HAS IQWIG'S 15% RESPONSE THRESHOLD MADE A MINIMALLY IMPORTANT DIFFERENCE TO BENEFIT ASSESSMENTS?

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INTRODUCTION

- In version 6.0 of its General Methods[1], IQWiG sought to address the increasing complexity of assessing minimally important differences (MIDs) for patient-reported outcomes (PROs), by stipulating that response thresholds for submitted responder analyses must be ≥ 15% of the scale range.
- This study investigated the impact of the General Methods update on IQWiG's assessments of PROs and how these have influenced G-BA's view on submitted PRO evidence.

METHODOLOGY

- Using IQVIA's HTA Accelerator, a comparison of IQWiG dossier assessments published 6 months before and 6 months after the publication of IQWiG's General Method v6.0 was conducted, focusing on the following analyses (see fig. 1):
  1) Proportion of all assessments, in which PRO results were accepted and analyzed in the report (hereafter called "assessments with PROs")
  2) Proportion of assessments with PROs, in which PROs impacted the benefit rating, meaning results were considered statistically significant and clinically relevant
  3) Proportion of assessments with PROs, in which a response threshold was rejected
  4) Proportion of assessments with PROs, in which an additional benefit was concluded overall, for any reason (not just due to PROs).
- The same analyses were performed for the corresponding G-BA assessments. In addition, since post hoc analyses using 15% as a response threshold could be submitted during commenting procedures, the impact of data in addenda to IQWiG's report was analyzed. Statistical significance was assessed by Fisher's exact test.

RESULTS

- There were no statistically significant differences between the proportion of assessments with PROs published 6 months before the update (21/51 assessments; 41%) and 6 months after the update (34/74 assessments; 46%) (see fig. 2).
- There were also no statistically significant differences in the proportions of assessments with PROs that had benefit ratings impacted by PROs (see fig. 3). However, there was a large numerical difference in the proportion of G-BA benefit ratings impacted by PROs (39% vs 60%). A difference can be seen depending on whether the addenda to IQWiG reports are included or not, which is likely due to the 15 instances of *post hoc* PRO analyses using a 15% response threshold being submitted during commenting procedures.
- The proportion of IQWIG assessments with rejected response thresholds was relatively high both before and after the method update, with no statistically significant difference observed between these (see fig. 4). G-BA on the other hand rejected substantially fewer MIDs both before and after the method update. In 12 assessments, G-BA accepted MIDs < 15% due to having accepted these previously.
- Finally, there were no statistically significant differences in the proportions of assessments with PROs, in which an additional benefit was concluded (see fig. 5).
- There were only 2 examples in which statistical significance was affected by the choice of response threshold. In the assessment of nivolumab + ipilimumab + platinum-based chemotherapy[2], a statistically significant difference in the EQ-5D VAS was seen in responder analyses using 7% and 10% thresholds, but not a 15% threshold. On the other hand, in the assessment of carfilzomib + daratumumab + dexamethasone[3], a statistically significant difference in the EQ-5D VAS was seen in responder analyses using 10% and 15% thresholds, but not a 7% threshold.

CONCLUSIONS

IQWiG's General Methods update has simplified IQWiG's process for assessing responder analyses but has not had a clear impact on the outcomes of benefit assessments in the first 6 months. There are indications that more benefit ratings are impacted by PROs following the update, but it may be too early to be conclusive

The proportion of positive G-BA outcomes has remained largely similar. It was seen in isolated cases that changes in response thresholds can affect the demonstration of statistical significance in PRO both negatively and positively.

A limitation of this study was the small sample size, which resulted in relatively wide confidence intervals. This can be addressed by repeating this analysis at a later stage when more assessments are available and General Method v6.0 is more established.

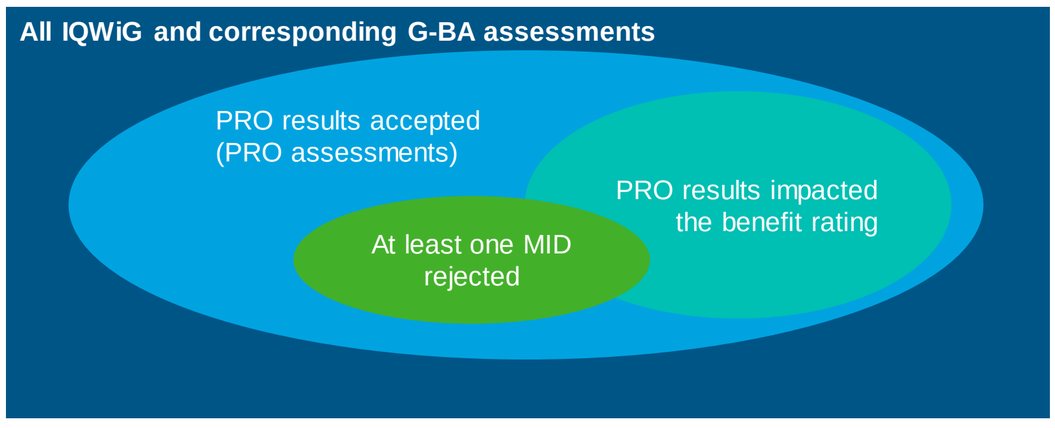

Figure 1: Venn diagram illustrating the different analyses performed in the study

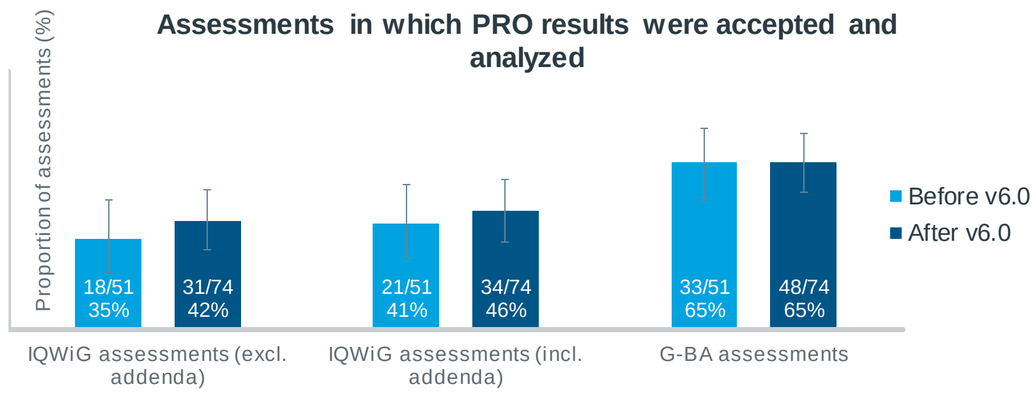

Figure 2: Comparison of proportions (with 95% confidence intervals) of assessments, in which PRO results were analyzed by IQWiG and G-BA. None of the differences were statistically significant (p > 0.05). The larger number G-BA assessments with PROs compared to IQWiG is caused by IQWiG not assessing PROs for drugs with an EMA orphan designation.

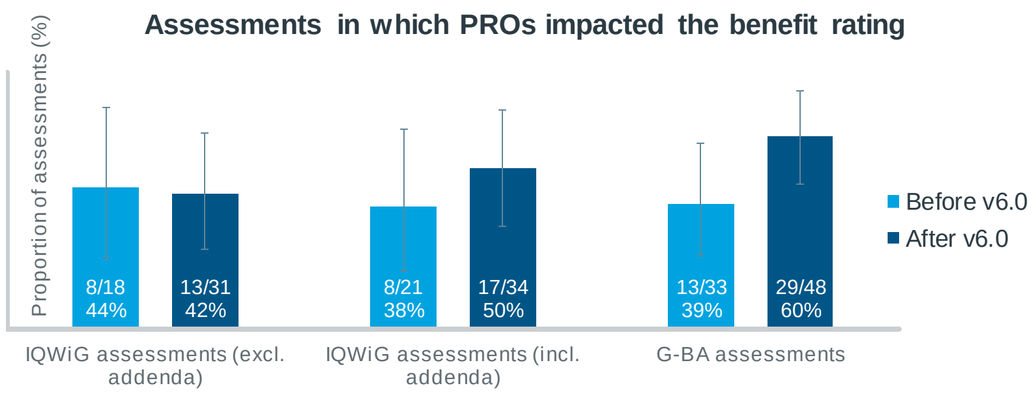

Figure 3: Comparison of proportions (with 95% confidence intervals) of assessments with PROs, in which PROs impacted the benefit rating. None of the differences were statistically significant (p > 0.05).

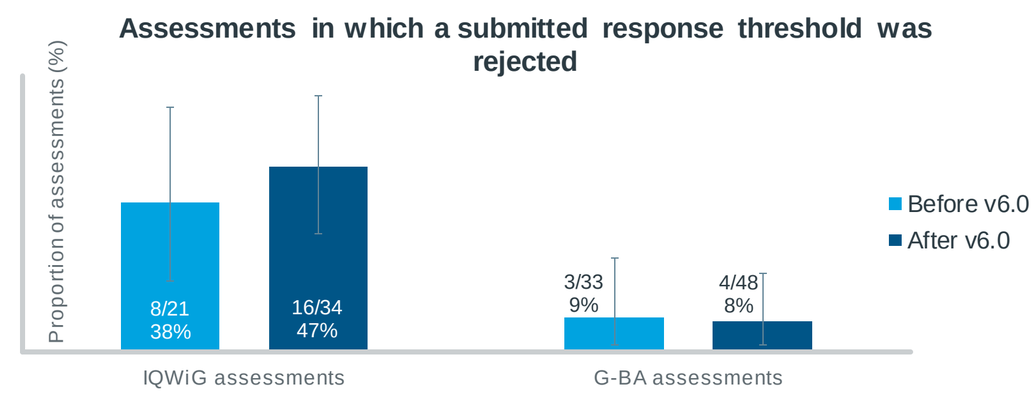

Figure 4: Comparison of proportions (with 95% confidence intervals) of assessments with PROs, in which a submitted response threshold was rejected. None of the differences were statistically significant (p > 0.05).

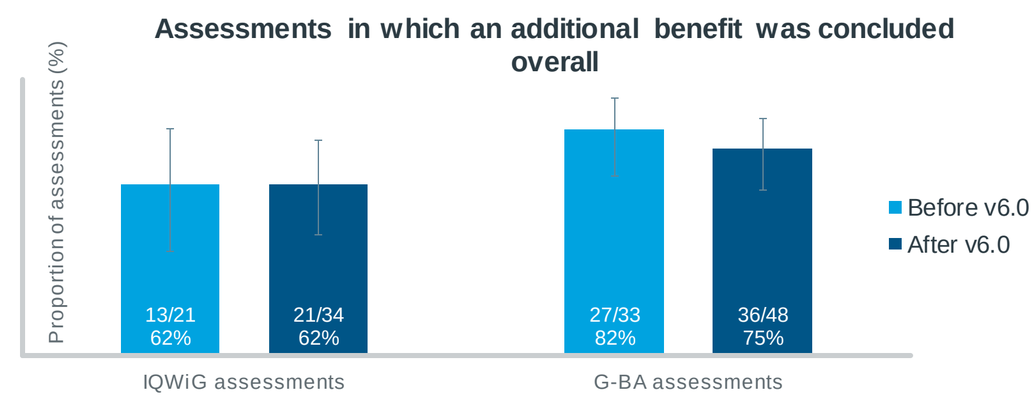

Figure 5: Comparison of proportions (with 95% confidence intervals) of assessments with PROs, in which an additional benefit was concluded overall. None of the differences were statistically significant (p > 0.05).

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0. 2020 [cited 08 November 2021]. Available from: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.
2. Gemeinsamer Bundesausschuss. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V; Nivolumab (Neues Anwendungsgebiet: Nicht-kleinzelliges Lungenkarzinom, Kombination mit Ipilimumab und platinbasierter Chemotherapie, Erstlinie). 2021 [cited 08 November 2021]. Available from: https://www.g-ba.de/downloads/39-261-4862/2021-06-03_AM-RL-XII_Nivolumab_D-628_BAnz.pdf.
3. Gemeinsamer Bundesausschuss. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V; Carfilzomib (Neues Anwendungsgebiet: multiples Myelom, mind. 1 Vortherapie, Kombination mit Daratumumab und Dexamethason). 2021 [cited 08 November 2021]. Available from: https://www.g-ba.de/downloads/39-261-4927/2021-07-15_AM-RL-XII_Carfilzomib_D-617_BAnz.pdf

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