

Treatment Effect Extrapolation Assumptions in NICE Highly Specialised Technology Appraisals

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Lay summary

- Clinical trials for treatments targeting rare diseases typically only provide short-term evidence on treatment effects.
- To understand long-term benefits, extrapolation is often used to estimate how long and how well a treatment continues to work once trial data end.
- This study reviewed how treatment effect extrapolation assumptions have been handled to date within NICE Highly Specialised Technology (HST) appraisals.
- Most appraisals assumed that treatment effects persisted beyond the trial period, with only some including a waning of effect over time.
- These assumptions substantially influenced cost-effectiveness estimates and, in turn, affected whether technologies could be recommended under NICE’s decision framework.
- The findings underline the need for transparent documentation and strong justification of extrapolation assumptions to maintain and build confidence in appraisal decisions.

Background

- Assumptions about treatment effect extrapolation are important for decision-making in NICE appraisals.
- To our knowledge, previous research on extrapolation assumptions has focused on Single Technology Appraisals (STAs).¹⁻³
- HST evaluations are of specific interest given the requirement for qualifying treatments to be cost-effective; in other jurisdictions, ultra-orphan treatments are not always subject to such rules.
- NICE HST recommendations were anticipated to rely on extrapolation assumptions, given the economics of technology development in this space and expected evidence gaps.

Study Objective & Methodology

- A systematic review was conducted of all HST topics with published NICE guidance up to April 24th, 2025.
- Each appraisal document was examined for references to treatment effect extrapolation or treatment effect waning.
- The following key information was extracted:
 - Company approaches to treatment effect extrapolation.
 - External Assessment Group (EAG)-preferred amendments to company assumptions.
 - Committee-preferred approaches (either implied or explicitly stated) that informed final decision-making.
 - Whether the final NICE recommendation was positive.
- We also examined reporting on how extrapolation assumptions were implemented within cost-effectiveness models.

Selected Results

HST topics

- A total of 33 HST topics were identified; three were updates, leaving 30 unique topics with published NICE guidance.
- These appraisals were published between 2015 and April 2025, with most published from 2020 onwards.
- Topics covered a mix of gene therapies, enzyme replacement treatments, and monoclonal antibodies for rare and ultra-rare diseases.

Abbreviations

EAG: External Assessment Group
HRQoL: Health-related quality of life
HST: Highly Specialised Technology
ICER: Incremental cost-effectiveness ratio
NICE: National Institute for Health and Care Excellence
STA: Single Technology Appraisal

Selected Results

Treatment effect waning and extrapolation

- Treatment effect waning was mentioned in 19 (63%) appraisals but appeared to inform the decision-making ICER in only 15 appraisals. Available documentation therefore implies that in 15 appraisals (50%), no waning of treatment effect was assumed over the cost-effectiveness model’s time horizon.
- Figure 1** illustrates how reporting of waning assumptions has evolved over time, with an apparent shift towards reporting of waning assumptions from 2019 onwards, perhaps as interest in these trends increased.
- Figure 2** shows how treatment effects were extrapolated beyond pivotal trial evidence in 29 of the 30 studies:
 - 22 of 30 extrapolated via health state occupancy.
 - 4 extrapolated via health-related quality of life (HRQoL) assumptions.
 - 3 extrapolated via health state occupancy and HRQoL assumptions.
- Scenario analyses exploring extrapolation assumptions were reported in 26 appraisals (87%).
- Overall, 28 of 30 topics (93%) resulted in a positive recommendation.
- Figure 3** shows that while extrapolation was critical to decision-making, its near-universal use means the impact of its presence or absence cannot be usefully interpreted.

Figure 1: Treatment effect waning in HST decision-making

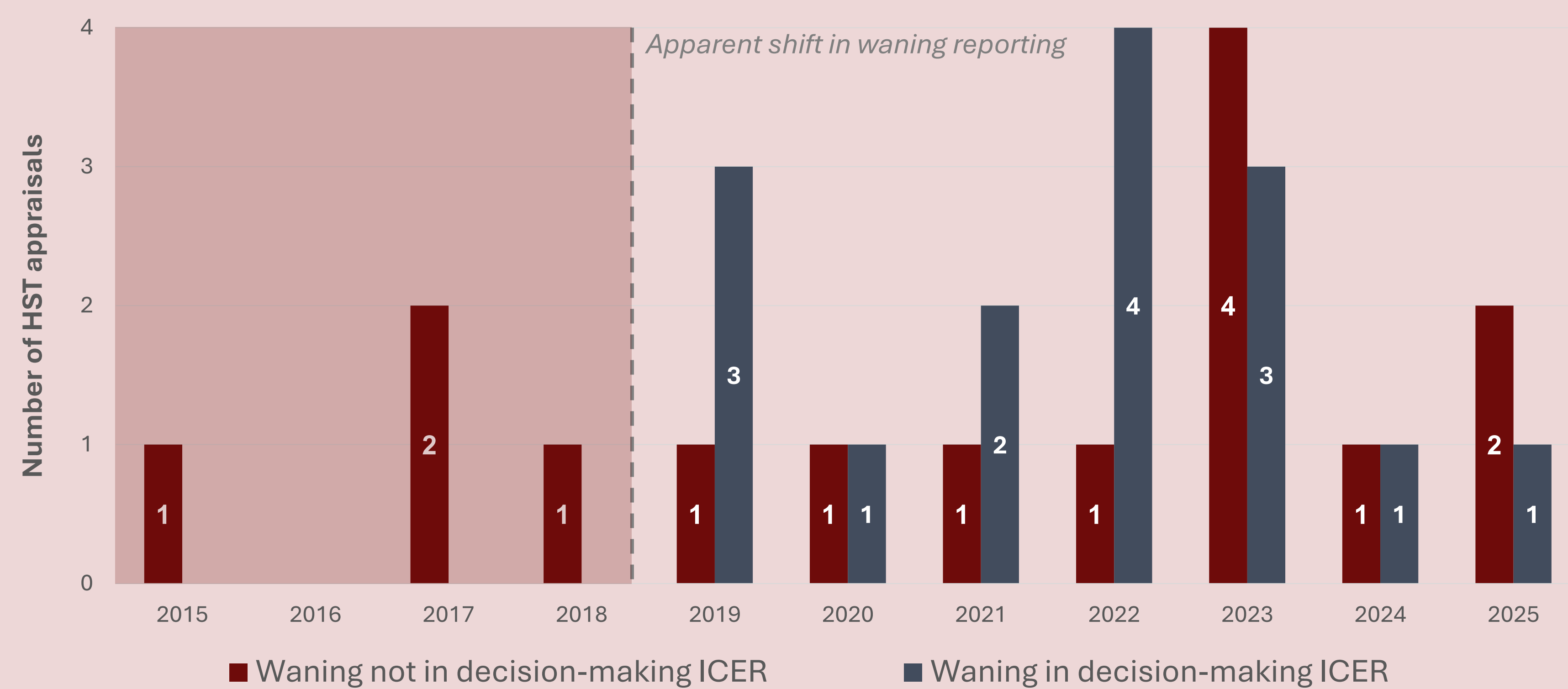


Figure 2: Extrapolation context

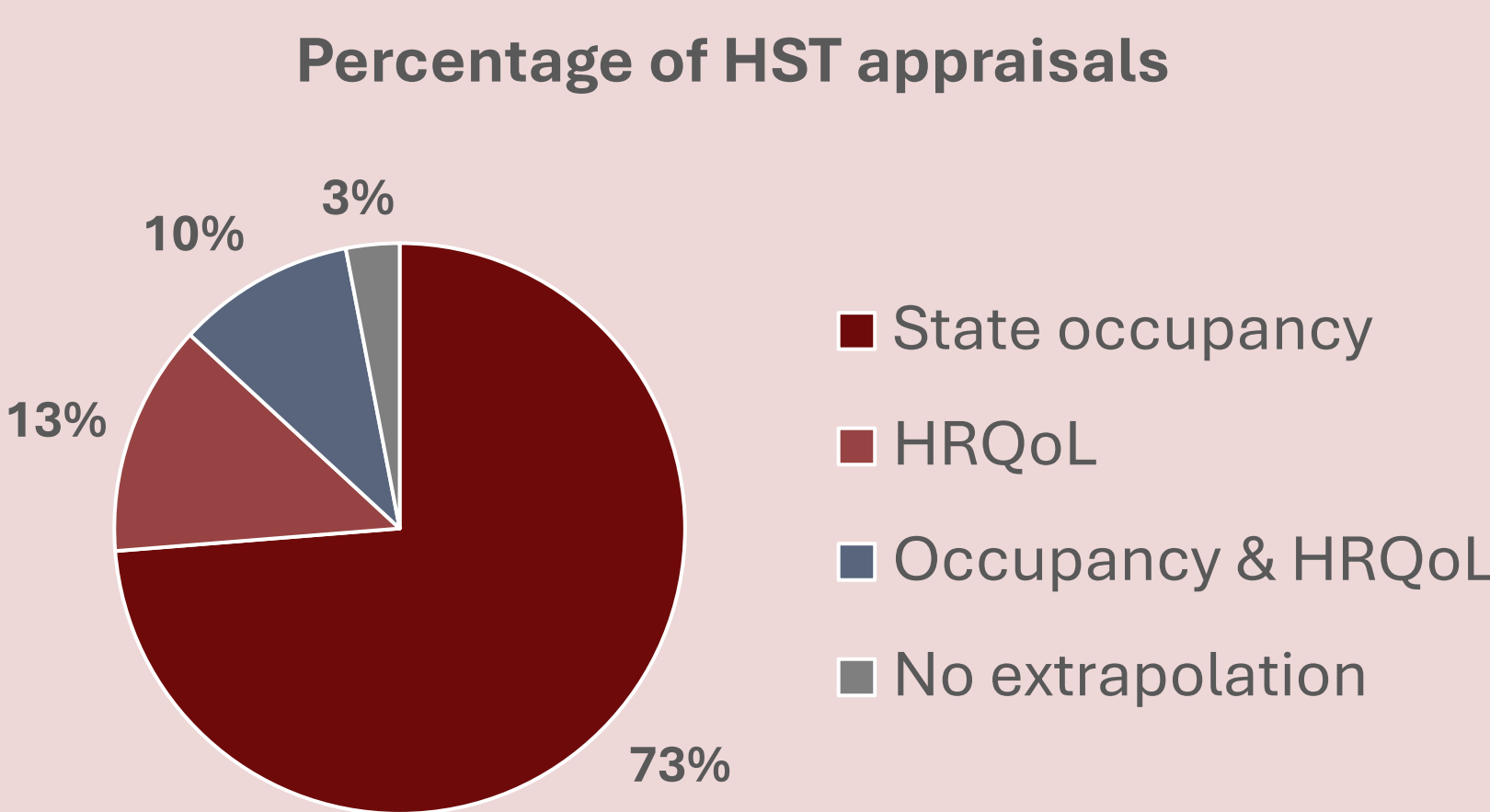
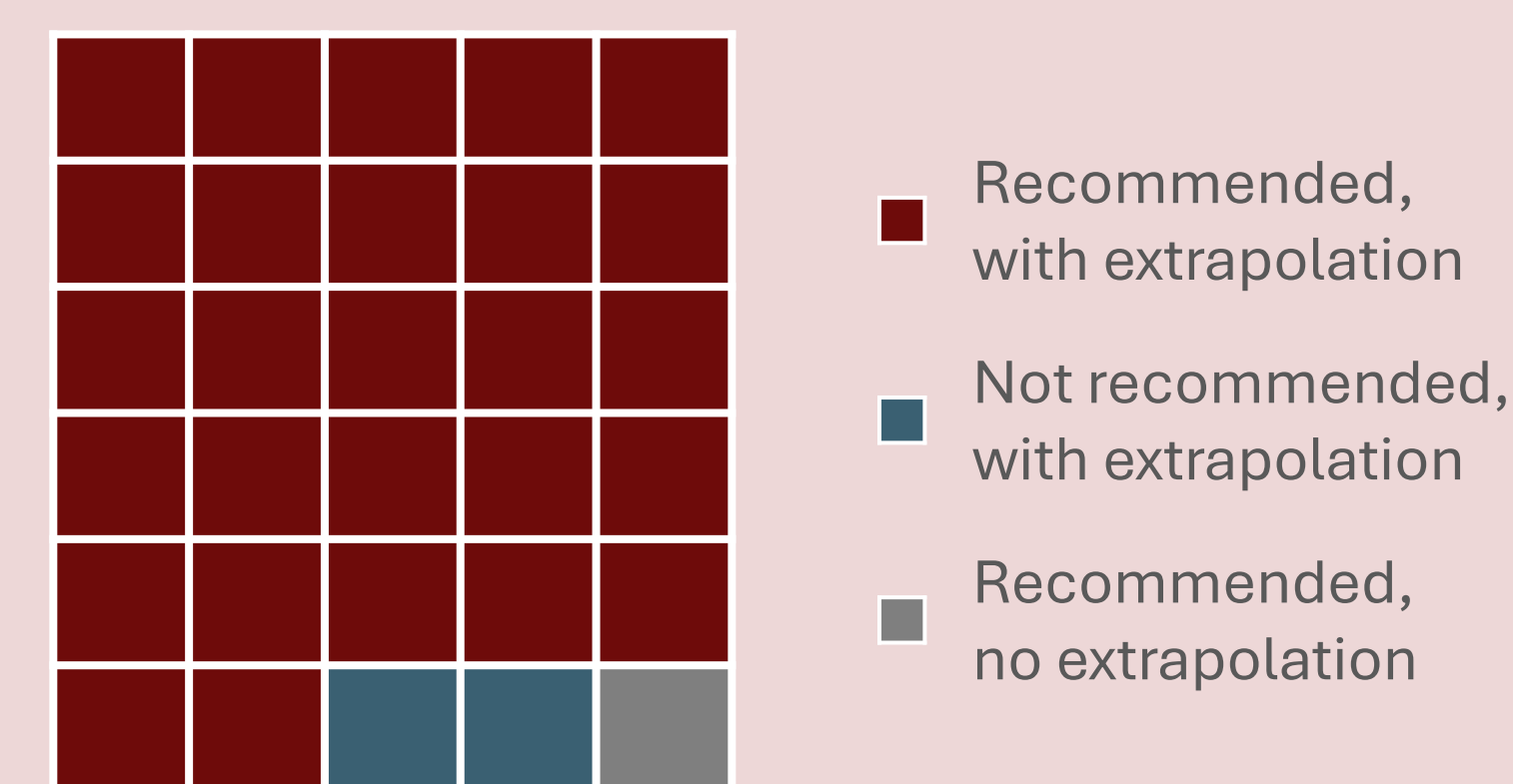


Figure 3: Relationship between extrapolation and recommendation



Interpretation

- Treatment effect extrapolation assumptions have been pivotal to nearly all positive NICE HST recommendations up to April 2025, underscoring their critical role in determining cost-effectiveness outcomes in HST appraisals.
- This reliance reflects both the economic realities of developing highly specialised technologies for small patient populations and the limited long-term clinical evidence available for rare diseases.
- Consistency in accepted extrapolation approaches may influence future NICE guidance and decision-making, potentially setting precedent for STAs.
- A limitation of our study is that three HSTs were updated during the study period, which may have influenced interpretation of temporal trends.
- Future research could examine differences in accepted treatment effect extrapolation assumptions across recent HST and STA appraisals.

References

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