A Gatekeeping Test on a Primary and a Secondary Endpoint in a Group Sequential Design with Multiple Interim Looks

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SUMMARY: Glimm et al. (2010) and Tamhane et al. (2010) studied the problem of testing a primary and a secondary endpoint, subject to a gatekeeping constraint, using a group sequential design (GSD) with $K = 2$ looks. In this paper we greatly extend the previous results to multiple ($K > 2$) looks. If the familywise error rate (FWER) is to be controlled at a preassigned α level then it is clear that the primary boundary must be of level α. We show under what conditions one α-level primary boundary is uniformly more powerful than another. Based on this result we recommend the choice of the O'Brien and Fleming (1979) boundary over the Pocock (1977) boundary for the primary endpoint. For the secondary endpoint the choice of the boundary is more complicated since under certain conditions the secondary boundary can be refined to have a nominal level $\alpha' > \alpha$, while still controlling the FWER at level α, thus boosting the secondary power. We carry out secondary power comparisons via simulation between different choices of primary-secondary boundary combinations. The methodology is applied to the data from the RALES study (Pitt et al., 1999; Wittes et al., 2001).

KEY WORDS: Familywise error rate; Gatekeeping; Lan-DeMets error spending function approach; Multiple comparisons; Multiple endpoints; O'Brien-Fleming boundary; Pocock boundary; Primary power; Secondary power.

1. Introduction

Gatekeeping procedures for testing multiple hierarchical objectives such as tests on multiple endpoints have been been studied by many authors in the last 15 years, see, e.g., Dmitrienko and Tamhane (2007, 2009). For the most part, these studies are restricted to fixed sample designs. However, group sequential designs (GSDs) have become increasingly more common in clinical trials since the early works of Pocock (1977) and O'Brien and Fleming (1979); Jennison and Turnbull (2000) have given a thorough overview of the subject. Tang and Geller (1999), Jennison and Turnbull (1993) and Maurer and Bretz (2013) have addressed certain aspects of multiple testing in GSDs. Still, there is a pressing need to develop procedures at the interface of gatekeeping and group sequential designs. This paper addresses a practically important problem at this interface.

Hung et al. (2007) were the first to study a gatekeeping test on a primary and a secondary endpoint using a GSD with two looks (or stages). They showed that the fixed-sequence testing strategy of propagating α from a rejected hypothesis to an unrejected one, used effectively in gatekeeping and graphical procedures (Bretz et al. (2009)), inflates the type I error rate when used in a GSD. Glimm et al. (2010) and Tamhane et al. (2010) studied this problem analytically and showed how to determine the critical boundaries for the two endpoints to control the familywise type I error rate (FWER). Both these papers focused on the two-look ($K = 2$) case. In this paper we study this problem in much greater depth and extend the previous results to multiple looks ($K > 2$).

The outline of the paper is as follows. Section 2 sets up the notation and gives the statement of the problem. Section 3 discusses the choice of the primary boundary. Section 4 discusses the choice of the secondary boundary. This section is divided into three subsections. The first subsection reviews the previous results for $K = 2$, while the second subsection gives new results for $K > 2$. Both these subsections consider the least favorable case (in terms of maximizing the

FWER) of the correlation ρ between the primary and the secondary endpoints equal to 1. The third subsection gives the secondary boundaries for the known ρ case to illustrate how much the secondary boundary can be relaxed if $\rho < 1$. Section 5 gives simulated power comparisons between different choices of primary and secondary boundaries. Section 6 gives a clinical trial example to illustrate the methodology presented in the paper. Section 7 gives an extension of the procedure studied in the paper. Section 8 gives concluding remarks. To keep the length of the paper within limits only a simpler and shorter proof of a special case of Theorem 1 is included in the Appendix; a longer and a more technical proof of that theorem is included in a Web Appendix, which also includes proofs of Theorems 4 and 5, and the R program to compute the various boundaries necessary to implement the proposed methodology.

2. Problem Formulation and Notation

We will assume the following normal theory set up, which applies asymptotically to broad types of data including survival and binary data. Consider a parallel arm trial to compare a treatment with a control or placebo on a primary and a secondary endpoint, which are to be tested hierarchically with the primary endpoint acting as a gatekeeper for the secondary endpoint. For each patient we observe a bivariate normal response on the primary and the secondary endpoints with means (μ_{t1}, μ_{t2}) for the treatment group and (μ_{c1}, μ_{c2}) for the control group; the variances (σ_1^2, σ_2^2) and the correlation coefficient ρ are assumed to be common for the two groups. Let $\delta_1 = \mu_{t1} - \mu_{c1}$ and $\delta_2 = \mu_{t2} - \mu_{c2}$ denote the primary and secondary treatment effects, respectively. We want to test two hypotheses, $H_1 : \delta_1 = 0$ and $H_2 : \delta_2 = 0$ against upper one-sided alternatives where H_2 is tested only if H_1 is rejected.

We use a GSD with $K \geqslant 2$ stages. In the ith stage of the trial we have n_i patients on each arm. Denote the cumulative sample sizes on each arm by $N_i = n_1 + \ldots + n_i$ and the information times by $t_i = N_i/N_K$ $(1 \leqslant i \leqslant K)$. We assume that the information times are the same for

the primary and secondary endpoints. All except one example (the RALES data example in Section 6) given in this paper assume equal group sizes and so $t_i = i/K \quad (1 \leqslant i \leqslant K)$; however. theoretical results apply more generally. This assumption will not be repeated in those examples.

Denote the critical boundary for the primary endpoint by $(c_1, \ldots, c_K)$ and that for the secondary endpoint by $(d_1, \ldots, d_K)$. We want to determine these decision boundaries so as to strongly control the FWER for any specified α (Hochberg and Tamhane, 1987):

$$\text{FWER} = P\{\text{Reject at least one true } H_i \ (i = 1, 2)\} \leqslant \alpha \tag{1}$$

regardless of whether H_1 or H_2 is true or both are true.

The Lan and Demets (1983) flexible error spending function approach used in the example in Section 6 does not require prespecification of the number or the timings of the looks. In that example we will adapt the fixed GSD boundaries to the flexible error spending function boundaries.

At the ith look, let (X_i, Y_i) denote the standardized sample mean test statistics for the two endpoints, which are assumed to be bivariate normal with mean vector $(\Delta_{1i}, \Delta_{2i})$ where

$$\Delta_{1i} = \frac{\delta_1}{\sigma_1}\sqrt{\frac{N_i}{2}} \quad \text{and} \quad \Delta_{2i} = \frac{\delta_2}{\sigma_2}\sqrt{\frac{N_i}{2}} \quad (1 \leqslant i \leqslant K)$$

and correlation coefficient ρ. Define the standardized treatment effects at Stage K for the two endpoints by

$$\Delta_1 = \Delta_{1K} = \frac{\delta_1}{\sigma_1}\sqrt{\frac{N_K}{2}} \quad \text{and} \quad \Delta_2 = \Delta_{2K} = \frac{\delta_2}{\sigma_2}\sqrt{\frac{N_K}{2}}.$$

Then $\Delta_{1i} = \gamma_i\Delta_1$ and $\Delta_{2i} = \gamma_i\Delta_2$ where $\gamma_i = \sqrt{t_i}$ $(1 \leqslant i \leqslant K)$. (We note that in Tamhane et al. (2010), Δ_1 and Δ_2 were defined as $\delta_1\sqrt{n_1}$ and $\delta_2\sqrt{n_1}$, respectively; also a single-sample study was assumed in contrast to the two-sample study assumed in the present paper.)

The correlation structure of $(X_1, \ldots, X_K)$ and $(Y_1, \ldots, Y_K)$ can be readily shown to be as

follows.

$$\begin{aligned} \text{corr}(X_i, X_j) = \text{corr}(Y_i, Y_j) &= \gamma_{ij} = \frac{\gamma_i}{\gamma_j} \quad (1 \leqslant i < j \leqslant K) \\ \text{corr}(X_i, Y_i) &= \rho \quad (1 \leqslant i \leqslant K) \\ \text{corr}(X_i, Y_j) = \text{corr}(X_j, Y_i) &= \rho\gamma_{ij} \quad (1 \leqslant i < j \leqslant K). \end{aligned}$$

We will restrict attention to what Glimm et al. (2010) called the stagewise hierarchical rule in which H_1 is tested using the primary decision boundary until either it is rejected, i.e., $X_i > c_i$ for some $i \leqslant K$ and then H_2 is tested or the trial terminates without rejecting H_1 and hence also H_2. If H_1 is rejected at the ith look then H_2 is rejected if $Y_i > d_i$; otherwise H_2 is retained and the trial terminates. We will denote this procedure by $\mathcal{P}_a$. See, however, see Section 7, which studies a more general procedure $\mathcal{P}_b$ that conducts sequential tests on H_2 until it is rejected or the trial stops.

3. Choice of the Primary Boundary

It is clear that since H_1 is a gatekeeper for H_2, the primary boundary must control the type I error under H_1 at level α. Any such α-level boundary can be chosen for this purpose. The following theorem tells how to choose a more powerful α-level boundary.

THEOREM 1: *Suppose* $(X_1, \ldots, X_K)$ *has a multivariate normal distribution as defined above. Consider two different* α*-level tests: Test A with group sequential boundary* $(a_1, \ldots, a_K)$ *and Test B with group sequential boundary* $(b_1, \ldots, b_K)$ *for testing* H_1*:* $\delta_1 = 0$ *vs* $\delta_1 > 0$*. If for some* $k^* \in \{1, \ldots, K-1\}$*,* $a_i > b_i$ *for* $i = 1, \ldots, k^*$ *and* $a_i < b_i$ *for* $i = k^* + 1, \ldots, K$*, and if the total sample size is the same for both the tests then Test A is uniformly more powerful than Test B for all* $\delta_1 > 0$*.*

An intuitive explanation for this result is that if test A tends to stop later than test B, then test A always makes a final decision based on more data than test B and so hs more

power. An extreme case for $k^* = K-1$ is when $a_1 = \ldots = a_{K-1} = \infty$ and so test A always takes the maximum possible sample size, while test B tends to take fewer observations. Then application of the Neymann-Pearson lemma implies that test A has a higher power. In the Appendix, we use a likelihood ratio argument to prove Theorem 1 for cases where $k^* = K-1$ and test A never stops earlier than test B. However, this method does not generalize to cases where k^*K-2 and it is possible for test A to stop before test B. Our proof for such cases is longer and more technical and is given in the Web Appendix.

Consider a corollary to this theorem for two classical group sequential boundaries: the O'Brien-Fleming (OBF) boundary and the Pocock (POC) boundary. It is clear that the OBF boundary corresponds to Test A and the POC boundary corresponds to Test B. So the OBF boundary is uniformly more powerful than the POC boundary. Thus given a choice between these two boundaries we choose the OBF boundary for the primary endpoint.

4. Choice of the Secondary Boundary

Now consider the choice of the secondary boundary to control the FWER under $H_2 : \delta_2 = 0$ when H_1 is false. This FWER (which we will also refer to as the secondary type I error probability) is a function of the joint distribution of the X_i's and the Y_i's, and so of the unknown parameters Δ_1 and ρ (as well as of the known information fractions). We denote it by $\alpha_2(\Delta_1, \rho)$, where

$$\alpha_2(\Delta_1, \rho) = \sum_{i=1}^{K} P_{H_2}\left\{X_1 \leqslant c_1, \ldots, X_{i-1} \leqslant c_{i-1}, X_i > c_i; Y_i > d_i\right\}. \tag{2}$$

Let $\alpha_2 = \max_{\Delta_1,\rho} \alpha_2(\Delta_1, \rho)$. Then we need to determine $(d_1, \ldots, d_K)$ such that $\alpha_2 \leqslant \alpha$.

4.1 *Summary of Results for $K = 2$*

We summarize the main results from Tamhane et al. (2010).

THEOREM 2: *If* $c_1 \geqslant d_1$ *then* $\alpha_2 = \max_{\Delta_1,\rho} \alpha_2(\Delta_1, \rho)$ *is achieved at* $\Delta_1 = \Delta_{11}^0 = (c_1 - d_1)/\gamma_1$ *and* $\rho = 1$ *and*

$$\alpha_2 = 1 - P_{H_2}(Y_1 \leqslant d_1, Y_2 \leqslant d_2) = 1 - \Phi_2(d_1, d_2|\gamma_1), \tag{3}$$

where $\Phi_2(\cdot, \cdot|\gamma)$ *denotes the standard bivariate normal c.d.f. with correlation coefficient* γ. *Thus in order to control* $\alpha_2 \leqslant \alpha$, (d_1, d_2) *must be an* α*-level boundary, i.e.,* $P_{H_2}(Y_1 \leqslant d_1, Y_2 \leqslant d_2) = \Phi_2(d_1, d_2|\gamma_1) = 1 - \alpha$.

This theorem shows that Hung et al.'s (2007) Strategy 1 will be liberal since it uses $d_1 = d_2 = z_\alpha$, the upper α critical point of the standard normal distribution. If $\alpha = 0.05$ then $z_{.05} = 1.645$ and $\alpha_2 = 1 - \Phi_2(1.645, 1.645|\sqrt{1/2}) = 0.08 > 0.05$.

Note that $\max_{\Delta_1,\rho} \alpha_2(\Delta_1, \rho)$ is independent of (c_1, c_2) although where this maximum occurs w.r.t. Δ_1 depends on (c_1, d_1). Any α-level boundary can be chosen for (d_1, d_2) as long as $c_1 \geqslant d_1$. For example, (c_1, c_2) can be the OBF boundary and (d_1, d_2) can be the POC boundary. The 0.05-level boundaries are $(c_1, c_2) = (1.678\sqrt{2}, 1.678)$ and $(d_1, d_2) = (1.876, 1.876)$. In this case $\max_{\Delta_1,\rho} \alpha_2(\Delta_1, \rho)$ is equal to 0.05 and is attained at $\Delta_1 = \Delta_{11}^0 = (1.678\sqrt{2} - 1.876)/\sqrt{0.5} = 0.703$ as shown in Figure 3 of Tamhane et al. (2010).

Next we consider the case $c_1 < d_1$ and $c_2 > d_2$. For example, (c_1, c_2) is the POC boundary and (d_1, d_2) is the OBF boundary.

THEOREM 3: *If* (c_1, c_2) *and* (d_1, d_2) *are* α*-level boundaries with* $c_1 < d_1$ *and* $c_2 > d_2$ *then* $\alpha_2 = \max_{\Delta_1,\rho} \alpha_2(\Delta_1, \rho)$ *is achieved at* $\Delta_1 = \Delta_{12}^0 = (c_2 - d_2)/\gamma_2 = c_2 - d_2$ *and the associated* $\alpha_2 < \alpha$. *So the secondary boundary can be refined to be more liberal with some nominal level* $\alpha' > \alpha$ *to make the associated* $\alpha_2 = \alpha$, *thus boosting the secondary power.*

To obtain the refined boundary (d_1, d_2), note that under the least favorable configuration $\rho = 1$, using $E(X_i) = \gamma_i \Delta_1$, we have $Y_i = X_i - \gamma_i \Delta_1 \ \ (i = 1, 2)$. So we can write

$$\alpha_2 = P\{Y_1 > \max(c_1 - \gamma_1 \Delta_1, d_1)\} + P\{Y_1 \leqslant c_1 - \gamma_1 \Delta_1, Y_2 > \max(c_2 - \gamma_2 \Delta_1, d_2)\}. \tag{4}$$

We can parameterize (d_1, d_2) by a single unknown d and solve the equation $\alpha_2 = \alpha$ for d. As an illustration, suppose for $\alpha = 0.05$, the primary boundary is POC with $c_1 = c_2 = 1.876$ and the secondary boundary is OBF with $d_1 = d\sqrt{2}, d_2 = d$ with $d = 1.678$. For this boundary it turns out that $\alpha_2 = 0.039$ using (4). We can find a refined OBF boundary (d_1, d_2) by setting (4) equal to $\alpha = 0.05$ and solving for d. The solution is $d = 1.570$. Thus the refined secondary boundary is $(1.570\sqrt{2}, 1.570)$. The nominal α level of this refined boundary is $\alpha' = 0.063 > 0.05$. These calculations are shown in the top panel of Table 1.

From these theorems we conclude that $\rho = 1$ is the least favorable configuration in that it maximizes $\alpha_2(\Delta_1, \rho)$. In practice, of course, ρ is always less than 1 (an exception being noninferiority-superiority testing, where the same statistic is used for both tests). So it is of interest to know how $\alpha_2(\Delta_1, \rho)$ behaves as a function of ρ. Figure 3 in Tamhane et al. (2010) indicates that $\max_{\Delta_1} \alpha_2(\Delta_1, \rho) < \alpha$ if $\rho < 1$, so a more liberal and more powerful secondary boundary can be used if ρ is known. We will extend these results to $K > 2$ in Section 4.3. If ρ is estimated from the first stage data then Tamhane et al. (2012) showed how an upper confidence limit on ρ can be used instead.

If $c_1 > d_1$ and $c_2 < d_2$ then it follows that $\Delta_{11}^0 > 0 > \Delta_{12}^0$. For example, for the OBF-POC boundary combination and $\alpha = 0.05$, we have $\Delta_{11}^0 = (1.678\sqrt{2} - 1.876)/\sqrt{0.5} = 0.703$ and $\Delta_{12}^0 = 1.678 - 1.876 = -0.198$. Thus, as Δ_1 is increased from $-\infty$, it crosses Δ_{12}^0 first when $\max(c_2 - \gamma_2\Delta_1, d_2)$ changes from $c_2 - \gamma_2\Delta_1$ to d_2, then it crosses Δ_{11}^0 when $\max(c_1 - \gamma_1\Delta_1, d_1)$ changes from $c_1 - \gamma_1\Delta_1$ to d_1. This gives us the following expressions for the two peak values of $\alpha_2(\Delta_1, \rho = 1)$:

$$\alpha_2(\Delta_1, \rho = 1) = \begin{cases} P(Y_1 > c_1 - \gamma_1\Delta_{12}^0) + P(Y_1 \leqslant c_1 - \gamma_1\Delta_{12}^0, Y_2 > d_2) & (\Delta_1 = \Delta_{12}^0) \\ P(Y_1 > d_1) + P(Y_1 \leqslant d_1, Y_2 > d_2) & (\Delta_1 = \Delta_{11}^0). \end{cases}$$

The overall maximum clearly occurs at $\Delta_1 = \Delta_{11}^0$ and equals α since (d_1, d_2) is an α-level boundary.

4.2 *New Results for $K > 2$*

We first derive a necessary and sufficient condition for the secondary boundary $\{d_1, \ldots, d_K\}$ to be an α-level boundary, i.e., $P_{H_2}\{Y_1 \leqslant d_1, \ldots, Y_K \leqslant d_K\} = 1 - \alpha$.

THEOREM 4: *The secondary type I error $\alpha_2(\Delta_1, \rho)$ is bounded above by*

$$1 - P_{H_2}\{Y_1 \leqslant d_1, \ldots, Y_K \leqslant d_K\},$$

and this bound is achieved if and only if

$$\Delta^0_{11} = \cdots = \Delta^0_{1,K-1} \geqslant \Delta^0_{1K} \quad \textit{and} \quad \rho = 1. \tag{5}$$

In all other cases, $\alpha_2 = \max_{\Delta_1,\rho} \alpha_2(\Delta_1, \rho) < \alpha$. So the secondary boundary can be refined to be more liberal with nominal level $\alpha' > \alpha$ to make the associated $\alpha_2 = \alpha$, thus boosting the secondary power.

Theorem 2 is a special case for $K = 2$ of the above theorem. In this case if (c_1, c_2) and (d_1, d_2) are both α-level boundaries and $c_1 \geqslant d_1$ then $c_2 \leqslant d_2$, and hence $\Delta^0_{11} \geqslant 0$ and $\Delta^0_{12} \leqslant 0$. So condition (5) is obviously satisfied. In most practical situations, condition (5) will not be satisfied for $K > 2$ unless the primary and secondary boundaries are the same. Hence α_2 will be less than α. Analogous to the $K = 2$ case, we can refine the secondary boundary to increase α_2 to α as follows.

Generalizing the formula (4) we can write

$$\alpha_2 = \sum_{i=1}^{K} P\{Y_1 \leqslant c_1 - \gamma_1\Delta_1, \ldots, Y_{i-1} \leqslant c_{i-1} - \gamma_{i-1}\Delta_1, Y_i > \max(c_i - \gamma_i\Delta_1, d_i)\}. \tag{6}$$

As before, given any α-level primary boundary $(c_1, \ldots, c_K)$, we can find a refined secondary boundary parameterized by a single unknown constant d by solving the equation $\alpha_2 = \alpha$ for d. For example, if we choose the secondary boundary to be the OBF boundary then $d_i = d/\gamma_i$ $(1 \leqslant i \leqslant K)$. We illustrate this calculation for $K = 3$ and $K = 4$ below.

Consider two boundary combinations: OBF for primary and POC for secondary (denoted

as OBF-POC) and POC for primary and OBF for secondary (denoted as POC-OBF). In both cases, the condition (5) is not satisfied and hence $\alpha_2 < \alpha$. The middle panel of Table 1 gives the original boundaries with $\alpha_2 < \alpha$ associated with them for $K = 3$. It also gives the refined secondary boundary with $\alpha_2 = \alpha$ and nominal level $\alpha' > \alpha$. The refined secondary boundary has the same form as the original secondary boundary (i.e., OBF or POC) but has $\alpha_2 = \alpha$. The bottom panel of Table 1 gives analogous results for $K = 4$.

[Table 1 about here.]

Generalizing the results for $K = 2$, the sharp peaks (where the derivative does not exist) in FWER plots for $\rho = 1$ occur at $\Delta_1 = \Delta_{1i}^0 = (c_i - d_i)/\gamma_i \ \ (1 \leqslant i \leqslant K)$. Thus there are exactly K such peaks and so the continuous problem of finding $\max_{\Delta_1} \alpha_2(\Delta_1, \rho = 1)$ reduces to the discrete problem of searching for the maximum of K values of $\alpha_2(\Delta_{1i}^0, \rho = 1)$ for $i = 1, \ldots, K$. Figure 1 illustrates this phenomenon for $K = 3$ with the OBF primary boundary and the refined POC secondary boundary with three sharp peaks. As shown in Figure 1, these peaks occur at $\Delta_1 = \Delta_{1i}^0$ $(i = 1, 2, 3)$, which are listed in Table 2 for the OBF-POC boundary combination under Refined Boundaries.

[Figure 1 about here.]

[Table 2 about here.]

In general, the ordering of the Δ_{1i}^0 values depends on the choice of the primary and secondary boundaries as well as the information times of the looks. For the OBF-POC boundary combination with equispaced information times of the looks, it is easy to show that $\Delta_{11}^0 > \cdots > \Delta_{1K}^0$, as seen in Table 2.

For $K > 2$, we can write the following expression for $\Delta_1 = \Delta_{1i}^0$:

$$\alpha_2(\Delta_{1i}^0, \rho = 1) \ = \ \sum_{j=1}^{i-1} P\{Y_k \leqslant c_k - \gamma_k \Delta_{1i}^0 \ (1 \leqslant k \leqslant j-1), Y_j > c_j - \gamma_j \Delta_{1i}^0\}$$

$$+\sum_{j=i}^{K} P\{Y_k \leqslant c_k - \gamma_k \Delta_{1i}^0 \ (1 \leqslant k \leqslant j-1), Y_j > d_j\}.$$

At $\Delta_1 = \Delta_{11}^0$, this expression equals

$$P(Y_1 > d_1) + P(Y_1 \leqslant d_1, Y_2 > d_2) + P(Y_1 \leqslant d_1, Y_2 \leqslant c_2 - \gamma_2 \Delta_{11}^0, Y_3 > d_3) + \cdots$$
$$+P(Y_1 \leqslant d_1, Y_2 \leqslant c_2 - \gamma_2 \Delta_{11}^0, \ldots, Y_{K-1} \leqslant c_{K-1} - \gamma_{K-1} \Delta_{11}^0, Y_K > d_K),$$

which is $< \alpha$ since $c_i - \gamma_i \Delta_{11}^0 < d_i$ for $i = 1, \ldots, K-1$ unless $\Delta_{11}^0 = \cdots = \Delta_{1,K-1}^0$ according to Theorem 4.

4.3 *Secondary Boundary Calculation for Known* ρ

The secondary boundary calculations given in the previous section have assumed the least favorable value of $\rho = 1$. As noted before, in practice ρ is generally less than 1. So it is of interest to determine how much the secondary boundary can be refined if $\rho < 1$ is assumed to be known. Analogous to Table 1 in Tamhane et al. (2010), we calculated the secondary boundary for selected values of ρ for $\alpha = 0.05$ in the top and the bottom panels of Table 3 for $K = 3$ and $K = 4$, respectively. This calculation involves simultaneous maximization with respect to Δ_1 and root finding with respect to d; the algorithm iterates between these two steps. The expression for $\alpha_2(\Delta_1, \rho)$ used in these calculations and its derivation are given in the Web Appendix.

[Table 3 about here.]

It is clear that the secondary boundary becomes more liberal as the assumed ρ gets smaller. However, if the true ρ is larger than the assumed ρ then the FWER under H_2 will not be controlled at level α. Therefore direct power comparisons between the secondary boundaries for different ρ are not possible. For example, if we compare the powers for the boundary combination OBF-POC for $\rho = 0.4$ and $\rho = 0.6$. Then clearly, the boundary combination for $\rho = 0.4$ will give a higher power than that for $\rho = 0.6$. However, if the true $\rho = 0.5$ then the

former will not control the FWER while the latter would. Thus the gain in power is obtained at the expense of excess secondary type I error.

5. Power Simulations

For studying secondary powers we will restrict attention to combinations of the OBF and POC boundaries. Since the OBF boundary is uniformly more powerful than the POC boundary for the primary endpoint, we will only consider OBF-POC and OBF-OBF combinations. If we choose the OBF-POC combination then since condition (5) in Theorem 4 is not satisfied, the POC boundary can be refined to level $\alpha' > \alpha$. If we use the OBF-OBF combination then condition (5) is satisfied; so the secondary OBF boundary cannot be refined. Thus we compare the powers of two primary-secondary boundary combinations: (1) α-level OBF boundary for the primary endpoint and α'-level POC boundary for the secondary endpoint, and (2) α-level OBF boundary for both the primary and secondary endpoints. Figure 2 gives the secondary power plots for these two combinations as functions of Δ_2 for $\alpha = 0.05, \rho = 0.5, \Delta_1 = 1.0, 3.0$ and $K = 3$. We see that for $\Delta_1 = 1.0$, the differences in the powers between the two boundary combinations are very small, but the boundary combination (1) is slightly more powerful. For $\Delta_1 = 3.0$, the boundary combination (1) is uniformly and substantially more powerful.

[Figure 2 about here.]

6. Example

To illustrate the methodology presented in this paper we use the data from the Randomized Aldactone Evaluation Study (RALES) (Pitt et al., 1999; Wittes et al., 2001). The goal of the study was to evaluate the efficacy of spironolactone for patients who had severe heart failure. The study used a multicenter double-blind randomized trial with 822 patients assigned to the treatment (25 mg of spironolactone daily) and 841 patients assigned to placebo. The

primary endpoint was death from all causes. The actual numbers of patients enrolled in the two arms were less than these numbers and are given in Table 4. There were a number of secondary endpoints, but none was evaluated formally. For illustration purposes we will use sudden cardiovascular (CV) deaths as the secondary endpoint.

The trial employed a group sequential design with Lan and Demets (1983) stopping boundary using the OBF error spending function: $\alpha(t) = 2[1-\Phi(z_{\alpha/2}/\sqrt{t})]$. The trial was monitored semi-annually by the Data Safety Monitoring Board (DSMB) and it was stopped early at the 5th look when the log-rank statistic for comparing the treatment and placebo group exceeded the critical threshold. The trial was planned assuming a total of 1080 all-cause deaths by the end of the trial. The looks occurred approximately at equal information times spaced 0.125 units (or 135 all-cause deaths) apart, which corresponds to $K = 8$ looks in a fixed GSD trial.

The one-sided 0.025-level critical values for the primary endpoint using the OBF error spending function are given in Table 4 along with the log-rank statistics for the observed number of deaths and the information fractions until the 5th look. We see that, in fact, the log-rank statistic crossed the boundary at the 4th look. In the actual trial this happened at the 5th look because the data on the number of deaths was not fully reported and thus was not up-to-date when the DSMB meetings took place.

Next we test the secondary endpoint at the 4th look. The data for the secondary endpoint is given in Table 5, where the information fractions are taken from Table 4, which are based on all-cause deaths. Since the expected total number of sudden CV deaths at the end of the trial was not specified, the information fractions based on sudden CV deaths cannot be computed. However, the total number of all-cause deaths and sudden CV deaths at each look are almost perfectly correlated with a correlation coefficient of 0.999. Therefore the correlations between the Y_i's needed to compute the secondary boundary, which are equal to the ratios of the total numbers of sudden CV deaths at different looks, are unaffected if we use all-cause

deaths instead. Another important point to note is that the alpha-spending for the secondary boundary is based on the information fractions for the primary boundary. But this change of time scale can be justified by the theory in Lan and Demets (1983) and also Proschan et al. (2006), pp. 87-89, and almost perfect correlation between the two sets of information fractions.

The log-rank statistic at the 4th look equals only 1.268 and fails to cross the Pocock boundary value of 2.505 calculated from the error spending function: $\alpha(t) = \alpha \ln[1+(e-1)t]$. At the 5th look, when the actual trial terminated, the log-rank statistic is 2.224, which still fails to exceed the Pocock critical value of 2.532. We could use the refined Pocock boundary by applying the method developed in Section 4.2 to the above error spending function. For this calculation we assumed that the number of looks is 8 and the timings of the future looks are equispaced at $(1-0.61)/3 = 0.13$ units apart, i.e., at $t_6 = 0.74, t_7 = 0.8, t_8 = 1$. The nominal significance level of the refined Pocock boundary turns out to be $\alpha' = 0.0473$. The corresponding critical value at the 5th look is 2.259, which is still not crossed by the secondary log-rank statistic. Thus we fail to declare statistical significance for the sudden CV death secondary endpoint.

In the above, we have assumed that the future looks are equispaced. For sensitivity analysis purposes, we considered two other sequences of future information times in which t_6-t_5, t_7-t_6 and t_8-t_7 are in 2:1:1 and 1:1:2 ratios. The corresponding information times are $t_6 = 0.81, t_7 = 0.90, t_8 = 1.$ and $t_6 = 0.71, t_7 = 0.81, t_8 = 1$. The α'-levels of the refined Pocock boundaries for these two sequences are 0.0480 and 0.0459, respectively, which don't differ very much from $\alpha' = 0.0473$ for the equispaced information fractions refined Pocock boundary. In making a positive claim for a secondary endpoint based on a refined test of the secondary endpoint, it could be advisable for investigators to report a similar sensitivity analysis.

[Table 4 about here.]

[Table 5 about here.]

7. Extensions

The procedure $\mathcal{P}_a$ tests H_2 only once and if it is not rejected then the trial stops. In practice, the DMC may choose not to stop the trial at the interim look when H_1 is rejected but H_2 is not rejected if the overall benefit/risk is not fully convincing. In that case a DMC may want to continue the trial and sequentially test H_2 until it is rejected or the trial stops. We denote this procedure by $\mathcal{P}_b$. Glimm et al. (2010) referred to this procedure as the overall hierarchical rule. They gave an expression for its secondary type I error for $K = 2$. Its straightforward generalization and an upper bound on it are given in the following theorem.

THEOREM 5: *Denote the secondary type I errors of procedures* $\mathcal{P}_a$ *and* $\mathcal{P}_b$ *by* $\alpha_2^a(\Delta_1, \rho)$ *and* $\alpha_2^b(\Delta_1, \rho)$*, respectively, where* $\alpha_2^a(\Delta_1, \rho)$ *is the same as* $\alpha_2(\Delta_1, \rho)$ *given by* (2)*. Then we have*

$$\begin{aligned}\alpha_2^b(\Delta_1, \rho) &= \alpha_2^a(\Delta_1, \rho) \\ &\quad + \sum_{i=1}^{K-1} \sum_{j=i+1}^{K} P(X_1 \leqslant c_1, \cdots, X_{i-1} \leqslant c_{i-1}, X_i > c_i, Y_i \leqslant d_i, \cdots, Y_{j-1} \leqslant d_{j-1}, Y_j > d_j) \\ &\leqslant 1 - P_{H_2}\{Y_1 \leqslant d_1, \ldots, Y_K \leqslant d_K\}. \end{aligned} \tag{7}$$

This upper bound is achieved if and only if $\rho = 1$ *and* $\Delta_1 \geqslant \max_{1 \leqslant i \leqslant K}(\Delta_{1i}^0)$.

The proof of the theorem is given in the Web Appendix. Note that this upper bound is equal to α if and only if $\{d_1, \ldots, d_K\}$ is an α-level boundary. Thus under the least favorable configuration of $\rho = 1$ and $\Delta_1 \geqslant \max_{1 \leqslant i \leqslant K}(\Delta_{1i}^0)$, the procedure $\mathcal{P}_b$ must use the regular α-level boundary for the secondary endpoint; any refinement is not possible.

Some other useful extensions that could be followed up include multiple primary and secondary endpoints, either unordered or hierarchically ordered.

8. Concluding Remarks

Some limitations of the proposed methodology stemming from the underlying assumptions should be noted here. One assumption is that ρ and Δ_1 are assumed to remain fixed throughout the trial. In practice, they might vary if the patient population changes over time. If the trial is designed under the least favorable configuration of $\rho = 1$ and $\Delta_1 = \text{argmax}\{\alpha_2(\Delta_1, \rho = 1)\}$ then the procedure will control the FWER for all ρ and Δ_1 and so will be robust to changes in these parameters.

Although the theory developed is for the case of a fixed GSD with a prespecified number and timings of the looks, we have shown through an example, how this theory can be applied to the flexible GSD using the error spending function approach of Lan and Demets (1983). Our general recommendation is to use this latter approach with a O'Brien-Fleming type boundary for the primary endpoint and a refined Pocock type boundary for the secondary endpoint.

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Supplementary Materials

Web Appendix referenced in Section 3 is available with this paper at the Biometrics website on Wiley Online Library.

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Appendix

Proof of a Special Case of Theorem 1. We consider the special case $k^* = K-1$, i.e., $a_i > b_i$ for $1 \leqslant i \leqslant K-1$ and $a_K > b_K$. However, we assume that the distribution of $(X_1, \ldots, X_K)$ has monotone likelihood ratio (MLR) thus relaxing the assumption of multivariate normality.

Denote by A the group sequential test defined by the boundary $(a_1, \ldots, a_K)$ and by B the group sequential test defined by the boundary $(b_1, \ldots, b_K)$, where $a_i > b_i$ $(1 \leqslant i \leqslant K-1)$ and $a_K < b_K$. Both A and B are α-level tests. Denote by $f_\delta(x_1, \ldots, x_K)$ the joint probability

density function (p.d.f.) of $(X_1, \ldots, X_K)$ under δ. When $\delta = 0$ this is the joint null p.d.f. under $H_1 : \delta_1 = 0$.

First consider the $K = 2$ case, where $a_1 > b_1, a_2 < b_2$. Equality of type I errors of A and B yields the equation

$$\int_{-\infty}^{b_1}\int_{-\infty}^{b_2} f_0(x_1, x_2)dx_1dx_2 = \int_{-\infty}^{a_1}\int_{-\infty}^{a_2} f_0(x_1, x_2)dx_1dx_2.$$

Write the LHS of the above equation as

$$\int_{-\infty}^{b_1}\int_{-\infty}^{a_2} f_0(x_1, x_2)dx_1dx_2 + \int_{-\infty}^{b_1}\int_{a_2}^{b_2} f_0(x_1, x_2)dx_1dx_2$$

and the RHS as

$$\int_{-\infty}^{b_1}\int_{-\infty}^{a_2} f_0(x_1, x_2)dx_1dx_2 + \int_{b_1}^{a_1}\int_{-\infty}^{a_2} f_0(x_1, x_2)dx_1dx_2.$$

Canceling the common term from both sides of the equation we get

$$\int_{-\infty}^{b_1}\int_{a_2}^{b_2} f_0(x_1, x_2)dx_1dx_2 = \int_{b_1}^{a_1}\int_{-\infty}^{a_2} f_0(x_1, x_2)dx_1dx_2. \tag{A.1}$$

The LHS of the above equation is the probability under H_1 that A rejects H_1 but B does not and the RHS is the probability under H_1 that B rejects H_1 but A does not.

To show that A is uniformly more powerful than B under $\delta > 0$ we need to show that

$$\int_{-\infty}^{b_1}\int_{a_2}^{b_2} f_\delta(x_1, x_2)dx_1dx_2 > \int_{b_1}^{a_1}\int_{-\infty}^{a_2} f_\delta(x_1, x_2)dx_1dx_2.$$

Let

$$r_\delta(x_1, x_2) = \frac{f_\delta(x_1, x_2)}{f_0(x_1, x_2)}$$

denote the likelihood ratio (LR) of the joint p.d.f.'s under $\delta > 0$ and under $\delta = 0$. Then since x_2 is a sufficient statistic for δ, $r_\delta(x_1, x_2)$ is a function only of x_2, so we can denote it simply by $r_\delta(x_2)$. Then by the monotone likelihood ratio (MLR) property, it follows that $r_\delta(x_2)$ is an increasing function of x_2. Therefore we can write

$$\int_{-\infty}^{b_1}\int_{a_2}^{b_2} f_\delta(x_1, x_2)dx_1dx_2 \;=\; \int_{-\infty}^{b_1}\int_{a_2}^{b_2} f_0(x_1, x_2)r_\delta(x_2)dx_1dx_2$$

$$
\begin{aligned}
&> r_\delta(a_2) \int_{-\infty}^{b_1} \int_{a_2}^{b_2} f_0(x_1, x_2) dx_1 dx_2 \\
&= r_\delta(a_2) \int_{b_1}^{a_1} \int_{-\infty}^{a_2} f_0(x_1, x_2) dx_1 dx_2 \quad \text{(from (A.1))} \\
&> \int_{b_1}^{a_1} \int_{-\infty}^{a_2} f_0(x_1, x_2) r_\delta(x_2) dx_1 dx_2 \\
&= \int_{b_1}^{a_1} \int_{-\infty}^{a_2} f_\delta(x_1, x_2) dx_1 dx_2,
\end{aligned}
$$

which was to be shown.

This result can be generalized to the $K > 2$ case by defining two sets of sample paths:

$$\mathcal{A} = \{(x_1, \ldots, x_{K-1}) : \text{Neither } A \text{ nor } B \text{ rejects in stages } 1, \ldots, K-1\}$$

and

$$\mathcal{B} = \{(x_1, \ldots, x_{K-1}) : B \text{ rejects but } A \text{ does not reject in stages } 1, \ldots, K-1\}.$$

In $\mathcal{A}$ we have $x_i \leqslant b_i < a_i$ and in $\mathcal{B}$ we have $b_i < x_i \leqslant a_i$ for $i = 1, \ldots, K-1$. For $K = 2$, $\mathcal{A} = [-\infty, b_1]$ and $\mathcal{B} = [b_1, a_1]$. If $(x_1, \ldots, x_{K-1}) \in \mathcal{A}$ and $x_K \in [a_K, b_K]$ then A rejects H_1 but B does not. On the other hand, if $(x_1, \ldots, x_{K-1}) \in \mathcal{B}$ and $x_K < a_K$ then B rejects H_1 but A does not. The proof then essentially proceeds as in the $K = 2$ case with obvious extensions (e.g., x_K replacing x_2). □

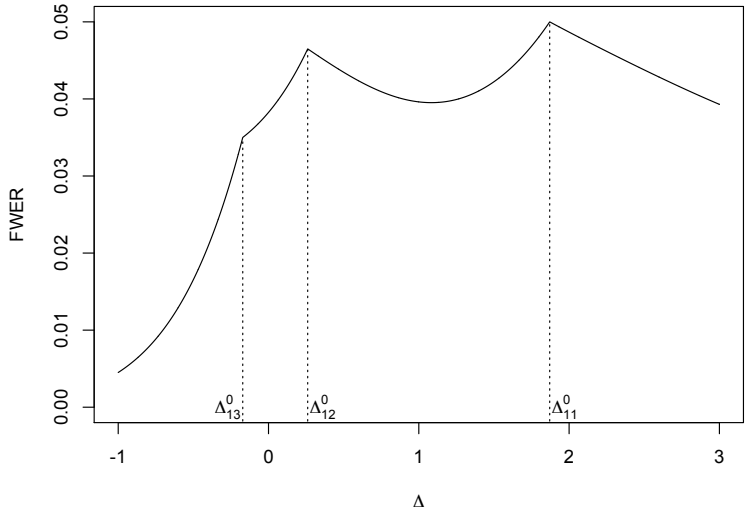

Figure 1. FWER Plot for OBF primary and Refined POC secondary boundary for $K = 3$

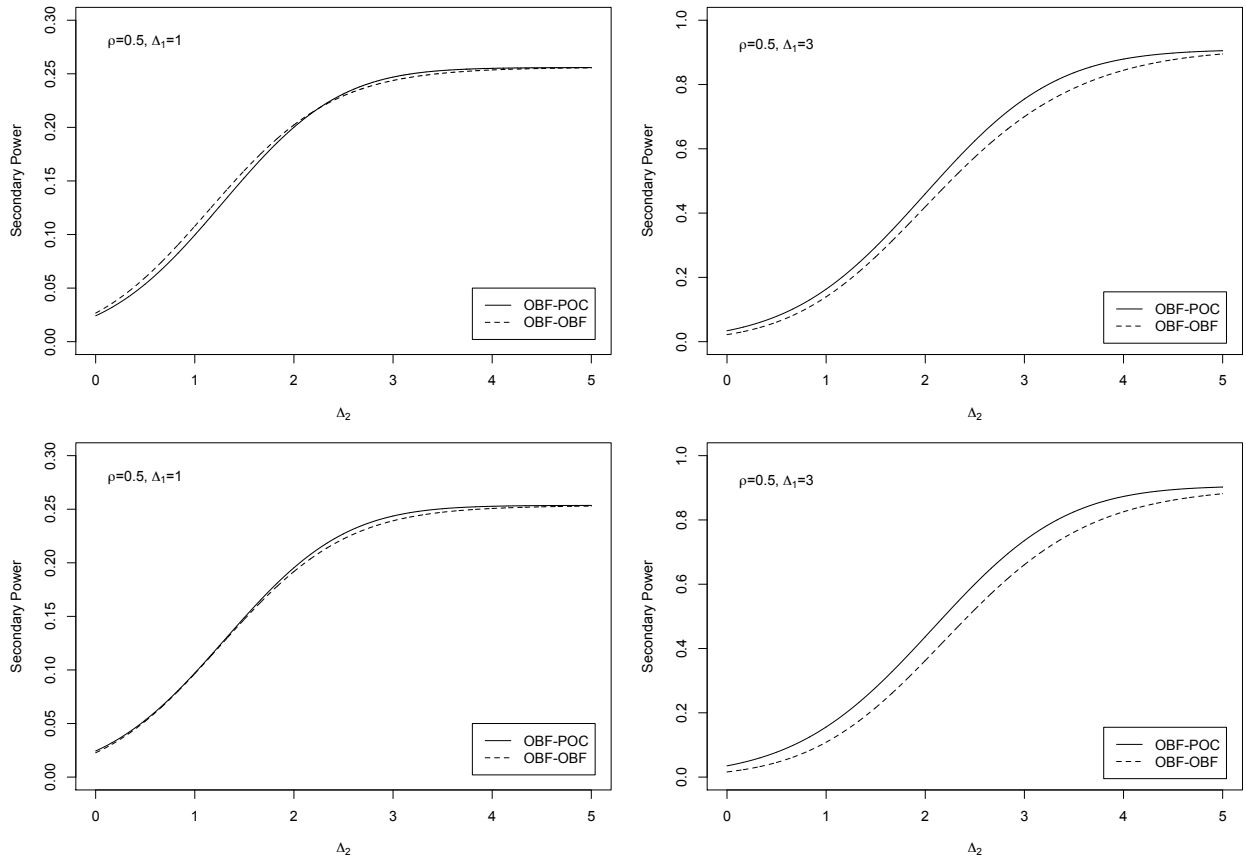

Figure 2. Secondary power as a function of Δ_2, $\rho = 0.5$. $K = 2$, $\Delta_1 = 1$ (top left panel) and $\Delta_1 = 3$ (top right panel), $K = 3$, $\Delta_1 = 1$ (bottom left panel) and $\Delta_1 = 3$ (bottom right panel)

Table 1
Original and refined boundaries[1,2,3] *($\alpha = 0.05$)*

$K = 2$	Original Boundaries		Refined Secondary Boundary	
Primary	Secondary	α_2	Secondary	α'
OBF: $c = 1.678$	POC: $d = 1.876$	0.050	Secondary boundary not refined	
POC: $c = 1.876$	OBF: $d = 1.678$	0.039	OBF: $d = 1.570$	0.063

$K = 3$	Original Boundaries		Refined Secondary Boundary	
Primary	Secondary	α_2	Secondary	α'
OBF: $c = 1.710$	POC: $d = 1.992$	0.039	POC: $d = 1.881$	0.063
POC: $c = 1.992$	OBF: $d = 1.710$	0.033	OBF: $d = 1.535$	0.073

$K = 4$	Original Boundaries		Refined Secondary Boundary	
Primary	Secondary	α_2	Secondary	α'
OBF: $c = 1.733$	POC: $d = 2.067$	0.033	POC: $d = 1.877$	0.075
POC: $c = 2.067$	OBF: $d = 1.733$	0.028	OBF: $d = 1.513$	0.080

[1] OBF primary boundary: $(c\sqrt{2}, c)$, OBF secondary boundary: $(d\sqrt{2}, d)$.
[2] POC primary boundary: (c, c), POC secondary boundary: (d, d).
[3] For the refined secondary boundary $\alpha_2 = \alpha = 0.05$ and $\alpha' > \alpha$ is its nominal α-level.

Table 2
Δ_{1i}^0 *Values for original and refined boundaries* ($K = 3, \alpha = 0.05$)

Boundary Combination	Original Boundaries			Refined Boundaries		
	Δ_{11}^0	Δ_{12}^0	Δ_{13}^0	Δ_{11}^0	Δ_{12}^0	Δ_{13}^0
OBF-POC	1.678	0.124	−0.283	1.871	0.261	−0.171
POC-OBF	−1.678	−0.124	0.283	−1.153	0.138	0.458

Table 3
Secondary boundary critical constants d for different combinations of the OBF and POC boundaries for $K = 3$ (top panel), $K = 4$ (bottom panel), $\alpha = 0.05$ and equispaced information times

$K = 3$	Primary Boundary	Secondary Boundary	ρ = 0.0	0.2	0.4	0.6	0.8	1.0
	OBF	OBF	1.356	1.378	1.408	1.451	1.519	1.710
			(2.945)	(2.481)	(2.062)	(1.524)	(1.002)	(0)
	OBF	POC	1.645	1.670	1.698	1.729	1.767	1.881
			(∞)	(4.376)	(3.561)	(2.940)	(2.596)	(1.871)
	POC	OBF	1.185	1.211	1.245	1.291	1.359	1.534
			(3.001)	(2.587)	(2.143)	(1.667)	(1.128)	(0.458)
	POC	POC	1.645	1.666	1.695	1.736	1.798	1.992
			(∞)	(3.807)	(2.987)	(2.148)	(1.319)	(0)

The OBF secondary boundary is $d_i = d\sqrt{3/i}$, the POC secondary boundary is $d_i = d$.

$K = 4$	Primary Boundary	Secondary Boundary	ρ = 0.0	0.2	0.4	0.6	0.8	1.0
	OBF	OBF	1.321	1.345	1.378	1.425	1.500	1.733
			(2.884)	(2.461)	(2.043)	(1.472)	(0.956)	(0)
	OBF	POC	1.645	1.669	1.695	1.726	1.767	1.877
			(∞)	(5.752)	(3.507)	(2.445)	(1.547)	(0.812)
	POC	OBF	1.140	1.166	1.201	1.249	1.323	1.513
			(3.011)	(2.597)	(2.160)	(1.655)	(1.145)	(0.554)
	POC	POC	1.645	1.674	1.712	1.761	1.835	2.067
			(∞)	(3.883)	(3.014)	(2.200)	(1.314)	(0)

The OBF secondary boundary is $d_i = d\sqrt{4/i}$, the POC secondary boundary is $d_i = d$.

Table 4
One-Sided 0.025-Level Lan-DeMets Boundary Using the O'Brien-Fleming Error Spending Function for the Primary Endpoint, Observed Number of All-Cause Deaths with Associated Log-Rank Statistics

Look	Placebo		Treatment		Information	Relative	Observed	Critical
No.	Enrolled	Deaths	Enrolled	Deaths	Fraction	Risk	X_i	c_i
1	563	81	543	59	0.130	0.755	1.820	6.117
2	830	189	809	139	0.304	0.755	2.719	3.903
3	830	254	810	199	0.419	0.803	2.744	3.278
4	830	327	811	251	0.535	0.786	3.357	2.876
5	831	380	811	279	0.610	0.752	4.414	2.704

Table 5

One-Sided 0.025-Level Lan-DeMets Boundary Using the Regular and Refined Pocock Error Spending Function for the Secondary Endpoint, Observed Number of Sudden CV Deaths with Associated Log-Rank Statistics

Look	Placebo		Treatment		Information*	Relative	Observed	Regular Pocock	Refined Pocock
No.	Enrolled	Deaths	Enrolled	Deaths	Fraction	Risk	Y_i	c_i	c_i
1	563	29	543	15	0.130	0.536	2.073	2.574	2.345
2	830	57	809	44	0.304	0.792	1.270	2.478	2.228
3	830	71	810	59	0.419	0.852	1.113	2.519	2.257
4	830	91	811	76	0.535	0.855	1.268	2.505	2.236
5	831	109	811	82	0.610	0.771	2.224	2.532	2.259

* These information fractions are based on all-cause mortality and are the same as in Table 4.