

# A Review of Survival Analysis Methods Used in NICE Technology Appraisals of Cancer Treatments: Consistency, Limitations, and Areas for Improvement

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**Objectives.** In June 2011, the National Institute for Health and Care Excellence (NICE) Decision Support Unit published a Technical Support Document (TSD) providing recommendations on survival analysis for NICE technology appraisals (TAs). Survival analysis outputs are influential inputs into economic models estimating the cost-effectiveness of new cancer treatments. Hence, it is important that systematic and justifiable model selection approaches are used. This study investigates the extent to which the TSD recommendations have been followed since its publication. **Methods.** We reviewed NICE cancer TAs completed between July 2011 and July 2017. Information on survival analyses undertaken and associated critiques for overall survival (OS) and progression-free survival were extracted from the company submissions, Evidence Review Group (ERG) reports, and final appraisal determination documents. **Results.** Information was extracted from 58 TAs. Only 4 (7%) followed all TSD recommendations for OS outcomes. The vast majority (91%) compared a range of common parametric models and assessed their fit to the data (86%). Only a minority of TAs included an assessment of the shape of the hazard function (38%) or proportional hazards assumption (40%). Validation of the extrapolated portion of the survival function using external data was attempted in a minority of TAs (40%). Extrapolated survival functions were frequently criticized by ERGs (71%). **Conclusions.** Survival analysis within NICE TAs remains suboptimal, despite publication of the TSD. Model selection is not undertaken in a systematic way, resulting in inconsistencies between TAs. More attention needs to be given to assessing hazard functions and validation of extrapolated survival functions. Novel methods not described in the TSD have been used, particularly in the context of immuno-oncology, suggesting that an updated TSD may be of value.

## Keywords

cancer, extrapolation, health technology assessment, survival analysis, technology appraisal

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Economic evaluation requires a comparison of the incremental costs and health effects of competing interventions. Health effects are typically defined in terms of quality-adjusted life-years, which involve the analysis of patient time-to-event outcomes such as death and progression-free survival in oncology. To avoid delays in obtaining marketing authorization and reimbursement

approval, and because it is usually impractical to run trials with an indefinite length, the time frame of trials is

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often shorter than the desired time horizon for economic evaluation. In these cases, it is necessary to extrapolate survival functions beyond the duration of a trial. Different assumptions about, and approaches to, modeling, the underlying hazard function, and resulting survival function can affect the estimates of population mean benefit and incremental cost-effectiveness ratios (ICERs),<sup>1-3</sup> particularly when there is a high proportion of unobserved events.<sup>3</sup> Consequently, demonstrating that appropriate survival models have been selected is important as this increases the likelihood that good funding decisions are made.

Extrapolation of hazard and survival functions is particularly relevant in the context of cancer health technology assessments (HTAs) because a proportion of overall survival (OS) events are often censored (i.e., have not yet been observed) at the end of trial follow-up. In the context of cancer HTAs, we require an estimate of the population mean survival over a time horizon that captures all differences in health benefit, which is usually lifetime.<sup>4-8</sup> To adopt a lifetime perspective, assumptions must be made about the hazard and survival functions beyond the collection of sample data.

There are many approaches that can be taken to extrapolate hazard and survival functions. Commonly, parametric models are fitted to the sample data to provide a lifetime extrapolation. However, model selection should depend not only on the goodness of fit of the model to the sample data but also on the clinical plausibility of the

extrapolated hazard and survival functions. Different models can provide very different extrapolated hazard and survival functions, and it is essential that the model is selected carefully to ensure that the cost-effectiveness analysis (CEA) is based on a plausible estimate of population mean survival.

Within England, the National Institute for Health and Care Excellence (NICE) conducts technology appraisals (TAs) and provides guidance to the National Health Service. A typical TA involves a company submission providing evidence on the clinical and cost-effectiveness of the technology appraised. This evidence is assessed by an independent Evidence Review Group (ERG), which produces its own report. These reports are considered by the NICE Appraisal Committee, which ultimately produces a final appraisal determination (FAD). The FAD document highlights concerns about the analysis or methodological shortcomings of the submission and reports the outcome of the appraisal. There are 3 possible outcomes of the FAD: the technology is or is not recommended as a treatment option or (for cancer appraisals only) it is recommended for use through the Cancer Drugs Fund. The Cancer Drugs Fund is a managed access fund. It is an option when both the clinical and cost-effectiveness evidence are too uncertain for a positive recommendation but the technology has the potential to be cost-effective with additional data collection. Further details on the process of NICE TAs is available on their web site.<sup>9</sup>

The NICE Decision Support Unit (DSU) published a Technical Support Document (TSD 14) in June 2011 to address problems with the inconsistency and application of survival analysis methods incorporated in TAs.<sup>10</sup> The TSD provided recommendations for choosing the appropriate survival modeling approach based on an assessment of the internal and external validity of the extrapolated hazard and survival functions. These recommendations intended to improve the quality and consistency of survival modeling in NICE submissions. However, it is not clear to what extent these recommendations are being followed in submissions to NICE since the TSD was published.

This article provides a review of models used to extrapolate hazard and survival functions in NICE cancer TAs, which commenced following the publication of the TSD. It aims to determine whether the TSD has been followed and has led to an improvement in terms of consistent and systematic application of assessments to inform the selection of appropriate survival extrapolation in NICE cancer TAs and to highlight areas where there is need for further progress.

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## Methods

The purpose of this review was to identify the number of Single Technology Appraisals (STAs) that followed the recommendations of TSD 14. TSD 14 made recommendations regarding the assessment of internal and external validity of survival models and incorporation of uncertainty into CEA.

The methods used for the review followed similar reviews of NICE TAs.<sup>10,11</sup> The scope was restricted to completed NICE STAs for cancer treatments that commenced between July 1, 2011, and June 30, 2017. STAs that involved company submissions made prior to July 1, 2011, were excluded from our review because it would not have been possible for these to follow the TSD recommendations. Multiple Technology Appraisals were considered to be out of scope because those submissions rely on network meta-analysis, which is not directly relevant to TSD 14. The STAs that were within scope were identified from the NICE web site.<sup>9</sup> Company submissions, ERG reports, and FAD documents were available for each STA and were obtained by information specialists and stored in a Mendeley online database.<sup>12</sup> When an STA had been updated by a more recent appraisal, evidence from both sources was extracted and counted as 1 submission, to avoid double counting.

A data extraction form was created by the review team to ensure that the necessary information was extracted to meet the aims and objectives of the review. Reviewers collected information on the compliance of company submissions and assessment group reports with the recommendations of the TSD, in terms of the extrapolation of OS and, where available, progression-free survival (PFS). Section headings of the data extraction form corresponded to the key recommendations from TSD 14<sup>10</sup> and align with the headings in Table 1. Information was also extracted on the extrapolation approaches used. In addition, information was extracted from ERG reports regarding criticisms of the models used to extrapolate hazard and survival functions applied in company submissions and regarding alternative approaches suggested or undertaken. From the FAD, issues relating to the extrapolation of survival functions that affected the final decision were highlighted. Most of the extraction required a binary “yes/no” response, although free text was extracted where additional detail was thought to be useful. Further details of the extraction form are provided in the Supplementary Appendix.

The TAs were divided between 4 reviewers, with each reviewer following the same prespecified process for data extraction as outlined above. Alongside the binary yes/no responses and free text, page numbers of the relevant

**Table 1** Compliance with TSD 14 Recommendations for Extrapolation of OS

	Number (%) of TAs					
	PFS			OS		
	<i>n</i> = 22	<i>n</i> = 25	<i>n</i> = 47	<i>n</i> = 24	<i>n</i> = 34	<i>n</i> = 58
	July 2011–2014	July 2014–2017	Total	July 2011–2014	July 2014–2017	Total
1. Internal validity	2 (9%)	11 (44%)	13 (28%)	5 (21%)	10 (29%)	15 (26%)
1(a). Assessed shape of the hazard	8 (36%)	13 (52%)	21 (45%)	10 (42%)	12 (35%)	22 (38%)
1(b). Assessed proportional hazards	7 (32%)	13 (52%)	20 (43%)	8 (33%)	15 (44%)	23 (40%)
1(c). Assessed the relative goodness-of-fit using AIC and/or BIC	19 (86%)	23 (92%)	42 (89%)	20 (83%)	30 (88%)	50 (86%)
1(d). Assessed the absolute goodness of fit	16 (73%)	22 (88%)	38 (81%)	16 (67%)	29 (85%)	45 (78%)
2. External validity	2 (9%)	2 (8%)	4 (9%)	4 (17%)	7 (21%)	11 (19%)
2(a). Validated extrapolation with external data	3 (14%)	6 (24%)	9 (19%)	8 (33%)	15 (44%)	23 (40%)
2(b). Validated extrapolation according to clinical plausibility	7 (32%)	10 (40%)	17 (36%)	9 (38%)	19 (56%)	28 (48%)
3. Other						
3(a). Considered structural uncertainty in sensitivity analyses	17 (77%)	19 (76%)	36 (77%)	18 (75%)	24 (71%)	42 (72%)

AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival; PFS, progression-free survival; TA, technology appraisal; TSD, Technical Support Document. The internal validity row (1) indicates the number (%) of TAs that performed assessments 1(a), 1(b), 1(c), and 1(d). The external validity row (2) indicates the number (%) of TAs that validated 2(a) and 2(b).

sections in the TA documents were also noted, to support the data extraction. All reviewers met after completing 2 reviews each to ensure that they were extracting the information consistently. At the end, 20% of each reviewer's TAs were allocated for second review by 2 other reviewers (i.e., 10% each) to check the quality of the data extraction. Final checks of each review were made by the lead reviewer to confirm the accuracy of the data extractions.

## Results

### *Compliance with TSD Recommendations*

There were 58 STAs within the scope of the review.<sup>13–71</sup> The first company submission was submitted in October 2011, 4 months after the publication of the TSD. All 58 of the STAs undertook an extrapolation of OS, and 47 of the STAs also undertook an extrapolation of PFS. Despite 39 (67%) of the STAs referencing TSD 14, only 4 (7%) STAs fully followed all of its recommendations for the extrapolation of OS, and none of the TAs fully followed the recommendations for the extrapolation of PFS. Table 1 provides a summary of assessments made in relation to each recommendation.

The internal validity of the OS model fit was fully assessed in 15 (26%) TAs and for PFS model fit in 13 (28%) TAs. Full assessment of internal validity included assessing the shape of the hazard function, the plausibility of the proportional hazards assumption, and the goodness-of-fit of the model to the data. Proportional hazards were assessed for OS in 23 (38%) TAs and for PFS in 20 (43%) TAs. Of those that did not assess proportional hazards, 5 (14%) fitted proportional hazard models for OS and 6 (22%) fitted proportional hazard models for PFS. The shape of the hazard function was formally assessed in 22 (38%) TAs for OS and 21 (45%) for PFS. In 50 (86%) of TAs, the relative goodness-of-fit of different parametric models for OS was assessed using AIC and/or BIC and in 42 (89%) TAs for PFS. The absolute goodness-of-fit of the OS to the sample data was assessed through visual inspection or using a test of Cox-Snell residuals in 45 (78%) TAs and in 38 (81%) TAs for PFS. Of these, visual inspection was the more commonly used approach.

With regard to the external validity of extrapolated OS hazard and survival functions, these were validated with both external data and using clinical opinion in the company submission in only 11 (19%) TAs and in only 4 (9%) TAs in the case of PFS. In 23 (40%) TAs, the OS extrapolated hazard and survival functions were validated using external data and in 9 (19%) TAs for PFS.

Of the company submissions that did not use external data to validate extrapolated OS hazard and survival functions, there were 2 cases (6%) in which the ERG used external data for validation.<sup>50,72</sup> In 28 (48%) TAs, the OS extrapolated hazard and survival functions were validated using clinical opinion and in 17 (36%) TAs for PFS. Additional assessments of the structural uncertainty about the OS extrapolated survival functions was done using sensitivity analyses in 42 (72%) TAs and in 36 (77%) TAs in the case of PFS.

To assess whether adherence to the TSD had improved over time, the TAs were split into 2 groups based on time of company submission (July 1, 2011, to June 30, 2014, and July 1, 2014, to June 30, 2017). The comparison did not show any overall substantive change in the proportion of submissions that adhered to the TSD recommendations. There was an increase in the proportion of TAs that used external data to validate the model and also the proportion that validated the model based on clinical opinion. More company submissions followed the TSD for the assessment of PFS in the more recent period.

### *Extrapolation Approaches Used*

A range of different approaches was used to extrapolate survival functions. In 53 (91%) TAs, common parametric distributions were used (i.e., exponential; Weibull; gamma; log-normal and log-logistic, which are members of the generalized gamma distribution family; and the Gompertz distribution) to extrapolate OS hazard and survival functions. This was the case with respect to PFS in 43 (91%) TAs. Another widely used method ( $n = 14$ , 23%) was to model the data using piecewise models, which split data at change (or cut) points, with extrapolations based on fitting parametric models to a subset of trial data and/or external data.<sup>15,20,40,54,68</sup> In 10 submissions, the company employed a specific type of piecewise model, known as a hybrid model, which typically split the observed data into 2 unique time periods. This uses Kaplan-Meier estimates for the first time period, with a parametric distribution used for both the second time period and for generating extrapolations. The hybrid method was also applied in 7 immunotherapy (IO) TAs for melanoma,<sup>17,30,38,41,49,56,66</sup> following the precedent for this method set by the first immunotherapy treatment assessed by NICE within this tumor type and reviewed by the Liverpool Reviews and Implementation Group (LRiG).<sup>17</sup>

In 3 appraisals, in which hazard functions were not compatible with commonly used parametric models, other more complex parametric models were used to

extrapolate hazard and survival functions. In TA414, a mixture-cure model was used to account for differences in the hazard for different subgroups of patients.<sup>64</sup> Flexible parametric spline-based models were used in TA374 and TA417 to account for changes in the hazard rate over time that cannot be captured using parametric distributions.<sup>66,72</sup>

### ERG Critique

ERGs criticized the resulting extrapolated survival functions in 41 (71%) of the 58 STAs. The ERGs identified 23 cases in which the TSD had been misinterpreted or not followed. These included situations in which proportional hazards had been assumed but there had been an incorrect assessment or no assessment of the plausibility of the assumption,<sup>22,27,40,41,55,66</sup> and/or in which the long-term treatment effect was deemed to be overestimated<sup>i</sup> or the hazard function was not regarded to be clinically plausible.<sup>20,38,41,45,69</sup> The proportional hazards assumption was mostly assumed when treatment-switching adjustment methods had been applied,<sup>31,32,55,60</sup> even though it is not a requirement for treatment-switching methods. The ERG criticized a submission in which the company had applied a hazard rate to a control group survival function to estimate the experimental group survival function, where the base function took the form of an accelerated failure time distribution, including log-normal or gamma parametric models.<sup>43</sup> ERGs also criticized 5 cases in which external data were not used to validate the extrapolation,<sup>22,28,32,40,51</sup> 3 cases in which the external data used were deemed to be inappropriate,<sup>38,62,68</sup> and 5 cases in which an assessment of goodness-of-fit was given priority over external validation of the extrapolated hazard and survival functions.<sup>30,31,39,40,63</sup> In 1 appraisal, the ERG suggested that there should have been more transparency around the elicitation of expert opinion.<sup>33</sup>

ERGs criticized applications of the hybrid method of extrapolation in which change-points had been arbitrarily selected rather than based on the shape of the hazard function or when sensitivity to the choice of change point was not assessed.<sup>15,19,54,69,68</sup>

The ERGs assessed the sensitivity of ICERs to both alternative parametric models<sup>15,26,51–53,66</sup> and more pessimistic assumptions about treatment effects during the extrapolated period (for example, assuming that there is no treatment benefit).<sup>29,32</sup> ERGs also assessed the impact of alternative change points as the piecewise models and

hybrid models have been criticized for arbitrary choice of change point, which can often influence the ICER.<sup>15,54,73</sup>

### FAD Considerations

The FAD documents provided information on the issues of extrapolating hazard and survival functions that were raised during the appraisal committee discussions. Issues relating to the extrapolation of survival functions were discussed in 41 (71%) of the 58 STAs. The main areas of discussion were the suitability of proportional hazards assumptions ( $n = 8$ )<sup>ii</sup> use of the nonparametric Kaplan-Meier estimator rather than parametric survival functions ( $n = 6$ ),<sup>15,26,40,46,47,54</sup> lack of validation with appropriate external data ( $n = 2$ ),<sup>28,45</sup> clinical plausibility of the extrapolated hazard and survival functions ( $n = 19$ ),<sup>iii</sup> structural uncertainty about the most plausible extrapolation (particularly when the duration of follow-up was short relative to patients' lifetime ( $n = 3$ ),<sup>21,42,65</sup> and treatment switching ( $n = 5$ ).<sup>16,19,20,22,55</sup> Situations in which there was little or no discussion regarding the extrapolated survival functions occurred when the sensitivity of the ICER had been assessed for a range of plausible models,<sup>24</sup> when the survival function was mature,<sup>15,26</sup> or in cases in which the treatment was dominated.<sup>20,43</sup>

### Discussion

Survival models make assumptions about the shape of the underlying hazard function. Therefore, it is important to assess the suitability of the model based on what was observed in the trial period and clinical knowledge of both the disease process and mechanism of action of the treatment.<sup>74</sup> These assessments will also inform what we expect to observe in the longer term. Sometimes, consideration of the underlying hazard function associated with different models could lead to some models being rejected as implausible before attempting any statistical analysis.<sup>75</sup> For example, if it is believed that the underlying hazard function is nonmonotonic, then survival models with monotonic hazard functions such as a Gompertz distribution can be ruled out. Presentation of the empirical hazard function provides a useful descriptive summary of the sample data and further aids the identification of an appropriate model.<sup>76</sup> Despite the fact that the TSD guidance advocates that model selection should be based on the hazard function, the shape of the empirical hazard function was considered in only about 40% of TAs.

<sup>ii</sup>References 13, 27, 33, 35, 38, 41, 55, 60.

<sup>iii</sup>References 18, 21, 23, 29, 34, 36, 38, 39, 41, 47, 49, 52, 53, 56, 57, 62, 63, 66, 69.

<sup>i</sup>References 23, 25, 26, 29, 36, 39, 43, 54, 56, 57, 61, 63, 65.

It is assumed that proportional hazards is a modeling assumption that is convenient for generating a single estimate of treatment effect for drug registration purposes. Although an assumption of proportional hazards used in an HTA may be a consequence of using summary statistics generated from a meta-analysis, assuming proportional hazards when hazards are not proportional will generate biased estimates of population mean time-to-event.<sup>77,78</sup> The underlying log hazards for each trial arm will not generally be parallel, and proportional hazards models can often be ruled out. Despite the TSD guidance that the proportional hazards assumption should be assessed, in some cases the assumption was applied without an assessment.

Statistical criteria can be used to assess absolute and relative goodness-of-fit, but a more important consideration is whether the models proposed are clinically plausible (both to the observed data as well as during the extrapolation phase). Despite the fact that the TSD recommends external validation using data and/or expert opinion, fewer than half of the TAs validated the extrapolation approach according to clinical opinion, and less than one-third of the TAs used external data to choose the modeling approach.

The apparent lack of consideration of these issues highlights the need for improvement in this area of assessment in NICE TAs. It is important to note that not all recommendations made in TSD 14 are relevant to all HTAs. For example, it is not necessary to assess whether hazards are proportional if there is no intention of making the proportional hazards assumption. In addition, for newer treatments with a novel mechanism of action, there may not be any relevant external sample data available with which to externally validate models. When these 2 issues (represented in Table 1 as 1b and 2a) were removed from our criteria, 19% of the TAs reviewed followed the remaining suggestions made by TSD 14.

Several ERGs consistently use common parametric models, whereas it is notable that the LRiG ERG often uses a hybrid approach based on an exponential survival function to extrapolate from a specified point in the tail of the Kaplan-Meier survival function. Whenever a piecewise model is used, uncertainty in the choice of change point should be assessed.<sup>79</sup> Both of the modeling approaches are consistent with TSD 14, provided—as for any extrapolation—internal and external validity have been considered appropriately. However, companies are aware of disparities in the approaches taken by different ERGs, and this has been highlighted by companies involved in writing submissions to NICE, with a

suggestion that this can be problematic.<sup>80</sup> However, in situations where extrapolation is required, it is important to consider alternative approaches to extrapolation, and the onus is on the company or ERG involved to justify the plausibility of the predictions.

In practice, it is possible that none of the commonly used parametric models described in TSD 14 will adequately represent expectations about the long-term hazards and those observed during the trial period. An observed hazard function, which is by definition an average over individuals, may exhibit odd shapes as a consequence of groups of patients with different underlying risk. For instance, strict entry criteria to clinical trials often result in a low short-term hazard function, which increases as individuals at higher risk experience an event, then decreases as a consequence of long-term survivors. In the longer term, the hazard might increase again if there are any extreme long-term survivors because of age-related mortality. None of the commonly used survival models can represent these 2 turning points, and it is necessary to consider more complex models in these circumstances.

The focus of this article was on compliance with TSD 14. TSD 14 was authored by the DSU, which has a specific role in supporting the NICE TA program. Other guides exist that provide recommendations for survival analysis and extrapolation within the context of HTA.<sup>79,81</sup> The content of these existing guides is similar.

Since the publication of TSD 14, more complex survival models have been used in TAs, such as flexible parametric spline models and mixture models (including mixture cure models).<sup>64,66</sup> There is some evidence to suggest that some of the more complex survival models are not well-understood by stakeholders in the NICE appraisal process. NICE TA483 was completed after the end date for our review, but in the company submission, the ERG report and in the FAD a spline model with 2 knots was interpreted as implying that there were 3 heterogeneous subgroups of patients, each with a different survival profile that can be expressed as a combination of 3 survival functions.<sup>82</sup> In fact, this description is more akin to a mixture model, whereas a spline-based model simply represents a way of modeling a complex hazard function. That is, a spline-based model describes only the population (marginalized) hazard function and cannot be used to make inferences about the unobserved hazard function for subgroups of patients. The current guidance in TSD 14 for these more complex survival models is not detailed. Therefore, it may be useful to publish a new TSD to provide additional advice to companies, the ERG, and Appraisal Committees on these more complex models.

Finally, TSD14 does not specify how parameters in survival models should be estimated, and we did not extract this information during the review. However, it is likely that parameters are being estimated mostly using maximum likelihood and that survival functions are generated using these estimates as plug-in values. Frequentist methods consider only sampling variation and do not deal with parameter uncertainty. Maximum likelihood estimates will generally correspond to the Bayesian posterior mode, whereas a Bayesian approach would estimate a survival function by taking the expectation with respect to the uncertain parameters. A maximum likelihood approach also requires an assumption of asymptotic multivariate normality to approximate joint posterior distributions with multivariate sampling distributions for use in probabilistic sensitivity analyses (which is inherently Bayesian). Although such approximations may be reasonable in some situations, it is precisely in situations in which there are few events and limited follow-up with which to estimate parameters that the Bayesian approach and the incorporation of external information is important to represent genuine uncertainty. The review did not assess whether the survival model parameter uncertainty was correctly incorporated in the economic models as this would be difficult to assess without access to the economic models. Indeed, if there is external information used to validate extrapolations, then it would be reasonable to include this in the analysis to strengthen inferences.


## Conclusions


Extrapolation of hazard and survival functions is a complex area. However, making use of clinical knowledge of the disease process and mechanism of action of the treatment and presenting the empirical hazard function should provide useful insights into plausible model selection. In general, our review has shown that while the majority of NICE cancer TAs assessed the absolute and relative goodness-of-fit of common parametric models to the sample data, other aspects such as consideration of the underlying hazard function and the use of external data have been given relatively little attention. Overall, there is scope for improvement in the application of survival analysis methods used in NICE cancer TAs to achieve greater transparency and consistency. An improvement could potentially be supported by explicit referencing in the NICE methods guide to TSD 14. Future research could investigate the reasons for nonadherence to the TSD.

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## Supplemental Material

Supplementary material for this article is available on the *Medical Decision Making* Web site at <http://journals.sagepub.com/home/mdm>.

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