Uncertainty in NICE Health Technology Appraisals for Rare Disease Products: A Review of Methodological Recommendations and How They Are Applied

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Introduction and background

- Rare diseases can be life threatening or impose a very high burden on patients and their families, however there are no effective treatments for 90% of rare diseases.[1]
- A significant hurdle for patient access of drugs for rare diseases (DRDs) is providing evidence to Health Technology Assessment (HTA) authorities. Generating the evidence required to demonstrate the value of DRDs can be challenging due to the inherent characteristics of rare diseases including small patient populations, heterogeneity in populations and clinical practice, and lack of comparative data against the standard of care. This leads to significant uncertainty for payers when assessing DRDs and providing recommendations for reimbursement.
- In recognition of these challenges, the National Institute of Health and Care Excellence (NICE) has implemented the Highly Specialised Technology (HST) appraisal route for DRDs. To be eligible for HST appraisal, a product must be for a very rare disease (<1 in 50,000 people in England) which significantly shortens lifespan, with no satisfactory treatment alternatives. These criteria result in most DRDs continuing to be appraised via the single technology appraisal (STA) pathway, which does not take into consideration the challenges associated with conducting evidence generation for DRDs.[1,2]
- DRDs that undergo assessment with the STA pathway must meet the same HTA requirements as non-DRDs. This includes not exceeding an incremental cost-effectiveness ratio (ICER) threshold of £20,000 to £30,000 per quality adjusted life-year (QALY)[1] which many DRDs fail to meet due to high research and development costs associated with developing innovative and breakthrough treatments.[2,3]
- In 2022, NICE introduced updated methods guidance which added a new severity of disease modifier to facilitate appraisals of products that have dramatic and far-reaching impacts on patients, such as DRDs, which would not have qualified for additional weighting under the previous criteria.[4,5] Such modifiers can increase the willingness to pay (WTP) threshold for drugs which meet specific criteria, aiding the demonstration of cost-effectiveness. The severity modifier has replaced the end of life (EOL) criteria implemented in 2009, which increased the acceptable ICER threshold to £50,000 for life-extending (≥3 months) treatments indicated for the treatment of diseases with small target populations (<7000) associated with a short life-expectancy (<24 months).[6]
- This research aims to summarise key areas of uncertainty as noted in NICE appraisals of DRDs via STA as well as an overview of the solutions to mitigate the issues identified.

Methods

Data sources

- All technical appraisals (TAs) conducted under the STA pathway between January 2022 and June 2024 were sourced from the NICE website. Appraisals for DRDs were tagged for subsequent data extraction.
- As there is no universal definition on the incidence or prevalence thresholds for a rare disease, DRDs were determined by whether they were indicated for a disease that was classified as rare by the European Medicines Agency (EMA) or in peer-reviewed published literature.

Data extraction

- We extracted the following information from each DRD TA:

1. Product name and indication
2. Recommendation
3. Areas of uncertainty on the analysis, as noted in the TA section entitled “why the committee made these recommendations”
4. Methods to address uncertainty

Data analysis

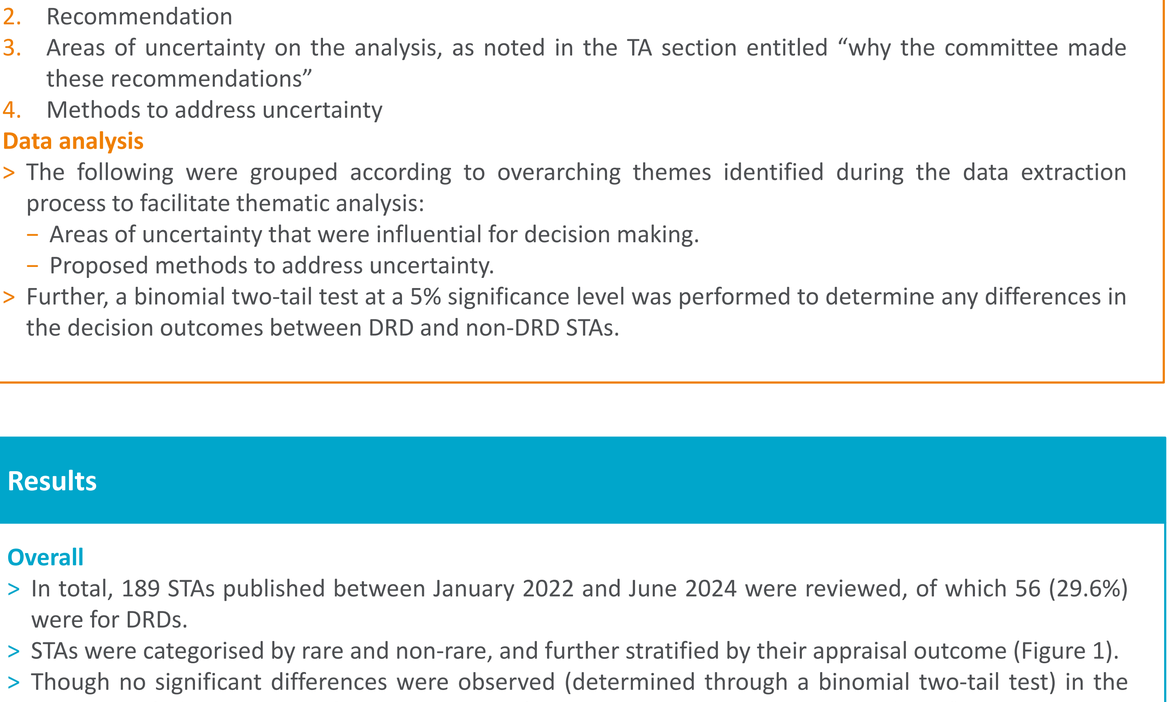
- The following were grouped according to overarching themes identified during the data extraction process to facilitate thematic analysis:
  - Areas of uncertainty that were influential for decision making.
  - Proposed methods to address uncertainty.
- Further, a binomial two-tail test at a 5% significance level was performed to determine any differences in the decision outcomes between DRD and non-DRD STAs.

Results

Overall

- In total, 189 STAs published between January 2022 and June 2024 were reviewed, of which 56 (29.6%) were for DRDs.
- STAs were categorised by rare and non-rare, and further stratified by their appraisal outcome (Figure 1).
- Though no significant differences were observed (determined through a binomial two-tail test) in the recommendation outcomes between DRD and non-DRD STAs, a greater proportion of DRD STAs were terminated.
  - A higher proportion of DRDs were recommended, and conversely fewer were not recommended.
  - Fewer DRD STAs resulted in recommendations for optimised indications when compared with non-DRD STAs.

Figure 1. Recommendation outcomes for DRD (56 appraisals) and non-DRD (133 appraisals) STAs



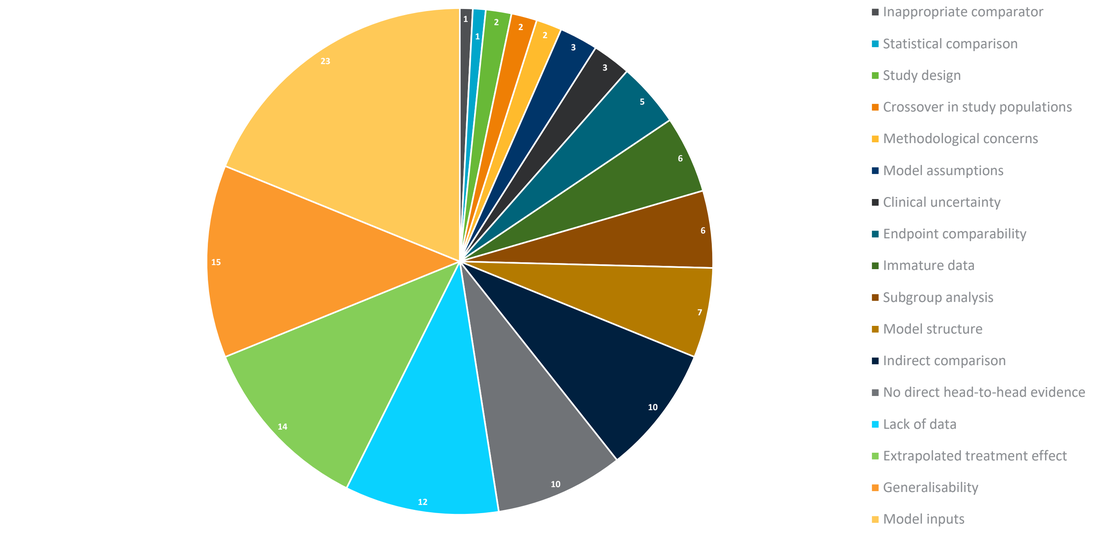
CDF: cancer drugs fund; DRD: drugs for rare diseases.

Results (continued)

Uncertainty and solutions

- As only two of the 56 DRD TAs were not recommended by NICE, the analysis focuses on those TAs that were submitted for appraisal and recommended.
- The main areas of uncertainty in TAs for DRDs which were recommended for use by NICE are presented in Figure 2.

Figure 2. Reasons for uncertainty in DRD TAs



- Model inputs were the most commonly cited source of uncertainty (n=23). The type of inputs introducing uncertainty varied, but included utility values (n=7), costs (n=3), and clinical values (n=4). Uncertainty on model inputs was often noted due to the paucity of associated data and lack of robust clinical trial data.
  - Structured expert elicitation was used to mitigate this uncertainty and provide greater confidence in the accuracy and reliability of inputs to the economic evaluation, as well as scenario analyses and adjustment of inputs to better reflect clinical practice or outcomes.
- The second most common source of uncertainty was generalizability, meaning the evidence was not representative of clinical practice or the UK general population.
  - Where the generalizability of the treatment population was the cause of uncertainty, solutions included the use of real-world data (RWD) to supplement trial data, conducting subgroup analyses to isolate a representative population, and conducting matched-adjusted indirect comparisons (MAIC).
- Where the generalizability to clinical practice was the cause of uncertainty, solutions included the use of RWD to validate model assumptions and elicitation of clinical opinion.

Discussion and conclusions

Discussion

- This research provides insights into the key elements that NICE considers when making reimbursement recommendations for DRDs and provides an overview of some of the common elements of uncertainty noted within the submission dossier for DRDs, as well as any methods accepted by NICE to mitigate this uncertainty.
- **Reasons for recommendations**
  - Despite the challenges associated with demonstrating cost-effectiveness for rare diseases, DRDs undergoing HTA via the STA pathway are still being recommended based on cost-effectiveness as the key criterion, with being below the ICER threshold as a key driver to positive recommendations.
    - Conditional modifiers, including end of life and severity, have been used in 14 of the TAs we reviewed and can help manufacturers demonstrate cost-effectiveness as the WTP threshold for drugs meeting specific criteria is raised.
  - The updated NICE HTA methods manual acknowledges that there are populations for which evidence generation is particularly difficult, including those affected by rare diseases. As such, the committee has cited these elements as reasons for positive recommendations despite significant uncertainty associated with the cost-effectiveness analysis. This includes rarity (n=1), severity of disease (n=5) and the unmet need and disease burden associated with the disease (n=12); all of which are elements applicable to rare diseases.
  - Despite some consideration, the vast majority of DRDs undergoing STAs are still subject to the same ICER requirements as those for non-rare. This is challenging as traditional aspects assessed under HTA do not take into consideration all elements of value associated with DRDs.
- **Uncertainty and solutions**
  - The evidence submitted for recommended DRDs included some key uncertainties, which were noted by NICE. These generally stemmed from a paucity of data to validate the use of model inputs within the economic evaluation.
    - Methods to mitigate this uncertainty noted by NICE included scenario analyses, clinical expert input via structured expert elicitation and the utilisation of RWD.
    - Though direct head-to-head randomized controlled trial (RCT) data is preferred, the evidence generation limitations for rare diseases mean indirect comparisons were accepted despite being associated with inherent uncertainty.

Conclusions

- HTA is often not fit for purpose for DRDs and does not take into account all of the considerable health benefits associated with these treatments. NICE considers this in their HTA processes with the HST pathway; however, the majority of DRDs still undergo assessment via the STA pathway. This review highlighted that for DRDs that undergo appraisal via STA, severity modifiers may be used during the assessment, but most TAs are still assessed against stringent cost-effectiveness criteria. Furthermore, HTA associated with DRDs generally include significant uncertainty, which is noted by NICE, although accepted to a degree. It is imperative for manufacturers to consider how to mitigate those uncertainties, where feasible, within the submission dossier to ensure positive reimbursement recommendations.

References

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