PharmaSUG 2025 — Paper ST-004

Promising Zone Designs for Sample Size Re-estimation in Clinical Trials: Graphical Approaches Using SAS

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Abstract

The promising zone design is a highly valuable tool for achieving more efficient and effective drug development. It allows for modifications of sample size based on unblinded interim data, enhancing trial efficiency and the likelihood of success. During the design stage of a trial, clear communication among various functional stakeholders is crucial to understand and align on the proposed promising zone design. Graphical displays can effectively facilitate this communication process. However, there are currently no resources in SAS to readily create these desired graphical displays. This paper presents SAS programs for producing these graphical displays and includes brief yet informative key underlying technical details. An example is provided to demonstrate its implementation. Hopefully, these accessible SAS programs will encourage broader application of promising zone designs, which are expected to play an increasingly important role in developing new therapies.

Keywords: Promising Zone; Sample Size Re-estimation; Clinical Trial; Conditional Power; SAS.

1 Introduction

In the drug development, ensuring the efficacy and safety of new therapies requires robust methodologies that can effectively balance the ethical considerations of patient welfare with the scientific rigor needed for reliable results. Among the various methodological innovations, the promising zone designs proposed by Hsiao et al. (2019) and Mehta and Pocock (2011) has emerged as notable approaches, aimed at enhancing the efficiency and ethical soundness of clinical trials.

The promising zone design represents an intriguing adaptive design strategy that allows for informed modification of sample size based on unblinded interim data analysis. This approach identifies a '*promising zone*', a range within which the treatment shows potential efficacy, thereby guiding decisions on whether to continue, modify, or terminate the trial. This strategy can maximize the probability of success in clinical trials while minimizing exposure to ineffective treatments. Unlike traditional fixed designs, promising zone designs offer greater flexibility and resource efficiency by enabling early adjustments, which can lead to faster and more cost-effective development of new treatments.

During the design stage of a trial, efficient communication across different functional stakeholders is critical to understanding and aligning on a proposed promising zone design. The graphical displays presented in

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Hsiao et al. (2019) and Mehta and Pocock (2011) can conveniently provide a tool to facilitate the process. However, there are limited resources in SAS to readily produce the desired graphical displays. In this paper, we presents the programs using SAS based on the underlying technical details of the promising zone design to create these graphical displays. We hope that providing these user-friendly SAS programs will support the expanded use of promising zone designs, which are likely to play an increasingly important role in developing emerging therapies.

The structure of this paper is as follows. Section 2 introduces a unified general technical notations used throughout the paper. Section 3 provides a detailed motivating example, which will be utilized to create graphical displays for the promising zone designs. Section 4, Section 5, along with Appendix 1, offer the technical details required for generating the graphical displays based on the promising designs proposed by Hsiao et al. (2019) and Mehta and Pocock (2011), respectively. Section 6 briefly describes the SAS programming used to produce these graphs, and all SAS macros and programs are available at `https://github.com/tonygit578/SAS-macro-for-promising-zone`. The paper concludes with final remarks in Section 7.

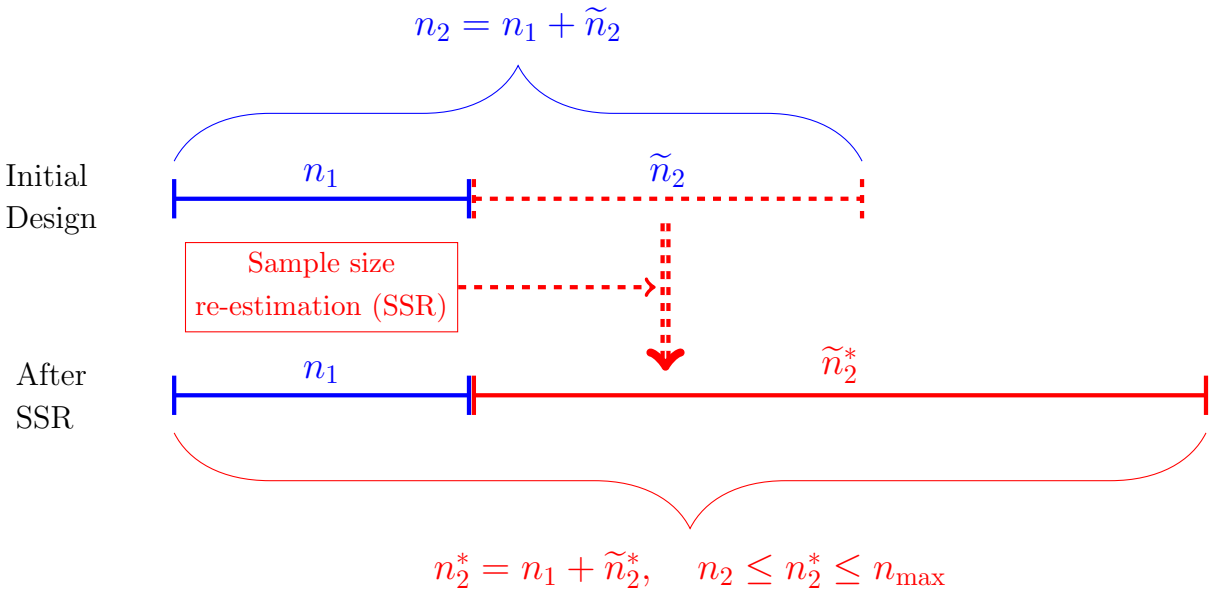


Figure 1: A general framework for a two-stage trial involves re-estimating the sample size for stage 2 based on the IA conducted in stage 1. The maximum allowable sample size for the trial, denoted as $n_{\max}$, is pre-specified.

2 General Notations

We generally follow the notations used in Mehta and Pocock (2011) and Hsiao et al. (2019). Suppose we initially design a two-stage trial with 1:1 randomization ratio between the treatment and the control groups. An interim analysis (IA) and a final analysis are conducted after enrolling n_1 patients for the first stage and n_2 patients for the entire study, respectively. Let $\widetilde{n}_2$ represent the incremental sample size between stage 1 and stage 2, so $n_2 = n_1 + \widetilde{n}_2$. Define $n_{\max}$ as the pre-specified maximum allowable sample size for the trial, generally determined by the feasible budget and patient recruitment capacity. At the end of stage 1, an unblinded interim analysis and sample size re-estimation (SSR) are performed, potentially increasing the incremental sample size from $\widetilde{n}_2$ to $\widetilde{n}_2^*$. Consequently, the adapted total sample size could be

$n_2^* = n_1 + \widetilde{n}_2^*$. Typically, we expect $n_2 \leq n_2^* \leq n_{\max}$. A general schematic setup is illustrated in Figure 1. Of note, in an event-driven trial, the power of study depends on the number of event of interest rather number of patients. Without loss of generality, the above notations can be interpreted accordingly based on specific scenario.

Let δ be the unknown true treatment effect between the test (t) group and the control (c) group. This effect can be expressed as the difference: $\delta = \mu_t - \mu_c$ where μ is mean of a normally distributed random variable, or as difference in porportion $\delta = p_t - p_c$ for a binary variable. It can also be expressed as the logarithm of hazard ratio (HR), such as $\delta = -\log(\text{HR})$ for time to event variable, or the logarithm of the odds ratio (OR), such as $\delta = -\log(\text{OR})$ for a binary variable. This approach easily unifies the subsequent development within a framework of normal distribution.

Then, let $\widehat{\delta}_1$ be the estimate of δ based on n_1 patients from stage 1, and its corresponding test statistic is $Z(t_1) = Z_1 = \widehat{\delta}_1/\text{s.e.}(\widehat{\delta}_1) = z_1$, where t_1 represents the information fraction for stage 1, as elaborated in Appendix 1, here $\text{s.e.}(\widehat{\delta}_1) = 2\widehat{\sigma}_1/\sqrt{n_1}$.

The IA at the end of stage 1 is designed to determine whether the final sample size of the trial, n_2^*, should be increased beyond the originally planned n_2. Conditional power is a tool used to aid in potential sample size re-estimation and adaption. The general formula to calculate the conditional power is

$$\text{CP}_\delta\left(z_1, \widetilde{n}_2\right) = P_\delta\left(Z_2 \geq z_{1-\alpha/2} | z_1\right) = \Phi\left[E\left[\text{Z}(t_1)\right]\sqrt{\frac{\widetilde{n}_2}{n_1}} - \frac{z_{1-\alpha/2}\sqrt{n_2} - \sqrt{n_1}z_1}{\sqrt{n_2 - n_1}}\right] \tag{1}$$

where $\Phi(\bullet)$ denotes the univariate standard normal cumulative distribution function, $z_{1-\alpha/2} = \Phi^{-1}(1-\alpha/2)$, and $Z_2 = \widehat{\delta}_2/\text{s.e.}(\widehat{\delta}_2)$ is the test statistic at the final analysis based on originally planned n_2 patients, and $\widehat{\delta}_2$ is the estimate of δ. The detailed derivation of (1) from Brownian motion perspective is included in Appendix 1.

The key component in (1) is $E\left[\text{Z}(t_1)\right]$ which can take different forms, hence, leading to various methods based on the conditional power. Using $\delta = -\log(\text{HR})$ as an example to illustrate the idea, the asymptotic variance for its estimate $\widehat{\delta}$ is $4/n_2$ where n_2 is the total number of events of interest. Given that the test statistic at IA is $\text{Z}(t_1) = \widehat{\delta}_1/\sqrt{4/n_1} = \widehat{\delta}\sqrt{n_1}/2$, we can express $E\left[\text{Z}(t_1)\right]$ in (1) as $E\left[\text{Z}(t_1)\right] = \delta\sqrt{n_1}/2$. Therefore, if we set δ as the minimum clinically meaningful treatment effect, i.e. $\delta = \delta_{\min}$, we then have $E\left[\text{Z}(t_1)\right] = \delta_{\min}\sqrt{n_1}/2$. This is the basic rationale used in Hsiao et al. (2019).

In terms of the promising zone designs for sample size re-estimation utilizing the tool of conditional power (1), the significant difference between the two proposals by Mehta and Pocock (2011) and by Hsiao et al. (2019) lies in how they calculate the conditional power, specifically the calculation of $E\left[\text{Z}(t_1)\right]$ in (1). Since the true treatment effect δ is unknown, the proposal for $E\left[\text{Z}(t_1)\right]$ is either to substitute an estimate obtained from the IA or to use a constant with desirable property. Namely, the proposal by Mehta and Pocock (2011) takes $E\left[\text{Z}(t_1)\right]$ as z_1 (i.e. corresponding to $\widehat{\delta}_1$) which is the observed test statistic from IA at the end of stage 1. In contrast, the proposal by Hsiao et al. (2019), set $E\left[\text{Z}(t_1)\right]$ to the test statistic corresponding to the minimum clinically meaningful treatment effect $\delta_{\min}$.

We now use a clinical trial design example to demonstrate the detailed implementation needed to generate the graphical displays like Figure 2 and Figure 3, which can be efficiently used to communicate with different stakeholders in a clinical trial team.

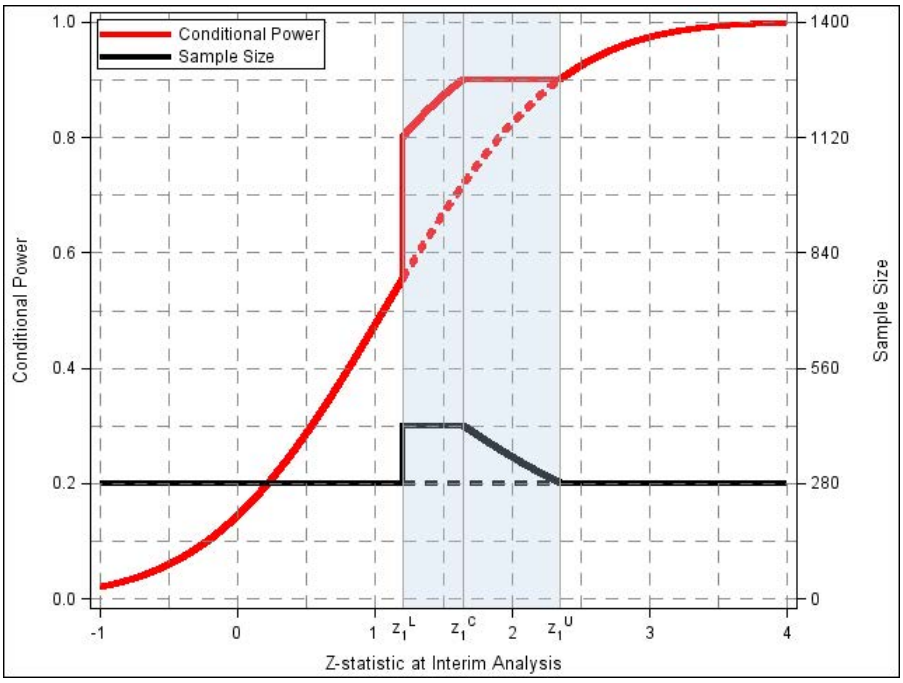


Figure 2: Conditional power and sample size of constrained promising zone design (Hsiao et al., 2019) with minimum clinically meaningful treatment effect of hazard ratio (HR) being 0.75, the following parameters are defined $\delta_{\min} = -\log(0.75) = 0.28768$, $\text{CP}_{\min} = 0.8$, and $\text{CP}_{\max} = 0.9$. The design results in the values of $z_1^{(L)} = 1.2065$, $z_1^{(C)} = 1.6464$, and $z_1^{(U)} = 2.3514$.

3 Motivating Example

We take the same example used in Hsiao et al. (2019) to demonstrate how to create Figure 2 and Figure 3. Consider a pivotal clinical trial designed for patients with advanced pancreatic cancer, where patients are randomized in 1:1 ratio to either the treatment group or the control group. The primary endpoint of the trial is progression-free survival (PFS), with median PFS for the control group being assumed as 8.5 months. While the treatment is believed to offer benefits, there is uncertainty about the extent of this benefit. Specifically, the HR is anticipated to range from an optimistic 0.67 to a pessimistic 0.75, with HR = 0.75 considered the minimum clinically meaningful treatment benefit. The implications of choosing either 0.67 or 0.75 affect the investment budget and project timeline differently. For a one-sided type I error rate of 0.025, we consider both optimistic and a pessimistic scenarios. That is,

1. in the pessimistic situation with HR = 0.75 (i.e. $\delta = -\log(0.75) = 0.28768$): assuming a 36-month accrual period and 48 months to complete the study, recruiting 600 patients to achieve 500 PFS events will provide a statistical power of 90% for the trial. This approach requires a substantial up-front financial commitment, which can be particularly challenging for smaller biotech companies. As an alternative,

2. in the optimistic situation with HR = 0.67 (i.e. $\delta = -\log(0.67) = 0.40048$): assuming 28-month accrual period and a total study duration of 40 months, 280 PFS events from 350 randomized patients will give a 92% statistical power for the study. However, if the true HR is actually 0.75 and other design parameters remain unchanged, the power will decrease to 67%. This scenario is more affordable and manageable, particularly for small biotech companies facing resource constraints.

A promising zone design can address the uncertainty about clinical benefit and facilitate milestone-based investment. Specifically, the study starts with a two-stage design based on the optimistic scenario with HR = 0.67. This leads to number of events for stage 1 $n_1 = 140$ and a planned number of events for final analysis $n_2 = 280$ as shown in Figure 1. An IA will be conducted after the first $n_1 = 140$ PFS events, if the conditional power at this IA falls within the pre-specified promising zone, additional investment will be made in the study. It is important to note that the maximum allowable number of PFS events for the trial is $n_{\max} = 420$ which is generally less than the number of PFS events required under the pessimistic situation (e.g. 500 in this example). Moreover, in this example, $\delta_{\min} = -\log(0.75) = 0.28768$.

4 Constrained Promising Zone Design by Hsiao et al. (2019)

Following the approach in Hsiao et al. (2019), we also use $\delta = -\log(\text{HR})$ to illustrate the concept. Substituting $E[\text{Z}(t_1)]$ with $\delta_{\min}\sqrt{n_1}/2$ in (1) yields the calculation of conditional power at IA as

$$\text{CP}_{\delta_{\min}}(z_1, \widetilde{n}_2) = \Phi\left[\delta_{\min}\frac{\sqrt{n_1}}{2}\sqrt{\frac{\widetilde{n}_2}{n_1}} - \frac{z_{1-\alpha/2}\sqrt{n_2} - \sqrt{n_1}z_1}{\sqrt{n_2 - n_1}}\right] = \Phi\left[\frac{\delta_{\min}}{2}\sqrt{\widetilde{n}_2} - \frac{z_{1-\alpha/2}\sqrt{n_2} - \sqrt{n_1}z_1}{\sqrt{n_2 - n_1}}\right] \quad (2)$$

With the constraint of $n_2 \le n_2^* \le n_{\max}$, the promising zone is defined as the region

$$\text{CP}_{\min} \le \text{CP}_{\delta_{\min}}(z_1, \widetilde{n}_2) \le \text{CP}_{\max} \quad (3)$$

where the values of $\text{CP}_{\min}, \text{CP}_{\max}$, and $\delta_{\min}$ are all *pre-specified* based on the clinical expectations. $\text{CP}_{\min}$ and $\text{CP}_{\max}$ are the minimum and maximum requirement for conditional power, respectively. Typically, $\text{CP}_{\max}$ is set to $1 - \beta$.

For promising zone in (3), with $\text{CP}_{\min}, \text{CP}_{\max}$, and $\delta_{\min}$ being pre-specified, and $\text{CP}_{\delta_{\min}}(z_1, \widetilde{n}_2)$ being a function of z_1 and $\widetilde{n}_2$ or $\widetilde{n}_2^*$, the implication of this promising zone is to find a new sample size $\widetilde{n}_2^*$ under which we can obtain the values of z_1 corresponding to their $\text{CP}_{\min}$ and $\text{CP}_{\max}$, respectively. Therefore, the task is essentially to find $\widetilde{n}_2^*$ and z_1. However, based on Figure 2 and Figure 3, we know the values of $\widetilde{n}_2^*$ at several hinging points. Then, to produce Figure 2 and Figure 3, the main objective is to find the values of z_1 to achieve the desired $\text{CP}_{\min}$ and $\text{CP}_{\max}$. This rationale leads to three key hinging points as $z_1^{(L)}$, $z_1^{(C)}$, and $z_1^{(U)}$, where $z_1^{(L)}$ marks the start of the promising zone, and $z_1^{(U)}$ marks the end of the promising zone.

Based on (2), the calculation of all three hinging points $z_1^{(L)}$, $z_1^{(C)}$, and $z_1^{(U)}$ depends on the equation (4). However, each $z_1^{(\bullet)}$ is obtained as shown in equation (5) by setting different values for $\widetilde{n}_{(\bullet)}$ and $\text{CP}_{(\bullet)}$ in (4), where $z_{\text{CP}_{(\bullet)}} = \Phi^{-1}[\text{CP}_{(\bullet)}]$.

$$\Phi\left[\frac{\delta_{\min}}{2}\sqrt{\widetilde{n}_{(\bullet)}} - \frac{z_{1-\alpha/2}\sqrt{n_2} - \sqrt{n_1}z_1^{(\bullet)}}{\sqrt{n_2 - n_1}}\right] = \text{CP}_{(\bullet)} \quad (4)$$

$$\Longrightarrow z_1^{(\bullet)} = z_{1-\alpha/2}\sqrt{\frac{n_2}{n_1}} - \sqrt{\frac{n_2 - n_1}{n_1}}\left(\frac{\delta_{\min}}{2}\sqrt{\widetilde{n}_{(\bullet)}} - z_{\text{CP}_{(\bullet)}}\right) \quad (5)$$

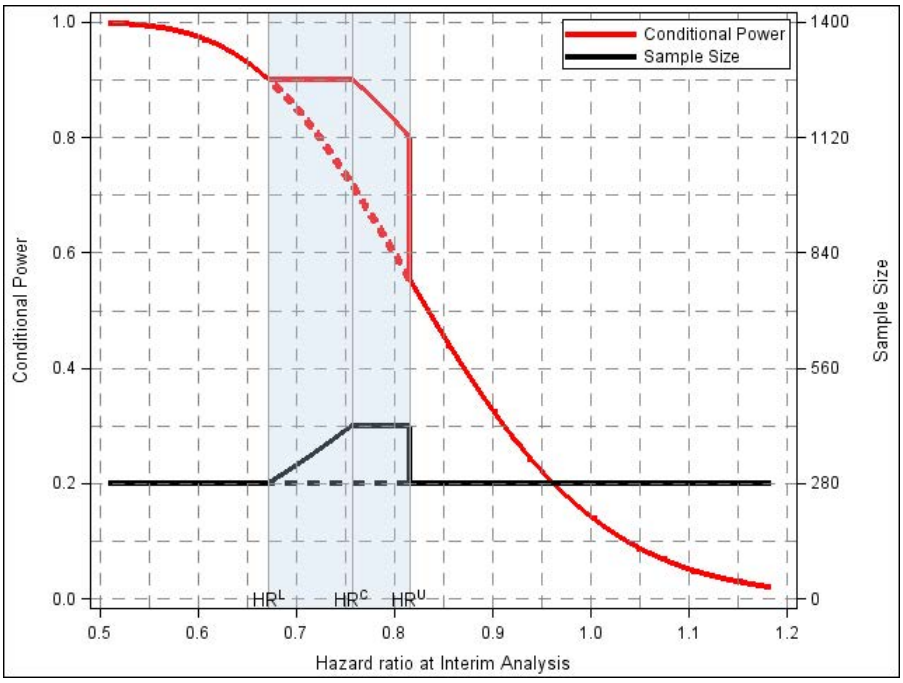


Figure 3: Conditional power and sample size of constrained promising zone design (Hsiao et al., 2019) with minimum clinically meaningful treatment effect of hazard ratio (HR) being 0.75, the following parameters are defined $\delta_{\min} = -\log(0.75) = 0.28768$, $\text{CP}_{\min} = 0.8$, and $\text{CP}_{\max} = 0.9$. The design results in the values of $\text{HR}^{(L)} = 0.67203$, $\text{HR}^{(C)} = 0.75708$, and $\text{HR}^{(U)} = 0.81551$.

4.1 Find $z_1^{(L)}$ with constraint of $\text{CP}_{\delta_{\min}}\left(z_1^{(L)}, \widetilde{n}_{\max}\right) = \text{CP}_{\min}$

The value of $z_1^{(L)}$ can be calculated from the constraint $\text{CP}_{\delta_{\min}}\left(z_1^{(L)}, \widetilde{n}_{\max}\right) = \text{CP}_{\min}$. That is, in equation (5), $\widetilde{n}_{(\bullet)}$ takes the value $\widetilde{n}_{\max}$, and $z_{\text{CP}_{(\bullet)}}$ takes the value $z_{\text{CP}_{\min}}$. Hence, the formula to calculate $z_1^{(L)}$ is

$$z_1^{(L)} = z_{1-\alpha/2}\sqrt{\frac{n_2}{n_1}} - \sqrt{\frac{n_2 - n_1}{n_1}}\left(\frac{\delta_{\min}}{2}\sqrt{\widetilde{n}_{\max}} - z_{\text{CP}_{\min}}\right)$$

The underlying rationale for this constraint, $\text{CP}_{\delta_{\min}}\left(z_1^{(L)}, \widetilde{n}_{\max}\right) = \text{CP}_{\min}$, is that if the conditional power evaluated at $\delta_{\min}$ and $\widetilde{n}_{\max}$ can be boosted to at least $\text{CP}_{\min}$. $z_1^{(L)}$ marks the start of the promising zone. The value of $z_1^{(L)}$ at IA suggests that the interim results are favorable (promising), indicating that it is worth increasing the sample size.

4.2 Find $z_1^{(C)}$ with constraint of $\text{CP}_{\delta_{\min}}\left(z_1^{(C)}, \widetilde{n}_{\max}\right) = \text{CP}_{\max}$

Since $\text{CP}_{\delta_{\min}}\left(z_1, \widetilde{n}_2^*\right)$ is a monotone function in terms of both z_1 and $\widetilde{n}_2^*$, if we keep sample size at $\widetilde{n}_{\max}$, achieving $\text{CP}_{\max}$ will lead to $z_1^{(C)}$. That is, in equation (5), $\widetilde{n}_{(\bullet)}$ takes the value $\widetilde{n}_{\max}$, and $z_{\text{CP}_{(\bullet)}}$ takes the value $z_{\text{CP}_{\max}}$. Therefore, the value of $z_1^{(C)}$ can be calculated from the constraint $\text{CP}_{\delta_{\min}}\left(z_1^{(C)}, \widetilde{n}_{\max}\right) = \text{CP}_{\max}$ as follows

$$z_1^{(C)} = z_{1-\alpha/2}\sqrt{\frac{n_2}{n_1}} - \sqrt{\frac{n_2 - n_1}{n_1}}\left(\frac{\delta_{\min}}{2}\sqrt{\widetilde{n}_{\max}} - z_{\text{CP}_{\max}}\right)$$

4.3 Find $z_1^{(U)}$ with constraint of $\mathrm{CP}_{\delta_{\min}}\left(z_1^{(U)}, \widetilde{n}_2\right) = \mathrm{CP}_{\max}$

Again, since $\mathrm{CP}_{\delta_{\min}}\left(z_1, \widetilde{n}_2^*\right)$ is a monotone function in terms of both z_1 and $\widetilde{n}_2^*$, if we maintain the desired conditional power at $\mathrm{CP}_{\max}$, we seek the largest value of z_1 (i.e. $z_1^{(U)}$) when the originally planned sample size $\widetilde{n}_2$ is used. Hence, in equation (5), $\widetilde{n}_{(\bullet)}$ takes the value $\widetilde{n}_2$, and $z_{\mathrm{CP}_{(\bullet)}}$ takes the value $z_{\mathrm{CP}_{\max}}$. Therefore, the value of $z_1^{(U)}$ can be calculated from the constraint $\mathrm{CP}_{\delta_{\min}}\left(z_1^{(U)}, \widetilde{n}_2\right) = \mathrm{CP}_{\max}$ as follows

$$z_1^{(U)} = z_{1-\alpha/2}\sqrt{\frac{n_2}{n_1}} - \sqrt{\frac{n_2-n_1}{n_1}}\left(\frac{\delta_{\min}}{2}\sqrt{\widetilde{n}_2} - z_{\mathrm{CP}_{\max}}\right)$$

As expected, $z_1^{(U)}$ marks the end of the promising zone.

The graphical display for the calculated $z_1^{(L)}$, $z_1^{(C)}$, and $z_1^{(U)}$ is presented in Figure 2 for the example in Section 3. Additionally, these calculated test statistics landmarks $z_1^{(L)}$, $z_1^{(C)}$, and $z_1^{(U)}$ can be converted to a different scale, such as HR for the example in Section 3. The relationship between a test statistic z_1 and HR can be described as follows

$$\mathrm{HR} = \exp\left(-\frac{z_1}{\sqrt{n_1 r(1-r)}}\right), \text{ where } r = \frac{R}{R+1}$$

here $R = n_t/n_c$ represents the randomization ratio between treatment and control group, where n_t is the number of patients in treatment group and n_c is the number of patients in control group. For $R = 1$, we have $r = 0.5$, leading to $\mathrm{HR} = \exp(-2z_1/\sqrt{n_1})$. Consequently, the corresponding $\mathrm{HR}^{(L)}$, $\mathrm{HR}^{(C)}$, and $\mathrm{HR}^{(U)}$ can be visually presented in Figure 3.

5 Promising Zone Design by Mehta and Pocock (2011)

In contrast to the proposal by Hsiao et al. (2019), the conditional power at IA in the proposal by Mehta and Pocock (2011) is calculated by replacing $E\left[\mathrm{Z}(t_1)\right]$ with z_1 in (1). Here, z_1 is the observed test statistic calculated for the estimated treatment effect $\widehat{\delta}_1$ at IA. Therefore, the conditional power $\mathrm{CP}_{\widehat{\delta}_1}\left(z_1, \widetilde{n}_2\right)$ proposed by Mehta and Pocock (2011) can be calculated as

$$\mathrm{CP}_{\widehat{\delta}_1}\left(z_1, \widetilde{n}_2\right) = 1 - \Phi\left(\frac{z_{1-\alpha/2}\sqrt{n_2} - z_1\sqrt{n_1}}{\sqrt{\widetilde{n}_2}} - \frac{z_1\sqrt{\widetilde{n}_2}}{\sqrt{n_1}}\right) = \Phi\left(\frac{z_1\sqrt{\widetilde{n}_2}}{\sqrt{n_1}} - \frac{z_{1-\alpha/2}\sqrt{n_2} - z_1\sqrt{n_1}}{\sqrt{\widetilde{n}_2}}\right) \quad (6)$$

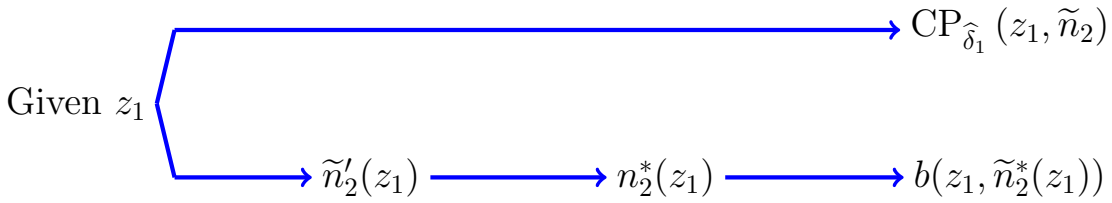
With the constraint of $n_2 \le n_2^* \le n_{\max}$, promising zone is specified to be the region of

$$\mathrm{CP}_{\min} \le \mathrm{CP}_{\widehat{\delta}_1}\left(z_1, \widetilde{n}_2\right) \le \mathrm{CP}_{\max} \quad (7)$$

where $\widehat{\delta}_1$ is the estimated treatment effect at IA. This approach differs from the proposal by Hsiao et al. (2019) in that only $\mathrm{CP}_{\max}$ is *pre-specified* based on the clinical expectations. $\mathrm{CP}_{\max}$ reflects the maximum requirement for conditional power and is typically set to $1-\beta$; we use this set up of $\mathrm{CP}_{\max} = 1-\beta$ for the convenience of subsequent discussion. In this context, we need to determine the value of $\mathrm{CP}_{\min}$ that allows us to use the conventional test statistic at the final analysis without inflating the study's overall type I error rate.

$\mathrm{CP}_{\min}$ depends on the ratios of $n_{\max}/n_2$ and n_1/n_2, and the targeted power $1-\beta$, finding the value of $\mathrm{CP}_{\min}$ is a two-step process. In the promising zone in (7), $\mathrm{CP}_{\widehat{\delta}_1}\left(z_1, \widetilde{n}_2\right)$ is a function of z_1 and $\widetilde{n}_2$ or $\widetilde{n}_2^*$. The first step involves fixing a value of z_1 and finding the corresponding sample size $\widetilde{n}_2^*$ that achieves

$\text{CP}_{\max}$. The second step is to use this value of $\widetilde{n}_2^*$ to determine the lower bound of promising zone, $\text{CP}_{\min}$. The requirement for $\text{CP}_{\min}$ is that if the conditional power calculated at IA is greater than $\text{CP}_{\min}$, even with sample size re-estimation, we can still use the conventional test statistic at the final analysis. The following provides additional details for each step in Section 5.1 and Section 5.2. Essentially, for a fixed z_1 at IA, it involves calculating several quantities as outlined in the visual flow below.



However, even after obtaining the value of $\text{CP}_{\min}$, we cannot follow the same procedure outlined in Section 4 to produce the desired graphical displays. Instead, a different algorithm is required, and the details are provided in Section 5.3.

5.1 Step 1: Find $\widetilde{n}_2^*$ with constraint of $\text{CP}_{\widehat{\delta}_1}(z_1, \widetilde{n}_2^*) = 1 - \beta$

For an observed test statistic z_1 at IA, the re-estimated sample size $\widetilde{n}_2^*$ is a function of z_1, denoted as $n_2^*(z_1)$. Then, the sample size $n_2^*(z_1)$ can be adjusted to

$$n_2^*(z_1) = \min\left[n_2'(z_1), n_{\max}\right]$$

where $n_2'(z_1)$ satisfies the condition of $\text{CP}_{\widehat{\delta}_1}(z_1, \widetilde{n}_2'(z_1)) = 1 - \beta$, which leads to

$$\Phi\left(\frac{z_1\sqrt{\widetilde{n}_2'(z_1)}}{\sqrt{n_1}} - \frac{z_{1-\alpha/2}\sqrt{n_2} - z_1\sqrt{n_1}}{\sqrt{\widetilde{n}_2}}\right) = 1 - \beta \Longrightarrow \widetilde{n}_2'(z_1) = \left(\frac{n_1}{z_1^2}\right)\left(\frac{z_{1-\alpha/2}\sqrt{n_2} - z_1\sqrt{n_1}}{\sqrt{n_2 - n_1}} + z_{1-\beta}\right)^2$$

$\text{CP}_{\min}$ depends on targeted power $1 - \beta$, this dependence is now transferred to the quantity of $\widetilde{n}_2'(z_1)$.

5.2 Step 2: Given $\widetilde{n}_2^*$, find $\text{CP}_{\min}$ with objective of using conventional test statistics at final analysis without inflating overall type I error rate

With z_1 and its corresponding $\widetilde{n}_2'(z_1)$ obtained in Step 1, we can calculate the test statistic at the final analysis as Z_2^*. It can then be shown (Gao et al., 2008) the following equation holds

$$P_{H_0}\left[Z_2^* \geq b(z_1, \widetilde{n}_2^*)\right] = \alpha$$

$$\text{where } b(z_1, \widetilde{n}_2^*(z_1)) = \frac{1}{\sqrt{n_2^*}}\left[\sqrt{\frac{\widetilde{n}_2^*}{\widetilde{n}_2}}\left(z_{1-\alpha/2}\sqrt{n_2} - z_1\sqrt{n_1}\right) + z_1\sqrt{n_1}\right]$$

Then, the promising zone can be defined as the region satisfying the criteria

$$\mathcal{P} = \left\{\text{CP}_{\widehat{\delta}_1}(z_1, \widetilde{n}_2) : b(z_1, \widetilde{n}_2^*(z_1)) \leq z_{1-\alpha/2}\right\} \tag{8}$$

The basic rationale for this definition is due to the following inequality

$$\alpha = P_{H_0}\left[Z_2^* \geq b(z_1, \widetilde{n}_2^*(z_1))\right] \geq P_{H_0}\left[Z_2^* \geq z_{1-\alpha/2}\right]$$

which ensures that the overall type I error rate will be preserved conservatively if we use the conventional test $Z_2^* \geq z_{1-\alpha/2}$ for the final analysis, even with the sample size re-estimation at the IA. Thus, (8) serves as the basis for determining $\text{CP}_{\min}$. Specifically, we can graphically present the relationship between $\text{CP}_{\widehat{\delta}_1}(z_1, \widetilde{n}_2)$ and $b(z_1, \widetilde{n}_2^*(z_1))$. The horizontal reference line $z_{1-\alpha/2}$ will intersect the curve at the axis for $b(z_1, \widetilde{n}_2^*(z_1))$, which in turn determines the $\text{CP}_{\min}$. The general idea is visually presented in Figure 4.

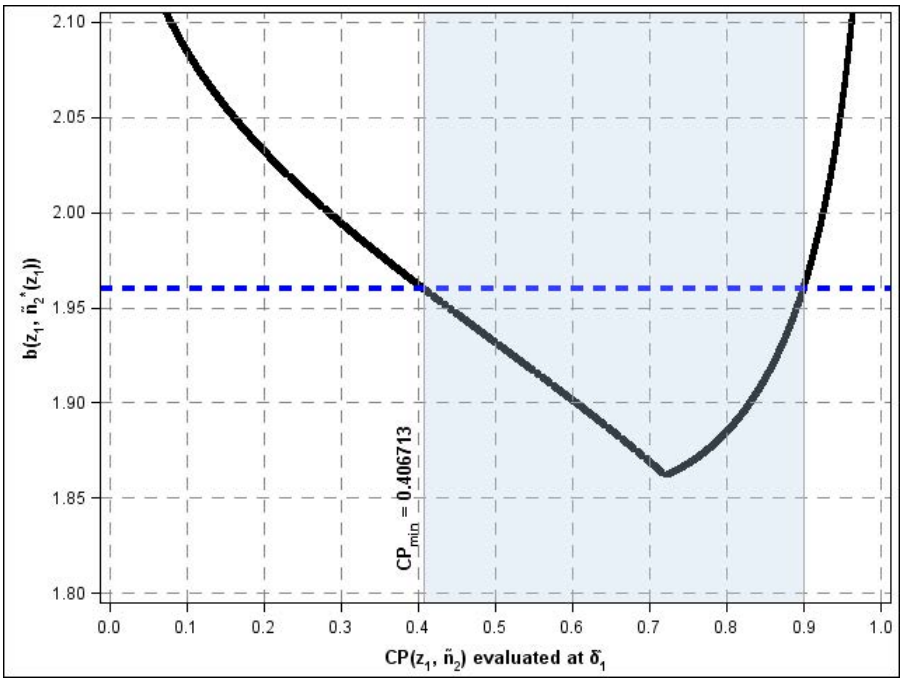


Figure 4: The relationship between $\mathrm{CP}_{\widehat{\delta}_1}(z_1, \widetilde{n}_2)$ and $b(z_1, \widetilde{n}_2^*(z_1))$ is illustrated, with a blue dashed horizontal line at $z_{1-\alpha/2} = z_{1-0.05/2} = 1.96$. The shaded area represents the desired promising zone. For parameters $n_1 = 140$, $n_2 = 280$, $n_{\max} = 420$, and $\mathrm{CP}_{\max} = 0.9$, the calculated $\mathrm{CP}_{\min}$ is $\mathrm{CP}_{\min} = 0.40671$. Additionally, the values $z_1^{(L)}$ and $z_1^{(U)}$, corresponding to $\mathrm{CP}_{\min}$ and $\mathrm{CP}_{\max}$, are found to be $z_1^{(L)} = 1.2679$ and $z_1^{(U)} = 2.0266$, respectively.

5.3 Algorithm to produce graphical displays in Figure 9 and Figure 10

To produce graphical displays similar to Figure 2 and Figure 3 for the promising zone design proposed by Mehta and Pocock (2011), the procedure and algorithm differ somewhat from those described in Section 4. This is because $\mathrm{CP}_{\min}$ is not pre-specified, and $E[\mathrm{Z}(t_1)]$ in (1) varies with z_1 as described in (6), rather than being a fixed value in (2) from the proposal by Hsiao et al. (2019).

As demonstrated in the procedure described in Section 5.2 for obtaining $\mathrm{CP}_{\min}$, a by-product of this procedure is that $z_1^{(L)}$ and $z_1^{(U)}$, which correspond to $\mathrm{CP}_{\min}$ and $\mathrm{CP}_{\max}$, can also be determined. Therefore, $z_1^{(C)}$ remains to be calculated.

Since $\mathrm{CP}_{\widehat{\delta}_1}(z_1, \widetilde{n}_2^*)$ is a monotone function in terms of both z_1 and $\widetilde{n}_2^*$, keeping the sample size at $n_2^*(z_1)$ and achieving $\mathrm{CP}_{\max}$ will lead to $z_1^{(C)}$. Note that the value of z_1 used in $\widetilde{n}_2^*(z_1)$ is actually $z_1^{(L)}$. Therefore, in equation (6), $z_1^{(C)}$ can be calculated from the constraint $\mathrm{CP}_{\widehat{\delta}_1}\left(z_1^{(C)}, \widetilde{n}_2^*(z_1^{(L)})\right) = \mathrm{CP}_{\max}$. Consequently, the $z_1^{(C)}$ can be obtained as follow

$$\Phi\left(\frac{z_1^{(C)}\sqrt{\widetilde{n}_2^*(z_1^{(L)})}}{\sqrt{n_1}} - \frac{z_{1-\alpha/2}\sqrt{n_2} - z_1^{(C)}\sqrt{n_1}}{\sqrt{n_2 - n_1}}\right) = \mathrm{CP}_{\max}$$

$$\Longrightarrow z_1^{(C)} = \left(\sqrt{\frac{\widetilde{n}_2^*(z_1^{(L)})}{n_1}} + \sqrt{\frac{n_1}{n_2 - n_1}}\right)^{-1}\left(z_{1-\alpha/2}\sqrt{\frac{n_2}{n_2 - n_1}} + z_{\mathrm{CP}_{\max}}\right)$$

Once the values of $z_1^{(L)}$, $z_1^{(C)}$, and $z_1^{(U)}$ have been determined, the corresponding $\text{HR}^{(L)}$, $\text{HR}^{(C)}$, and $\text{HR}^{(U)}$ can be similarly obtained as described in Section 4.3. The graphical displays can then be produced in Appendix 2 as Figure 9 and Figure 10 for the example in Section 3.

6 SAS Programs

All the SAS macros and programs used to generate the Figure 2, Figure 3, Figure 4, Figure 9, and Figure 10 can be found at `https://github.com/tonygit578/SAS-macro-for-promising-zone`. Here we provide a brief overview of these programs.

As illustrated in Section 4, the values of $\text{CP}_{\min}$, $\text{CP}_{\max}$, and $\delta_{\min}$ are all *pre-specified* based on the clinical expectations in the promising zone design proposed by Hsiao et al. (2019). Therefore, the programming set up to produce Figures 2 and 3 is relatively straightforward. The SAS macro `Data4PZGraph`, along with the procedure of `proc sgplot`, is used to generate Figures 2 and 3 for the example in Section 3. A detailed description of the parameters used in the macro `Data4PZGraph` is provided in Figure 5.

```
**-------------------------------------------------------------------------------------------------------------------
** Promising Zone Designs for Sample Size Re-estimation in Clinical Trials: Graphical Communication using SAS--
** PharmSUG paper by Zhao Yang and Shivani Nanda ----------------------------------------------------------------
** It is a SAS implementation to the optimal promising zone design proposed by Hsiao et al (2019) -------------
** --------------------------------- Details for macro parameters ---------------------------------------------
    n1:     total # of events/sample size at the interim analysis
    n2:     total # of events/sample size at final analysis based on the original design
    cpmin:  expected minimal conditional power
    cpmax:  expected maximal conditional power
    hrmin:  the minimal clinically meaningful treatment effect, here it is HR
    nmax:   the total affortable maximal # of events/sample size at final analysis
    alpha:  target two-sided significance level
    randR:  randomization ratio between treatment vs control, i.e. ratio of treatment/control
    dsout:  the final datasets name to be produced
**-------------------------------------------------------------------------------------------------------------------;
%macro Data4PZGraph(n1 =, n2 =, cpmin = 0.8, cpmax = 0.9, hrmin =, nmax =, alpha = 0.05, randR = 1, dsout = );
   *********
%mend;
%Data4PZGraph(n1 = 140, n2 = 280, cpmin = 0.8, cpmax = 0.9, hrmin = 0.75, nmax = 420, alpha = 0.05,
                                                                    randR = 1, dsout = PrepData4PZ3);
```

Figure 5: A snapshot of the parameters used in the SAS macro `Data4PZGraph` is provided. This macro is used to create a dataset which will be further used to produce Figures 2 and 3 for the example in Section 3.

In contrast, for the promising zone design proposed by Mehta and Pocock (2011), we first need to determine $\text{CP}_{\min}$. The SAS macro `FindingCPmin` is developed to find the value of $\text{CP}_{\min}$ based on the technical details presented in Section 5.1 and Section 5.2. The description of the parameters used in the macro `FindingCPmin` is provided in Figure 6. This macro prepares a dataset, which is then used to produce Figure 4 using the procedure of `proc sgplot` with its annotation capabilities. Once $\text{CP}_{\min}$ is obtained, the algorithm described in Section 5.3 can then be applied. The SAS macro `Data4PZGraph_Mehta`, along with the procedure of `proc sgplot`, is used to generate Figure 9 and Figure 10 in Appendix 2 for the example in Section 3. A detailed description of the parameters used in the macro `Data4PZGraph_Mehta` is provided in Figure 7.

Remark 1: When we compare Figure 2 vs Figure 9 and Figure 3 vs Figure 10, it is evident that the promising zone obtained from the proposal by Mehta and Pocock (2011) is narrower than the promising zone obtained from the proposal by Hsiao et al. (2019). For example, considering the test statistic z_1 in Figure 2 vs Figure 9, the ranges $(z_1^{(L)}, z_1^{(U)})$ of z_1 for promising zone are $(1.2065, 2.3514)$ and $(1.2679, 2.0266)$

```
**-------------------------------------------------------------------------------------------------------------------
** Promising Zone Designs for Sample Size Re-estimation in Clinical Trials: Graphical Communication using SAS---
** PharmSUG paper by Zhao Yang and Shivani Nanda ----------------------------------------------------------------
** It is a SAS implementation to obtain the CPmin based on promising zone design proposed by Mehta et al (2011)-
** --------------------------------- Details for macro parameters ------------------------------------------
    n1:     total # of events/sample size at the interim analysis
    n2:     total # of events/sample size at final analysis based on the original design
    cpmax:  expected maximal conditional power
    nmax:   the total affortable maximal # of events/sample size at final analysis
    alpha:  target two-sided significance level
    dsout:  the final datasets name to be produced
**-------------------------------------------------------------------------------------------------------------------;

%macro FindingCPmin(n1 =, n2 =, cpmax = 0.9, nmax =, alpha = 0.05, dsout = );
   •••••••
%mend;

%FindingCPmin(n1 = 140, n2 = 280, cpmax = 0.9, nmax = 420, alpha = 0.05, dsout = PrepData4CPmin);
```

Figure 6: A snapshot of the parameters used in the SAS macro `FindingCPmin` is provided. This macro is designed to create a dataset that will be further used to produce Figure 4 for the example in Section 3.

```
**-------------------------------------------------------------------------------------------------------------------
** Promising Zone Designs for Sample Size Re-estimation in Clinical Trials: Graphical Communication using SAS--
** PharmSUG paper by Zhao Yang and Shivani Nanda ----------------------------------------------------------------
** It is a SAS implementation to the optimal promising zone design proposed by Mehta et al (2011) -------------
** --------------------------------- Details for macro parameters ------------------------------------------
    n1:     total # of events/sample size at the interim analysis
    n2:     total # of events/sample size at final analysis based on the original design
    cpmax:  expected maximal conditional power
    nmax:   the total affortable maximal # of events/sample size at final analysis
    alpha:  target two-sided significance level
    randR:  randomization ratio between treatment vs control, i.e. ratio of treatment/control
    dsout:  the final datasets name to be produced
**-------------------------------------------------------------------------------------------------------------------;

%macro Data4PZGraph_Mehta(n1 =, n2 =, cpmax = 0.9, nmax =, alpha = 0.05, randR = 1, dsout = );
    ••••••••••
%mend;
%Data4PZGraph_Mehta(n1 = 140, n2 = 280, cpmax = 0.9, nmax = 420, alpha = 0.05, randR = 1, dsout = PrepData4PZ3);
```

Figure 7: A snapshot of the parameters used in the SAS macro `Data4PZGraph_Mehta` is provided. This macro is designed to create a dataset which will be further used to produce Figures 9 and 10 in Appendix 2 for the example in Section 3.

for Hsiao et al. (2019) and Mehta and Pocock (2011), respectively. Because of the larger value of $z_1^{(L)}$, it results in a smaller CP_{min} (i.e. 0.40671) for the design by Mehta and Pocock (2011) as shown in Figure 9 and Figure 10. A similar pattern is observed with the HR scale in Figure 3 vs Figure 10.

The implication of the above observation pertains to the control of the overall type I error rate. A key motivation for determining CP_{min} in the design by Mehta and Pocock (2011) is that, when CP exceeds CP_{min}, it is common practice to use the conventional test statistic at the final analysis without inflating the study's overall type I error rate. The design by Hsiao et al. (2019) expands the promising zone established in the design by Mehta and Pocock (2011). Consequently, the conditional rejection probability (CRP) method (Müller and Schäfer, 2001, 2004) or the CHW combination method (Cui et al., 1999) are commonly employed to control the overall type I error rate of the study.

This naturally raises a question: in the example using the design proposed by Hsiao et al. (2019), CP_{min}

is set to 0.8, but it is calculated as only 0.40671 when using the design proposed by Mehta and Pocock (2011). Why are commonly used methods different? The aforementioned details help us understand that what matters in selecting a method to control the overall type I error rate is the value of the test statistic z_1 or HR scale. Although the value of z_1 or HR can eventually lead to a corresponding CP, the detailed calculation of CP differs between the proposals by Hsiao et al. (2019) and Mehta and Pocock (2011). Therefore, focusing solely on the CP value may result in a misleading interpretation to the utilization of methods to control the overall type I error rate, a good practice when applying a design in real clinical trial is to understand and concentrate on the underlying setting of the design. □

7 Concluding Remarks

The exploration of promising zone designs in clinical trials underscores their potential to enhance the efficiency of drug development. By incorporating adaptive features that allow for modifications of sample size based on interim data, there are two most attractive features of this type of designs (i) optimize resource allocation by identifying and focusing on the most promising zones, reducing unnecessary expenditures on less promising zones, hence improve the likelihood of trial success. This is particularly important in the context of limited funding and resources often encountered in small biotech; (ii) minimize patient exposure to ineffective treatments, thus enhancing overall safety and addressing ethical concerns more effectively than traditional fixed designs. While promising zone designs offer numerous advantages, their implementation requires careful planning and adherence to regulatory guidelines (FDA, 2019). Collaboration with regulatory bodies and thorough documentation are essential to ensure the acceptability and integrity of the trial outcomes.

As expected, promising zone design often results in a potential increase in sample size at the interim analysis if the accumulating data indicate a treatment effect lower than anticipated. This approach functions as a form of remedial strategy in drug development; however, the communications to external stakeholders following the interim analysis and the subsequent decision may not convey a positive message to investors. If there is such kind of concerns for promising zone designs, the 2-in-1 adaptive phase 2/3 design (Chen et al., 2018) could be a good alternative, it starts with a Phase 2 study, then it can be seamlessly expanded to a Phase 3 study based on the IA results, eventually, data from the first Phase 2 will be included in final analysis of the Phase 3. As we can see, expanding to Phase 3 based on favorable IA results can deliver a more encouraging message to external stakeholders. For the 2-in-1 design, there are multiple extensions, including embedding into the group sequential and multiple endpoints situation (Fan et al., 2020; Jin and Zhang, 2021; Zhang et al., 2024), especially the most recent advancement of incorporating the sample size re-estimation to the 2-in-1 framework (Li et al., 2024).

In conclusion, promising zone design is an invaluable tool for achieving more efficient and effective drug development. The easily accessible SAS program presented in this paper aims to enhance communication among functional stakeholders in a clinical trial using promising zone design and to promote its broader application, which is expected to play an increasingly significant role in the development of new therapies.

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Appendix 1: Technical Derivation of Conditional Probabilities Based on Brownian Motion

In clinical trials employing group sequential design, four commonly used monitoring devices are identified (Proschan et al., 2006): (1) the S-process, which involves partial sums (e.g. score function); (2) E-process, which focuses estimation (e.g. MLE); (3) Z-process, which uses test statistic; and (4) B-process, which is based on Brownian motion. The relationship among these monitoring tools are illustrated in the right panel of Figure 8. This appendix offers a concise yet informative overview of key technical aspects of the methods discussed in this paper, grounded in the concept of Brownian motion.

Assuming $\widehat{\theta}$ is the point estimate of parameter θ from an underlying probability distribution based on a sample of data from N patients. Then, Fisher's information $I_\theta(\bullet)$ quantifies the curvature at $\widehat{\theta}$. Specifically, $I_\theta(1)$ represents the total information available with the full sample size N; while $I_\theta(\tau_1)$ and $I_\theta(\tau_2)$ denote the interim information at stages τ_1 and τ_2, respectively, where τ indicates the progression of the trial (with $\tau = 0$ at the start and $\tau = 1$ at the end). A trial can be evaluated at a point t (known as the trial information fraction), where $0 \leq t \leq 1$, and is defined as $t = I(\tau)/I(1)$. The concept of Fisher's information $I_\theta(\bullet)$ is graphically illustrated in the left panel of Figure 8, demonstrating that information increases along with sample size, leading to reduced variability and a more concentrated curvature around $\widehat{\theta}$.

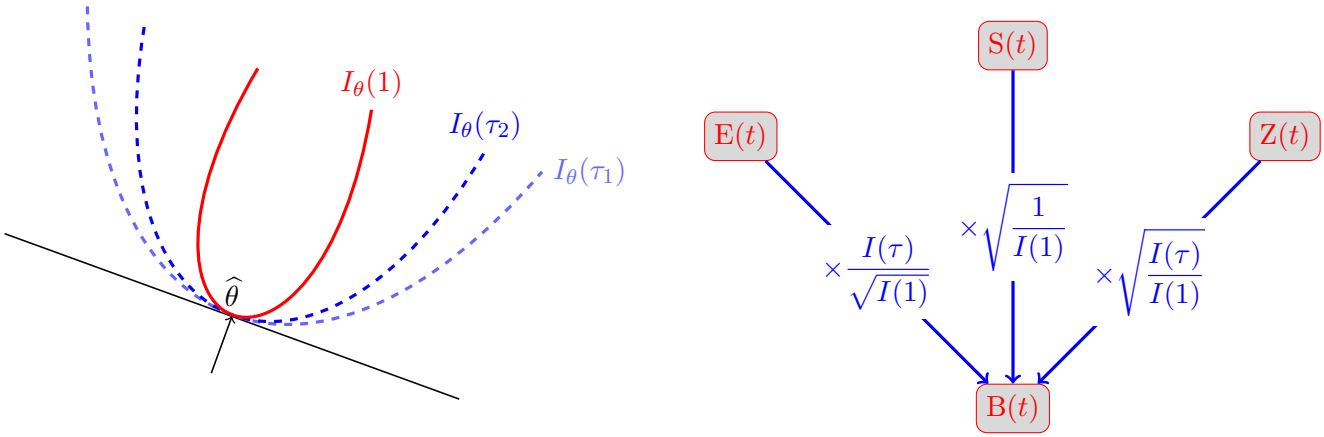

Figure 8: Left panel: Fisher's information $I_\theta(\bullet)$ measures the curvature at $\widehat{\theta}$. Right panel: relationship among 4 commonly used monitoring devices in a clinical trial using group sequential design, as detailed by Proschan et al. (2006).

Based on the relationship among 4 commonly used monitoring devices (Proschan et al., 2006) shown in the right panel of Figure 8, a key pragmatic relationship at t between test statistic $\mathrm{Z}(t)$ and Brownian motion $\mathrm{B}(t)$ is $\mathrm{B}(t) = \sqrt{t}\mathrm{Z}(t)$. Here, $\mathrm{B}(t)$ represents a Brownian motion with drift θ, where θ is typically considered as the treatment effect. Let θ as the expected value of the $\mathrm{Z}(t)$ at the end of trial (i.e. $t = 1$), that is, $\theta = E\left[\mathrm{Z}(1)\right]$, then $E\left[\mathrm{B}(t)\right] = \theta t$ as derived in (10). This result uses the equation of $E\left[\mathrm{E}(t)\right] = E\left[\mathrm{E}(1)\right]$ from (9) to (10). Clearly, under the null hypothesis H_0, where $\theta = 0$, $\mathrm{B}(t)$ is a standard Brownian motion.

$$E\left[\mathrm{B}(t)\right] = E\left[\sqrt{t}\mathrm{Z}(t)\right] = E\left[\sqrt{\frac{I(\tau)}{I(1)}}\mathrm{Z}(t)\right] = E\left[\sqrt{\frac{I(\tau)}{I(1)}}\sqrt{I(\tau)}\mathrm{E}(t)\right] \tag{9}$$

$$= \sqrt{\frac{I(\tau)}{I(1)}}\sqrt{I(\tau)} \times E\left[\mathrm{E}(1)\right] = \sqrt{\frac{I(\tau)}{I(1)}}\sqrt{I(\tau)} \times E\left[\frac{1}{\sqrt{I(1)}}\mathrm{Z}(1)\right] = \frac{I(\tau)}{I(1)}E\left[\mathrm{Z}(1)\right] = \theta t \tag{10}$$

Conditioned on the Past

Given $0 \le t_1 \le t_2 \le 1$ and $B(t_1) = b$, the increment $B(t_2) - B(t_1)$ is independent of $B(t_1)$, this property is extremely useful for calculating the conditional probabilities in the group sequential or adaptive design. Since $B(t_2) = B(t_1) + [B(t_2) - B(t_1)]$, we have

$$\begin{aligned} E\left[B(t_2) - B(t_1)\right] &= \theta t_2 - \theta t_1 = \theta(t_2 - t_1) \\ \text{Var}\left[B(t_2) - B(t_1)\right] &= \text{Var}\left[B(t_2)\right] + \text{Var}\left[B(t_1)\right] - 2\text{Cov}\left[B(t_2), B(t_1)\right] = t_2 + t_1 - 2t_1 = t_2 - t_1 \end{aligned}$$

Then, the mean and variance for the conditional variable of $B(t_2)|B(t_1) = b$ can be obtained as follows

$$\begin{aligned} E\left[B(t_2)|B(t_1) = b\right] &= E\left\{B(t_1) + [B(t_2) - B(t_1)]\,|B(t_1) = b\right\} \\ &= E\left\{B(t_1) + [B(t_2) - B(t_1)]\right\} = b + \theta(t_2 - t_1) \\ \text{Var}\left[B(t_2)|B(t_1) = b\right] &= \text{Var}\left\{B(t_1) + [B(t_2) - B(t_1)]\,|B(t_1) = b\right\} = \text{Var}\left[B(t_2) - B(t_1)\right] = t_2 - t_1 \end{aligned}$$

A general conditional probability can be calculated as

$$\begin{aligned} C_p(\theta) &= \Pr\left[B(t_2) \ge b_2 | B(t_1) = b\right] = \Pr\left[\frac{B(t_2) - [b + \theta(t_2 - t_1)]}{\sqrt{t_2 - t_1}} \ge \frac{b_2 - [b + \theta(t_2 - t_1)]}{\sqrt{t_2 - t_1}}\right] \\ &= \Pr\left[N(0,1) \ge \frac{b_2 - [b + \theta(t_2 - t_1)]}{\sqrt{t_2 - t_1}}\right] = 1 - \Phi\left[\frac{b_2 - [b + \theta(t_2 - t_1)]}{\sqrt{t_2 - t_1}}\right] \end{aligned}$$

Conditional Power

The conditional power is the conditional probability $C_p(\theta)$ at the end of trial (i.e. $t_2 = 1$), that is,

$$\begin{aligned} \text{CP}_p(\theta) &= \Pr\left[B(1) \ge z_{1-\alpha/2} | B(t_1) = b\right] = \Pr\left[\frac{B(1) - [b + \theta(1 - t_1)]}{\sqrt{1 - t_1}} \ge \frac{z_{1-\alpha/2} - [b + \theta(1 - t_1)]}{\sqrt{1 - t_1}}\right] \\ &= \Pr\left[N(0,1) \ge \frac{z_{1-\alpha/2} - [b + \theta(1 - t_1)]}{\sqrt{1 - t_1}}\right] = 1 - \Phi\left[\frac{z_{1-\alpha/2} - [b + \theta(1 - t_1)]}{\sqrt{1 - t_1}}\right] \\ &= \Phi\left[\frac{[b + \theta(1 - t_1)] - z_{1-\alpha/2}}{\sqrt{1 - t_1}}\right] \end{aligned} \tag{11}$$

where $t_1 = n_1/n_2$, n_1 is the number of patients at t_1, $n_2 = n_1 + \widetilde{n}_2$ represents the total number of patients, and $\widetilde{n}_2$ is the number of additional patients needed after t_1. Next, let's examine the pertinent quantities in the final equation of (11), which are

$$\begin{aligned} \text{CP}_p(\theta) &= \Pr\left[B(1) \ge z_{1-\alpha/2} | B(t_1) = b\right] = \Phi\left[\frac{[b + \theta(1 - t_1)] - z_{1-\alpha/2}}{\sqrt{1 - t_1}}\right], \quad \text{where} \\ & b = \sqrt{t_1} Z(t_1) = \sqrt{t_1} z_1,\ z_1 \text{ is the observed test statistic at interim analysis (IA) at } t_1, \\ & \theta = E\left[\text{Z}(1)\right] \text{ is the expectation of test statistic at final analysis} \\ & E\left[\text{Z}(t_1)\right] \text{ is the expectation of test statistic at IA} \end{aligned}$$

We need to determine the relationship between $E\left[\text{Z}(t_1)\right]$ and $\theta = E\left[\text{Z}(1)\right]$, which can be derived as shown in (12). In this derivation, we again utilize the equation $E\left[\text{E}(t_1)\right] = E\left[\text{E}(1)\right]$.

$$\begin{aligned} E\left[\text{Z}(t_1)\right] &= E\left[\sqrt{I(\tau)}\text{E}(t_1)\right] = \sqrt{I(\tau)} \times E\left[\text{E}(1)\right] = \sqrt{I(\tau)} \times E\left[\frac{1}{\sqrt{I(1)}}\text{Z}(1)\right] = \sqrt{\frac{I(\tau)}{I(1)}} E\left[\text{Z}(1)\right] = \theta\sqrt{t_1} \\ \Longrightarrow \theta &= \frac{1}{\sqrt{t_1}} E\left[\text{Z}(t_1)\right] \end{aligned} \tag{12}$$

With (12), the conditional power in (11) can be further calculated as

$$\begin{aligned}
\mathrm{CP}_p(\theta) &= \Phi\left[\frac{[b+\theta(1-t_1)]-z_{1-\alpha/2}}{\sqrt{1-t_1}}\right] = \Phi\left[\frac{\left[\sqrt{t_1}z_1+\theta(1-t_1)\right]-z_{1-\alpha/2}}{\sqrt{1-t_1}}\right] \\
&= \Phi\left[\theta\sqrt{1-t_1}-\frac{z_{1-\alpha/2}-\sqrt{t_1}z_1}{\sqrt{1-t_1}}\right] = \Phi\left[\frac{1}{\sqrt{t_1}}E\left[\mathrm{Z}(t_1)\right]\sqrt{1-t_1}-\frac{z_{1-\alpha/2}\sqrt{n_2}-\sqrt{n_1}z_1}{\sqrt{\widetilde{n}_2}}\right] \\
&= \Phi\left[E\left[\mathrm{Z}(t_1)\right]\sqrt{\frac{1-t_1}{t_1}}-\frac{z_{1-\alpha/2}\sqrt{n_2}-\sqrt{n_1}z_1}{\sqrt{n_2-n_1}}\right] \\
&= \Phi\left[E\left[\mathrm{Z}(t_1)\right]\sqrt{\frac{\widetilde{n}_2}{n_1}}-\frac{z_{1-\alpha/2}\sqrt{n_2}-\sqrt{n_1}z_1}{\sqrt{n_2-n_1}}\right] \qquad (13)
\end{aligned}$$

The equation in (13) is directly applicable to calculating conditional power in promising zone designs. The main distinction between different promising zone designs lies in the value assigned to $E\left[\mathrm{Z}(t_1)\right]$. For example, if $E\left[\mathrm{Z}(t_1)\right] = z_1$, this corresponds to the design proposed by Mehta and Pocock (2011). Conversely, if $E\left[\mathrm{Z}(t_1)\right]$ is set to the expectation of the test statistic evaluated at the minimal treatment effect δ_{min}, it aligns with the design proposed by Hsiao et al. (2019).

Additionally, the conditional rejection probability (CRP) (Müller and Schäfer, 2001, 2004) obtained at the interim analysis under the null hypothesis H_0 (i.e. $E\left[\mathrm{Z}(t_1)\right] = 0$) is given by

$$\mathrm{CRP} = \mathrm{CP}_p(\theta) = \Phi\left(\frac{\sqrt{n_1}z_1 - z_{1-\alpha/2}\sqrt{n_2}}{\sqrt{n_2-n_1}}\right) \qquad (14)$$

This CRP represents the preserved type I error rate and can be spent for the subsequent stages of the study (i.e. beyond t_1).

The CRP method or the CHW combination method (Cui et al., 1999; Mehta and Pocock, 2011; Hsiao et al., 2019) can be employed to control the overall type I error rate of the study. When the study consists of only two stages, the CRP method is equivalent to the CHW combination method (Cui et al., 1999). A notable limitation of the CHW method is that it does not allow for adjustments to the number of future interim analyses after a potential sample size adaptation at the first stage. In contrast, CRP method can accommodate such changes. Specifically, the CRP is preserved beyond the first stage analysis. For instance, after the first stage analysis, if two additional analyses are planned after the first stage (e.g., a second interim analysis and a final analysis), the O'Brien-Fleming method can be utilized to schedule these analyses and utilize the preserved CRP. The CHW method, however, cannot address this situation.

Appendix 2: Graphical Displays for Promising Zone Design Proposed by Mehta and Pocock (2011)

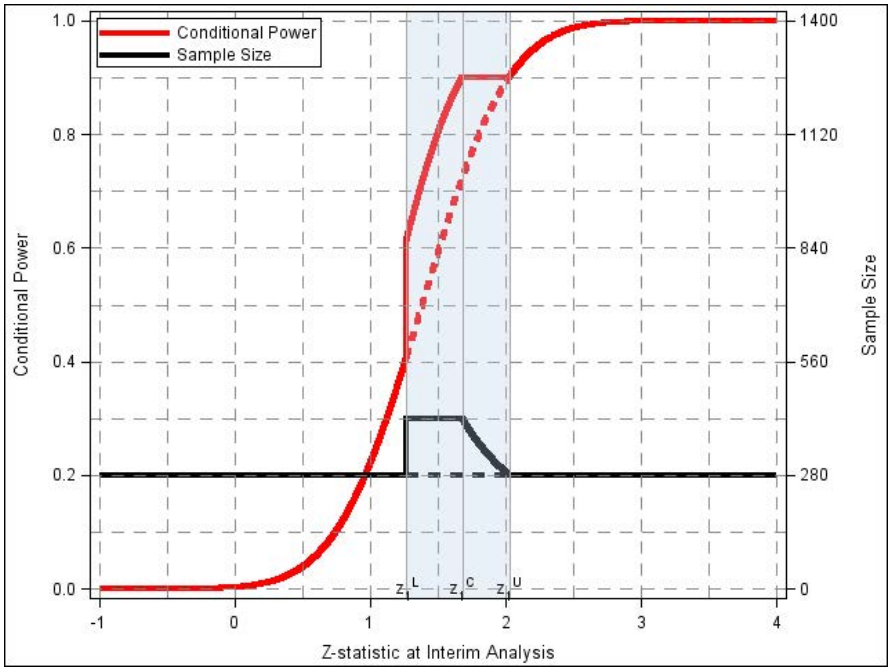

Figure 9: Conditional power and sample size of promising zone design based on observed treatment effect $\widehat{\delta}_1$ and test statistic z_1 at IA. With CP_{min} calculated as $\text{CP}_{\text{min}} = 0.40671$ and CP_{max} set to 0.9, the design results in $z_1^{(L)} = 1.2679$, $z_1^{(C)} = 1.679$, and $z_1^{(U)} = 2.0266$.

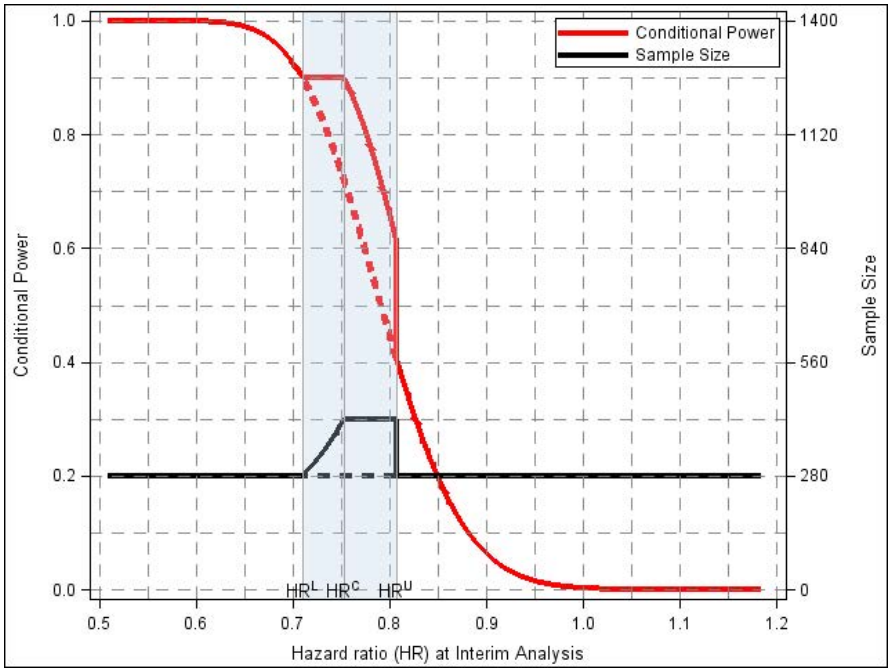

Figure 10: Conditional power and sample size of promising zone design based on observed treatment effect $\widehat{\delta}_1$ and test statistic z_1 at IA. With CP_{min} calculated as $\text{CP}_{\text{min}} = 0.40671$ and CP_{max} set to 0.9, the design results in $\text{HR}^{(L)} = 0.70995$, $\text{HR}^{(C)} = 0.75292$, and $\text{HR}^{(U)} = 0.80709$.