Use of time to event data in health economic analyses

Version 1

Introduction

This guide specifies the implementation of parametrization with extrapolation of the clinical time to event data beyond the actual study period. Health economic analyses sent to the Medicine Council for evaluation must be carried out according to the specifications outlined below. This applies regardless of whether the relative efficacy has been obtained by direct or indirect comparisons.

Time-to-event data refers to all data where the time of the event is the endpoint. Examples are time to progression in oncology, such as progression-free survival (PFS) and time to death, such as overall survival (OS). Time to other disease related events is also time to event data. The randomization time point is usually the starting point in time to event analyses.

In the presence of censoring in the clinical data, health economic analyses often use a form of parametrization to extrapolate data beyond the study follow-up period.

Parametrization of data from clinical studies

In the health economic part of the application it is required to describe the future state of the investigated issue. Extrapolation of the time to event data beyond the study follow-up period is often done with a parametric function. Parametric functions assume that the underlying risk of the event (baseline risk) follows a given distribution, in contrast to non-parametric (e.g., Kaplan-Meier) or semi-parametric (e.g., Cox model) functions. Different parametric functions can give very different estimates.

The choice of a parametric function is based on statistical analyses of best mathematical fit, in combination with biological criteria related to knowledge of how the risk of event is expected to develop for the current condition/disease and endpoint. For example, some conditions will have a high risk of an event initially, but will the decrease (biphasically), while for others the risk of event will increase or decrease in monotonously.

Parametrization must be based on the actual data from the clinical studies, thus highlighting the direct effect of the treatment under consideration.

Statistical tests and graphic evaluations must be carried out systematically to allow the choice of the most accurate parametric function.

For a given function to fit satisfactorily, the following two criteria must be fulfilled:

1. The function must fit well with the observed efficacy data from the study or studies
2. The extrapolated part is clinically and biologically plausible

Justify in detail the choice of a function considering the two criteria above. Functions which do not fulfill both these criteria are probably not suitable.

Curve fitting to observed study data

By curve fitting, means how well suited a parametric function is to the clinical data from the study or studies (usually Kaplan-Meier data). All the points in the list below *must* be delivered as a minimum for documenting the adjustment to the observed study data:

- Log-cumulative hazard plot for the different parametric functions as a guide for the choice of parametric function and the choice between proportional hazard model (PH) and accelerated failure time model (AFT).

- Statistical tests and graphical presentation of proportional hazard (PH) if such a model is chosen. Examples are log-cumulative hazard plot and plot based on Schoenfeld residuals, but if other graphical methods are more suitable, these must be used.

- If neither PH nor AFT appears suitable, another, more flexible function must be considered, such as a piecewise function, Royston-Palmer models, spline models.

- Akaike's Information Criteria (AIC), Bayesian Information Criteria (BIC) and/or other suitable tests for those functions which are relevant based on the criteria described above.

- Graphical presentation of time to event data curves, where both Kaplan-Meier (KM) data and the parametric distribution is shown in the same figure.

- In some cases, curves with KM data for the first part of the study period can be appropriate, and then a parametric tail which shows the extrapolation beyond this point (transition point). The transition point must be evaluated in the individual case. As a minimum requirement an analysis must be presented where the tail is set at the time point where 50 % of the included population in each treatment arm is still "at risk".

Plausibility of the extrapolated part of the curve

The plausibility of the extrapolated part of the survival curve must be documented and justified biologically and clinically for the patient group in question. External data can be used to evaluate the assumptions made in the extrapolation. External data can include data from another study of a similar patient group or data from a national/international registry with long-term follow-up of a relevant patient group. The patient population must be relevant in terms of patient characteristics, pre-treatment and treatment. External data can only be seen as indicative. Use of external data requires a balanced discussion of how far any differences in long-term survival between the projected survival curve and the external data source is due to:

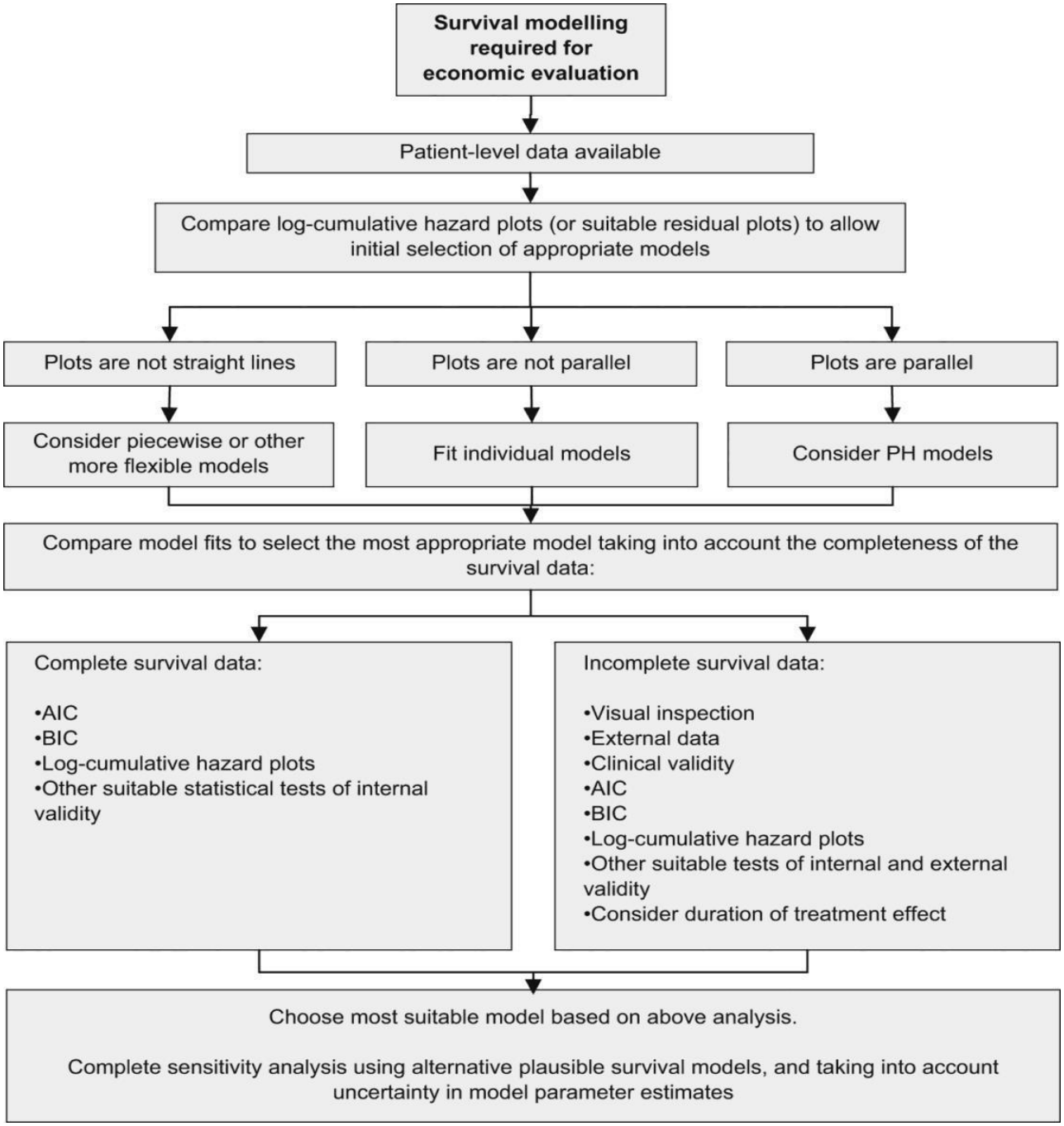
- Weaknesses in the chosen parametric function and/or
- Limitations in the external data source

External data will most likely, only be available for the comparator arm, and will therefore be most useful for evaluating the plausibility of projecting the comparator arm. Therefore, the clinically valid assumptions on the duration of treatment effect will be necessary for extrapolating the effect of the intervention. The assumptions can be sourced from clinical expert statements, evaluation of the mechanism of action and biological plausibility. Different assumptions must be tested in the scenario analyses. The significance of each of these factors in assessing plausibility will depend on the current issue and will vary from case to case.

Algorithm and implementation in the health economic model

The figure below shows the algorithm for selection of a parametric model in time to event data analysis.

Figure 1: Algorithm for selection of a parametric model. From Latimer 2013 (1)



(1) Latimer NR. Survival analysis for economic evaluations alongside clinical trials—extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. Medical Decision Making. 2013;33(6):743-54.