A Bayesian Model for the Endpoint Event Incidence Rate in Analysis of Futility to Assess Treatment Efficacy

Let n_k and T_k denote, respectively, the event count and the observed total person-time at risk at the time of the k-th futility analysis, pooling over all treatment arms. Additionally, let T^* denote the estimated total person-time at risk for the primary efficacy analysis. Let the prior distribution of the treatment arm-pooled incidence rate p be $\mathsf{Ga}(\alpha, \beta)$ parametrized such that the prior mean $E\,p = \alpha/\beta$ (the same Bayesian method applies to treatment arm-specific incidence rates).

Generally, assuming that, conditional on p, the times to event follow $\mathsf{Exp}(p)$, the posterior mean of p at the time of the k-th analysis equals

$$\begin{aligned} E[p \,|\, \text{data}] &= \frac{\alpha + n_k}{\beta + T_k} \\ &= \frac{\alpha}{\beta}\,\frac{\beta}{\beta + T_k} + \frac{n_k}{T_k}\,\frac{T_k}{\beta + T_k}, \end{aligned} \tag{1}$$

i.e., the posterior mean can be interpreted as a convex combination of the prior mean and the observed incidence rate. For a given $\beta > 0$, the weight on the prior mean at the first analysis depends on the accumulated person-time at risk (T_1), and the weight will decrease at subsequent analyses because $\beta/(\beta + T_k)$ is a decreasing function of T_k, which is a desirable Bayesian property.

In order to identify α and β, it is desirable that the prior mean equals the pre-trial assumed treatment arm-pooled incidence rate p^* (e.g., under $TE = 60\%$, $p^* = (1/3) \times 0.055 + (2/3) \times 0.4 \times 0.055 = 0.033$ in HVTN 703/HPTN 081), i.e.,

$$\frac{\alpha}{\beta} = p^*.$$

Furthermore, we propose to consider three values of β that correspond to the weights $w = \frac{1}{2}$, $\frac{1}{3}$ and $\frac{1}{4}$ on the prior mean at the time when 50% of the estimated total person-time at risk has been accumulated, i.e., for each value of w, β is defined as the solution to the equation

$$\frac{\beta}{\beta + T^*/2} = w.$$

It follows that

$$\beta = \beta(w, T^*) = \frac{wT^*}{2(1-w)}\,,$$

and the estimation of T^* is described in the next section. For $w = \frac{1}{2}$, $\frac{1}{3}$ and $\frac{1}{4}$, we obtain $\beta = \frac{T^*}{2}$, $\frac{T^*}{4}$, and $\frac{T^*}{6}$, respectively.

At the k-th futility analysis and for each of the three values of β, we will sample the incidence rate from $\mathsf{Ga}(\alpha + n_k, \beta + T_k)$ for generating future data and report the weight $\frac{\beta}{\beta+T_k}$ on the prior mean in the convex combination (1).

Estimation of the Total Person-Years at Risk (T^*)

We consider the standard right-censored failure time analysis framework. Denoting the failure and censoring times as T and C, respectively, we assume that T is independent of C, $T \sim \mathsf{Exp}(p^*)$, and $C \sim \mathsf{Exp}(d^*)$. It follows that $X := \min(T, C) \sim \mathsf{Exp}(p^* + d^*)$ and

$$\begin{aligned} T^* &= N \times E[\min(X, \tau)] \\ &= N \times \left\{E[X \mid X \le \tau]\, P(X \le \tau) + \tau\, P(X > \tau)\right\} \\ &= N \times \left\{(p^* + d^*) \int_0^\tau x \mathrm{e}^{-(p^*+d^*)x} \mathrm{d}x + \tau \mathrm{e}^{-(p^*+d^*)\tau}\right\} \\ &= N \times \frac{1 - \mathrm{e}^{-(p^*+d^*)\tau}}{p^* + d^*}\,. \end{aligned}$$

To illustrate, we consider the total target sample size $N = 1,500$ with a 2:1 randomization ratio to treatment vs. placebo, the duration of follow-up per participant $\tau = 80/52$ years, the pre-trial assumed dropout rate $d^* = 0.1$ dropouts per person-year at risk (PYR), and, in the $TE = 60\%$ scenario, the pre-trial assumed treatment arm-pooled endpoint event incidence rate $p^* = (1/3) \times 0.055 + (2/3) \times 0.4 \times 0.055 = 0.033$ cases per PYR.

These assumptions result in $T^* = 2086.91$ PYRs. For comparison, if all N participants were followed for τ years, the total PYRs would be $N\tau = 2307.69$ years.

Subsequently, for $T^* = 2086.91$ PYRs, if $T_1 = 0.2\,T^*$, the weights $\frac{\beta}{\beta+T_1}$ on the prior mean at the first futility analysis corresponding to $w = \frac{1}{2}$, $\frac{1}{3}$, and $\frac{1}{4}$ are 0.71, 0.56, 0.45, respectively. If $T_1 = 0.3\,T^*$, the respective weights on the prior mean are 0.63, 0.45, and 0.36.