Clinical Evidence Quality in Appraisals of Drugs for Rare Diseases in England and Germany

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Introduction

Health technology assessment (HTA) processes and evaluation methods for rare disease treatments differ between England and Germany [1-2]. However, systematic comparisons of the quality of clinical evidence in appraisals of rare disease treatments are lacking.

Objective

To systematically analyse clinical evidence quality characteristics in appraisals of rare disease treatments published by the National Institute for Health and Care Excellence (NICE) in England and the Federal Joint Committee (GBA) in Germany.

Methods

Appraisal selection

- We analysed RDT appraisals completed between 2011-2023.
  - England: appraisals published under the Technology Appraisal guidance of treatments listed in the UK Orphan Register of the Medicines & Healthcare products Regulatory Agency, and all appraisals published under the Highly Specialised Technology appraisal guidance
  - Germany: appraisals of rare disease treatments published by the GBA
- From selected appraisals, we identified indications for which an HTA outcome was documented in both countries to construct 'medicine-indication pairs'.

Data extraction

- We developed a coding manual describing variable definitions for clinical evidence quality characteristics (availability of alternative treatments, design of the main study, use of indirect treatment comparisons, applicability, risk of bias, and maturity of survival data).
- The coding manual was validated by external researchers and disagreements were resolved by discussion.

Table 1: Overview of extracted data

	Germany (GBA)	England (NICE)
Alternative treatment	The use of an active, licensed and pharmacological comparator in the appraisal recorded as a proxy for the availability of an alternative treatment.	
Main study	Pivotal study informing the effectiveness of the intervention that was accepted by the GBA in the appraisal.	Study that was used to inform the intervention arm of the economic model.
Study design	The design of the main study categorised as randomised control trials or other (single-arm or observational studies or appraisals for which no evidence was submitted by the manufacturer).	
Comparison	The directness of the main study categorised as direct or indirect.	
Indirect treatment comparison	Whether an indirect treatment comparison was used to derive the clinical benefit rating in the appraisal.	Whether an indirect treatment comparison was used to estimate the treatment effect in the economic model.
Applicability	The applicability of the main study to the patient population and clinical practice categorised as questionable, moderate or acceptable.	
Risk of bias	The risk of bias of the main study categorised as low or other.	
Maturity of survival data	The proportion of deaths in the intervention arm of the main study categorised as very immature (proportion of deaths < 20%), immature (proportion of deaths between 20-50%), or mature (proportion of deaths > 50%).	

GBA = Federal Joint Committee; NICE = National Institute for Health and Care Excellence

Data analysis

We descriptively analysed clinical evidence quality characteristics. We used Kappa scores to measure the level of agreement, calculated the proportion of appraisals for which there was agreement or disagreement, and highlighted similarities and differences in approaches between the two countries.

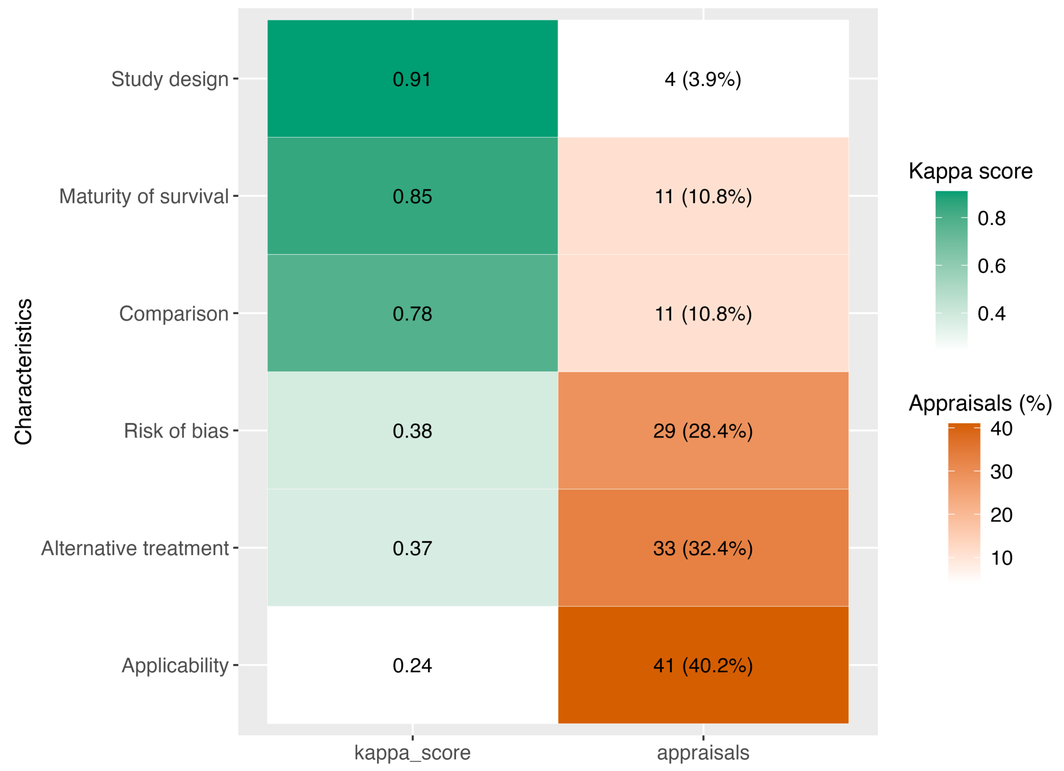
Results

Table 2: Clinical evidence quality characteristics in appraisals of rare disease treatments published by the GBA and NICE (n=102)

	GBA – N (%)	NICE - N (%)
Alternative treatment		
Yes	43 (42.2)	58 (56.9)
No	59 (57.8)	44 (43.1)
Study design		
Randomised controlled trial	66 (64.7)	66 (64.7)
Other	36 (35.3)	36 (35.3)
Comparison		
Direct	65 (63.7)	56 (54.9)
Indirect	37 (36.3)	46 (45.1)
Indirect treatment comparison		
No	95 (93.1)	51 (50.0)
Yes	7 (6.9)	51 (50.0)
Risk of bias		
Low	35 (34.3)	38 (37.3)
Other	67 (65.7)	64 (62.7)
Applicability		
Acceptable	26 (25.5)	25 (24.5)
Moderate	15 (14.7)	12 (11.8)
Questionable	61 (59.8)	65 (63.7)
Maturity of survival data		
Mature	22 (21.6)	19 (18.6)
Immature	19 (18.6)	23 (22.5)
Very immature	61 (59.8)	60 (58.8)

GBA = Federal Joint Committee; NICE = National Institute for Health and Care Excellence

Figure 1: Kappa scores and number of appraisals (%) with no agreement between the GBA and NICE (n=102)



GBA = Federal Joint Committee; NICE = National Institute for Health and Care Excellence

Table 3: Key similarities and differences in appraisals of rare disease treatments in England and Germany (n=102)

Key similarities
1) In 96.1% of appraisals, the design of the main study was the same.
2) In 92.1% of appraisals, the main study was the same.
3) In more than half of appraisals, the main study was a randomised controlled trial (64.7%). However, only slightly more than half of these randomised controlled trials in each country had a low risk of bias.
4) In 89.2% of appraisals, the maturity of survival data was the same.
Key differences
1) There was no agreement about the applicability of the main study to clinical practice in 40.2% of appraisals.
2) There were more appraisals without an alternative treatment in the appraisal in Germany than in England (57.8% vs 43.1%).
3) Submitted evidence was not accepted by the GBA in 13.7% of appraisals and thus not used to derive the clinical benefit rating.
4) Only few indirect treatment comparisons were accepted by the GBA to derive the clinical benefit rating (6.9%). Indirect treatment comparisons played a bigger role in England as they informed the economic model in half of the appraisals (50.0%).

GBA = Federal Joint Committee

Limitations

- We focused on comparing characteristics of the main study to allow for a systematic comparison; we recognise, however, that appraisals may have been informed by additional evidence.
- The analysis relied on data extracted from publicly available appraisal documents only; information considered during appraisal discussions but not captured in reports was not taken into account.

Conclusion

- The GBA and NICE approach evidentiary uncertainty in different ways. They employ different processes and methods affecting the type of clinical evidence considered, and they evaluate clinical evidence differently despite despite evidence being to some extent similar.
- Understanding cross-country differences can inform the development and improvement of approaches to HTA.

1. Stafinski T, Glennie J, Young A, et al. HTA decision-making for drugs for rare diseases: comparison of processes across countries. Orphanet J Rare Dis. 2022;17(1):258. doi: 10.1186/s13023-022-02397-4
2. Nicod E, Whittal A, Drummond M, et al. Are supplemental appraisal/reimbursement processes needed for rare disease treatments? An international comparison of country approaches. Orphanet J Rare Dis. 2020;15(1):189. doi: 10.1186/s13023-020-01462-0