Adoption of Piecewise Modelling: A Review of NICE Health Technology Appraisals in Oncology

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OBJECTIVE

- To review the adoption of the piecewise modelling approach in recent assessments of oncology drugs submitted to the National Institute for Health and Care Excellence.

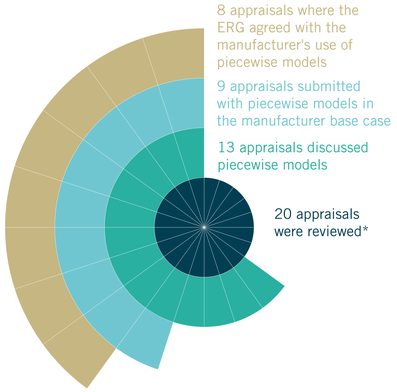
BACKGROUND

- Survival analysis is crucial for modelling the health benefit of a novel drug in order to provide smooth estimates of survival that extend over the patients' lifespan. A number of standard parametric models can be used for this survival analysis but these may fail to capture the complexity of the survival function, particularly for novel therapies.
- 10 years ago, National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Support Document 14 noted the underutilization of piecewise models as an alternative to fully parametric models for survival extrapolations and recommended their consideration where more flexible survival models are required.[1] More recently, NICE DSU Technical Support Document 21 provided further detail on the motivation, methods and limitations of piecewise models.[2]
- Piecewise models split the data at defined cut-point(s), modelling each time period separately before "stitching" these together to overall produce more flexible survival profiles.[1,3]

METHODS

- The survival extrapolation methods used in the 20 most recent oncology submissions to NICE (as of December 10th, 2021) were reviewed.
- For each appraisal, a pre-formatted extraction grid was used to capture detailed information regarding:
  - Whether the submitting manufacturer considered piecewise models and used these in their survival analyses
  - How the cut-points were determined if piecewise models were used
  - The rationale for the manufacturer's chosen modelling approach
  - The responses from the Evidence Review Group (ERG) and the NICE Committee
- The data were extracted by one reviewer and the extractions were then verified by a second independent reviewer. Where there were discrepancies in opinion, consensus was reached through discussion.
- Qualitative and quantitative analysis was conducted in order to understand utilization rates of piecewise models, rationale for their use and learnings for methodological implementation.

1 Adoption of piecewise models among the 20 most recent NICE oncology submissions



*20 most recent as of December 10th, 2021.

1 Summary of ERG and NICE Committee concerns for piecewise models

Appraisal No.	TA692	TA707	TA739
ERG's comment on the use of piecewise model	Though the ERG agreed with the use of a piecewise approach, they did not agree with the rationale of non-constant hazards alone being sufficient for use of a piecewise model for overall survival, as many parametric curves assume a hazard profile that changes at different rates over time. However, the ERG ultimately agreed that a piecewise approach was justified as the behaviour of the cumulative hazard was different in early and late follow-up.	The ERG agreed with the use of a piecewise model but also noted that the hazards in the taxane arm remained constant over time so using a fully parametric model could still be reasonable.	The ERG rejected the piecewise approach and instead preferred using fully parametric curves for the base case due to the large uncertainty associated with the piecewise approach resulting from the small sample size.
NICE Committee's response to the use of piecewise model	The Committee accepted the piecewise modelling approach.	The Committee agreed with the piecewise approach but noted that the optimal method to extrapolate the overall survival was still uncertain.	The Committee concluded that both the manufacturer and ERG's approaches were acceptable; the two approaches both gave similar, clinically plausible survival estimates and this was the main concern of the Committee.

RESULTS

- **Figure 1** presents a summary of the level of adoption of piecewise models in the 20 most recent NICE oncology submissions.
- Among the 9 (45%) appraisals where the manufacturer's submitted base case used piecewise models, the justification for the choice of the piecewise approach by the manufacturer almost always (8/9) included consideration of visual fit and/or the clinical plausibility of the resultant extrapolations. This approach was recommended by the NICE DSU and was well-accepted by ERGs.[2] However:
  - In the one case (TA692) where the manufacturer used a different justification, the ERG rejected the justification (though ultimately agreed with the piecewise approach) – see **Table 1**.
  - In two further cases (TA707, TA739), the ERG either had comments/reservations or rejected the manufacturer's use of piecewise models over fully parametric models – see **Table 1**.
- Selection of the cut-point(s) is an important feature of piecewise models and uncertainty in the choice of cut-point should be assessed.[3,4] Of the 9 submissions where the manufacturer used piecewise analysis in their base case, 8 specified the timepoint for the cut-off. **Table 2** summarizes the handling of cut-point(s) in these 8 appraisals.

CONCLUSIONS

- Piecewise modelling is seeing frequent usage by manufacturers submitting to NICE in recent oncology appraisals.
- Where used and justified on the basis of better model fit and/or clinical plausibility, it is well accepted.
- Careful consideration of the selected cut-point(s) is warranted due to the focus placed on this in critical review. Factors including timepoint of change in hazards and preservation of sufficient sample size are important in justifying the cut-point for ERGs, but this remains a balance of factors with no single statistical test having been used in the appraisals evaluated to determine a definitive 'best' cut-point.

2 Summary of justifications for cut-point(s) selection and ERG comment

Appraisal No.	TA742	TA737	TA736	TA724	TA716	TA709	TA707	TA692
Manufacturer justification for selected cut-point(s)	Cut-point chosen based on precedent from a prior appraisal (TA535).	A **Chow test** was performed to determine the appropriate cut-point for the piecewise models by choosing the cut-point with the highest test statistic.	A log-cumulative hazards plot was used to identify where a **change in hazard** occurred. Week 96 was chosen over other cut-points as the optimal cut-point to better **utilize the observed trial data**.	Month 13 was chosen as the preferred cut-point due to the **large amount of censorship after Month 13**. Month 18 was explored in scenario analysis as an alternative cut-point.	Month 6.44 was chosen as the preferred cut-point due to the **observed change in hazard profile** after the cut-point.	Week 10 and 20 were chosen as potential cut-points. Week 20 was ultimately chosen as the cut-point for its **superior visual fit and clinical plausibility**.	Month 2.99 was chosen as the preferred cut-point to capture the difference in hazard before and after the second assessment that was scheduled for 12 weeks.	Week 24 was chosen as the cut-point based on the **change in hazard profile** observed after the cut-point. Week 40 was explored in the scenario analysis as alternative cut-point.
Were alternative cut-points presented in the manufacturer submission?	No	No	Yes	Yes	No	Yes	No	Yes
ERG's comment on manufacturer approach to cut-point(s)	The ERG agreed with the cut-point for the comparator arm based on precedent. Some uncertainty in the piecewise approach for the intervention arm was noted due to limited data.	This approach was rejected by the ERG, who stated that the Chow test was designed to identify the presence of structural breaks rather than identify the optimal cut-off point, and hence the cut point should not be based on Chow test statistics alone.	The ERG agreed with the choice of Week 96 as the cut-point.	The ERG agreed with the choice of Month 13 as the cut-point.	The ERG agreed with the choice of Month 6.44 as the cut-point.	The ERG agreed with the choice of Week 20 as the cut-point as it appropriately captures the change in the hazard observed in the log-cumulative hazard plots.	The ERG preferred Month 5.75 as the cut-point. Although the ERG acknowledged a later cut-point reduced sample size for extrapolation, Month 5.75 was ultimately chosen because it avoided the potential issues in selecting a cut-point close to where the Kaplan-Meier curves cross and provided more realistic survival estimates.	The ERG agreed with the choice of Week 24 as the cut-point.

References

1. Latimer N. NICE DSU Technical Support Document 14: Survival Analysis for Economic Evaluations Alongside Clinical Trials – Extrapolation With Patient-Level Data, Version 2: National Institute for Health and Care Excellence, Decision Support Unit, 2013.
2. Rutherford MJ, Lambert PC, Sweeting MJ. *et al.* NICE DSU Technical Support Document 21: Flexible Methods for Survival Analysis: National Institute for Health and Care Excellence, Decision Support Unit, 2020.
3. Gorrod HB, Kearns B, Stevens J, *et al.* A Review of Survival Analysis Methods Used in NICE Technology Appraisals of Cancer Treatments: Consistency, Limitations, and Areas for Improvement. Medical Decision Making 2019;39:899–909.
4. Ishak KJ, Kreif N, Benedict A, *et al.* Overview of Parametric Survival Analysis for Health-Economic Applications. Pharmacoeconomics 2013;31:663–75.

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