The Impact of Patient-Reported Outcomes on German HTA Outcome: A Matter of Calculation or Coincidence?

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T. WIEMER, D. FIMM, S. BERGNER

AstraZeneca GmbH, Germany

INTRODUCTION

In recent years, there has been a growing emphasis on incorporating patient experience into the processes of pharmaceutical approval and health technology assessment (HTA) [1,2]. In order to assess the additional benefit of new therapies, the German HTA body, the Federal Joint Committee (G-BA), categorizes study outcomes into four patient-relevant benefit dimensions: mortality, morbidity, health-related quality of life (HRQoL), and safety. In the field of oncology, efficacy is typically determined by overall survival (mortality) [3]. However, the impact of patient-reported outcomes (PROs), which are reviewed under morbidity and HRQoL, remains uncertain in German HTA.

OBJECTIVE

The objective of this study is to understand the role of PROs in the benefit assessment of new oncology therapies within the framework of HTA in Germany. Therefore, the study examines how frequently pharmaceutical companies presented PROs in their dossiers and how often the G-BA considered them for the assessment. Additionally, the study aims to evaluate if and how advantages and disadvantages in PROs affect the additional benefit rating.

METHOD

A systematic review of early benefit assessments from January 2011 to February 2024, based on at least one randomized controlled trial, was conducted with a focus on authorized oncological non-orphan drugs. The database of Pharm-Analytics GmbH was used to identify relevant procedures. Data on presentation, consideration and assessment of PROs, and procedure characteristics were extracted for each evaluation. Logistic regression analysis on the outcome of additional benefit was performed using IBM SPSS Statistics Version 29.0.2 including the presented and considered number and type of PROs with their number of advantages and disadvantages for each procedure as predictor variables. For regression analysis and Chi-square test, the levels of additional benefit "Additional benefit not quantifiable", "Minor additional benefit", "Considerable additional benefit", and "Major additional benefit" were consolidated into a single category called "Additional benefit". The remaining categories "Less benefit" and "Additional benefit not proven" together form the category "No additional benefit". In addition, the association between the four benefit dimensions and the additional benefit was analyzed in cases where the non-PROs of morbidity did not have an impact in terms of advantages or disadvantages. The analyses considered the assessments of the G-BA, which indicate whether there were advantages or disadvantages, whether there was no difference between the treatments, or whether the data submitted could not be used or evaluated. Effect measures were not included in the calculations.

RESULTS

Between 2011 and 2024, a total of 186 assessments on oncological sub-indications were identified. The pharmaceutical company submitted at least one PRO as part of the dossier in 177 cases (95.2%). In 162 procedures (87.1%), at least one PRO was recognized and considered by the G-BA for the early benefit assessment.
There has been a rise in frequency with which PROs are presented in the dossier and their acceptance by the G-BA (Fig. 1). In 2014 and 2015, at least one PRO was presented in all submitted dossiers. However, only in 50.0% and 75.0% of the procedures at least one PRO was considered for the assessment. In contrast, in 2022, PROs were both presented and recognized by the G-BA in all procedures. Furthermore, there has been a notable increase in the number of PROs presented and considered over time, with an average of 2 to 3 PROs per procedure being submitted and accepted in recent years (Fig. 2).

Submission and consideration of PROs

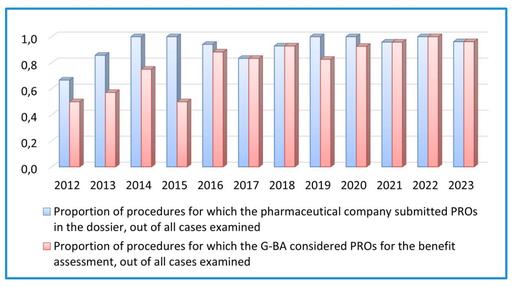


Fig. 1: Frequencies of submission and consideration of PROs
The number of procedures with at least one presented or accepted PRO was collected for each year of the benefit assessments and the proportion of these procedures relative to all submitted procedures in each respective year was calculated.

Number of PROs submitted and considered

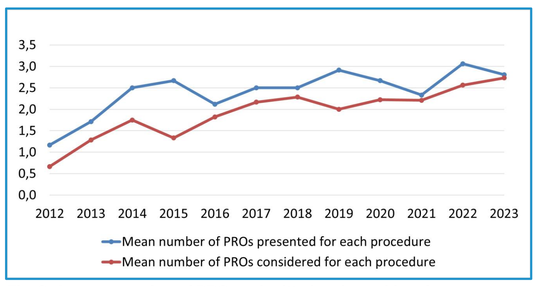


Fig. 2: Average number of PROs submitted and considered
Both the number of presented and accepted PROs were collected for each sub-indication of the procedures. For each year since 2011, a separate mean was calculated based on the respective procedures decided in that year.

At least one PRO of the benefit dimension HRQoL was presented in 171 (91.9%) of the dossiers, in 154 cases (82.8%) together with at least one PRO of morbidity. In 133 of the evaluations at least one PRO was considered by G-BA. PROs of the benefit dimension morbidity were presented in 160 (86.0%) of the dossiers, in 6 of them without further PROs related to HRQoL. In 157 of the 160 cases, the G-BA considered at least one of the submitted PROs for the assessment of morbidity; in 8 cases, PROs were instead evaluated as part of the HRQoL benefit dimension.

Submission and acceptance of PROs in different therapy areas

For all selected procedures, the most frequently assessed therapy areas were genitourinary cancer (22.0%), breast cancer (20.4%), and lung cancer (16.1%) with the majority of therapies evaluated in a palliative context (86.0%) and only 14.0% in a curative setting. In all procedures with hematologic or other less common indications, at least one PRO was included in the dossier (Fig. 3). For assessments conducted in the therapy area lung cancer 29 out of 30 procedures included PROs.
However, for hematological indications, the G-BA only considered PROs in 81.0% of the assessments. In contrast, for all lung cancer assessments in which PROs were presented at least one PRO was accepted by G-BA. The therapy area breast cancer got the lowest proportion of procedures with presented (89.0%) and accepted (74.0%) PROs.

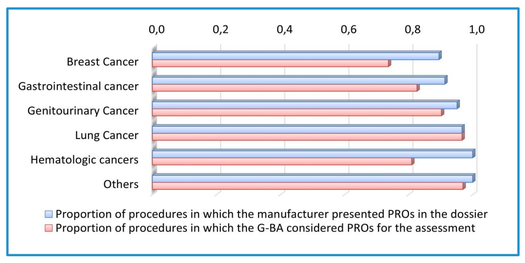
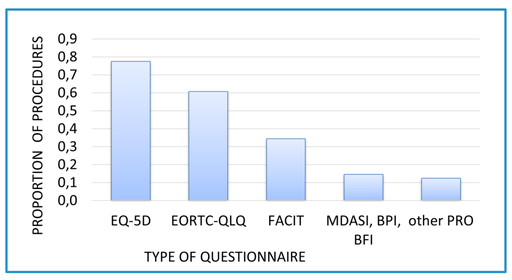


Fig. 3: Submission and acceptance of PROs in different therapy areas
The number of procedures in which the pharmaceutical company presented at least one PRO or in which the G-BA accepted at least one PRO was collected for each therapeutic area. The proportion of these procedures relative to all submitted procedures in the respective therapy area was calculated.

PROs presented in the dossier categorized by questionnaire type

The EQ-5D questionnaire was used in 144 procedures (77.4%), making it the most frequently submitted questionnaire among the procedures examined (Fig. 4). The EORTC questionnaire was submitted in 60.8% of cases, and the FACIT questionnaire in 34.4% of cases. Pharmaceutical companies rarely introduced other questionnaires for the benefit assessment.

Fig. 4: PROs presented in the dossier categorized by questionnaire type
Frequency of dossiers with the different PRO questionnaire types presented by the pharmaceutical companies as proportion relative to all dossiers in which PROs were presented.



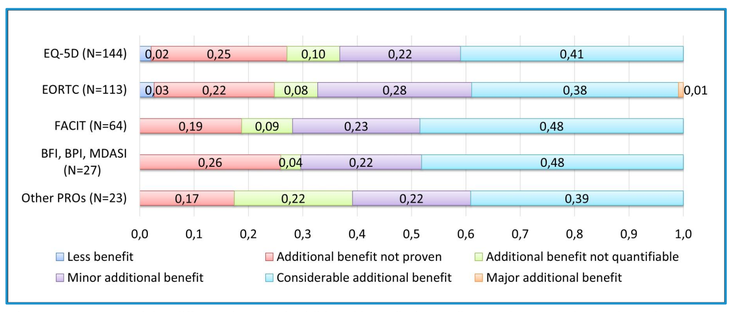


Fig. 5: Frequency of the different levels of additional benefit depending on the type of questionnaire presented in the dossier (%).

Extent of additional benefit according to the type of questionnaire

Treatments were often recognized as providing considerable (39.2%) or minor (27.4%) additional benefit. A single procedure was identified providing major additional benefit, while 4 procedures were found to have less benefit for partial indications. Some questionnaires occur more frequently than others. However, there is little difference in the extent of additional benefit according to the type of questionnaire submitted by the pharmaceutical company (Fig. 5). It is striking that the proportion of procedures with rare PROs and an unquantifiable added benefit is higher (22.0%) than for all other questionnaires (10.0%). Nevertheless, most procedures had considerable benefits, irrespective of the questionnaire type.

Extent of additional benefit depending on beneficial or harmful effects of PROs

Advantages in PROs were only recognized by the G-BA in 72 (40.7%) of all procedures in which PROs were submitted (N=177). Disadvantages in PROs were identified in 44 (24.9%) of the assessments. 87 procedures were identified in which the pharmaceutical company had included at least one questionnaire in the dossier, but the G-BA did not recognize any advantages or disadvantages for PROs.

In only 4 of the 72 procedures in which the G-BA identified PRO-advantages, the treatment's indication failed to receive an additional benefit (Fig. 6). Among the procedures with advantages in PROs a considerable additional benefit was granted in the majority of cases (66.2%). However, the situation differs for the 44 procedures with disadvantages in PROs. An additional benefit was granted for 29 of the procedures, with the majority of these cases providing a considerable extent of benefit. “Additional benefit not proven” or “Less benefit” was awarded in only 15 procedures showing disadvantages in the PROs.

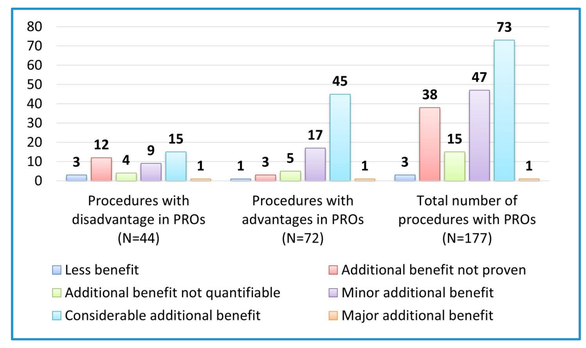


Fig. 6: Extent of additional benefit depending on positive or negative effects in PROs.
Procedures in which at least one PRO was submitted by the pharmaceutical company were analyzed (N=177). Advantages and disadvantages in PROs were counted if the G-BA recognized at least one statistically significant positive or negative effect in the PROs - regardless of the extent of the effect - and listed it in its resolution.

PROs of morbidity or HRQoL and the additional benefit

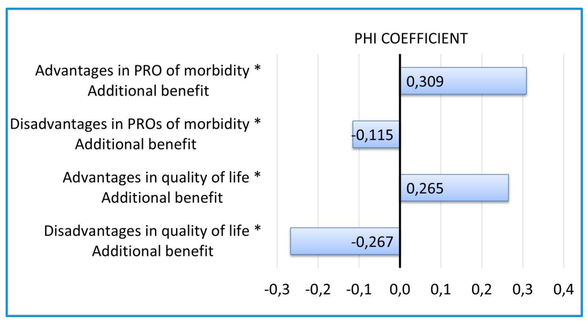


Fig. 7: Association between advantages and disadvantages in PROs and the additional benefit.
Chi-square tests were conducted to examine the association between the recognition of advantages and disadvantages in PROs of morbidity and HRQoL by the G-BA and the awarding of additional benefit in the early benefit assessments. The Phi coefficient (Φ) was calculated to determine the effect size of the association.

Procedures where the G-BA recognized advantages in PROs of the benefit dimension morbidity were significantly more likely to receive an additional benefit ($\Phi = 0.309$, $p < 0.001$) (Fig. 7). Specifically, 61 of 65 procedures (93.8%) with advantages in morbidity PROs were awarded an additional benefit, compared to 80 out of 121 procedures (66.1%) without such advantages. Recognition of advantages in PROs of HRQoL was also significantly associated with the awarding of additional benefit ($\Phi = 0.265$, $p < 0.001$). Among procedures with advantages in HRQoL, 39 of 40 (97.5%) received an additional benefit. No statistically significant association was found between recognized disadvantages in morbidity PROs and the awarding of additional benefit ($\Phi = -0.115$, $p = 0.116$). Despite disadvantages, 28 out of 42 procedures (66.7%) still received an additional benefit. Disadvantages in the benefit dimension HRQoL were significantly associated with not receiving an additional benefit ($\Phi = -0.276$, $p < 0.001$). Only 5 out of 14 procedures (35.7%) with disadvantages were awarded an additional benefit.

Correlation across the assessment of the benefit dimensions and the additional benefit

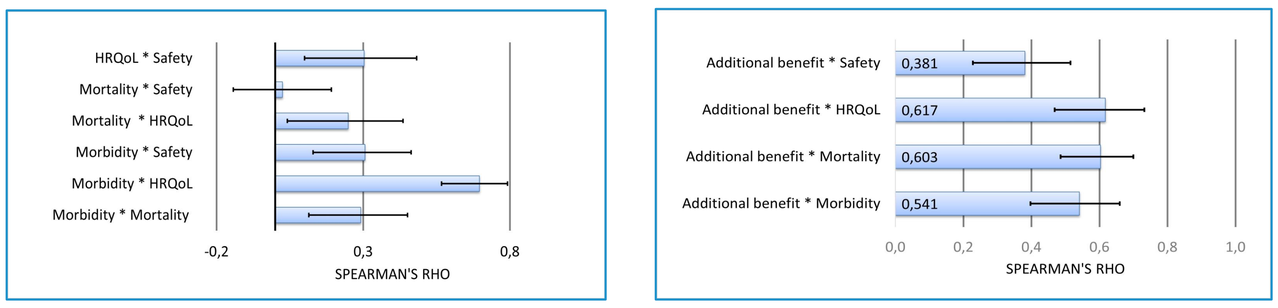


Fig. 8; Fig. 9 : Correlation across the assessment of the benefit dimensions and of the additional benefit.
Spearman's rank-order correlations were computed using pairwise case exclusion if no data were available for one of the benefit dimensions or if the data were classified by the G-BA as not assessable. The relationships between the assessments of the four benefit dimensions morbidity, mortality, HRQoL and safety was investigated (Fig. 8) as well as their association with the additional benefit assessment by the G-BA (Fig. 9). Only those cases in which the accepted non-PROs in the morbidity category demonstrated neither advantage nor disadvantage were subjected to analysis.

There was a strong correlation between morbidity and HRQoL assessments ($\rho = 0.696$, $p < 0.001$, 95% CI [0.567, 0.792], $N = 90$), but only moderate correlations between other benefit dimensions (Fig. 8). No significant correlation was found for the association of mortality and safety ($\rho = 0.025$, $p = 0.767$, 95% CI [–0.143, 0.191], $N = 146$), indicating that improvements in survival outcomes may not necessarily be associated with changes in side effect profiles.

All 4 benefit dimensions show significant positive correlation with the additional benefit (Fig. 9). The highest association was determined for the assessment of HRQoL ($\rho = 0.617$, $p < 0.001$, 95% CI [0.468, 0.732], $N = 93$). The correlation between mortality and the outcome of the benefit assessment was only slightly weaker with ($\rho = 0.603$, $p < 0.001$, 95% CI [0.485, 0.699], $N = 147$). The weakest correlation was found between the assessment of safety and the additional benefit ($\rho = 0.381$, $p < 0.001$, 95% CI [0.228, 0.515], $N = 146$).

Impact of PROs on the additional benefit

Fig. 10: Regression analysis of the impact of PROs on the additional benefit
The logistic regression model was statistically significant ($\chi^2(4) = 33.706$, $p < 0.001$] and explained between 17.3% (Cox & Snell R^2) and 26.2% (Nagelkerke R^2) of the variance in the awarding of additional benefit. It correctly classified 79.7% of cases, with a sensitivity of 95.6% for predicting additional benefit and a specificity of 26.8% for predicting no additional benefit. The model included 177 cases in which at least one PRO was submitted by the pharmaceutical company.

Logistic regression revealed that an increased number of statistically significant advantages in PROs per procedure was positively associated with the G-BA granting an additional benefit (Fig. 10). Specifically, each additional advantage in PROs increased the odds of receiving an additional benefit by 65% (odds ratio [OR]: 1.651; 95% confidence interval [CI]: 1.144-2.383; $p = 0.007$).

Conversely, each additional statistically significant disadvantage in PROs per benefit assessment decreased the odds of an additional benefit by 34% (OR: 0.662; 95% CI: 0.493-0.889; $p = 0.006$).

In addition, the total number of PROs submitted by the pharmaceutical company per procedure was negatively associated with the granting of an additional benefit by the G-BA. This implies that for each additional PRO submitted, the odds of receiving an additional benefit decreased by 43% (OR: 0.575; 95% CI: 0.366-0.903; $p = 0.016$).
The number of PROs accepted by the G-BA per case showed a positive association with the granting of an additional benefit, although this did not reach statistical significance (OR: 1.507; 95% CI: 0.982-2.312; $p = 0.060$).

CONCLUSIONS

The study demonstrates that both the presentation of PROs and their acceptance have increased in recent years, reflecting the growing importance of the patient's perspective in the evaluation of medical treatments. The granting of an additional benefit by the G-BA is significantly influenced by positive outcomes in all four benefit dimensions morbidity, mortality, safety and HRQoL, suggesting, that not only mortality is the primary driver for positive benefit assessment outcomes. However, there were also interconnected effects found, where positive outcomes in one benefit dimension may influence or reflect benefits in another. The analysis demonstrates that recognized advantages in PROs significantly increase the probability of oncological therapies receiving an additional benefit from the G-BA. Conversely, the recognized disadvantages reduce the likelihood of an additional benefit. It also highlights that recognized advantages in the outcomes of both benefit dimensions morbidity and HRQoL play a crucial role in the G-BA's decision to grant an additional benefit. Conversely, only recognized disadvantages in HRQoL could negatively impact the likelihood of receiving an additional benefit. The presence of disadvantages in PROs evaluated as part of the benefit dimension morbidity does not necessarily preclude the awarding of an additional benefit.

Notably, simply submitting a higher number of PROs does not enhance the chances of obtaining an additional benefit; the **quality and relevance of the PROs are crucial**. These findings highlight the importance for pharmaceutical companies to prioritize the submission of robust and meaningful PRO data to improve the likelihood of favorable assessments in the early benefit assessment process.

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CONTACT INFORMATION

AstraZeneca GmbH
Friesenweg 26
22763 Hamburg
www.astrazeneca.de

Tabea Wiemer
tabea.wiemer@astrazeneca.com
Désirée Fimm
desiree.fimm1@astrazeneca.com

AstraZeneca