Associations of Product-Specific and Clinical Evidence Quality Characteristics with HTA Outcomes: A Quantitative Assessment of Appraisals for Drugs for Rare Diseases in England and Germany

HTA49

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Introduction

Health technology assessment (HTA) outcomes for rare disease treatments (RDTs) vary across countries [1-2] but how product-specific and clinical evidence characteristics of RDTs are associated with HTA outcomes remains unclear.

Objective

To explore associations of product-specific and clinical evidence quality characteristics with the HTA outcome in RDT appraisals.

Hypotheses

Product-specific characteristics
1) Appraisals for ATMPs were associated with a positive HTA outcome.
2) Appraisals for oncology RDTs were associated with a positive HTA outcome.
3) Appraisals for RDTs indicated for adults and children, or children only were associated with a positive HTA outcome.
4) Appraisals for which no alternative active treatment was available were associated with a positive HTA outcome.
Clinical evidence quality characteristics
5) Appraisals in which the main study was a randomised controlled trial were associated with a positive HTA outcome.
6) Appraisals in which the risk of bias in the main study was low were associated with a positive HTA outcome.
7) Appraisals in which the applicability of the main study was acceptable were associated with a positive HTA outcome.
8) Appraisals in which survival data was mature were associated with a positive HTA outcome.

ATMP = advanced therapy medicinal product; HTA = health technology assessment; RDTs = rare disease treatment

Methods

Appraisal selection

- We analysed RDT appraisals completed in England and Germany between 2011-2023.
- 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 product-specific and clinical evidence quality characteristics.
- The coding manual was validated by external researchers and disagreements were resolved by discussion.

HTA outcome definition

- Primary analysis:
  - England: recommended (positive); optimised, recommended only in research, recommended in the Cancer Drugs Fund (CDF) or under a Managed Access Agreement (MAA), or not recommended (negative)
  - Germany: major, considerable or minor added benefit (positive); non-quantifiable, no added benefit, benefit less than the comparator (negative)
- Secondary analysis:
  - England: recommended or optimised (positive); recommended only in research, recommended in the CDF or under a MAA, or not recommended (negative)
  - Germany: major, considerable, minor or non-quantifiable added benefit (positive); no added benefit, benefit less than the comparator (negative)

Statistical analysis

- We performed descriptive statistics and cross-tabulations.
- We explored associations between the independent variables and the HTA outcome separately in each country using logistic regression.
- We tested multicollinearity using Pearson's chi-squared tests.
- We excluded variables strongly correlated with other independent variables from the final model.
- To account for clustering at RDT level, we used clustered standard errors.
- To adjust for multiple hypothesis testing, we applied the Bonferroni correction.

Results

Table 3: Characteristics associated with HTA outcomes in Germany and England: results of binary logistic regression analyses (n=102)

	Primary analysis				Secondary analysis			
	Germany		England		Germany		England	
Variables	AOR (p-value)	95% CI	AOR (p-value)	95% CI	AOR (p-value)	95% CI	AOR (p-value)	95% CI
ATMP								
No	-	-	-	-	-	-	-	-
Yes	0.79 (1.000)	0.09, 6.80	0.49 (1.000)	0.08, 3.04	0.64 (1.000)	0.08, 5.30	0.12 (0.133)	0.01, 1.31
Patient age								
Adults	-	-	-	-	-	-	-	-
Adults and children	2.78 (0.602)	0.58, 13.88	0.27 (0.392)	0.05, 1.63	0.43 (1.000)	0.05, 3.83	0.60 (1.000)	0.05, 8.03
Alternative treatment								
Yes	-	-	-	-	-	-	-	-
No	1.15 (1.000)	0.21, 6.17	0.68 (1.000)	0.14, 3.34	44.16 (<0.001)	5.21, 374.04	0.11 (0.021)	0.01, 0.78
Study design								
Other	-	-	-	-	-	-	-	-
Randomised controlled trial	13.12 (<0.001)	2.18, 78.88	1.34 (1.000)	0.37, 4.84	8.49 (0.402)	0.39, 185.42	4.12 (0.532)	0.50, 33.65
Applicability								
Other	-	-	-	-	-	-	-	-
Acceptable	0.75 (1.000)	0.17, 3.21	1.53 (1.000)	0.46, 5.05	0.58 (1.000)	0.14, 2.32	1.03 (1.000)	0.25, 4.27
Maturity of survival data								
Other	-	-	-	-	-	-	-	-
Mature	2.11 (1.000)	0.43, 10.33	0.59 (1.000)	0.12, 2.90	2.38 (1.000)	0.20, 27.91	1.74 (1.000)	0.17, 17.68
Process								
Regular / TA	-	-	-	-	-	-	-	-
Limited / HST	0.98 (0.973)	0.27, 3.56	8.41 (0.013)	1.57, 45.11	NA	NA	108.64 (0.018)	2.23, 5289.82

AOR = adjusted odds ratio; ATMP = advanced therapy medicinal product; CI = confidence interval; HST = Highly Specialised Technology appraisal guidance; TA = Technology Appraisal guidance
Note: 95% CIs and p-values account for clustering at RDT level and are Bonferroni-adjusted

- In our primary analysis, more appraisals had positive HTA outcomes in England than in Germany (46.1% vs 33.3%); however, in the secondary analysis, Germany had more positive outcomes (85.3% vs 77.5%).
- The alignment of the results with the initially specified hypotheses was mixed.
- After adjusting for evidence quality and process-specific characteristics, product-specific factors alone may not be sufficient to achieve a positive HTA outcome (as defined in our primary analysis).

Table 2: Characteristics of GBA and NICE appraisals (n=102)

	GBA – N (%)	NICE - N (%)
HTA outcome (primary analysis)		
Positive	34 (33.3)	47 (46.1)
Negative	68 (66.7)	54 (52.9)
HTA outcome (secondary analysis)		
Positive	87 (85.3)	79 (77.5)
Negative	15 (14.7)	23 (22.5)
Process		
Regular (Germany) / TA (England)	29 (28.4)	75 (73.5)
Limited (Germany) / HST (England)	73 (71.6)	27 (26.5)
Patient age		
Adults	65 (63.7)	63 (61.8)
Adults and/or children	37 (36.3)	39 (61.7)
ATMP		
Yes	14 (13.7)	
No	88 (86.3)	
Oncology indication		
Non-oncological	52 (51.0)	
Oncological	50 (49.0)	
Study design		
Randomised controlled trial	66 (64.7)	66 (64.7)
Other	36 (35.3)	36 (35.3)
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)
Other	76 (74.5)	77 (75.5)
Maturity of survival data		
Mature	22 (21.6)	19 (18.6)
Other	80 (78.4)	83 (81.4)

ATMP = advanced therapy medicinal product; CDF = Cancer Drugs Fund; GBA = Federal Joint Committee; HST = Highly Specialised Technology; MAA = Managed Access Agreement; NICE = National Institute for Health and Care Excellence; TA = Technology Appraisal

Conclusion

- Studies comparing HTA outcomes across countries should be interpreted in light of the definition of the HTA outcome, as the associated characteristics are likely to be sensitive to this definition.
- The findings improve our understanding of the characteristics influencing HTA decision-making for rare disease treatments specifically, providing insights for HTA specialists, policymakers, and manufacturers.

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