BAST approach to parametric time-to-event (PTTE) modelling.

BAST Inc Limited, Loughborough, UK

12th July 2017

Table of Contents

1. Parametric time-to-event modelling – summary

1.1 Background

Time-to-event (TTE) data is unique because the outcome of interest is not only whether or not an event occurred, but also when that event occurred. Traditional methods of logistic and linear regression are not suitable to include both the event and time aspects. More traditional regression methods also are not equipped to handle censoring, a special type of missing data that occurs in time-to-event analyses when the event of interest is either not observed within the follow-up time (right censoring), or the event is known to have happened between two time points (interval censoring). Special analysis methods for TTE data have been developed to utilize also the partial information of censored data and to provide unbiased survival estimates.

Interesting questions can be addressed when TTE data are analysed properly:

1. How many individuals remain event free after a certain time?
2. What proportion of individuals will have the event after a certain time?
3. What is the risk of an event at a certain time, among those who have survived without event until that point in time?

These questions can be answered with the following functions commonly used in survival analysis:

1. Probability density function (pdf) f(t): The probability of observing an event.
2. Survival function S(t): The probability that an individual will have a survival time T beyond time t [Pr(T> t)].
3. Cumulative distribution function (cdf) F(t): The probability that an individual will have a survival time T less than or equal to t [Pr(T≤ t)].
4. Hazard function h(t): The instantaneous potential of experiencing an event at time t, having survived without event up to that time.

These functions are related via the following equalities:

$$S(t) = \int_t^{\infty} f(u)\, du = 1 - F(t),$$

$$h(t) = \frac{f(t)}{S(t)}$$

There are 3 main approaches to the analysis of TTE data: Non-parametric, semi-parametric and parametric approaches. A common example of a non-parametric approach is the Kaplan Meier (KM) estimator. The Cox proportional hazard model applies a semi-parametric approach to modelling TTE data. It is frequently used in drug development to explore exposure-response relationships [1]. A strength of the Cox-proportional approach is the speed with which many covariate factors can be evaluated simultaneously, resulting in each factor's contribution to the hazard [2].

The approach presented in this guiding document is built on parametric models, which have the advantage over non- and semi- parametric approaches that hazard models of competing risks can be woven together into realistic simulations of the possible outcomes of a clinical

trial of a certain design. Possible questions that can be explored through simulations of competing risks include e.g.:

- How many patients will still be treated in each arm of the study two years after its start?
- What proportion of patients in treatment arm X will have had adverse events of type Y and grade ≥3 two years into the study?
- What would be the benefit/risk of patients after two years of treatment if the exposure of drug X was changed by using a relaxed dosing schedule?

The central assumption of the parametric approach is that the probabilities follow pre-defined distributions. The flip side is that an incorrect choice of the underlying probability density function can introduce bias. Well-established probability distributions are: exponential, Gompertz, Weibull, Lomax, and log-logistic.

For an exponential distribution we have:

Probability density function: $f(t) = \lambda e^{-\lambda t}$, with $\lambda > 0$

Cumulative distribution function: $F(t) = 1 - e^{-\lambda t}$

Survival function: $S(t) = e^{-\lambda t}$

Hazard function: $h(t) = \lambda$

The choice of the best probability function is typically guided by maximum likelihood estimation. Care should be taken that the underlying cumulative distribution function equals one as $t \to \infty$.

1.2 Analysis of competing risks

The design of clinical trials and the definitions of outcomes are currently tailored to the limitations of traditional non-parametric and semi-parametric analysis methods. However, more advanced methods exist that allow the investigation of outcomes that are the results of several types of events. Special methods are needed for the analysis of competing risks, and it has been shown that analysing each event separately can lead to bias [3]. Competing risks analysis utilizes the cumulative incidence method, in which the overall event probability at any time is the sum of the event-specific probabilities [4].

Within a certain study, event times may or may not compete with one another. For example, an adverse event X of grade 2 and anther adverse event Y of grade 3 would not be competing events. On the other hand, time to death from tumour progression, time to death due to another cause, and time to withdrawal from the study are indeed competing events. In order to simulate realistic and meaningful study outcomes competing risks models must be employed.

2. The PTTE modelling approach

2.1 Overview

The methodology presented here can be applied to a mixture of competing and non-competing events, and the influence of covariates on the hazard of certain events can be investigated. The sequence of the typical modelling tasks will be explained. We start with a "NONMEM ready" data file consisting of 4 different timed event types and 6 covariates in a hypothetical population of 200 patients. We identify base models for each event type before going on to testing the covariates. Various plots for visual predictive checks (VPC) will qualify the models.

2.2 Data

2.2.1 Data overview

Data for a single study were simulated, containing time-to-event records for 200 patients. Four event types were included: two pairs of two event types which are competing with each other. For the purposes of this analysis, we call them event 1, event 2, competing event 1, and competing event 2. The exact times that patients had either event 1 or competing event 2 are known; however, for event 2 and competing event 1, the exact times of the events are not known and they are assumed to occur between a patient's assessment visits. Table 2-1 provides a summary of the simulated data.

Table 2-1: Summary of data

Event type	Other event type(s) that compete	Number of patients with event[#]	% of total
Event 1	Competing event 1 and Competing event 2	76	38%
Event 2	Competing event 1 and Competing event 2	104	52%
Competing event 1	Competing event 2	36	18%
Competing event 2	Competing event 1	142	71%

[#] 200 patients in total minus the number of patients with an event equal the number of patients which were right-censored.

2.2.2 Covariates

The following covariates were included in the data file:

1. Patient's age in years,
2. Baseline neutrophil count ($/mm^3$),

3. Number of pre-treatments,
4. Diameter of largest lesion (mm).
5. AUC of drug treatment given within the first week (ug·h/L)
6. Cmax of drug treatment given after the first dose (ug/L)

2.3 Methods

PTTE model development was conducted using maximum likelihood estimation with NONMEM software (ICON Development Solutions, version 7.3).

2.3.1 Base models

The following distributions were tested as base models for each event type:

$$Exponential: h(t) = \lambda$$

$$Gompertz: h(t) = \lambda \cdot exp(\alpha \cdot t)$$

$$Weibull: h(t) = \lambda \cdot exp((\alpha - 1) \cdot \ln(t))$$

$$Lomax: h(t) = \frac{\lambda}{\alpha + t}$$

$$Log - logistic: h(t) = \frac{\alpha \cdot \lambda^{\alpha} \cdot t^{\alpha-1}}{1 + \lambda^{\alpha} \cdot t^{\alpha}}$$

$$Log - normal: h(t) = \frac{f(t)}{1-F(t)}, \qquad f(t) = \frac{1}{t \cdot \lambda \cdot \sqrt{2\pi}} e^{-\frac{\left(\log\left(\frac{t}{\alpha}\right)\right)^2}{2 \cdot \lambda^2}}, \qquad F(t) = \frac{1}{2} + \frac{1}{2} \cdot \mathrm{erf}\left[\frac{\log\left(\frac{t}{\alpha}\right)}{\sqrt{2}\lambda}\right]$$

Where "t" is the time in days since the beginning of treatment. The unknown parameters, λ and α, in the above equations were estimated using maximum likelihood. Working with each candidate hazard function in turn, the hazard function *h(t)* was integrated from zero to the time of each observed event (*T*), giving the cumulative hazard *H(T)* for each event. The contribution of an event to the total likelihood is given by:

$$likelihood\ contribution\ of\ an\ event = h(T) \cdot \exp(-H(T))$$

When the end of the observation period (*T*) of a particular patient was reached before an event was observed, that particular situation constituted a censoring event, and the likelihood contribution was calculated using:

$$likelihood\ contribution\ of\ a\ censoring\ event = \exp(-H(T))$$

The diagnosis of event 2 or competing event 1 was only possible at a patient's assessments which were spaced at regular time intervals. For example, if a patient was assessed with no sign of event 2 after 60 days on treatment and subsequently was diagnosed with event 2 at 120 days, then event 2 must have occurred at some time between 60 and 120 days. This is known as interval censored data, and the likelihood contribution was calculated as follows:

$$likelihood\ contribution\ of\ an\ interval\ censored\ event$$

$$= \exp\left(-H(T_{PrevVisit})\right) - \exp\left(-H(T_{ObsVisit})\right)$$

where $T_{ObsVisit}$ is the time of the assessment when event 2 was observed and $T_{PrevVisit}$ is the time of the previous assessment.

NONMEM estimates the unknown parameter values in the hazard function by maximising the sum of all likelihood contributions with respect to the parameter values. This process corresponds to determining the parameter values within the hazard function that have the greatest probability of producing the observed distribution of event times.

In general, for any base model to be accepted it had to satisfy the following basic acceptance criteria:

1) The value of the objective function should converge successfully to a minimum along with a successful covariance step.
2) The absolute values of the gradients in the last iteration should be all smaller than 10 and greater than 10^{-6}.
3) The number of significant digits of parameter estimates should be ≥ 3.
4) The correlation between parameter estimates in the correlation matrix of the model output should be ≥ -0.95 and ≤ 0.95.
5) The ratio of maximum/minimum eigenvalues of the correlation matrix of the parameter estimates should be ≤ 1000.
6) The standard error of each parameter estimate provided by the covariance step should be less than 50% of the estimated parameter value. This implies that zero is excluded from the 95% confidence interval of the parameter estimate (assuming normality).

The comparison of structurally different base hazard models necessitated the calculation of the Akaike Information Criterion (AIC):

$$AIC = OFV_{model\ A} - OFV_{model\ B} + 2(n_{model\ A} - n_{model\ B})$$

where n_{modelA} and n_{modelB} denote the number of model parameters, and $OFV_{\text{model A}}$ and $OFV_{\text{model B}}$ the objective function values of model A and B, respectively. Model A was considered statistically superior to model B if AIC<0. The selection of the base hazard model on the basis of AIC was further supported by the subjective evaluation of a graphical display of the candidate models in comparison with a Kaplan-Meier plot of the observed event data.

Note: The BAST survival function "Models_summary" in BAST_surv_funtions.R was used during base model selection.

2.3.2 Covariate models

Once acceptable base models had been identified for describing the hazards of each of the four event types, the 6 covariates were tested for influence on each hazard function according to the formula:

$$h_{cov}(t) = \gamma \cdot h(t), \quad \gamma = \exp\left(\gamma_1 \cdot (COV - \overline{COV})\right),$$

Where COV is the covariate of interest, $\overline{COV}$ is the median value over all patients and γ_1 is a parameter to be estimated.

The structures of all covariate models were nested with respect to the corresponding base models; i.e. fixing of the additional parameter in a covariate model to its null value reduced the model to the corresponding base model. Such pairs of expanded and reduced models were compared by a likelihood ratio test where the difference in the objective function value (ΔOFV) follows the χ^2-distribution with k degrees of freedom, where k is the difference in the number of estimated parameters in the expanded and the reduced model.

During modelling, each covariate was tested in univariate models; each univariate model was then ranked by the largest change in OFV (ΔOFV). The strongest covariate (largest ΔOFV) was then retained in the hazard model and the second strongest covariate was added by introducing a multiplicative factor depending on the covariate as shown above. The ΔOFV compared to the base model determined if also the second covariate was retained. A significance level of $p<0.01$ was required for selection of the covariate model at each stage. Following the χ^2-distribution with k degrees of freedom, this corresponds to a $\Delta OFV \leq -6.6$ for k=1, -9.2 for k=2 and so on.

As for the base model, the final covariate model had to satisfy the following acceptance criteria:

1) The value of the objective function should converge successfully to a minimum along with a successful covariance step.
2) The absolute values of the gradients in the last iteration should be all smaller than 10 and greater than 10^{-6}.
3) The number of significant digits of parameter estimates should be ≥ 3.
4) The correlation between parameter estimates in the correlation matrix of the model output should be ≥ -0.95 and ≤ 0.95.
5) The ratio of maximum/minimum eigenvalues of the correlation matrix of the parameter estimates should be ≤ 1000.
6) The standard error of each parameter estimate provided by the covariance step should be less than 50% of the estimated parameter value. This implies that zero is excluded from the 95% confidence interval of the parameter estimate (assuming normality).

2.3.3 Model validation by visual predictive checks (VPC)

It was recognised that the use of Kaplan-Meier displays was not ideal for the qualification of the covariate influences in a parametric hazard model, and simulations of competing risks were summarised instead in a new visual predictive check (VPC) which was stratified according to the value of the influencing covariate.

For each event type and its competing event type, sets of 1000 event times were simulated: For each of the 200 patients, the hazard functions (with inclusion of covariate information as required by the model) were first numerically integrated to generate the survival functions. Since each survival function follows a uniform distribution on the interval from 0 to 1, an event time can be determined by taking random draws from the uniform distribution between

0 and 1 and finding the time at which the survival function becomes less than or equal to the sampled random draw. The outcome of each patient was the event or competing event with the earliest simulated event time. If the event type of interest is simulated at a time before any competing event type, its time is counted in pre-selected time bins. If the event type of interest is simulated after a competing event type then the event type is right-censored at the time of the simulated competing event.

Two types of VPC were produced:

1. Cumulative VPC: The y-axis was calculated as the number of simulated patients (with 90% confidence interval) that experience an event before bin time *t.* These were plotted together with the event counts from the observed data.
2. Discrete VPC: For this VPC, the number of patients that experienced an event *between* the various bin times was used. This gave a slightly different assessment of the model that focused more on specific time intervals instead of the overall event count.

For the interval censored events (event 2 and competing event 1) the time of each simulated event was shifted to the time of the next scheduled assessment for that patient. This allowed a realistic simulation of the interval censored events so that the model simulation output could be compared to the data.

In order to determine whether the model had identified covariate relationships correctly, stratified VPCs were produced by splitting the patients into two groups according to their covariate value being above and below the population median. The predicted and observed event rates within the stratified patient groups were then compared in a single VPC plot. This was done for each VPC type.

The following functions in the BAST survival analysis functions (BAST_surv_functions.R) were used in the creation of the VPCs:

- *Hazard() – Returns the hazard function based on input label and parameters.*
- *CumHaz() – Calculates cumulative hazard.*
- *IntHaz() – A wrapper for Hazard() and CumHaz() for calculating survival curves.*
- *Sim_events() – Calculates a set of events and survival curves for each patient.*
- *Repeated_sim_events() – Produces replicate simulated events for each patient.*
- *adjust_repeat_events_to_appointment_times() – Adjusts the event times to the next assessment time for each patient.*
- *CompeteEvents() – Carries out analysis of competing events leading to an adjustment of simulated events to give realistic results.*
- *calcEventVPC() – Calculates the VPC data to be used for plotting both types of VPC.*
- *plotEventVPC() – Plots both types of VPC.*

2.4 Results

2.4.1 Base models

The six base models were compared to the Kaplan-Meier (KM) survival function of the event data.

The base model selection was done using the BAST survival function Models_summary().

Event 1

Testing of the various parametric models resulted in an exponential distribution being chosen as a base model. Figure 2-1 gives an overview of the different candidate distributions together with a plot of the KM survival function of the event data.

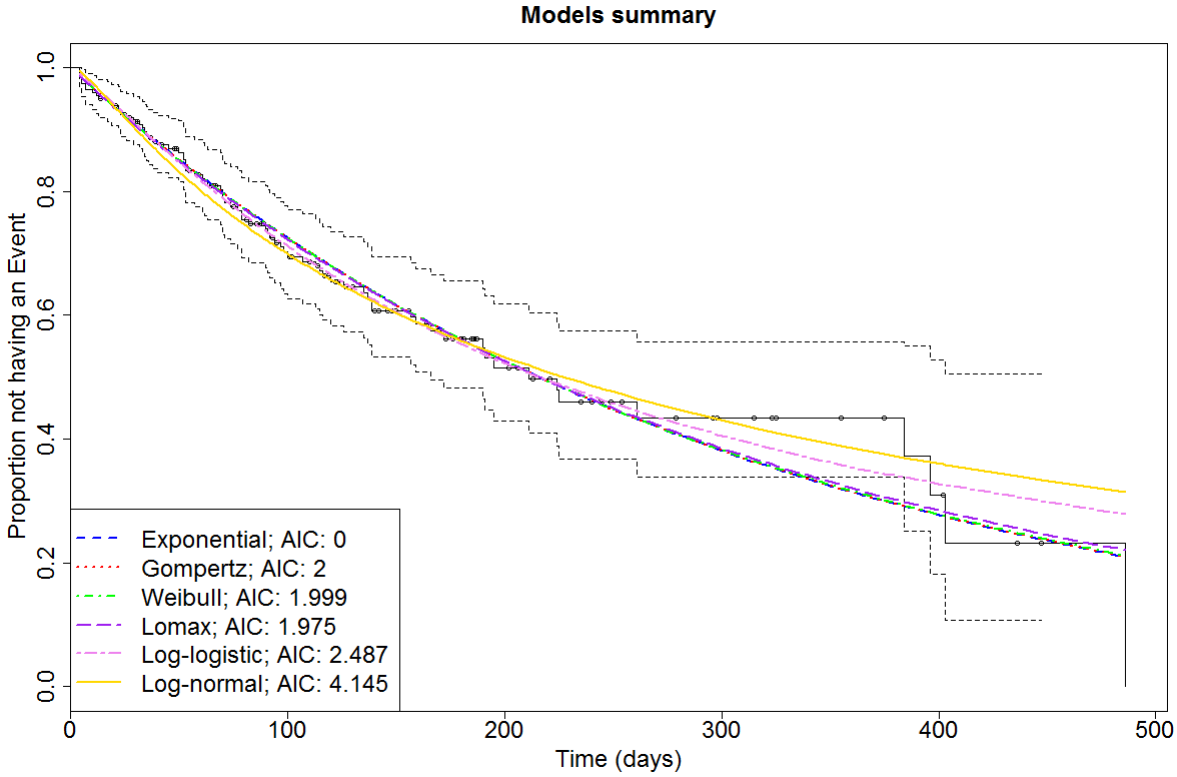

Figure 2-1: Overview of candidate distributions compared to the KM plot of Event 1.

Event 2

Testing of the various parametric models resulted in a Gompertz distribution being chosen as a base model. Figure 2-2 gives an overview of the different candidate distributions together with a plot of the KM survival function of the event data. Note the characteristic step-like nature of the KM function derived from the observed data due to the interval censoring. This interval-censoring has been accounted for during model inference. However, the base model

visualisation in Figure 2-2 displays survival functions of the inferred base models in the scenario where the event can be observed at any point in time rather than only at assessment visits. (The VPC simulations are more thorough such that simulated event times are withheld until the time of the next assessment).

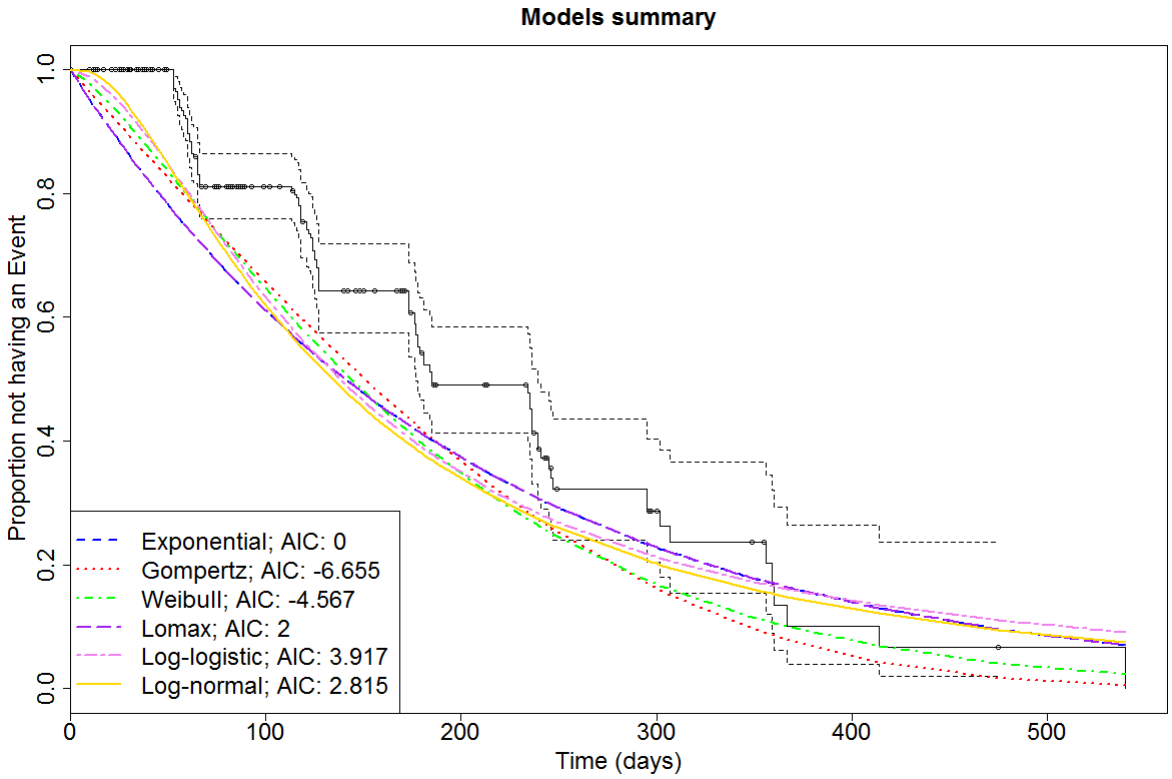

Figure 2-2: Overview of candidate distributions compared to the KM plot of Event 2.

Competing Event 1

Testing of the various parametric models resulted in a log-normal distribution being chosen as a base model. Figure 2-3 gives an overview of the different candidate distributions together with a plot of the KM survival function of the event data. Again the characteristic pattern of interval-censored data is evident.

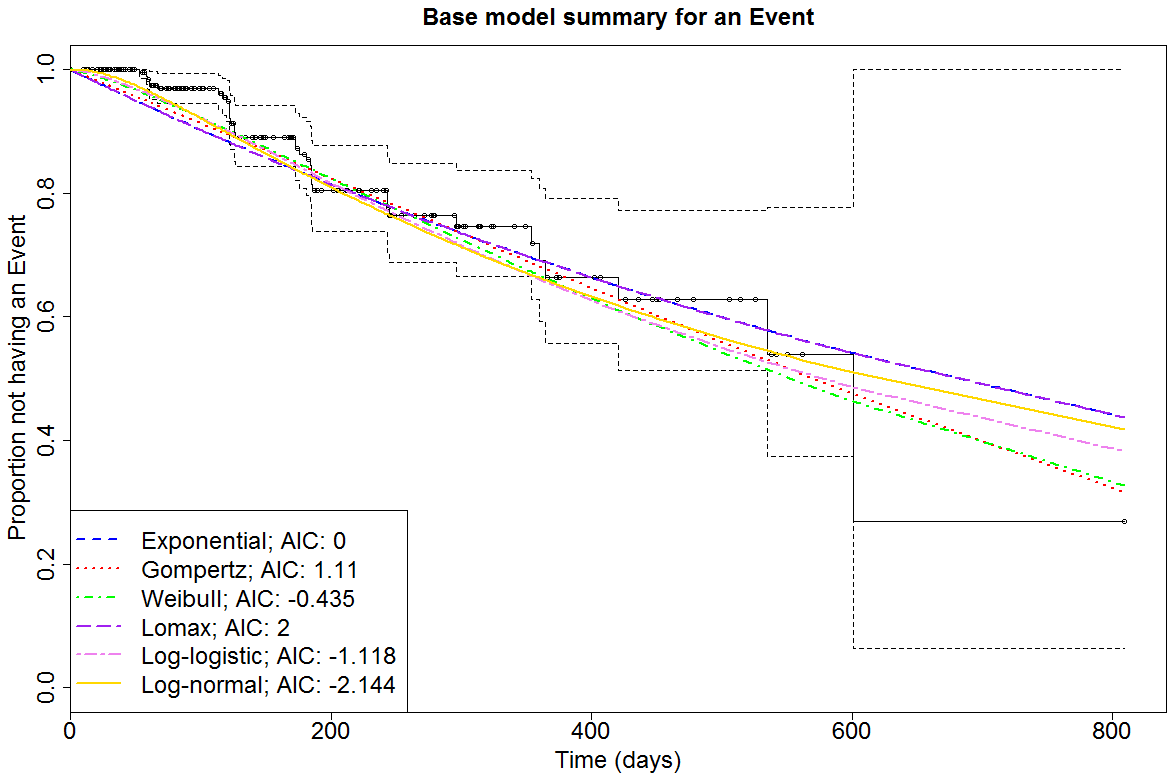

Figure 2-3: Overview of candidate distributions compared to the KM plot of Competing Event 1.

Competing Event 2

Testing of the various parametric models resulted in a log-normal distribution being chosen as a base model. Figure 2-4 gives an overview of the different candidate distributions together with a plot of the KM survival function of the event data.

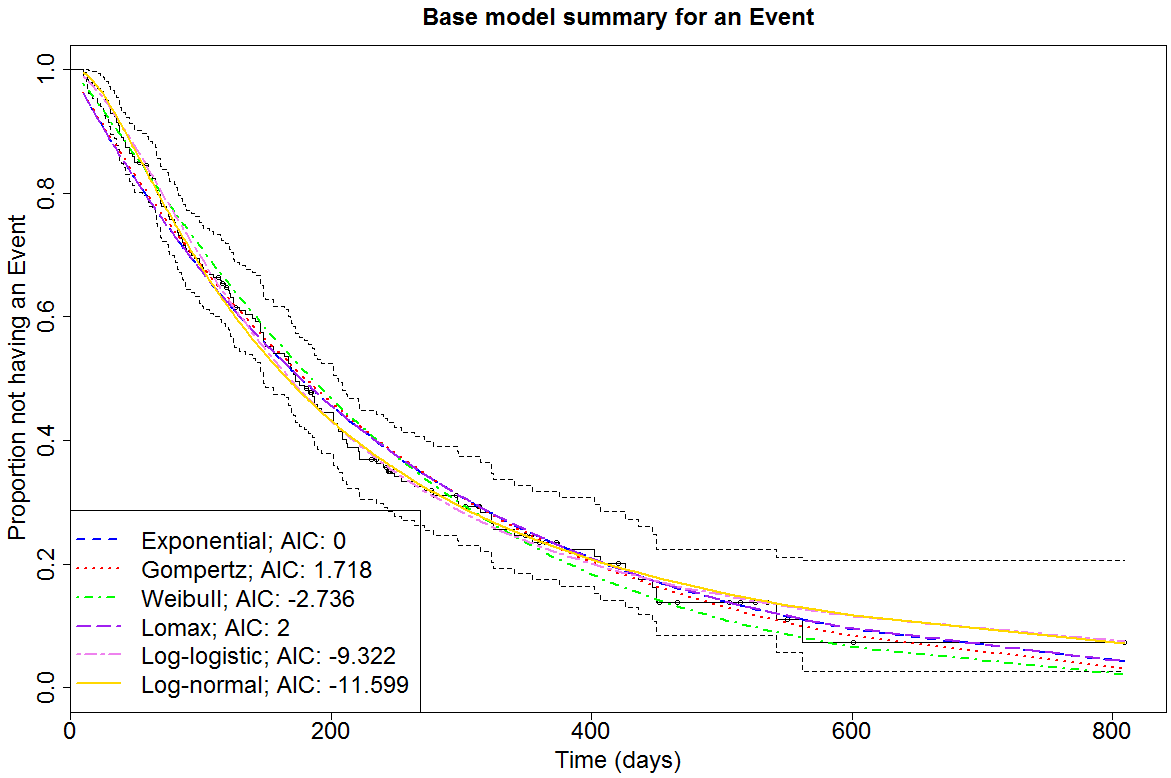

Figure 2-4: Overview of candidate distributions compared to the KM plot of Competing Event 2.

2.4.2 Covariate models

Event 1

Testing of the 6 covariates on the selected base model for Event 1 resulted in both age and baseline neutrophil count being found significant. Age was then retained and baseline neutrophil count was also tested, giving an OFV drop of -22.69 and so was selected as a final model. Table 2-2 shows the results of the covariate modelling.

The result file of the final selected model run is runEV1_201.res.

Table 2-2: Results of covariate modelling for event 1.

Covariate model number	Covariate	ΔOFV
EV1_101	Age	-16.39
EV1_102	Baseline neut. count	-7.6
EV1_103	No. of pre-treatments	-0.6
EV1_104	Max. lesion size	-4.1
EV1_105	1st week AUC	-0.21
EV1_106	1st dose Cmax	-4.01
EV1_201	Age + base neut. count	-22.69

Both cumulative and discrete type VPCs were created in order to assess model bias (Figure 2-5, Figure 2-6, Figure 2-7 and Figure 2-8). Due to two covariates being in the final model, two sets of VPCs were created with the first stratified by patient age above (CAT=1) and below (CAT=0) the median, and the second stratified by baseline neutrophil count above and below the median.

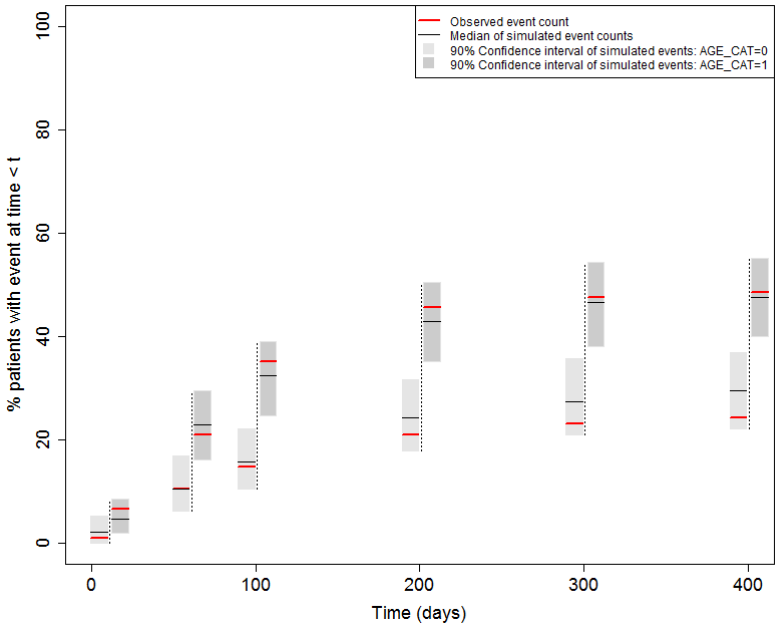

Figure 2-5: Cumulative VPC for Event 1, stratified by patient age.

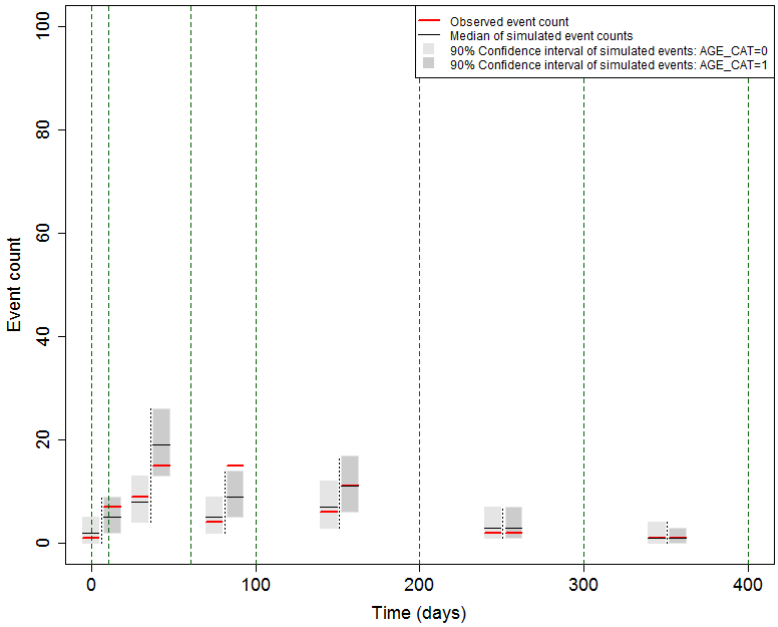

Figure 2-6: Discrete VPC for Event 1, stratified by patient age.

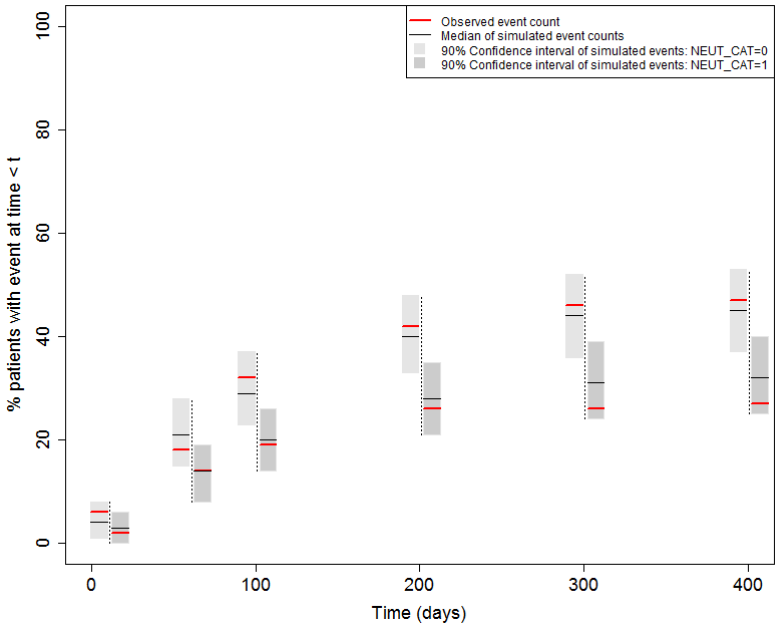

Figure 2-7: Cumulative VPC for Event 1, stratified by patient baseline neutrophil count.

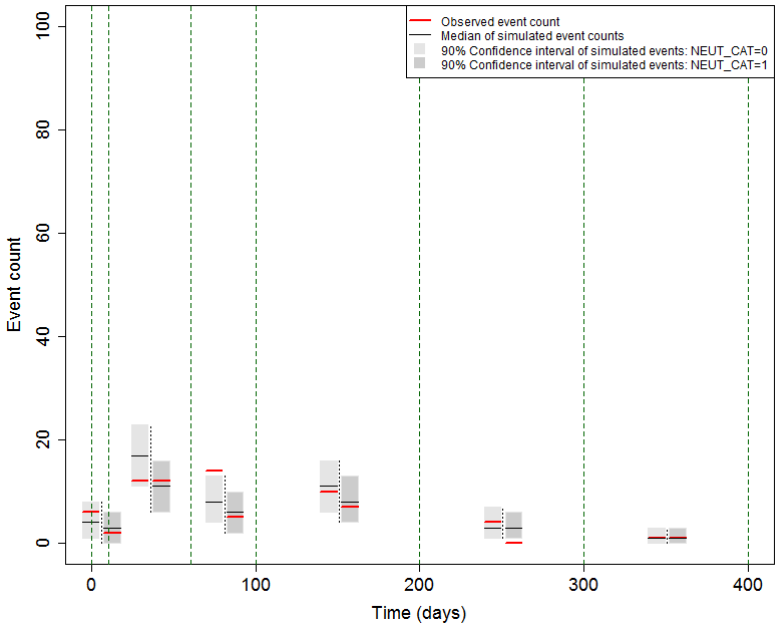

Figure 2-8: Discrete VPC for Event 1, stratified by patient baseline neutrophil count.

In general, the VPCs show a satisfactory fit and absence of bias for the final model for Event 1. The stratification of the VPCs clearly show the model's ability to explain the event rate within patient sub-groups defined by their covariate values being below and above the median of baseline neutrophil count and age.

Event 2

Testing of the 6 covariates on the selected base model for Event 2 resulted in AUC of the first week of treatment being found significant; giving an OFV drop of -9.775 and so was selected as a final model. Table 2-3 shows the results of the covariate modelling.

The result file of the final selected model run is runEV2_105.res.

Table 2-3: Results of covariate modelling for event 2.

Covariate model number	Covariate	ΔOFV
EV2_101	Age	-0.18
EV2_102	Baseline neut. count	-0.17
EV2_103	No. of pre-treatments	-0.07
EV2_104	Max. lesion size	-0.08
EV2_105	1st week AUC	-9.775
EV2_106	1st dose Cmax	-0.19

Both cumulative and discrete type VPCs were created in order to assess model bias (Figure 2-9 and Figure 2-10). Patients were stratified by their 1st week AUC, where CAT=0 is below median AUC and CAT=1 is above median AUC.

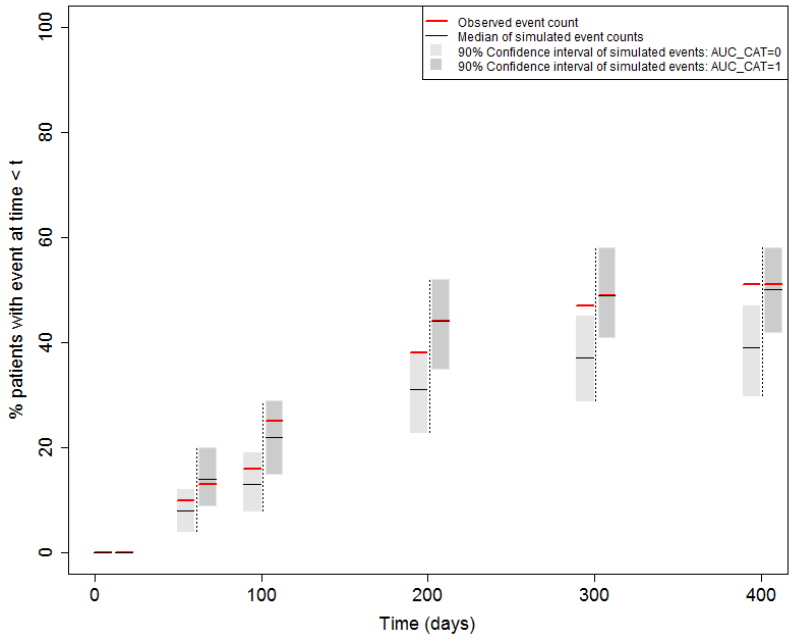

Figure 2-9: Cumulative VPC for Event 2, stratified by 1st week AUC.

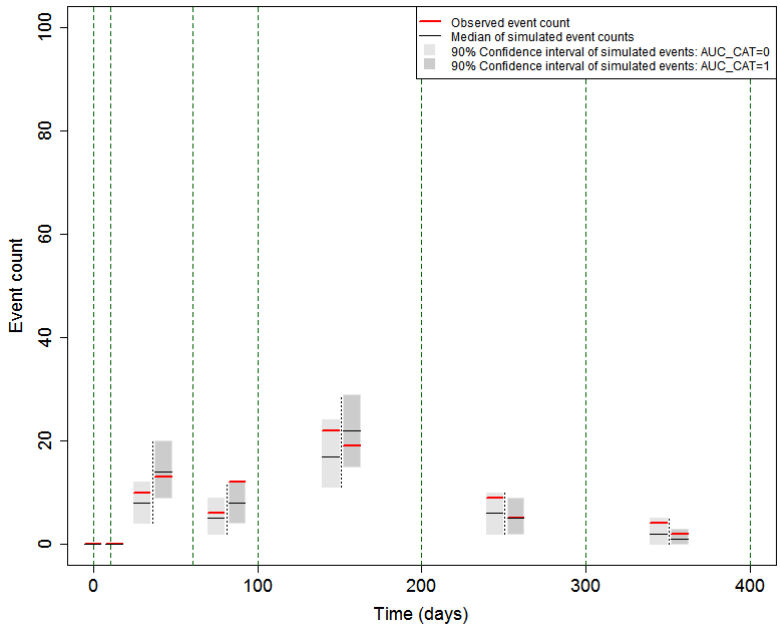

Figure 2-10: Discrete VPC for Event 2, stratified by 1st week AUC.

In general, the VPCs show a satisfactory fit of the data. However, the model appears to underestimate the event rate for those patients with a first week AUC less than the median. Identifying such model weaknesses is one of the benefits of stratified VPCs. The discrete VPC identifies the time (about 100 days after start of treatment) when the covariate influence on the event rate is reversed. Such granularity cannot be derived from a ΔOFV alone.

Competing Event 1

Testing of the 6 covariates on the selected base model for Competing Event 1 resulted in patient age being found significant; giving an OFV drop of -14.822 and so was selected as a final model. Table 2-4 shows the results of the covariate modelling.

The result file of the final selected model run is runCOMPEV1_101.res.

Table 2-4: Results of covariate modelling for competing event 1.

Covariate model number	Covariate	ΔOFV
COMPEV1_101	Age	-14.822
COMPEV1_102	Baseline neut. count	-0.106
COMPEV1_103	No. of pre-treatments	-0.698
COMPEV1_104	Max. lesion size	-0.255
COMPEV1_105	1st week AUC	-0.01
COMPEV1_106	1st dose Cmax	-0.1

Both cumulative and discrete type VPCs were created in order to assess model bias (Figure 2-11 and Figure 2-12). Patients were stratified by patient age, where CAT=0 is below median age and CAT=1 is above median age.

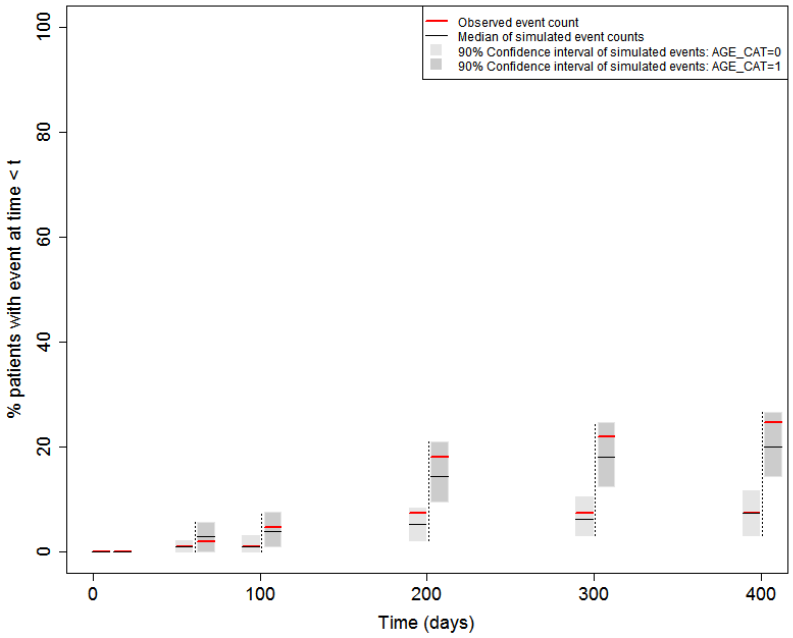

Figure 2-11: Cumulative VPC for Competing Event 1, stratified by patient age.

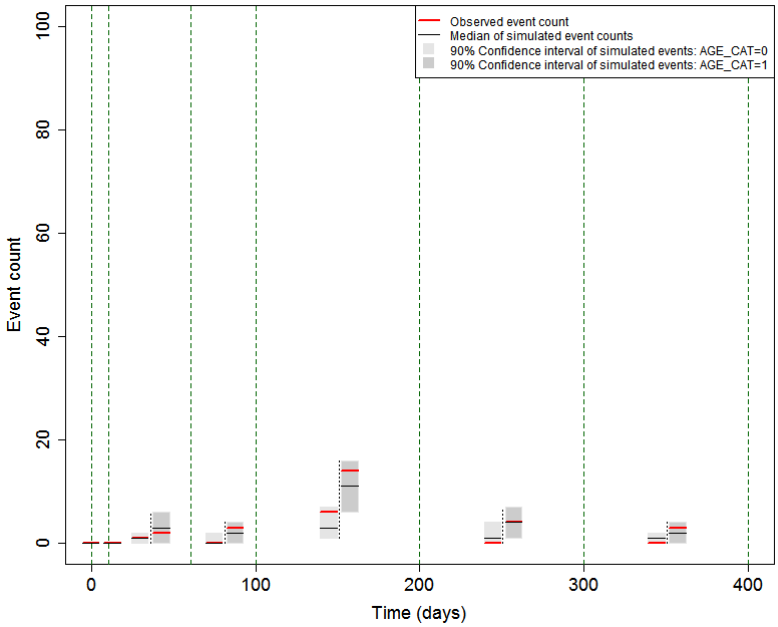

Figure 2-12: Discrete VPC for Competing Event 1, stratified by patient age.

The VPCs show a satisfactory fit of the data, within patient sub-groups defined by their covariate values being below and above the median age.

Competing Event 2

Testing of the 6 covariates on the selected base model for Competing Event 2 resulted in no covariate being found significant. Table 2-5 shows the results of the covariate modelling.

The result file of the final selected model run is runCOMPEV2_005.res.

Table 2-5: Results of covariate modelling for competing event 2.

Covariate model number	Covariate	ΔOFV
COMPEV2_101	Age	-2.705
COMPEV2_102	Baseline neut. count	-3.145
COMPEV2_103	No. of pre-treatments	-0.232
COMPEV2_104	Max. lesion size	-0.441
COMPEV2_105	1st week AUC	-3.81
COMPEV2_106	1st dose Cmax	-0.793

Both cumulative and discrete type VPCs were created in order to assess model bia. No stratification was required.

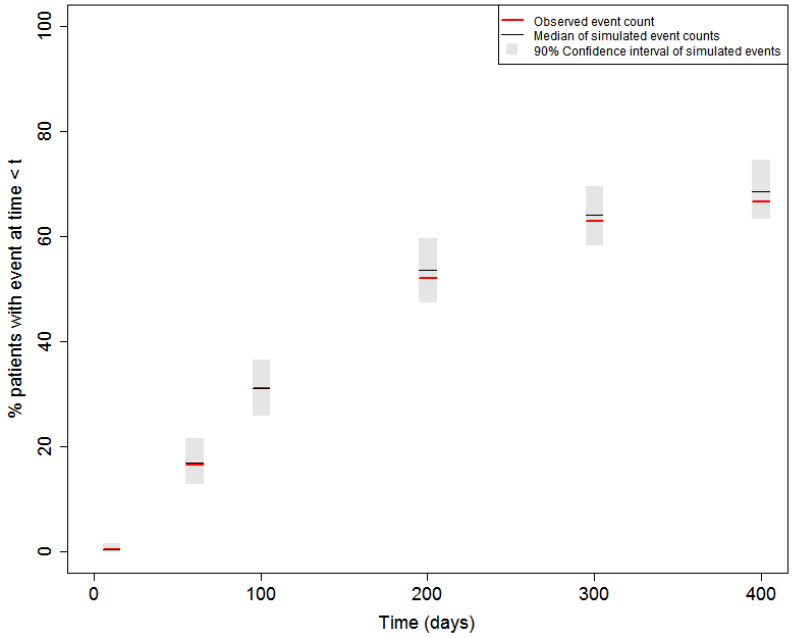

Figure 2-13: Cumulative VPC for competing event 2.

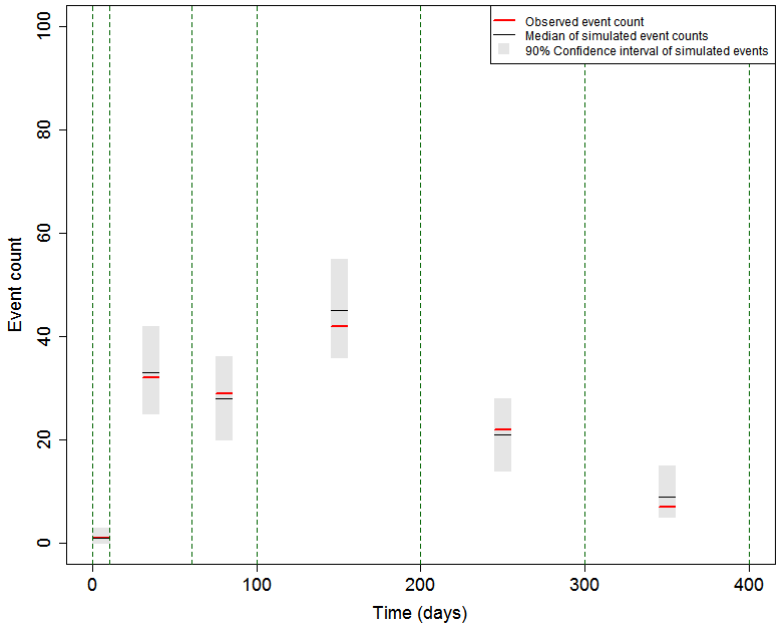

Figure 2-14: Discrete VPC for competing event 2.

Figure 2-13 and Figure 2-14 show the VPCs for Competing Event 2. The VPCs show a satisfactory fit of the data without bias.

2.5 A comment on the suitability of KM plots to identify covariate influences

The KM estimator provides a graphical display of the survival without an event in an imaginary world which is only threatened by the risk of a single event. The world of clinical trials is, however, different. The VPC scripts which are discussed here produce displays that can take into account several competing risks. It is during simulation of trial outcomes that knowledge of the specific competing risks is required (for parameter inference one does not need to know exactly what competing risks are present).

There is an option in the BAST survival analysis function, calcEventVPC(), which allows the user to simulate events without competing risks.

Figure 2-15 shows a VPC without competing risks for Event 1. We see that although the event rate is initially described fairly accurately, later on there is a dramatic over-estimation of the event rate when compared to the observed events. This is because in reality many of the simulated events of type 1 cannot be observed as they are preceded by events from the Competing Events types 1 or 2.

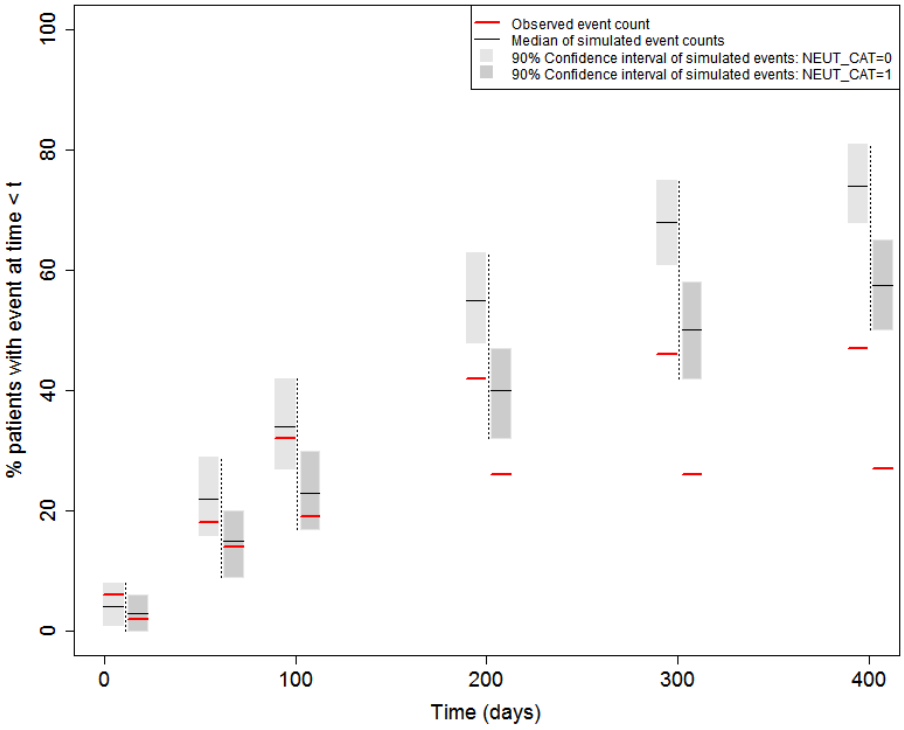

Figure 2-15: Stratified VPC of Event 1 without considering competing risks.

It is imperative to consider all competing risks whenever any predictive simulation work is done. Failure to do so could result in a dramatic over-estimation of the event rate. The extent of this over-estimation is best shown through an illustrative example.

Example:

Consider a simple scenario where there are two competing events:

1. Time to response,
2. Time to grade 4 adverse event causing patients to leave the study (competing event).

Patients are given 50mg a week IV infusions on a bi-weekly dosing schedule. Modelling shows that there is a relationship between drug exposure and the time to both event types, with higher exposure being related to higher event rates. Simulations of the number of patients with a response within the first year of treatment with a higher dose of 80mg/week are performed, both with and without considering competing events. The outcomes of these simulations are compared in terms of number of responders. Table 2-6 illustrates the bias of failing to account for competing events: although higher exposure increases the response rate, it increases even more the rate of grade 4 adverse events that causes patients to withdraw.

Table 2-6: Illustrative example of simulating events with and without competing events.

Number of responders in the study - (50mg/week)	75
Simulated median number of responders – (80mg/week, competing events considered)	71
Simulated median number of responders – (80mg/week, no competing events considered)	86

3. Reference list

1. Wang, X. *et al.* Quantitative Characterization of the Exposure–Response Relationship for Cancer Immunotherapy: A case ctudy of nivolumab in patients with advanced melanoma. CPT: Pharmacometrics Syst Pharmacol. 2017 Jan; 6(1): 40-48.
2. Bender, R., Augustin, T., and Blettner, M. Generating survival times to simulate Cox proportional hazards model. Statist. Med. 2005; 24:1713-1723.
3. Putter, H., Fiocco, M. and Geskus, R. B. (2007), Tutorial in biostatistics: competing risks and multi-state models. Statist. Med., 26: 2389–2430. doi:10.1002/sim.2712
4. Haller, B., Schmidt, G. & Ulm, K. Applying competing risk regression models: an overview. Lifetime Data Anal (2013) 19: 33. doi:10.1007/s10985-012-9230-8

A Appendix – Overview of the BAST PTTE modelling package

The BAST PTTE modelling package consists of the following:

1. *Event_data.csv*: An example time-to-event data file consisting of 4 different event types, 2 of which are competing events.
2. *Assessment_times.csv*: A data file of patient assessment times to accompany event_data.csv.
3. NONMEM files used to identify which probability density function fits the data best (base model).
4. NONMEM files used for covariate modelling.
5. A control file automation executable file together with example run tables for fast creation of the NONMEM control files.
6. NONMEM result files of the four final models in this document.
7. An R script containing the BAST survival functions.
8. An R script used to create TTE model VPCs.
9. A guiding document, *BAST_PTTE_modelling.pdf*, for the analysis of *event_data.csv* together with references to the BAST PTTE modelling package.

B Appendix – Commonly used parametric models

For modelling in NONMEM, only the hazard function is required. This section lists the hazard functions in *BAST_surv_functions.R* with their specific parameterisation. The probability density, cumulative distribution, and survival functions are not all shown but can be easily derived or are commonly available in the literature.

Exponential

$$h(t) = \lambda, \qquad \lambda > 0.$$

Gompertz

$$h(t) = \lambda \cdot \exp(\alpha \cdot t), \qquad \lambda, \alpha > 0.$$

Weibull

$$h(t) = \lambda \cdot \exp((\alpha - 1) \cdot \log(t + \Delta)), \qquad \lambda, \alpha > 0, \qquad \Delta = 10^{-8}.$$

Lomax

$$h(t) = \frac{\lambda}{\alpha + t}, \qquad \lambda, \alpha > 0.$$

Log-logistic

$$h(t) = \frac{\alpha \cdot \lambda^{\alpha} \cdot (t+\Delta)^{\alpha-1}}{1 + \lambda^{\alpha} \cdot (t+\Delta)^{\alpha}} \qquad \lambda, \alpha > 0, \qquad \Delta = 10^{-8}.$$

Log-normal

$$h(t) = \frac{f(t)}{1 - F(t)},$$

where,

$$f(t) = \frac{1}{(t+\Delta) \cdot \lambda \cdot \sqrt{2\pi}} e^{-\frac{\left(\log\left(\frac{t+\Delta}{\alpha}\right)\right)^2}{2 \cdot \lambda^2}},$$

$$F(t) = \frac{1}{2} + \frac{1}{2} \cdot \operatorname{erf}\left[\frac{\log\left(\frac{t+\Delta}{\alpha}\right)}{\sqrt{2}\lambda}\right],$$

$$\lambda, \alpha > 0, \qquad \Delta = 10^{-8}.$$

Here, erf is the Gauss error function and is defined as:

$$\operatorname{erf}(t) = \frac{2}{\sqrt{\pi}} \int_0^t e^{-u^2}\, du.$$

This can be written in NONMEM using the inbuilt "PHI" function that recalls the values of the cumulative distribution function for the normal distribution.

Log-Cauchy

$$h(t) = \frac{f(t)}{1 - F(t)},$$

where,

$$f(t) = \frac{1}{(t+\Delta)\cdot\pi}\left[\frac{\lambda}{\left(\log\frac{t+\Delta}{\alpha}\right)^2 - \lambda^2}\right],$$

$$F(t) = \frac{1}{\pi}\arctan\left(\frac{\log\frac{t+\Delta}{\alpha}}{\lambda}\right) + \frac{1}{2},$$

$$\lambda, \alpha > 0, \qquad \Delta = 10^{-8}.$$

Note: The log-Cauchy distribution can be used to model certain survival processes where significant outliers or extreme results may occur and should thus be tested as a base model when none of the other distributions give a satisfactory fit.