A Bayesian Model for the Endpoint Event Incidence Rate in an Interim Analysis of Operational Futility

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). For the treatment arm-pooled incidence rate, we additionally consider a robust prior distribution described in Section 1.

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., in a trial in which participants are randomized to treatment and placebo in the 2:1 ratio, assuming the incidence rate of 0.055 endpoints per person-year at risk in the placebo group and $TE = 60\%$, $p^* = (1/3) \times 0.055 + (2/3) \times 0.4 \times 0.055 = 0.033$), i.e.,

$$
\frac{\alpha}{\beta} = p^*.
\tag{2}
$$

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

$$\beta = \beta(w, T^*) = \frac{wT^*}{2(1-w)} \,, \tag{3}$$

and the estimation of T^* is described in Section 2. 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).

1 A Robust Mixture Prior Distribution for the Endpoint Event Incidence Rate

The robust prior model (Schmidli et al., 2014) is implemented since it is designed to maximize the probability of meeting, e.g., an enrollment expansion guideline for large downward deviations from the protocol-assumed incidence rates, while minimizing a false trigger for protocol-assumed incidence rates.

The prior distribution of p is defined as a weighted mixture of two gamma distributions,

$$(1 - w_R)\mathsf{Ga}(\alpha_I, \beta_I) + w_R\mathsf{Ga}(\alpha_V, \beta_V),$$

where we set, e.g., $w_R = 0.2$, and $\mathsf{Ga}(\alpha_V, \beta_V)$ and $\mathsf{Ga}(\alpha_I, \beta_I)$ represent the weakly informative and informative component of the mixture prior, respectively. The parameters β_V and β_I are calculated following (3) with, e.g., $w = 1/1000$ and $w = 1/3$, respectively (and T^* per Section 2). Subsequently, α_V and α_I are calculated following (2) with p^* set to the pre-trial assumed treatment arm-pooled incidence rate for both components of the mixture.

The posterior distribution at the time of the k-th analysis is derived following the conjugacy principle, as in (1), which results in a mixture of conjugate posteriors with updated weights

$$(1 - \widetilde{w}_{R,k})\mathsf{Ga}(\alpha_I + n_k, \beta_I + T_k) + \widetilde{w}_{R,k}\mathsf{Ga}(\alpha_V + n_k, \beta_V + T_k),$$

where

$$\widetilde{w}_{R,k} \propto w_{R,k}f_V / \left\{ w_{R,k}f_V + (1 - w_{R,k})f_I \right\}$$

with $f.$ equal to

$$f. = \frac{\Gamma(\alpha. + n_k)/(\beta. + T_k)^{\alpha. + n_k}}{\Gamma(\alpha.)/\beta.^{\alpha.}}$$

(see, e.g., Bernardo and Smith, 2000, Section 5.2.3, pages 279–282).

2 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 the pre-trial assumed constant incidence rate of 0.055 endpoints/PYR in the placebo group. Then, in the $TE = 60\%$ scenario, the pre-trial assumed treatment arm-pooled endpoint event incidence rate is $p^* = (1/3) \times 0.055 + (2/3) \times 0.4 \times 0.055 = 0.033$ endpoints/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.

References

J. M. Bernardo and A. F. M. Smith. *Bayesian Theory*. Wiley Series in Probability and Statistics, 2000.

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