The National Institute for Health and Care Excellence's Highly Specialised Technologies process: a review of past submissions and recommendations for the future

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Background

- Treatments for very rare chronic conditions represent a unique challenge to payers, necessitating the development of specialised frameworks for evaluating cost-effectiveness.
- Extremely low patient numbers mean that often only Phase 1/2 trial data are available, and that natural history, quality of life and resource use data are limited.
- Combined with high acquisition costs, these evidence challenges result in estimates of cost-effectiveness that are subject to a greater degree of uncertainty.
- In the UK, the National Institute for Health and Care Excellence's (NICE's) Highly Specialised Technologies (HST) process assesses the clinical and cost-effectiveness of specialised therapies for rare chronic conditions [1].To be eligible for consideration through the HST process, all seven of the following criteria must apply:
  1. The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS
  2. The target patient group is distinct for clinical reasons
  3. The condition is chronic and severely disabling
  4. The technology is expected to be used exclusively in the context of a highly specialised service
  5. The technology is likely to have a very high acquisition cost
  6. The technology has the potential for lifelong use
  7. The need for national commissioning of the technology is significant.
- Evidence submissions for the HST process are reviewed by Evidence Review Groups (ERGs), who critique the evidence provided and the methods employed by the manufacturer to estimate cost-effectiveness.
- Following the completion of the first 10 appraisals, and ahead of a review of HST methods in 2020, it was of interest to identify common themes and issues to help guide manufacturers in making future evidence submissions to the HST process.

Objective

- To review published HST ERG reports and develop recommendations for future submissions.

Methods

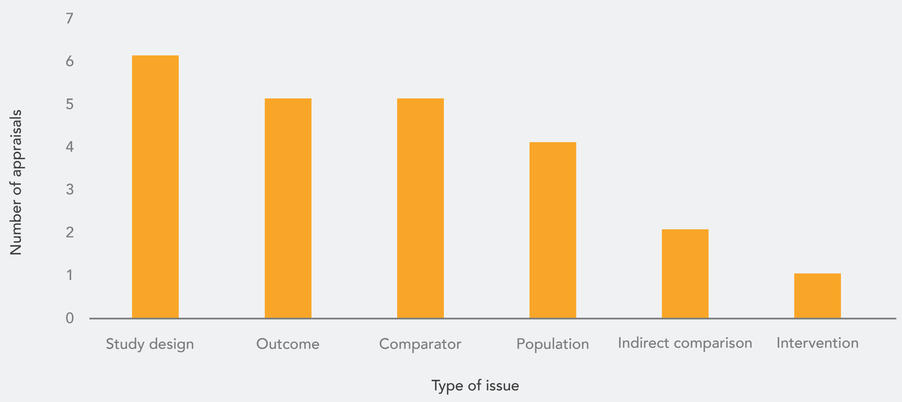
- ERG reports from the 10 published HST appraisals were reviewed (those which were 'in development' were not included).
- Common methodological issues and evidence limitations raised by the ERGs were identified; specifically, we searched for criticisms on systematic literature reviews (SLR), and clinical and economic evidence.
- The issues identified were grouped into themes, enabling us to identify the most frequently raised issues in the HST process.
- Based on the issues identified, recommendations were made for manufacturers considering future submissions.

Results

Clinical evidence

- The clinical evidence issues identified were grouped into the subcategories of the PICOS criteria (patient population, intervention, comparator, outcomes, study design), in addition to issues associated with indirect comparisons performed as part of the NICE evidence submission.
- The frequency of each type of issue by number of appraisals is presented in **Figure 1**, and these are discussed in further detail below.

Figure 1: Frequency of clinical evidence issues



Study design

- Study design issues were identified in 6/10 submissions; these included:
  - Issues related to trial statistics:
    - Missing data not being accounted for
    - Statistical analyses being conducted differently for each outcome
    - Non-inferiority margins being wider than would normally be accepted
    - Trials being underpowered due to underestimation of the standard deviation of the primary outcome measure
  - Trials being open label
  - Lack of independent assessment of treatment-emergent adverse events.

Outcomes

- Outcome issues were identified in 5/10 submissions; these included:
  - Lack of clarity about clinical relevance thresholds
  - Primary outcomes not being relevant to clinical practice (e.g. biochemical or surrogate outcomes)
  - The potential for placebo effects
  - Overestimation of effectiveness when using an overall survival endpoint, due to counting of patients who failed on treatment but who received successful subsequent treatment.

Comparators

- Comparator issues were identified in 5/10 submissions; these included:
  - The absence of control arms
  - Heterogeneity in the comparator due to variations in definition between countries.

Populations

- Population issues were identified in 4/10 submissions; these included:
  - Heterogeneity in the patient population
  - The patient population not being fully representative of those in clinical practice
  - Small sample sizes.

Indirect comparison

- Indirect comparison issues were identified in 2/10 submissions; these included:
  - Issues around comparability of results from treated patients with those from historical control patients
  - Unreliability of naïve comparisons due to differences in inclusion criteria between studies.

Intervention

- Intervention issues were identified in one submission; with doses being significantly higher than those used in clinical practice.

Systematic literature reviews

- Key issues in the reporting of SLRs included:
  - A lack of comprehensive search strategies:
    - No proper attempt made to search for comparators
    - Inappropriate limits applied to searches
    - Not all alternative terms and synonyms used for intervention under consideration
  - Transparency in reporting:
    - A lack of clarity about how many reviewers completed screening process and data extraction
    - Limitations in reporting of quality assessment
    - No reasons for exclusion of full text articles
  - Inconsistencies in PRISMA flow diagrams:
    - PRISMAs not conforming to PRISMA statement
    - Numbers in the PRISMA not following a logical progression
    - Discrepancies in search result numbers and numbers provided in PRISMA

Economic evidence

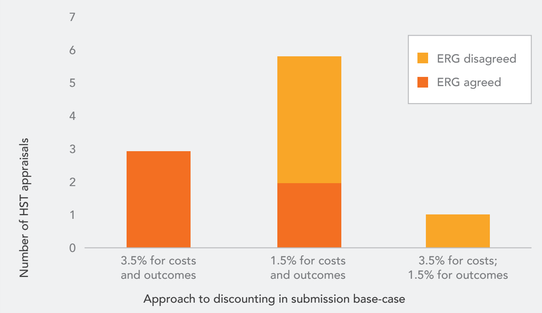
Discount rate

- In line with the NICE guide to the methods of technology appraisal [2], interim HST guidance states that discount rates of 1.5% may be used if:
  - treatment restores people to full or near full health when they would otherwise die or have a very severely impaired life, and this is sustained over a very long period (normally at least 30 years); and
  - the introduction of the technology does not commit the NHS to significant irrecoverable costs [1].
- The approach to discounting across appraisals is summarised in **Figure 2**.
- Discount rates of 3.5% were presented in the model base-case of 3/10 submissions.
- Discount rates of 1.5% were presented in the model base-case of 6/10 HST submissions.
  - In two cases this was accepted.
  - In four cases, discount rates of 1.5% were rejected because:
    - the conditions for a 1.5% discount rate were not considered to be met; or
    - the ERG's interpretation of NICE guidance was that discount rates of 1.5% should be presented as a scenario only; or
    - both of the above.
- One submission applied a 3.5% discount rate for costs, and a 1.5% discount rate for outcomes.
  - The ERG stated that differential discounting is not considered appropriate, and both discount rates were set to 3.5%.

Utility data

- The approach to generating utility values was a key concern in 3/10 HST submissions:
  - In one submission, utility values were estimated by six clinical experts based on health state vignettes; the ERG stated that it would have been preferable to have derived utility values based on responses from the patients themselves, or from the parents of patients.
  - In another submission, the ERG criticised the use of EQ-5D values based on Brazilian general population preferences and questioned whether these values would be transferable to the UK setting.
  - In a third submission, an ordinary least squares regression model was fitted to EQ-5D-5L data collected in the pivotal clinical trial; the ERG had concerns about the specification of the statistical model, the implementation of utility 'caps' to ensure realistic values, and the assumptions made for utility values in the comparator arm.

Figure 2: Approach to discounting across appraisals



Conclusions and recommendations

- All appraisals completed thus far have resulted in a recommendation, however all but one include a managed access arrangement and/or a patient access scheme. Managed access arrangements allow therapies to be made available to patients while further data is collected, with the aim of minimising uncertainty.
- Despite unavoidable uncertainties, some of the issues identified could be mitigated in the future by adopting the following recommendations during clinical trial design and/or development of the NICE submission:
  - SLR strategies should be comprehensive, and SLRs should be reported in a fully transparent manner, allowing the methods to be reproduced.
  - Appropriate statistical methods should be used when comparing single-arm trial data against historical control data.
  - Novel endpoints should be fully justified, and well-established secondary endpoints should be used in conjunction with these.
  - The use of 1.5% discount rates should be carefully justified, and a scenario should be included assuming discount rates of 3.5%.
  - De novo utility studies should align as closely as possible with NICE's reference case if appropriate utility values are not available from trials or the literature.
- Due to the nature of the conditions being appraised, some of the limitations identified were unavoidable. These included small sample sizes, heterogeneity in patient populations between trial arms, and the lack of utility data completely fulfilling the NICE reference case.

References

1. National Institute for Health and Care Excellence (2017) Interim Process and Methods of the Highly Specialised Technologies Programme - Updated to reflect 2017 changes.
2. National Institute for Health and Care Excellence (2013) Guide to the methods of technology appraisal

International Society for Pharmacoeconomics and Outcomes Research Europe, 2-6 November 2019, Copenhagen