Does Size Matter? Impact of Population Size on Evidence Quality and Negotiation Outcome for Orphan Drugs in Germany

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Objectives

Providing high quality evidence is considered extremely challenging in rare diseases, inter alia due to substantially low patient numbers and a high burden of disease. However, high-quality comparative evidence is essential for a favorable outcome of the benefit assessment by the G-BA and the subsequent price negotiations in Germany. Currently, existing orphan privileges to acknowledge the abovementioned circumstances are under debate.

This analysis aims to identify whether there is an evident correlation of a decreasing population size and reduced evidence quality for orphan drugs in Germany. In addition, the respective outcomes of the price negotiations and annual therapy costs were analyzed for the potential impact of a decreasing population size and reduced quality of evidence on negotiation success.

Methods

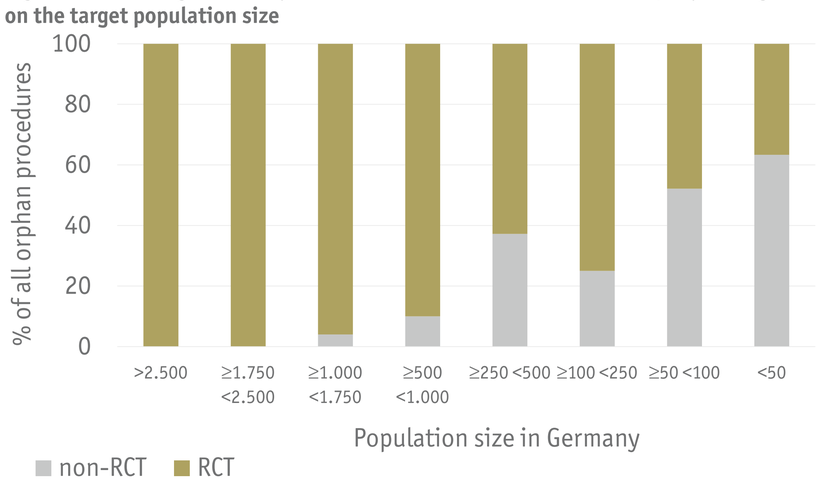
All orphan benefit assessments in Germany (until Sep 2022) were analyzed regarding population size, quality of submitted evidence, G-BA rating and price negotiation outcome by using publicly available data, combining all dossier assessments in Germany and IQWiG/G-BA rulings with GKV-SV price negotiation outcomes (LAUER-TAXE®).

The following assumptions were made to allow for generalization: Evidence quality was categorized in Ia/Ib as "RCT" or ≥II as "non-RCT"; in case of multiple studies the highest category was assigned; the same study can be included twice in case of re-assessments; differently assessed subgroups were included separately, if applicable; average population size was used in case of a min-max range.

Results

The trend is clear: In smaller target populations, randomized controlled trials are conducted less often.

Figure 1: Percentage of G-BA procedures incl. RCT vs. non-RCT studies, depending on the target population size



- Figure 1 describes the evidence quality of studies submitted in relation to the population size according to the G-BA resolution in all orphan assessments. Within each population size group, the number of included trials ranges from 22 to 43 (Median: 27, Ø: 28,8). The total number is 230.
- In a patient population of ≥ 1,750 patients in > 95 % of cases, an RCT was submitted. As the number of patients in the indication decreased, so did the quality of the evidence in terms of a decreasing RCT/non-RCT ratio.
- Although it becomes increasingly challenging to collect randomized controlled evidence for a smaller target population, still for a population size of < 100 patients approximately 50 % of the submitted studies included RCTs.

In orphan diseases, an RCT increases the likelihood of a quantifiable G-BA rating.

Figure 2: Added benefit in correlation to population size for RCT studies

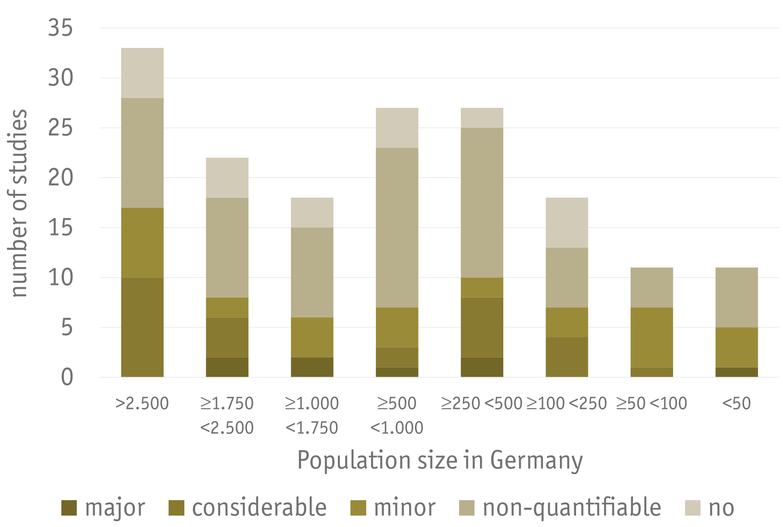
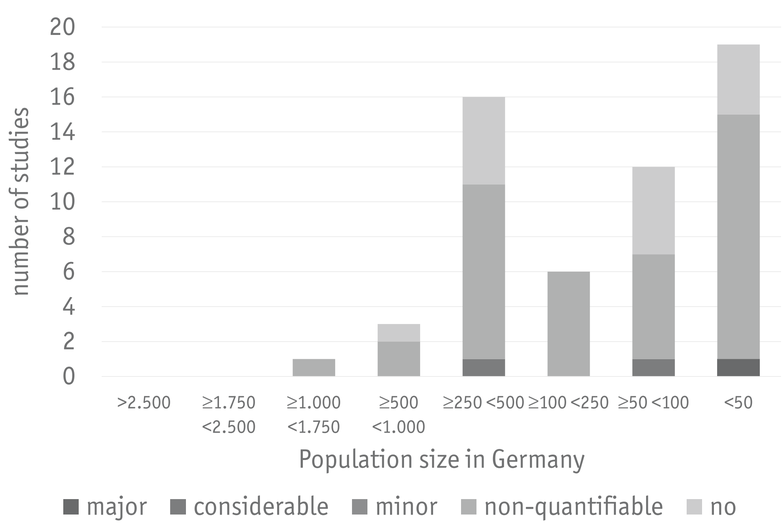


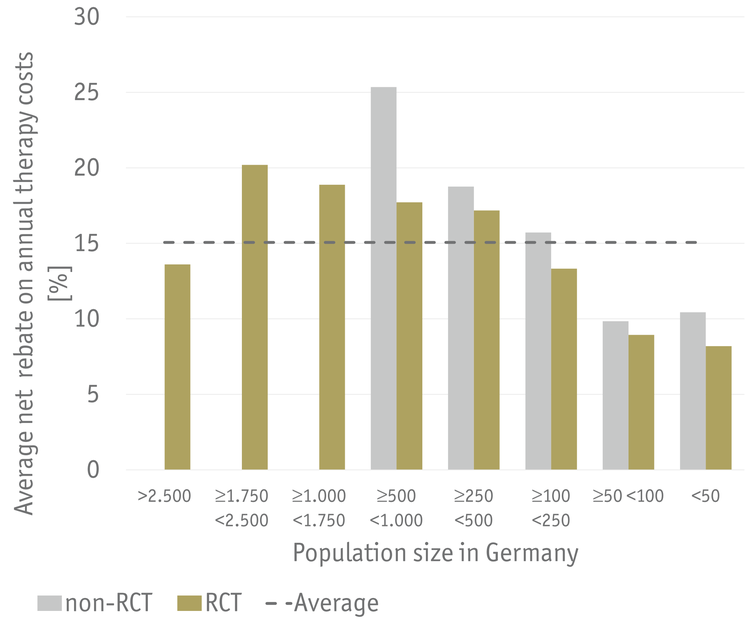
Figure 3: Added benefit in correlation to population size for non-RCT studies



- Figure 2 and 3 describe the outcomes of the German HTA in terms of the G-BA rating in relation to the population size.
- Of note, in Germany all orphan drugs are granted a minimal non-quantifiable added benefit (lowest category) by law. A rating of "no added benefit" is therefore only possible under a regular assessment, e.g., after exceeding the 50 Mio € revenue annual threshold. In 75 % of cases with non-RCT evidence and 48 % with RCT evidence, a non-quantifiable added benefit was granted. In total, in only 3 % of all non-RCT orphan procedures a higher added benefit category was granted.
- On average, a higher ratio of RCT/non-RCT slightly improves the G-BA rating, albeit the room for interpretation is limited due to small sample numbers - especially in a separate assessment of RCT and non-RCT procedures.
- In Germany, the initial benefit assessment by the G-BA ends with the G-BA resolution including the added benefit rating. This outcome is then a key influencing factor for the subsequent price negotiations (see Figure 4).

The smaller the population, the smaller the rebate – especially with RCT evidence.

Figure 4: Average net rebate in correlation to population size



- Figure 4 describes the average negotiated rebate in relation to the quality of the submitted evidence and the population size. To allow for generalization, apparent outliers and non-regular negotiations were excluded, such as individual case decisions, exceptional and potentially distorting contract conditions, biasing jointly negotiated rebates.
- Within each population size group, the number of included trials ranges from 14 to 30 (Median: 20,5, Ø: 21,9). The total number is 175. The overall average net rebate on annual therapy costs for all orphan drugs is 15,06 %.
- The data shows a trend in terms of an improving rebate (↓) with a decreasing population size. For a population size of 500-1000 patients in Germany, an average net rebate on the annual therapy costs of 21.5 % was negotiated. In procedures with < 50 patients, the average net rebate was 9.3 %.
- In general, an improvement in evidence concurrently led to a reduction in the negotiated rebate. However, the effect was only of minor extent: For a population size of < 50 patients in Germany, an average net rebate on the annual therapy costs of 10.4 % was negotiated for non-RCT evidence, while 8.2 % was negotiated on average for RCT evidence.
- Cautious interpretation is required since the sample numbers in single categories are low and individual cases can have a significant impact.

Conclusion

- Despite the evident hurdles in a rare disease setting, high quality evidence for orphan drugs is often submitted for the HTA in Germany. Nevertheless, as the population size in the indication decreased, so did the quality of the evidence in terms of an increasing proportion of non-RCTs submitted to the G-BA. This outcome highlights the substantial challenges and even impossibilities in terms of evidence generation when it comes to (ultra-)orphan diseases.
- A substantial impact of the evidence quality on the G-BA rating was not observed. Nevertheless, a higher ratio of RCT/non-RCT slightly improved the average G-BA rating. These results can partially be seen as biased since in Germany all orphan drugs are granted a minimal non-quantifiable added benefit (lowest category) by law.
- Within all orphan drugs assessed by the G-BA in Germany, the negotiation outcome on average improved with a decreasing target population, although the evidence quality continuously decreased. This outcome can be interpreted as a (partially legally-forced) acknowledgement of the special circumstances in an orphan disease setting by the HTA bodies in Germany. On the other hand, it can be interpreted as the pharmaceutical manufacturers spending high effort to provide best possible evidence in the respective orphan setting, providing solid data even in extremely rare diseases.
- Anticipation of the achievable price range is essential and should ideally already be taken into account when planning the phase II/III studies. In order to do so, precedence and peer group analyses are essential.

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All analyses have been conducted with our own comprehensive MAIS database that contains and links AMNOG information of all completed and ongoing benefit assessment procedures according to §35a SGB V of the German Federal Joint Committee (G-BA).