Reply to Comments

The comments from Englert and Kieser considered an adaptive design, where the over enrollment of the second stage can potentially depend on the observed responses in the first stage. However, such an adaptive design could be challenging because it involves the change of the original two-stage design and hypothesis setting, while the trial is already ongoing. The study protocol may need to be amended, and hence, the integrity of the trial becomes questionable. Furthermore, our method is applicable to the case for which the study team may want to add more subjects after claiming success of the trial based on the Simon two-stage design.

On the other hand, our method can be easily extended to accommodate this design by allowing the second stage enrollment size n_2' to depend on x_1, denoted as $n_2'(x_1)$. The overall Type I error is

$$\text{Type I error} = \sum_{x_1=R_1}^{n_1} \binom{n_1}{x_1} \pi_0^{x_1}(1-\pi_0)^{n_1-x_1} \sum_{x_2=R_2'(x_1)}^{n_2'(x_1)} \binom{n_2'(x_1)}{x_2} \pi_0^{x_2}(1-\pi_0)^{n_2'(x_1)-x_2}.$$

Thus, for a given set of $\{n_2'(x_1)\}$, we can still use the same approximation in the paper to choose $\{R_2'(x_1)\}$ so that this Type I error is controlled below α, while the power is maximized. For this particular example, if we decide to only increase enrollment from 31 to 46 in the second stage when $R_1 = 6$ while stick to the original Simon's design, the critical values using our method and Koyoma and Chen's method are given in the following table. We can observe that our method is still more likely, although slightly in this setting, to reject the null. Indeed, the Type I error from our method is 0.0446 with power 0.8110, while the Type I error from Koyama and Chen's method is 0.0441 with power 0.8106.

Table I. One Example of $R_2'(x_1)$.

	AG		KC	
$X_1 = x_1$	$R_2'(x_1)$	$R_t'(x_1) = R_2'(x_1) + x_1$	$R_2'(x_1)$	$R_t'(x_1) = R_2'(x_1) + x_1$
6	19	25	19	25
7	12	19	12	19
8	11	19	11	19
9	10	19	10	19
10	8	18	9	19
11	7	18	8	19
12	6	18	7	19
13	5	18	6	19
14	4	18	5	19
15	2	17	4	19

DONGLIN ZENG, FEI GAO, JOSEPH G. IBRAHIM
Department of Biostatistics
University of North Carolina
Chapel Hill, NC 27599

KUOLUNG HU, CATHERINE JIA
Global Biostatistical Science, Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320