HTA 23

# Addressing payer concerns: Opportunities for HEOR in orphan drug development

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## Objectives

- Orphan drugs present unique challenges to the health technology assessment (HTA) process due to small patient populations, posing challenges to the conduct of traditional clinical trials. This leads to evidence packages with inherent uncertainties.
- This study aims to assess common HTA bodies' (HTAb) criticisms of the orphan drugs evidence package and to identify HEOR opportunities to ensure optimal HTA outcomes.

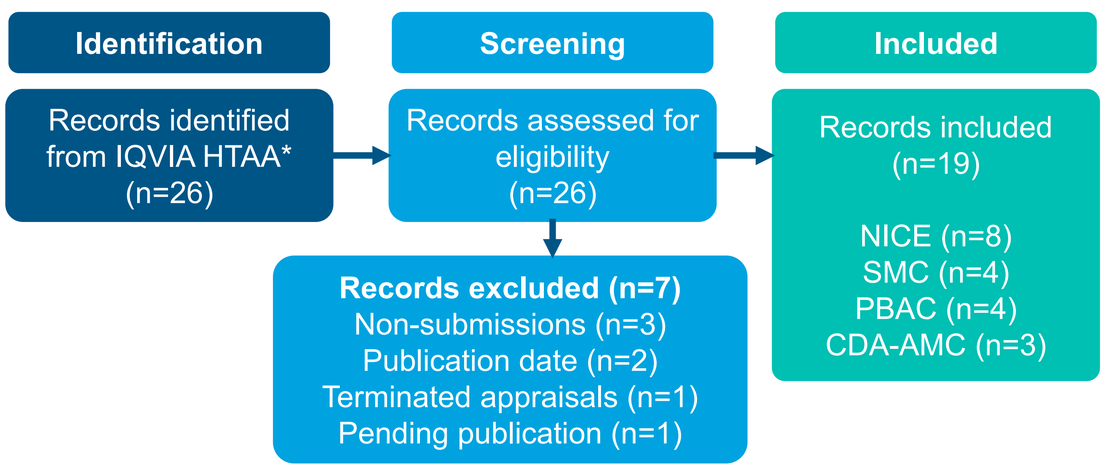
## Methods

- Completed National Institute for Health and Care Excellence (NICE) appraisals of highly specialised technologies (HSTs) for endocrine and metabolic disorders since 2023 were identified.
- Appraisals of the same technologies identified from NICE were expanded to Canada's Drug Agency (CDA-AMC), Scottish Medicines Consortium (SMC) and Pharmaceutical Benefits Advisory Committee (PBAC) of Australia.
- Key criticisms were identified across *population, clinical and economic value* domains and summarised qualitatively.

## Results

- A total of 19 HTA reports were reviewed (eight NICE, four SMC, three CDA-AMC and four PBAC) (Figure 1).

### Figure 1: Selection process flow-chart



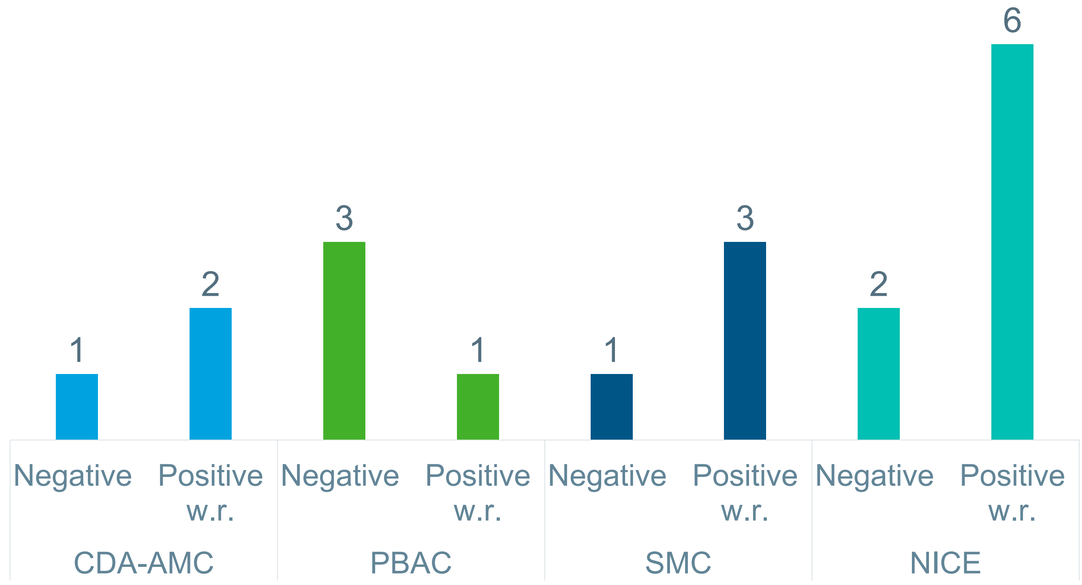

**Abbreviations**: HTAA: health technology assessment accelerator.

- Criticisms were identified across seven endocrine or metabolic diseases (Table 1, Table 2):
  - Key ***population-related criticisms*** included baseline imbalances between treatment arms and inappropriate subgroup classification or underrepresentation (n=10, 53%).
  - ***Clinical evidence criticisms*** included inappropriate validation of surrogate endpoints (n=5, 26%) and reliance on non-disease specific health-related quality of life (HRQoL) (n=6, 32%).
  - ***Economic evidence critiques*** highlighted utility value uncertainty (use of vignette studies and carer or bereavement disutility) (n=11, 58%) and overreliance on expert opinion or surrogate endpoints to derive disease progression and utilities in the model (n=5, 26%).
- Certain differences were observed between HTAb criticisms:
  - NICE and SMC permitted the use of carer disutility in economic models of paediatric patients (only in genetic disorders with perinatal, infantile, or juvenile onset [n=6, 32%])
  - PBAC and CDA-AMC consistently emphasised uncertainties associated with surrogate endpoints, while NICE showed greater acceptance when supported by robust evidence and thorough validation.
- Criticisms of the evidence package contributed to a higher proportion of negative final recommendations in PBAC submissions (75%), compared to CDA-AMC (33%), NICE (25%) and SMC (25%) submission (Figure 2).
- Positive recommendations were generally restricted based on a commercial agreement consisting of a simple discount.

### Table 1: Number of appraisals by indication

| Indication | No. of appraisals | Indication | No. of appraisals |
|---|---|---|---|
| Mineral disorders | 3 | Glycoprotein disorders | 2 |
| Carbohydrates-related disorders | 3 | Porphyrin disorders | 2 |
| Weight disorders | 1 | Sphingolipid-related disorders | 6 |
| Amino acid disorders | 2 | | |

### Figure 2: Final recommendation by HTAb




**Abbreviations**: w.r.: with restrictions.

### Table 2: Summary of HTAbs' critiques and observations

| | Critique/observations summarised | NICE | SMC | CDA-AMC | PBAC |
|---|---|---|---|---|---|
| Population | Inappropriate disease classification into clinical subgroups or lack of subgroup analysis. | ✓ | ✓ | | ✓ |
| | Baseline imbalances between treatment arms and over-reliance on age-matching. | ✓ | ✓ | ✓ | |
| | Definition of disease severity being based on clinical judgement. | ✓ | | | |
| | Limited data presented for paediatric population subgroup. | | ✓ | | ✓ |
| | Uncertainty surrounding disease subtype distribution. | ✓ | ✓ | | ✓ |
| Clinical evidence | Inappropriate validation of surrogate endpoints. | ✓ | | ✓ | ✓ |
| | Outcomes compared solely to baseline data, lacking RCT design or ITC comparison. | ✓ | | | |
| | Lack of disease specific mortality rate and long-term data leading to uncertain and overly optimistic survival gain. | ✓ | ✓ | ✓ | ✓ |
| | Reliance on non-disease specific HRQoL. | ✓ | | ✓ | ✓ |
| | Use of flawed disease specific HRQoL tools developed by the submitting company. | | ✓ | | |
| Economic evidence | Use of vignette studies for utilities considered reasonable (when there is insufficient health state data) but surrounded by uncertainty. | ✓ | ✓ | ✓ | ✓ |
| | Uncertainty of using surrogate endpoints in the model for deriving health state transitions and utilities. | | | ✓ | ✓ |
| | Carer disutility was inclued in the model and considered in decision making in paediatric populations. | ✓ | ✓ | | |
| | Bereavement disutility accepted in the model in paediatric populations. | ✓ | | | |
| | Overreliance on expert opinion to inform model structure parameters. Uncertainty of agreement between experts. | ✓ | ✓ | | |

## Conclusions

- The findings of this study highlight several opportunities for HEOR in addressing payer evidence needs and optimise HTA outcome:
  - Strategies addressing payer evidence needs should be implemented early in the technology's lifecycle to optimise optimize evidence readiness according to payers' needs.
  - Scientific advice alongside HTA analysis of analogue diseases can identify relevant subgroups and optimise design of pivotal trials.
  - Ensuring balanced randomisation across treatment arms based on key prognostic factors to minimise bias in the evidence.
  - Surrogate endpoint validation helps demonstrate the clinical and economic value of the technology amid high uncertainty.
  - In the absence of disease-specific HRQoL tools, use of validated tools in suitable proxy conditions can reduce model uncertainties and reliance on vignette studies.
- This study included only published HTAs in endocrine and metabolic disorders. Consequently, the findings may not be generalisable to other therapeutic areas.