PT4

Patient-Reported Outcomes in German AMNOG Assessments: Impact of Increasing the Response Threshold to 15%

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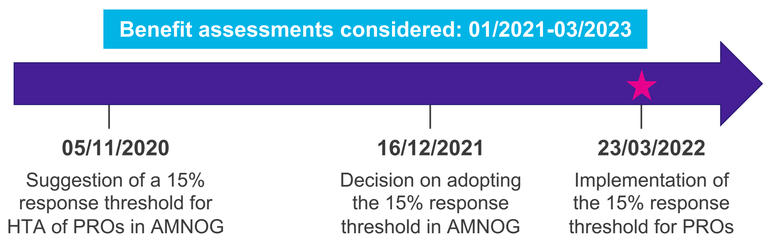
Background

- Defining a standardized and reliable minimal clinically important difference (MCID) for the evaluation of patient-reported outcomes (PROs) is challenging.
- In March 2022, the Federal Joint Committee (G-BA) adopted a new response threshold of ≥15% of the scale range of the questionnaire for binary analyses of PROs (**Figure 1**).[1]

Figure 1. Timing of the 15% threshold coming into force



Objective

- The aim of our study was to evaluate how the new response threshold affects the assessment of the added medical benefit of PROs in Germany.

Methods

- The G-BA website was searched for benefit assessments published in the transition period 01/2021-03/2023.
- The search terms were limited to EQ-5D, SF-36, and FACT as these questionnaires represent the most common PROs affected by the adoption.
- Only assessments including data on both analyses, the previously accepted MCID, and the newly introduced threshold of ≥15%, and those that were methodologically accepted by the G-BA were considered.

Info Box: Exceptional cases of PROs

SF-36
• Due to the scale structure of the SF-36, a change of approximately 10 points corresponds to the 15% response threshold.[2]
EORTC QLQ-C30 (and disease-specific versions)
• The majority of the 15 scales consists of only 1 item with 4 possible answers (corresponding to a score change of at least 33.33 points). • In consequence, it has no effect whether 10 points or 15 points (=15%) are used as the response criterion.
Conclusion The G-BA continues to accept the previously used response criterion of 10 points for both questionnaires.

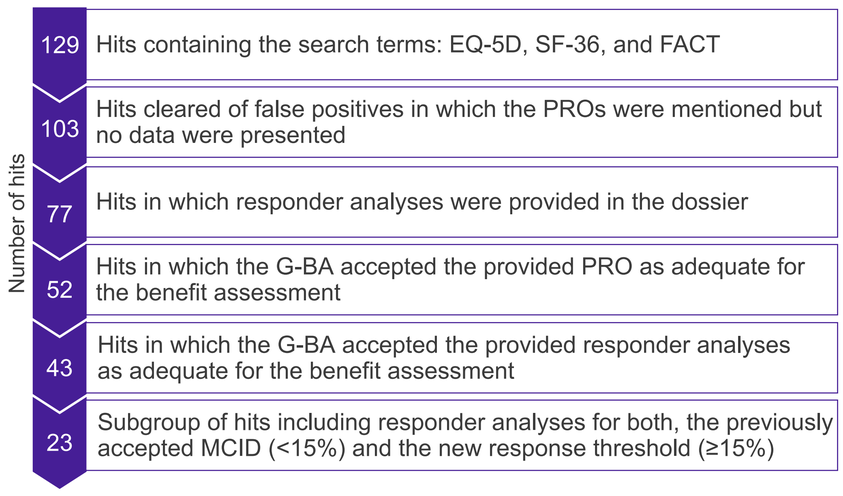
Conclusions

- Overall, only in 7 assessments did the PROs achieve a significant treatment benefit. This demonstrates how challenging it is to achieve an added medical benefit through PROs.
- This might be explained by the fact that the majority of assessments (16/23) covered oncology drugs for which maintaining health status or quality of life is already considered a treatment success.
- The new response threshold of ≥15% represents a higher hurdle to prove an added medical benefit based on PROs.
- Consequently, minor but yet patient-relevant benefits might not be valued appropriately.

Results

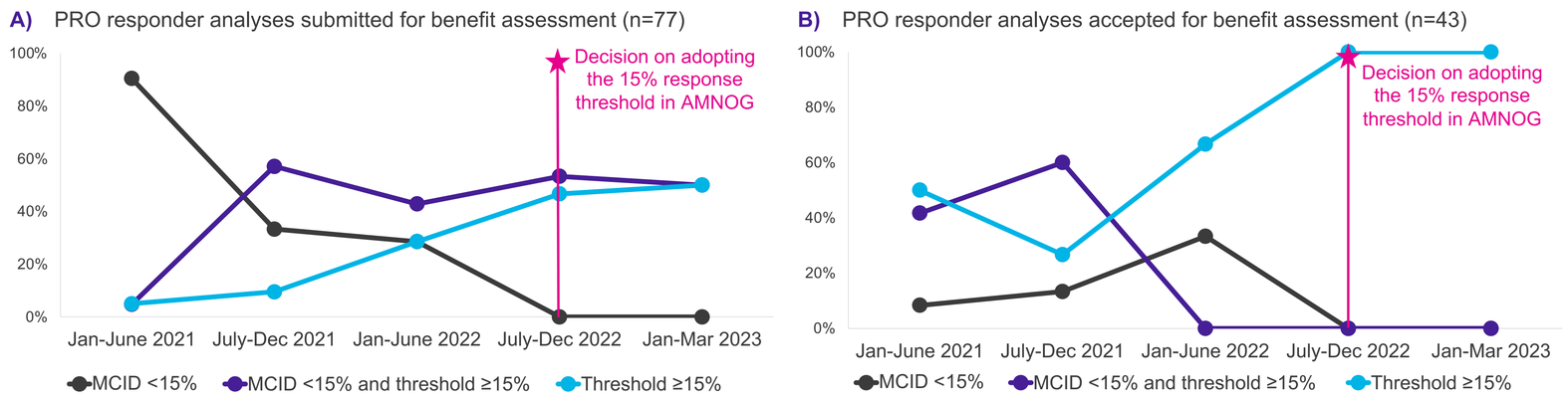
- In 129 benefit assessments, a hit on at least one of the PROs included in the search (**Table 1**) was identified. A full-text search revealed that PRO data was presented in only 103 of the included assessments.

Table 1. Benefit assessment selection



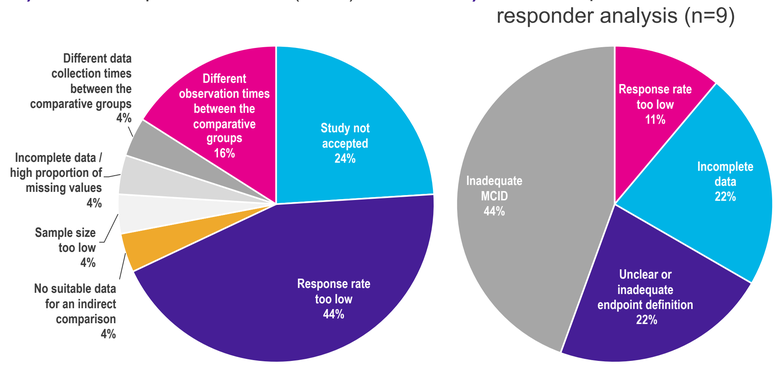
- Responder analyses of PROs were reported in 77 assessments and considered relevant for benefit assessment by the G-BA in 52 procedures.
- The G-BA considered responder analyses in 43 of 52 procedures as relevant for benefit assessment. In 9 of 52 procedures, continuous data (e.g. MMRM) was considered instead.
- To compare the effect of the new response threshold on the assessment of the added medical benefit, a subgroup of 23 assessments showing both an MCID <15% and a response threshold ≥15% was selected.

Figure 2. Change in presentation of response thresholds during the transition period



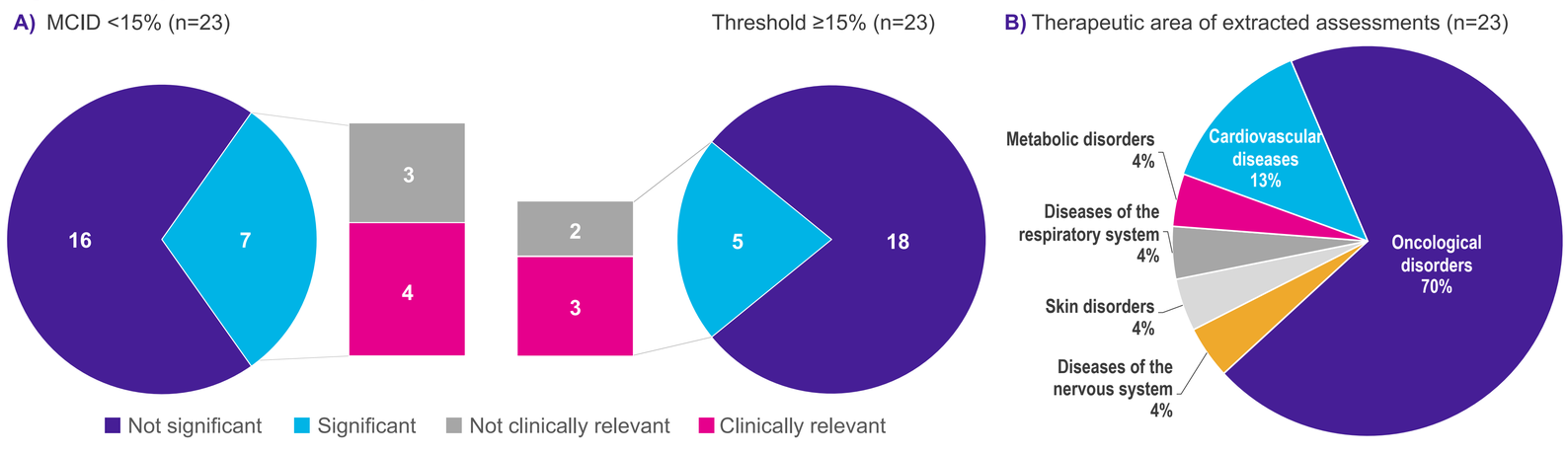
- While at the beginning of 2021, in almost all dossiers an MCID <15% was presented, pharmaceutical manufacturers quickly adapted, with multiple response thresholds (MCID <15%; response threshold ≥15%) being presented in half of the dossiers within the following half year. From the second half of 2022, almost all dossiers included at least the response threshold ≥15% (**Figure 2A**).
- In the benefit assessment in which the G-BA accepted a PRO responder analysis, the transition occurred even faster. G-BA considered the response threshold of ≥15% from the start, if available. From 2022 onwards, almost exclusively the response threshold of ≥15% was applied in the assessment (**Figure 2B**).

Figure 3. Reasons for non-consideration of PRO data in benefit assessment



- The three most common reasons for non-acceptance of a PRO by the G-BA were: response rate too low (44%), study not accepted (24%), and different observation times between the comparative groups (16%) (**Figure 3A**).
- The reasons for non-acceptance of responder analyses by the G-BA for the benefit assessment were: inadequate MCID (44%), incomplete data (22%), inadequate endpoint definition (22%), or response rate too low (11%) (**Figure 3B**).

Figure 4. Impact of different response thresholds on added benefit



- In 16 out of 23 assessments for which both an MCID <15% and a response threshold ≥15% were presented, no significant PRO results were demonstrated, regardless of the response threshold applied. Seven assessments revealed a significant treatment benefit for the responder analysis of the PRO based on the previously accepted MCID <15%. Five of these 7 assessments revealed a significant treatment benefit based on the new threshold of ≥15% (**Figure 4A**).
- Considering the clinical relevance of the results, 4 of 7 assessments based on the MCID <15% and 3 of 5 assessments based on the response threshold ≥15% showed clinically relevant effects based on the criteria applied by the G-BA.
- Most assessments (16/23) covered oncology drugs. The other therapeutic areas covered cardiovascular diseases (3), diseases of the nervous system (1), skin disorders (1), diseases of the respiratory system (1), and metabolic disorders (1) (**Figure 4B**).

References

1. BMG (Bundesministerium für Gesundheit). Bekanntmachung eines Beschlusses des Gemeinsamen Bundesausschusses über eine Änderung der Verfahrensordnung: Änderung der Modulvorlage in der Anlage II zum 5. Kapitel. December 16, 2021. Accessed September 22, 2023. https://www.bundesanzeiger.de/pub/publication/8JgVtHxgy0ED31usNCE/content/8JgVtHxgy0ED31usNCE/BAnz%20AT%2022.03.2022%20B2.pdf?inline.
2. G-BA (Gemeinsamer Bundesausschuss). Zusammenfassende Dokumentation zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Verfahrensordnung: Änderung der Modul-vorlage in der Anlage II zum 5. Kapitel. December 16, 2021. Accessed September 22, 2023. www.g-ba.de /downloads/40-268-8140/2021-12-16_VerfO_Aenderung-Modulvorlage-Anlage-II-Kap-5_ZD.pdf

Key: AMNOG – Arzneimittelmarktneuordnungsgesetz; BMG – Bundesministerium für Gesundheit; EORTC QLQ-C30 – European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EQ-5D – European Quality of life questionnaire – 5 Dimensions; FACT – Functional Assessment of Cancer Therapy; G-BA – Gemeinsamer Bundesausschuss; HTA – Health Technology Assessment; MCID – Minimal Clinically Important Difference; MMRM – Mixed Model for Repeated Measures; PRO – Patient Reported Outcome; SF-36 – Short Form Health Survey 36-Items

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