Correction to Derivation of Sample Size Requirements for Evaluating Heart Valves with Constant Risk Events

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To show a satisfactory performance of a new heart valve in a non-randomized clinical study, the complication rates of the new device are statistically compared to the past-experience values listed in the FDA Draft Replacement Heart Valve Guidance [2]. The required number of follow-up years is determined by the specified values, called Objective Performance Criteria (OPCs). In Grunkemeier et al. [4], the method for computing the required number of valve-years for any OPC is presented. The idea of the method is to use a Gamma distribution to approximate the Poisson distribution. We claim that this approximation results in over-estimation of type I error and under-estimation of type II error. We suggest to use an exact continuous interpolation instead. Both the approximation and the exact interpolation, however, result in the same number of required patient-years. Thus, for all practical purposes it is largely irrelevant which formula is used, but for the sake of mathematical preciseness and accuracy we propose to use the exact interpolation.

To determine whether a tested heart valve is efficient, the statistical hypotheses testing should be performed. According to guidelines worked out in [2], the null hypothesis is that the true complication rate of a new heart valve (R) is equal to or greater than twice the OPC rate ($R_{\rm OPC}$) shown by commercially available valves. Thus, the clinical data are accumulated with the hope to reject $\mathrm{H}_0 : R \geq 2\,R_{\rm OPC}$ in favor of the alternative hypothesis $\mathrm{H}_1 : R < 2\,R_{\rm OPC}$. The derivation of the required minimum number of patient-years in [4] is based on the assumption that the number of complication events E in a clinical trial over a fixed time period T has a Poisson distribution with a fixed rate $\lambda = R_{\rm OPC}\,T$. The rate λ can be computed if the type I and type II errors in the hypotheses testing are specified. Consequently, the total number of patient-years corresponding to a particular OPC rate is determined by $T = \lambda/R_{\rm OPC}$. The type I error, denoted by α, is defined as the probability to reject the null hypothesis provided it is true. Type II error, denoted by β, is the other possible error in hypotheses testing, that is to accept H_0 when it is false. The type II error depends on a particular value of R under the alternative hypothesis. We are assuming $R = R_{\rm OPC}$. It is usually desirable for type I error not to exceed 5%, and for type II error not to exceed 20%, that is $\alpha \leq 0.05$ and $\beta \leq 0.20$. From the theory of hypotheses testing, the null hypothesis is rejected if an observed number of valve-related complications is less than or equal to some critical value CV, and accepted (failed to be rejected) otherwise. Therefore,

$$\alpha = \mathbb{P}(E \leq CV | R \geq 2\,R_{\rm OPC}),$$

and

$$\beta = \mathbb{P}(E > CV | R = R_{\rm OPC}).$$

For fixed CV, the largest α corresponds to the case $R = 2\,R_{\rm OPC}$. The formulas for α and β define a system of two non-linear equations with two unknowns, CV and λ:

$$0.05 = \sum_{k=0}^{CV} \frac{(2\lambda)^k}{k!}\, e^{-2\,\lambda} \qquad (1)$$

and

$$0.20 = \sum_{k=CV+1}^{\infty} \frac{\lambda^k}{k!}\, e^{-\lambda}. \qquad (2)$$

These equations cannot be solved exactly since the critical value CV for a discrete Poisson distribution must be an integer. However, a continuous interpolation of a Poisson distribution can be used to rewrite the above sums as appropriate integrals.

Suppose $N_t \sim Poisson(\tilde{\lambda}\, t)$ where t denotes a time interval and N_t is the random number of events in this interval. Let T_n be the waiting time for the nth event. It is known that $T_n \sim Gamma(n+1, \tilde{\lambda})$. Thus,

$$\mathbb{P}(N_t > n) = \mathbb{P}(N_t \geq n+1)$$

$$= \mathbb{P}(T_{n+1} < t) = \int_0^t \frac{\tilde{\lambda}^{n+1}\, y^n}{\Gamma(n+1)}\, e^{-\tilde{\lambda}\, y}\, dy$$

$$= \int_0^{\tilde{\lambda}\, t} \frac{u^n}{\Gamma(n+1)}\, e^{-u}\, du \qquad (3)$$

where $\Gamma(x) = \int_0^{\infty} y^{x-1}\, e^{-y}\, dy$ is the gamma function, $x > 0$.

Also,
$$\mathbb{P}(N_t \leq n) = 1 - \mathbb{P}(N_t > n)$$
$$= 1 - \mathbb{P}(T_{n+1} < t)$$
$$= \int_{\tilde{\lambda}\, t}^{\infty} \frac{u^n}{\Gamma(n+1)}\, e^{-u}\, du. \qquad (4)$$

The value of n in the integrals in (3) and (4) can now be any real number, not necessarily integer. Hence, these formulas determine an exact continuous interpolation for the Poisson probability function. Indeed, for any integer n,

$$\mathbb{P}(N_t = n) = \mathbb{P}(N_t \geq n) - \mathbb{P}(N_t \geq n+1)$$

$$= \mathbb{P}(T_n < t) - \mathbb{P}(T_{n+1} < t)$$

$$= \int_0^t \frac{\tilde{\lambda}^n y^{n-1}}{\Gamma(n)}\, e^{-\tilde{\lambda} y} dy - \int_0^t \frac{\tilde{\lambda}^{n+1} y^n}{\Gamma(n+1)}\, e^{-\tilde{\lambda} y} dy$$

$$= \int_0^{\tilde{\lambda}\, t} \left(\frac{u^{n-1}}{\Gamma(n)} - \frac{u^n}{\Gamma(n+1)} \right) e^{-u}\, du$$

$$= \int_0^{\tilde{\lambda}\, t} \frac{n u^{n-1} - u^n}{\Gamma(n+1)}\, e^{-u} du$$

$$= \frac{(\tilde{\lambda} t)^n}{\Gamma(n+1)}\, e^{-\tilde{\lambda} t} = \frac{(\tilde{\lambda} t)^n}{n!}\, e^{-\tilde{\lambda} t}. \qquad (5)$$

Now, in view of (3) and (4), equations (1) and (2) become

$$0.05 = \int_{2\lambda}^{\infty} \frac{u^{CV}}{\Gamma(CV+1)}\, e^{-u}\, du \qquad (6)$$

and

$$0.20 = \int_0^{\lambda} \frac{u^{CV}}{\Gamma(CV+1)}\, e^{-u}\, du. \qquad (7)$$

The solution of these equations is $CV = 11.296$ and $\lambda = 9.287$. It was obtained numerically using *Mathematica*.

In defining the minimum required number of patient-years, FDA used the OPC rate of 1.2%/year – the smallest OPC rate in [2]. Thus, $T = \lambda / R_{\text{OPC}} = 9.287/0.012 \approx 774$ patient-years. The approximate solution of the Poisson-based equations (1) and (2) is $\lambda = 9.72$ and $CV = 12$ with the left-hand sides equal to 0.05 and 0.183, respectively. This results in $T = 9.72/0.012 = 810$ patient-years. The quantities 774 and 810 valve-years gave rise to the FDA requirement of the minimum 800 patient-years in a non-randomized clinical study of a new heart valve.

Grunkemeier et al. [4] proposed a different Gamma-based continuous approximation to the Poisson distribution. The idea is borrowed from Cox [1]. In the notation described in the paragraph proceeding equation (3), Cox suggests to use the approximation

$$\mathbb{P}(N_t > n) \approx \mathbb{P}(T_{n+0.5} < t).$$

In this case, the equations (6) and (7) become

$$0.05 = \int_{2\lambda}^{\infty} \frac{u^{CV-0.5}}{\Gamma(CV+0.5)}\, e^{-u}\, du$$

and

$$0.20 = \int_0^{\lambda} \frac{u^{CV-0.5}}{\Gamma(CV+0.5)}\, e^{-u}\, du.$$

The solution of these equations is $CV = 11.796$ and $\lambda = 9.287$, which differs from the solution for the exact interpolation only in the value of CV. Since the λ's are the same, the number of patient-years is intact. The fact that the CV proposed by Grunkemeier et al. [4] is larger than ours by 0.5 results in over-estimation of α and under-estimation of β.

The difference between this approximation and the proposed exact interpolation is negligibly small only for large values of λ, but for the obtained value of 9.287 the difference is noticeable (see Figure 1 and Figure 2).

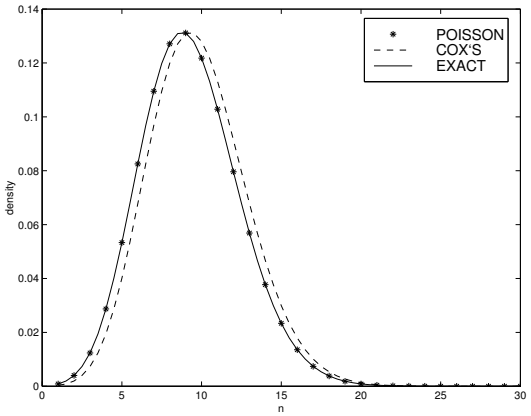

Figure 1: Cox's approximation curve is shifted with respect to the exact interpolation curve.

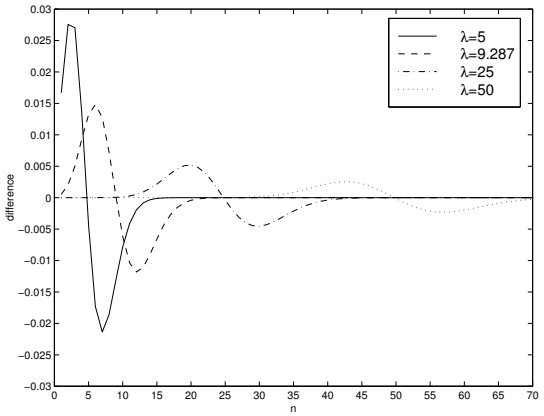

Figure 2: Difference between Cox's approximation and the exact interpolation as function of n.

To prove the behavior of this difference analytically, first compute $\mathbb{P}(N_t = n)$ for Cox's approximation,

$$\begin{aligned}\mathbb{P}(N_t = n) &= \mathbb{P}(N_t > n-1) - \mathbb{P}(N_t > n)\\ &= \mathbb{P}(T_{n-0.5} < t) - \mathbb{P}(T_{n+0.5} < t)\\ &= \int_0^t \frac{\tilde{\lambda}^{n-0.5}\, y^{n-1.5}}{\Gamma(n-0.5)}\, e^{-\tilde{\lambda}y} dy\\ &\quad - \int_0^t \frac{\tilde{\lambda}^{n+0.5} y^{n-0.5}}{\Gamma(n+0.5)}\, e^{-\tilde{\lambda}y} dy\\ &= \int_0^{\tilde{\lambda}\,t} \left(\frac{u^{n-1.5}}{\Gamma(n-0.5)} - \frac{u^{n-0.5}}{\Gamma(n+0.5)}\right) e^{-u}\, du\\ &= \int_0^{\tilde{\lambda}\,t} \frac{(n-0.5)u^{n-1.5} - u^{n-0.5}}{\Gamma(n+0.5)}\, e^{-u} du\\ &= \frac{(\tilde{\lambda}t)^{n-0.5}}{\Gamma(n+0.5)}\, e^{-\tilde{\lambda}t}. \qquad (8)\end{aligned}$$

The difference between the probabilities in (5) and (8) is

$$\begin{aligned}&\frac{(\tilde{\lambda}t)^n}{\Gamma(n+1)}\, e^{-\tilde{\lambda}t} - \frac{(\tilde{\lambda}t)^{n-0.5}}{\Gamma(n+0.5)}\, e^{-\tilde{\lambda}t}\\ &= \frac{(\tilde{\lambda}t)^n}{\Gamma(n+1)}\, e^{-\tilde{\lambda}t}\left(1 - \frac{1}{\sqrt{\tilde{\lambda}t}}\frac{\Gamma(n+1)}{\Gamma(n+0.5)}\right).\end{aligned}$$

If we denote $\lambda = \tilde{\lambda}t$, then the difference equals

$$\frac{(\lambda)^n}{\Gamma(n+1)}\, e^{-\lambda}\left(1 - \frac{1}{\sqrt{\lambda}}\frac{\Gamma(n+1)}{\Gamma(n+0.5)}\right),$$

which decreases as λ goes to infinity, and is still considerably large for the moderate value of 9.287. In Figure 2, this expression is plotted as a function of n for different values of λ. From the graph, the maximum difference for $\lambda = 9.287$ is about 0.015.

Comments

For the Bayesian analysis of a non-randomized clinical study of a new heart valve, Grunkemeier et al. [3] proposed to use the gamma approximation to the Poisson distribution as a guideline for choosing the prior distribution for R. The CV plays a crucial role as a constraint for determining parameters of the prior distribution. The usage of the CV obtained with the approximation formula results in a slight underestimation of the posterior probabilities of the true alternative hypothesis. We suggest to use the exact interpolation value of CV.

References

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