Letter to the Editor

Comment on derivation of sample size requirements for evaluating heart valves with constant risk events

In order to show a satisfactory performance of a new heart valve in a non-randomized clinical study, the complication rates of the new device are compared statistically to the past-experience values listed in the FDA Draft Replacement Heart Valve Guidance (1). The required number of follow up years is determined by the specified values, called Objective Performance Criteria (OPCs). In Grunkemeier et al. (2), 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. This approximation results in an over-estimation of type I error, and an under-estimation of type II error. Instead, we suggest the use of an exact continuous interpolation. Whilst the approximation and exact interpolation result in the same number of required patient-years, the suggestion is to use exact interpolation for the sake of mathematical precision and accuracy.

To determine whether a tested heart valve is efficient, the statistical hypotheses testing should be performed. According to guidelines worked out in (1), 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 (ROPC) shown by commercially available valves. Thus, the clinical data are accumulated with the hope to reject H0: $R \geq 2\ R$OPC in favor of the alternative hypothesis H1: $R < 2\ R$OPC. The derivation of the required minimum number of patient-years in (2) 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 $\lambda = R\text{OPC}\ T$. 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 $T = \lambda/R\text{OPC}$. In defining the minimum required number of patient-years, FDA used the OPC rate of 1.2% per year (1).

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 H0 when it is false. The type II error depends on a particular value of R under the alternative hypothesis, here taken as $R = R$OPC. It is usually desirable that $\alpha \leq 0.05$ 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,
$\alpha = P(E \leq CV \mid R \geq 2\ R\text{OPC})$ and $\beta = P(E > CV \mid R = R\text{OPC})$. For fixed CV, the largest α corresponds to the case $R = 2\ R$OPC. The formulas for α and β define a system of two non-linear equations with two unknowns, CV and λ:

$$0.05 = \sum_{k=0}^{CV} \frac{(2\lambda)^k}{k!} e^{-2\lambda} \qquad \text{and } 0.20 = \sum_{k=CV+1}^{\infty} \frac{\lambda^k}{k!} e^{-\lambda} \qquad (1)$$

These equations cannot be solved exactly since the critical value CV for a discrete Poisson distribution must be an integer.

Grunkemeier et al. (2) proposed a Gamma-based continuous approximation to the Poisson distribution, using the idea of Cox (3). Denote $N_t \sim$ Poisson (), where t is the time and N_t is the random number of events in the interval $[0,t]$. Let T_n be the waiting time for the nth event. Then, . Since $T_n \sim$ Gamma $(n,)$, Eq. (1) are approximated by

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

$$\text{and } 0.20 = \int_{0}^{\lambda} \frac{u^{CV+0.5}}{\Gamma(CV+0.5)} e^{-u} du \qquad (2)$$

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

Alternatively, an exact continuous interpolation of the Poisson distribution can be used to rewrite the sums in Eq. (1). Indeed

$$P(N_t > n) = P(T_{n+1} < t) = \int_0^t \frac{\bar{\lambda}^{n+1} y^n}{\Gamma(n+1)} e^{-\bar{\lambda}y} dy = \int_0^{\bar{\lambda}t} \frac{u^n}{\Gamma(n+1)} e^{-u} du, \quad (3)$$

so that Eq. (1) become

$$0.05 = \int_{\bar{\lambda}}^{\infty} \frac{u^{CV}}{\Gamma(CV+1)} e^{-u} du \text{ and } 0.20 = \int_0^{\bar{\lambda}} \frac{u^{CV}}{\Gamma(CV+1)} e^{-u} du \quad (4)$$

The solution of these equations is CV =11.296 and λ=9.287, and this was obtained numerically using *Mathematica*. On the other hand, the solution of the approximate Eq. (2) is CV = 11.796 and λ = 9.287. In particular, $T = \lambda/\text{ROPC} = 9.287/0.012 \approx 774$ patient-years in both cases, but the value of CV is smaller for the exact interpolation. A larger value of CV in (2) results in an over-estimation of α and an under-estimation of β. In general, the difference between the Cox approximation and the exact interpolation tends to zero as the value of λ grows, however, for λ = 9.287 the difference is still noticeable.

References

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2. Grunkemeier GL, Johnson DM, Naftel DC. Sample size requirements for evaluating heart valves with constant risk events. J Heart Valve Dis 1994;3:53-58
3. Cox DR. Some simple approximate tests for Poisson variates. Biometrika 1953;40:354-360

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Author's response

The letter by Korosteleva and Lototsky (KL) discusses the relationship between the Poisson and gamma distributions that were used to compute the minimum patient-years required by the FDA for clinical studies to evaluate new heart valves.

The problem was framed as a hypothesis test based on the Poisson distribution, with a standard way of estimating the sample size needed to attain given probabilities of type 1 (alpha=.05) and type 2 (beta=.20) errors for an OPC (linearized event rate) of 1.2%/year. The Poisson distribution describes the number of events expected to occur in a fixed number of patient-years, and yielded 810 patient years; but because the Poisson is a discrete distribution, alpha and beta were not both exact. So we employed an approximation to the Poisson, the continuous gamma distribution suggested by Cox, to produce a sample size corresponding to the desired alpha and beta. KL provides a well-written, more detailed formulation of this procedure.

The resulting gamma distribution (shape parameter 12.296) resulted in a sample size of approximately 774 patient years. KL used an exact gamma approximation, rather than the Cox approximation, and obtained the same sample size. The only difference in our two approaches is the critical value (CV), an intermediate value used to determine the trade-off between alpha and beta for a given sample size and OPC. To get the CV, we (per Cox) subtracted 0.5 from the shape parameter and KL subtracted 1.0. Derivation of the sample size does not depend on CV. And, in fact, in the present case, both CV's give the same alpha (0.042, a bit under the .05 target) and beta (0.226, a bit over the .20 target) using the Poisson formulation (equations [1] of KL).

We thank the authors for their interest in this area of research, and for this stimulating letter pointing out an improvement in the method of interpolation. Fortunately, both methods produce the same sample size, which was the purpose of our paper.

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