Acceptance of flexible survival models by the Swedish Dental and Pharmaceutical Benefits Agency (TLV) and the Norwegian Medical Products Agency (NOMA)

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HTA196

Background

Long-term extrapolating clinical trial data is crucial to inform health technology assessments (HTAs). Guidelines such as the technical support document (TSD) 14 [1] have suggested standard parametric models for this task. However, these survival models can only model specific types of hazards. They cannot accurately model hazards with more than one turning point. Therefore, more flexible survival models are required for complex hazard shapes. These have become widely used within health technology assessments (HTA), and TSD 14 has been complemented with TSD 21 [2].

The present study aimed to analyze how frequently two agencies responsible for HTAs in Norway and Sweden, the Norwegian Medicine Agency (NOMA) and the Dental & Pharmaceutical Benefits Agency (TLV), use flexible models to extrapolate survival outcomes in their base case scenario

Methods

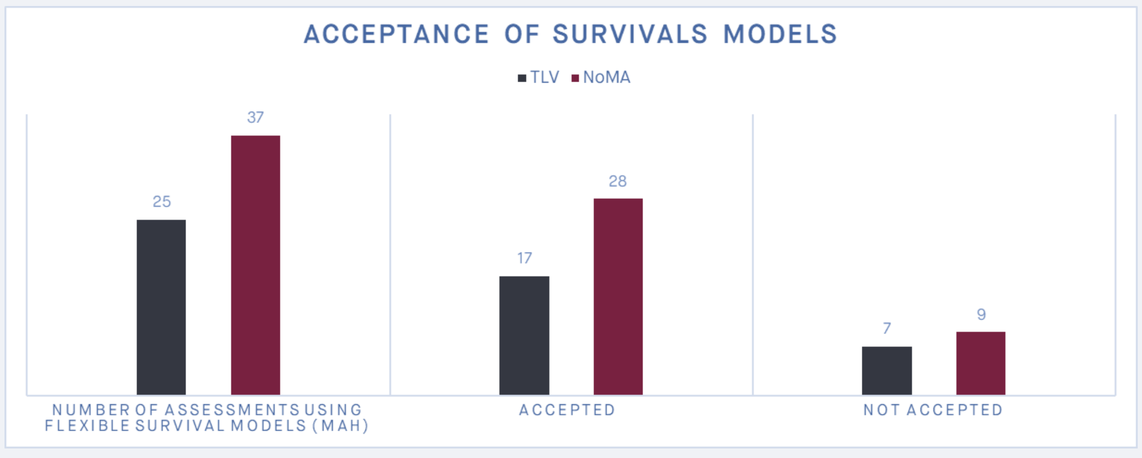
The study used a bespoke HTA database (NMA*i*) containing all the drug assessments published on TLV's and NOMA's websites. This database allows for keyword searches within all the published assessments up to the present (November 2024). NMA*i* was used to systematically identify assessments where the market authorization holder (MAH) submitting evidence had used flexible models using advanced keyword searches (combination of keywords and filtering).

The identified assessments were then analyzed to determine if TLV and NOMA used the flexible models in their base case analyses. Only assessments in which the MAH introduced a flexible survival model in the base case were included in the analysis.

Results and discussion

Overall, flexible survival models were used extensively in the agencies' base cases in Sweden and Norway, which shows that both agencies are open to using more complex survival models. In Sweden, 17 out of 24 (72%) proposed flexible models were accepted, and similarly, in Norway, 28 of 37 (76%) applications with flexible survival modelling, were accepted (Figure 1). The various models and their definitions are described below.

Figure 1 Acceptance of Survival models

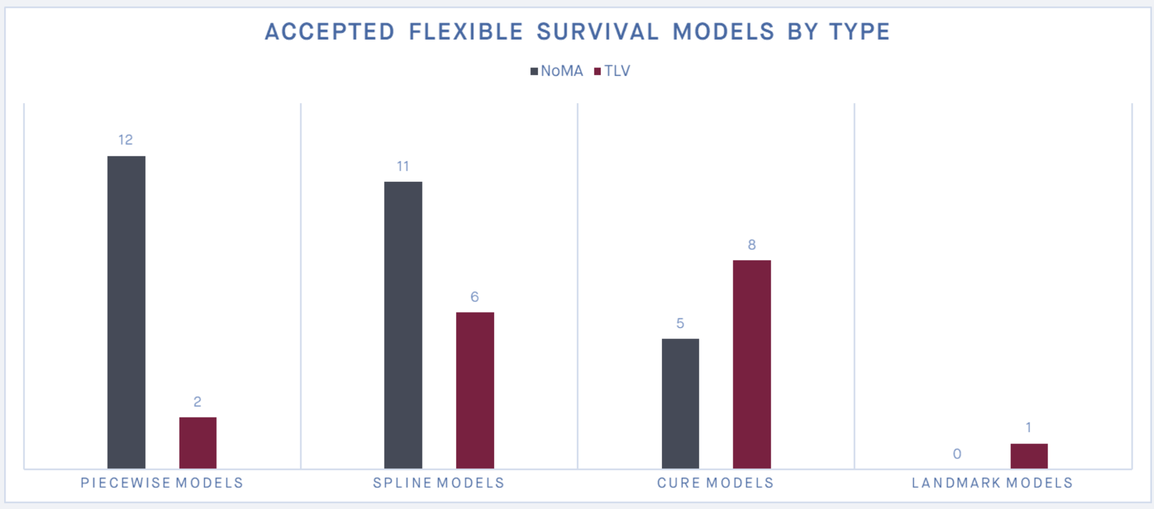


- **Spline model:** This model uses piecewise functions with specified "knots" to model non-linear relationships. It provides smooth, flexible fits in regression for capturing complex trends.
- **Mixture cure model**: assumes a fraction of the population is "cured" and will not experience the event, combining a cure model with a survival model to address individuals at no risk over time
- **Landmark model:** predicts based on patient status at a specific "landmark" time, conditioning on survival to this point. Useful for handling time-dependent covariates in survival analysis.
- **Piecewise model:** divides data into segments with separate models for each, allowing different hazard rates in each interval. Enhances flexibility by capturing hazard changes over time.

Concerning the types of flexible models accepted, most in both countries were splines and (mixture-) cure models (Figure 2), used in more than 50% of both countries, with piecewise models being more common in Norway than Sweden.

In all the evaluated assessments, whenever the authorities rejected a flexible model, both in Norway and in Sweden, the survival analysis was based instead on a standard parametric distribution, e.g., the exponential, gamma, Weibull, lognormal, log-logistic, Gompertz, or the generalized gamma. The primary cause of rejection in both countries was the concern that using a more complex survival model would increase the uncertainty of the survival projections.

Figure 2 Accepted flexible survival models by type



The majority of pharmaceuticals that utilized a flexible survival model were monoclonal antibodies (Mabs) and chimeric antigen receptor T-cells (CAR-Ts). All groups are listed in Table 1. Even in the smaller rejected samples for both countries, Mabs were still the largest group of pharmaceuticals to submit a flexible model. This highlights the need for these products to use complex models in their health economics assessments. The disease area where flexible survival modelling was most frequent, regardless of acceptance, was haematology.

Table 1 Types of pharmaceuticals using flexible survival models

Type of pharmaceuticals	Norway	Sweden
Monoclonal antibody	*16*	*9*
CAR-T	*5*	*2*
BRAF inhibitor	2	0
PARP inhibitor	1	2
Others*	4	4

**Tyrosine kinase inhibitor, Multiple protein kinase inhibitor, Androgen receptor antagonist, RNA antisense molecule, Theranostic medications*

Conclusion

With the development of new therapies and the need to model different shapes of hazards, several HTAs are currently using complex and more flexible survival models to assess pharmaceuticals. In Sweden and Norway, the HTA authorities TLV and NOMA show a similar acceptance of flexible models. While these models represents a minority of all the submitted applications for the period explored, the trend is increasing in the more recent years, and their acceptance rate highlight a positive response by the authorities.

Within these two countries, the majority of pharmaceuticals which presented a flexible survival model in their base case were Mab and CAR-T, predominantly used for blood cancer. Since new recommendations following the NICE TSD 21 have been around for a few years, it is possible to foresee an increasing use of these models within the Nordics HTAs assessments, which are now becoming the new standard practice.

References:
1. Technical Support Document 14: Survival Analysis For Economic Evaluations Alongside Clinical Trials - Extrapolation With Patient-Level Data Report By The Decision Support Unit June 2011, NICE DSU
2. Technical Support Document 21: Flexible Methods For Survival Analysis Report By The Decision Support Unit 23 January 2020, NICE DSU