to-event responder analyses. The use of a validated MCID is critical to demonstrate a clinically relevant difference in an HrQoL analysis (**Table 3**). In case a validated MCID is not available, G-BA/IQWiG refers to MMRM analyses (combined with Hedges' g) to assess the clinical benefit. However, if the formal criteria postulated by G-BA (eg, appropriate comparator, adequate indirect comparison) are not met, even methodologically adequate HrQoL analyses are not considered for benefit assessment as they were not considered relevant for the decision process.

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