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N-of-1 Trials of Expensive Biological Therapies: A Third Way (Random-Effects Model)

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#### **Publication Date**

2007-08-17

## Random Effects Models

In order to assess the sensitivity of the results presented in Table 3 for the Primary Model with respect to the assumption that the outcomes are statistically independent across treatment episodes, we conducted sensitivity analyses under random effects models that allowed the outcomes to be statistically correlated across treatment episodes. We describe below the model specifications and analysis procedures.

Let  $X_{ji} = 0$  (failure) or 1 (success) denote the success/failure outcome for the  $i$ -th trial in the  $n$ -of-1 trial conducted for the  $j$ -th patient, where the between-patient index  $j=1, \dots, J$  denotes the patients,  $J$  denotes the total number of patients, and the within-patient index  $i=1, 2, 3, 4$  denotes the four trials in the  $n$ -of-1 trial sequence for the  $j$ -th patient. Let  $P_{ji} = P(X_{ji} = 1)$  denote the success probability for the  $i$ -th trial in the  $j$ -th patient. Let us assume that the outcome  $X_{ji}$  is determined from an underlying continuous propensity to succeed,  $Y_{ji}$ , as follows:

$$(1) \quad \begin{aligned} X_{ji} &= 1 \text{ if } Y_{ji} \geq T_{ji}, \\ X_{ji} &= 0 \text{ if } Y_{ji} < T_{ji}, \end{aligned}$$

where the propensity to succeed,  $Y_{ji}$ , follows a standard normal distribution with mean zero and variance one,

$$(2) \quad Y_{ji} \sim N(0, 1),$$

and  $T_{ji}$  is the threshold that determines the success/failure status  $X_{ji}$  for the  $i$ -th trial in the  $j$ -th patient. It follows that the success probability  $P_{ji}$  is given as follows:

$$(3) \quad P_{ji} = P(Y_{ji} \geq T_{ji}) = 1 - \Phi(T_{ji}),$$

where  $\Phi$  is the cumulative distribution function for the standard normal distribution. Therefore,

$$(4) \quad T_{ji} = \Phi^{-1}(1 - P_{ji}).$$

For the Treatment Sequence A (MEME) in Figure 2, the success probabilities for the Treatment Sequence A are given as follows in Table 1:

$$(5) \quad P_{j1} = P_{j3} \equiv 0.35, P_{j2} = P_{j4} \equiv 0.40;$$

the corresponding thresholds are given as follows:

$$(6) \quad \begin{aligned} T_{j1} &= T_{j3} \equiv \Phi^{-1}(1 - 0.35) = \Phi^{-1}(0.65) = 0.3853, \\ T_{j2} &= T_{j4} \equiv \Phi^{-1}(1 - 0.40) = \Phi^{-1}(0.60) = 0.2533. \end{aligned}$$

(For the other three Treatment Sequences, the success probabilities and thresholds are permuted according to the specific Treatment Sequence.)

Let us assume further that the propensity vector  $(Y_{j1}, Y_{j2}, Y_{j3}, Y_{j4})$  follows a random effect model,

$$(7) \quad Y_{ji} = A_j + B_{ji}, \quad j=1, \dots, J; \quad i=1, 2, 3, 4,$$

where  $A_j$  denotes the random effect at the individual level,  $B_{ji}$  denotes the residual variation for each trial within the same individual, with the following distributions:

$$(8) \quad A_j \sim N(0, \tau^2),$$

$$(9) \quad B_{ji} \sim N(0, \sigma^2),$$

where

$$(10) \quad \tau^2 + \sigma^2 = 1,$$

and  $A_j, B_{j1}, B_{j2}, B_{j3}, B_{j4}$  are statistically independent. The between-patient variance component,  $\tau^2$ , can be interpreted as the intra-class correlation at the individual level, i.e.,  $\tau^2 = \text{corr}(Y_{ji}, Y_{ji'})$  for any two trials (say, trials  $i$  and  $i'$ ) taken on the same individual patient.

Under the primary model presented in Table 3, and also shown in Table 2 as the column “Expected Proportion (Product of Probabilities),” the trial outcomes  $X_{ji}$ ’s are assumed to be statistically independent across trials, i.e., the between-individual variance component  $\tau^2$  is assumed to be zero. Under this assumption, the joint probability for the outcome vector  $(X_{j1}, X_{j2}, X_{j3}, X_{j4})$  is the product of the marginal probabilities,  $P(X_{j1}) \times P(X_{j2}) \times P(X_{j3}) \times P(X_{j4})$ . For example, the joint probability for the outcome sequence SSSS ( $X_{j1}=1, X_{j2}=1, X_{j3}=1, X_{j4}=1$ ) in Table 2 is given by  $0.35 \times 0.40 \times 0.35 \times 0.40 = 0.0196$ .

For the sensitivity analyses, we assume alternative values for the between-individual variance component  $\tau^2$ . In particular, we assume two scenarios,  $\tau^2 = 0.20$  and  $\tau^2 = 0.50$ , with the results shown in Table 3, footnote, and in Table 2 under the columns “Expected Proportion (20% Shared Variance)” and “Expected Proportion (50% Shared Variance)”. The first scenario assumes a modest correlation in the treatment outcomes across treatment episodes, to capture the propensity for some patients to respond to treatments and other patients not to respond to treatments. The second scenario assumes a strong correlation across treatment episodes.

The joint probabilities reported in table 2 are derived using Monte Carlo integration. The algorithm is summarized below:

(a) We simulate a random value for  $A$  from the distribution (8), call it  $A_j$ .

(b) We derive the conditional probability for the outcome vector  $(X_{j1}, X_{j2}, X_{j3}, X_{j4})$  for the simulated value  $A_j$ , call it  $CP_j$ . For example, for the outcome vector SSSS, we have

$$(11) \quad P(\text{SSSS}) = E[P(\text{SSSS} \mid A_j)],$$

$$(12) \quad \begin{aligned} \text{CP}_j &= P(\text{SSSS} \mid A_j) \\ &= \prod_i P(B_{ji} \geq T_{ji} - A_j) \\ &= \prod_i \Phi((A_j - T_{ji}) / \sigma), \end{aligned}$$

where the multiplication  $\prod_i$  is taken over the index  $i=1, 2, 3, 4$ .

We repeat steps (a) and (b) 10,000 times, and save the results in a dataset as  $(A_j, \text{CP}_j)$ ,  $j=1, \dots, 10,000$ . We then analyze this simulated dataset to obtain the point estimates for the (unconditional) joint distribution for  $X_i$ 's by taking the average for  $\text{CP}_j$ 's across  $j$ 's. We also examine the Monte Carlo standard errors to ascertain that the number of iterations (10,000) for the Monte Carlo integration is adequate.