The use of data from published Kaplan-Meier survival curves in NICE HTAs

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Objective
Reporting of survival outcomes from clinical trials is often limited to median survival times, hazard ratios, Kaplan-Meier (K-M) curves and numbers at risk. The numerical results are not always sufficient for meta-analysis and cost-effectiveness analysis. Further information can be obtained by digitizing and analysing the K-M curves. The most basic analysis approach is to fit a non-linear model to the K-M curve and use this to estimate parameters such as the mean survival time. Methods have recently been developed for estimating individual patient data (IPD) from K-M curves. Once individual patient data is estimated, standard survival analysis approaches can be used to estimate parameters and also provide estimates of uncertainty in the curve fits. The objective of this study was to review methods commonly used and assess the impact of the improved methods, where IPD is estimated, on the inferences drawn.

Methods
We conducted a targeted review of the methods that have been used in NICE HTAs to obtain data from published K-M curves. We examined the frequency of each method, how results were used and any feedback from Evidence Review Groups. Two STAs were selected for further investigation. For each of these STAs we digitized the K-M curves and used standard methods and IPD methods to model the curves. The impact of the IPD methods was assessed. The methods for the estimation of survival curves are described below.

Standard method: regression
The standard method for estimating survival curves is to fit a regression model to the digitized points of the K-M curve. Non-linear regression can be used to directly estimate standard survival curves; for example, exponential, Weibull, lognormal or loglogistic. Model fit statistics such as the Akaike information criterion (AIC) can be used to help select the best model. An alternative is to re-parameterise the curves and fit the models using standard linear regression.

The key disadvantage of this method is that it gives equal weight to all parts of the K-M curve. The beginning of a K-M curve includes more patients (fewer patients have been censored) and so should be given more weight. Estimates of mean survival can be sensitive to the end of the curve, so it is important that this information is properly weighted.

IPD methods: survival analysis
Two methods have recently been proposed for the reconstruction of IPD from published K-M curves (1,3). Once IPD has been estimated, ordinary survival analysis models can be applied. This method has the advantage that survival analysis methods will give proper weight to different parts of the K-M curve and allow for better measurement of the uncertainty in the estimates.

Guyot et al. (3) published an alternative method in 2012. Their method requires the total number of patients and the K-M curve. Estimation of the IPD can be improved if the numbers at risk and/or the total number of events are available. Guyot et al. recommend taking readings, where possible, at each step of the K-M curve. Their method assumes that censoring occurs at a constant rate between time intervals for which the numbers at risk were reported. If these are not available and the total number of events has been reported it can be used to estimate the number of censored observations. Otherwise the method assumes that there were no censored observations. Guyot et al. have published R code to implement their method.

We applied both the standard method and the IPD methods to two case studies (see below).

Case studies
A review of existing HTA submissions demonstrated that most HTAs used non-linear models to approximate the Kaplan-Meier curves. It also showed that the improved methods, estimating IPD can, in theory, have a significant impact on conclusions drawn from survival results. In order to empirically test this, two case studies were selected. We chose two examples of oncology models where full K-M curves were published, along with a reported number at risk at various timepoints. The two examples were:

i. An adjunctive treatment to pegylated liposomal doxorubicin hydrochloride (PLDH) versus PLDH alone in the treatment of metastatic ovarian cancer;

Illustrative Markov model
To test the impact of different approaches toward the estimation of survival parameters, a simple Markov model was developed. It should be noted that the model was designed purely to test the impact of the different approaches and was intended to approximate, not replicate, existing economic evaluations of the interventions (indeed, the analysis below uses K-M data that included trial crossover, which was not considered to be appropriate for an HTA economic evaluation). The Markov model followed a typical approach for oncology, by using a three-state approach and incorporating progression-free survival and overall survival. Costs and outcomes associated with adverse events were not included in the analysis, nor was treatment discontinuation accounted for. As such, the cost-effectiveness results presented below are for illustrative purposes only and should be used only to assess how different approaches to survival curve modelling can impact upon the results.

Results
Results of the standard (regression) and IPD methods are shown in Table 1, below.

Table 1: Impact of survival analysis

<table>
<thead>
<tr>
<th>Method</th>
<th>Breast cancer</th>
<th>Ovarian cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard (SC)</td>
<td>$42,846.04</td>
<td>$17,034.04</td>
</tr>
<tr>
<td>H&amp;H: SC + NAR</td>
<td>$39,232.05</td>
<td>$17,034.04</td>
</tr>
<tr>
<td>G: SC + NAR + NOE</td>
<td>$48,338.05</td>
<td>$17,034.04</td>
</tr>
<tr>
<td>G: SC + NOE</td>
<td>$42,110.01</td>
<td>$12,422.24</td>
</tr>
<tr>
<td>G: SC</td>
<td>$46,657.02</td>
<td>$106,068.27</td>
</tr>
</tbody>
</table>

Conclusions
The results demonstrate that the method used to estimate parametric fits to survival data can have a significant impact upon the results. By using techniques to generate quasi-patient-level data, the results of a cost-effectiveness model were shown to vary substantially.

The estimation of IPD from Kaplan-Meier curves is a valuable method that is currently underutilised. It has the potential to provide more accurate estimates of survival parameters and to improve the characterisation of uncertainty in such estimates. This is especially important when survival curves are extrapolated.

References

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