Event prediction in event-driven trials

MedianaDesigner package

1. Introduction

This document provides a description of the statistical methodology used in the event prediction module (EventPred function).

For more information on the MedianaDesigner package, visit the following web pages at

http://www.mediana.us/medianadesigner

http://medianasoft.github.io/MedianaDesigner

2. Event prediction in event-driven trials

2.1. Trial design

Consider a Phase II or Phase III trial with an event-driven design where the timing of decision points (interim and final analyses) is determined based on a pre-defined number of events of interest. Event-driven designs arise when the primary efficacy endpoint is defined as the time to a specific event such as death or disease progression. From an operational perspective, it is important to develop tools for predicting the number of events at a given time point.

A popular method for event forecasting in trials with event-driven designs is presented in this module. This method enables the trial's sponsor to project the number of events at a future time point from blinded trial data. Since event predictions rely on blinded data, the method could be applied by the sponsor (rather than an external organization) and event forecasting could be performed at any point during the trial.

The event prediction methodology based on a Bayesian approach is presented in Section 2.2 and is illustrated in Section 3.

2.2. Event prediction methodology

The event prediction method featured in this module relies on the framework proposed in Bagiella and Heitjan (2001).

Considering a trial with an event-driven design, let t_1 denote the time point at which the blinded data (patient enrollment, times to event or censoring, event and patient dropout indicators) are available and let t_2 denote the time point in the future at which a prediction for the number of

events needs to be computed. The event prediction method makes the following parametric assumptions:

- The time to the event of interest and the time to patient dropout/loss to follow up both follow exponential distributions. Let λ and ν denote the hazard rates for the event and dropout times, respectively.
- The patient enrolment is governed by a homogenous Poisson process and the intensity parameter of this process is denoted by μ.

To enable Bayesian predictions, prior distributions for the three parameters (λ, ν and μ) need to be assumed. It is convenient to assume that each parameter follows a gamma distribution. In particular, let α_λ and β_λ denote the shape and rate parameters of the prior gamma distribution for λ. Since conjugate priors are used, the posterior distributions of the three parameters are easily found as follows. Using λ as an example, the posterior distribution for this parameter is also a gamma distribution with the shape and rate parameters given by

$$\alpha_\lambda + d \text{ and } \beta_\lambda + t,$$

respectively, where d is the total number of events and t is the sum of the observed times to event or censoring at the time point t_1. The posterior distributions for the other two parameters are defined in a similar way, see Bagiella and Heitjan (2001).

A Bayesian prediction for the number events is easy to perform by computing the posterior distributions for λ, ν and μ from the blinded trial data available at t_1 and sampling from these posterior distributions to find the distribution of the number of events at t_2. The mean number of events and a 95% predictive interval are computed from this distribution.

The Bayesian event prediction method is illustrated in Section 3 using a Phase III oncology trial. This section also describes a simple set of rules for selecting the parameters of the prior distributions for λ, ν and μ.

3. Case study

A two-arm Phase III trial for the treatment of colorectal cancer will be used to illustrate the process of applying the event prediction method introduced in Section 2.2. The primary efficacy analysis in this trial focuses on the comparison of overall survival in the two trial arms. A blinded database snapshot that includes the patient enrollment, event and dropout information on 457 patients was taken at 12 months after the study start (the blinded data are included in the data set named EventPredData). The trial's sponsor is interested in predicting the number of events at 18 and 24 months.

The mean event counts with 95% predictive intervals were computed at the two time points using the Bayesian event prediction method. The following rule was applied to select the shape and rate parameters of the prior gamma distributions for the three key parameters (λ, ν and μ). Beginning with the hazard rate for the event times (λ), let λ_0 denote the expected hazard rate (note that the overall hazard rate computed from blinded data is used in this case) and let λ_1 denote the uncertainty parameter. Using the general framework introduced by Herson (1979), the uncertainty parameter of 0.1 defines a high-confidence prior distribution and larger values of this parameter correspond to decreasing levels of confidence, e.g., the uncertainty parameter of 0.5 defines a low-confidence prior distribution. The shape and rate parameters of the prior distribution (α_λ and β_λ) were selected to ensure that the mean of the resulting distribution is equal to λ_0 and the coefficient of variation is equal to λ_1. Assuming that

$$\lambda_0 = \frac{\log(2)}{15} = 0.0462 \text{ and } \lambda_1 = 0.3,$$

which corresponds to a medium-confidence prior, the shape and rate parameters were given by

$$\alpha_\lambda = \frac{1}{\lambda_1^2} = 11.11 \text{ and } \beta_\lambda = \frac{\alpha_\lambda}{\lambda_0} = 240.5.$$

The prior gamma distributions for the other two parameters (ν and μ) were found using a similar approach. The expected median dropout time was assumed to be 80 months, which corresponds to an annual dropout rate of 10%, and the expected patient enrollment rate was set to 35 patients per month. The coefficients of variation for both parameters were equal to 0.3.

The prediction results are summarized in Table 1 and Figure 1. The table presents the mean event counts and 95% predictive intervals at 18 and 24 months whereas the figure depicts the predicted monthly event counts over a longer time period (from 12 to 24 months).

In addition, a simulation study was carried out to assess key characteristics of the event prediction method defined in Section 2.2. Using a setting similar to the one described above, a clinical trial with 900 patients was considered and the times to an event of interest and patient dropout were assumed to be exponentially distributed with the median times of 15 and 100 months, respectively. The 900 patients were assumed to be enrolled in a uniform manner over a 24-month period, i.e., the enrollment rate was 37.5 patients per month. A snapshot of the trial's database was taken at 12 months to predict the number of events at 24 months. The prior distributions for the event and patient dropout hazard rates (λ and ν) as well as the patient enrollment rate (μ) were selected using the rules outlined above. The means of the prior gamma distributions were found assuming the medians of 15 and 80 months for the times to event and patient dropout and the intensity rate of 35 patients per month for the patient enrollment process. The coefficient of variation for all three gamma distributions was set to 0.3, i.e., medium-confidence priors were assumed.

The simulation study relied on 100 simulation runs, i.e., a hundred complete data sets were created with patient enrollment, event and dropout outcomes for the entire 24-month period. For each data set, the average number of events and a 95% predictive interval at $t_2 = 24$ months were computed from the subset extracted at $t_1 = 12$ months. The number of events and 95% predictive interval were obtained based on 1,000 draws from the posterior distributions. A comparison of the actual number of events at 24 months and corresponding 95% interval for the predicted number of events in each simulation run is presented in Figure 1. The actual number of events was covered by the predictive interval 95% of the time in this simulation study, which is consistent with the expectations. The difference between the actual and predicted number event counts was computed in each simulation run. The mean and median differences were 4.6 and 5.1, respectively. Since the mean number of events at 24 months was about 350, these results correspond to a relative precision of about 1.5%.

References

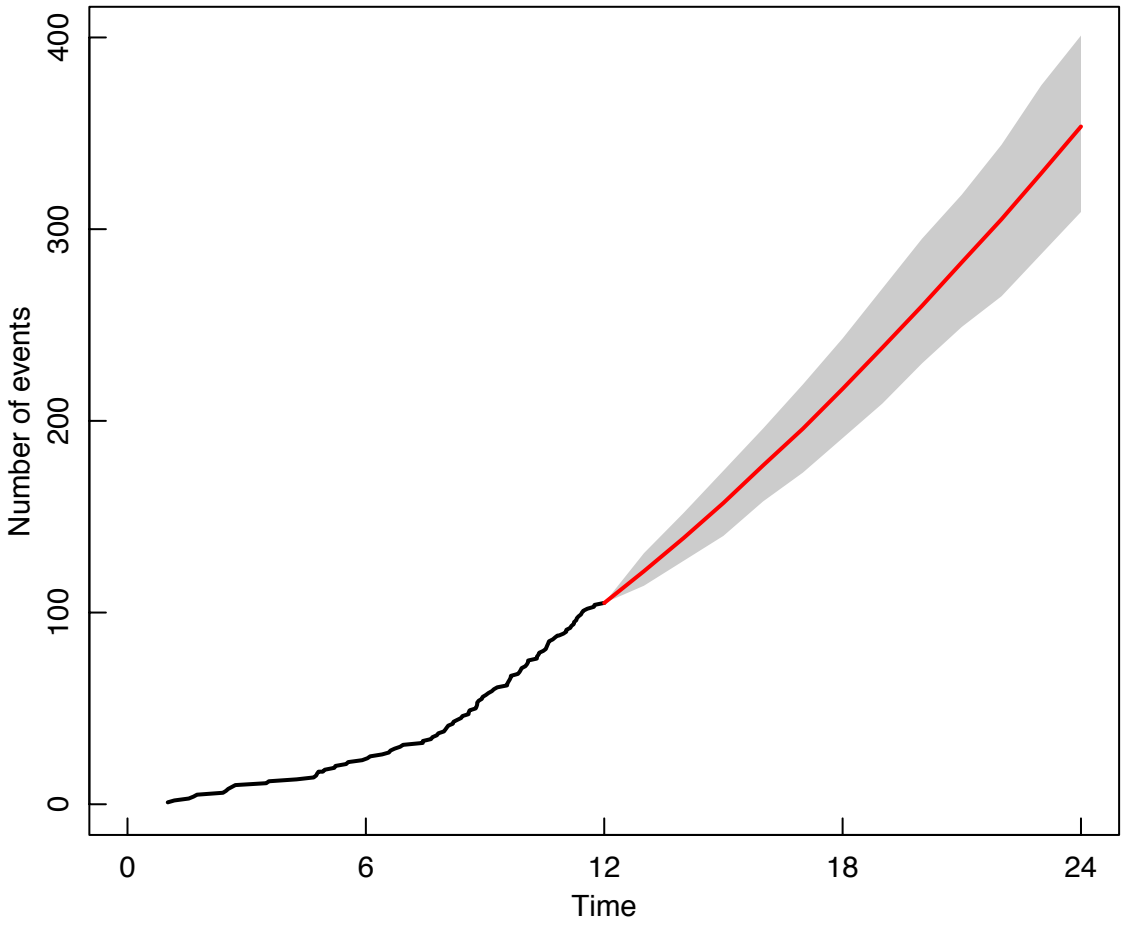
Bagiella, E., Heitjan, D.F. (2001). Predicting analysis times in randomized clinical trials. Statistics in Medicine. 20, 2055-2063.

Herson, J. (1979). Predictive probability early termination plans for Phase II clinical trials. Biometrics. 35, 775-783.

Table 1. Event prediction at 18 and 24 months in the Phase III oncology trial

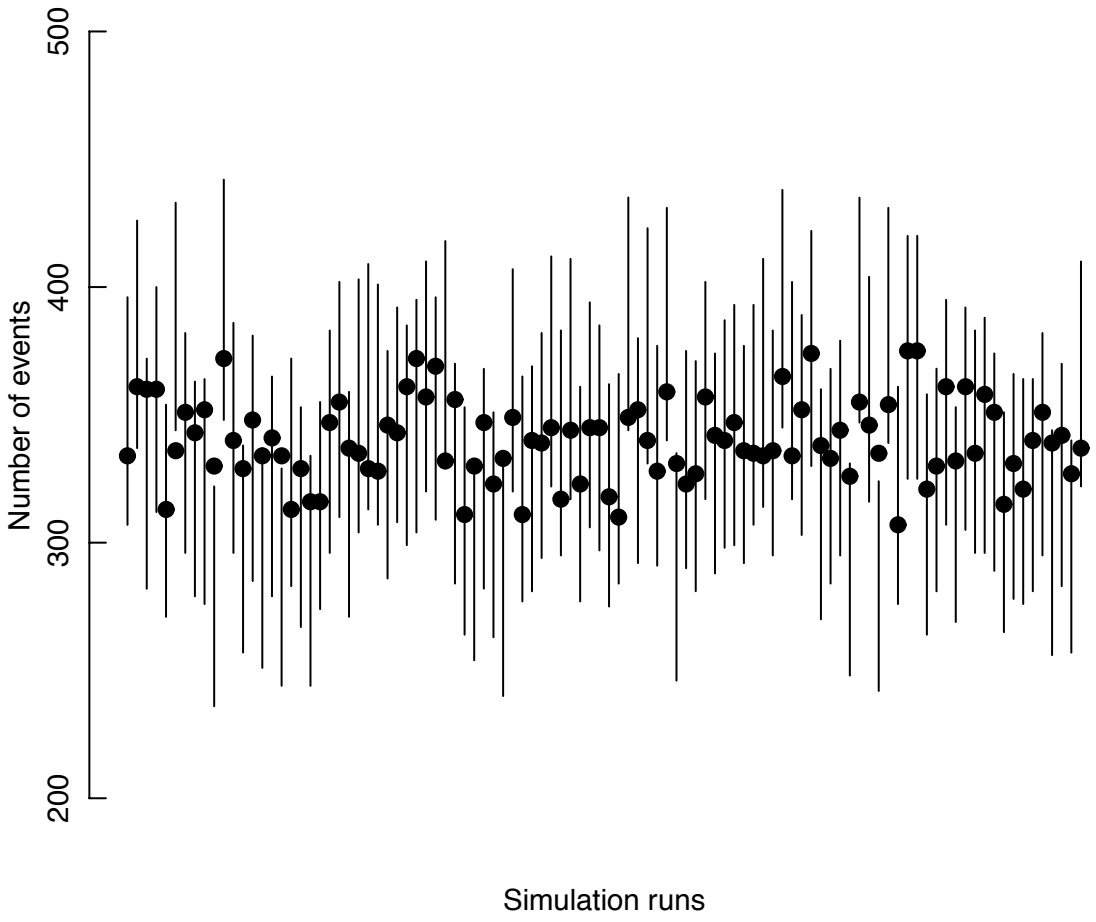
Time point	Average number of events	95% predictive interval
18 months	216.7	(191, 243)
24 months	353.5	(309, 401)

Figure 1. Event prediction in the Phase III oncology trial



Black curve: Observed events. Red curve: Predicted mean number of events. Gray band: 95% predictive interval.

Figure 2. Comparison of actual and predicted event counts in a simulation study



Dots: Actual event counts in each simulation run. Intervals: 95% predictive intervals in each simulation run.