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Sample Size Estimation/Re-Estimation Under a Promising Zone Design in Clinical Trials

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Abstract

The promising zone design is a novel adaptive clinical trial design that focuses on the interim analysis test statistic and its conditional power. The term promising zone defined an interval of interim analysis test statistics and its corresponding conditional power. The use of promising zone design could reduce the cost and duration of the trials by adaptively reducing the sample size when the interim analysis result is satisfied. While it could also increase the probability of success of the trials by increasing the sample size when the interim analysis result is not sufficient to support the desired result [1]. Provided a general scheme to determine the promising zone by preserving the overall Type-I error rate [2] proposed more specified methodology and algorithm for clinical studies with time-to-event endpoint based on optimizing the conditional power while control the budget limit and power requirement. However, the validation of the concept of optimal promising zone is not fully discussed. This study mainly focuses on the validation of this method and formula derivation of conditional power and sample size.

Introduction

Pre-study power analysis for sample size calculation (power calculation) is an integral part of randomized clinical trial. In clinical trials, based on the primary study endpoint, power calculations are typically performed following the steps:

i. It is to set up appropriate hypotheses for clinical investigation

ii. It is to derive an appropriate statistic under a valid study design and the null hypothesis to be tested

iii. It is to evaluate power function under the alternative hypothesis

iv. It is to select an appropriate sample size by fixing all the parameters in the power function for achieving a desired power (e.g., 80%) at a pre-specified level of significance (e.g., 5%).

Thus, power calculation depends upon the study design, the study objective (or hypotheses), and the primary study endpoint of the intended clinical trial. In practice, commonly used study designs for clinical investigation include, but are not limited to, a crossover design, a parallel design, or a complex innovative design such as an adaptive trial design. The study objectives could be the demonstration of non-inferiority, superiority, or equivalence (e.g., therapeutic equivalence or bioequivalence). The data types of the commonly considered study endpoints could be continuous variable, binary response, or time-to-event data. More details regarding power calculation for testing non-inferiority hypothesis, superiority hypothesis, and equivalence hypothesis with various data types of study endpoints can be found in [3].

In clinical trials, interim analysis is often performed regardless the study design used. The purpose of interim analysis is multi-fold. First it is to verify the assumptions made for power calculation at the planning stage of the intended study. Second, it is to make sure the intended trial will achieve the desired power if the observed clinically meaningful difference (or treatment effect) preserves until end of the study. Thus, a blinded sample size re-estimation is often performed at interim. Third, if an adaptive trial design is used, some adaptations (modifications or changes) may be recommended after the review of interim data. For sample size re-estimation [3] pointed out that one could consider alternative methods in addition to the method of conditional power. These alternative methods include, but are not limited to

i. Maintain treatment effect

ii. Controlling variability

iii. Reaching a desired probability of reproducibility.

Maintaining treatment effect is to make sure that the test treatment under investigation is efficacious while controlling variability is for post-approval quality control and assurance. Reaching a desired probability of reproducibility is to make sure the observed positive result is not by chance alone and hence is reproducible.

In practice, it is desirable to maintain treatment effect and control variability at the same time when performing sample size calculation at the planning stage and/or sample size re-estimation sample size for achieving the objectives of maintaining treatment effect and/or controlling variability is studied under a promising zone design. In the next section, the concept of promising zone is briefly outlined. Moreover, the construction of Brownian Motion of the promising zone will also be demonstrated in Section 2. Under a promising zone design, formulas of conditional power, adjusted critical value, adjusted sample size are derived in Section 3. Section 4 summarizes the results of simulated studies with parameters from two real protocol under a promising zone design. Some concluding remarks are given in Section 5.

Statistical Assumptions

Concept of Promising Zone Design

In this article, the promising zone design is based on a two-stage and two-arm parallel clinical trial design with continuous endpoints. However, this methodology is surely applicable for multi-stage trials and trials with binary and time-to-event endpoints. The statistical assumptions mainly follow the article of [1]. This two-arm, two-stage trial is assumed to study the responses of participants to a newly developed compound. Suppose that all the participants entered the study at the beginning of stages and no subjects were recruited in the middle of the study. After the recruitment, participants were randomly assigned to the control arm and experimental arm and there is no drop-out in this ideal trial. The responses of individuals are considered as independent variables that identically followed a normal distribution. To start with a simple case, the variables of responses are assumed to follow a normal distribution with equal variance. To be more specific, let $X_e i \sim N(\mu_e, \sigma^2)$ and $X_c i \sim N(\mu_c, \sigma^2)$ be the response of i^{th} subject in two arms where i denote the i^{th} subjects. Then, a treatment effect difference can be defined as $\delta = \mu_e - \mu_c$. To check whether this difference is statistical significance, hypothesis testing for difference is applied with a null hypothesis $H_0 : \delta = 0$ and a one-sided alternative hypothesis $H_A : \delta > 0$. The reason why the one-sided alternative hypothesis is considered is that non-inferiority is the desired target. Since this trial is a two-stage design, an interim analysis is performed after data was recorded with n_1 subjects and a final analysis is performed after n_2 response data is accumulated. Considering the α-level and predefined power $(1-\beta)\%$, the planned total sample size can be derived as

$$n_2 = \frac{4\sigma^2\left(z_\alpha + z_\beta\right)}{\delta_0}$$

where the $Z_k = \Phi(1-k)$ is the Z-score and δ_0 is a pre-specified, clinical-meaningful treatment effect. And define the maximal sample size n_{max} as the upper bound of sample size limited by the budget and regulation of sponsor.

In terms of interim analysis and final analysis, let $Di_j = X_{eij} - X_{cij}$ where j denotes j^{th} stage, $j = 1,2$ and $D_{ij} \sim N(\delta, 2\sigma^2)$. Consequently, the mean of treatment difference between two groups D_j is also normally distributed and $\overline{D_j} \sim N\left(\delta_0, \frac{2\sigma^2}{n_j}\right)$ where n_J is the sample of data accumulated at J^{th} stage. Then the maximum likelihood estimates of treatment effect difference at two stages are $(P1)\, E(\overline{D_I}) = \delta_0$ and variance of $\hat{\delta}_j$ is $\text{var}(\hat{\delta}_j) = \frac{2\sigma^2}{n_j}$. Considering a Wald statistic at j^{th} stage denoted as $W_j = \left(\hat{\delta} - \delta_0\right) / se\left(\overline{\sigma_j}\right) = \frac{\left(\overline{D_j} - \delta_0\right)\sqrt{n_j}}{\sqrt{2}\sigma} \sim N(0,1)$.

The null hypothesis is rejected when $W_j > Z_\alpha$ to assure the hypotheses testing reaches the α-level. And whether the interim analysis result is promising is defined by the power of hypotheses testing condition on the interim statistic W_1 and the maximum loglikelihood estimator of treatment effect at stage one $\hat{\delta}_1$. By Mehta and Pocock (2011), it can be written as

$$CP_0\left(W_1, n_2\right) = \Pr\hat{\delta}_1\left(W_2 > Z_\alpha / W_1\right) = \Pr\hat{\delta}_1\left(\frac{\hat{\delta}_2}{se\left(\hat{\delta}_2\right)} > Z_\alpha / W_1\right).$$

One important requirement of clinical trials with multiple stages is that the overall type-I error should not be inflated. Small conditional power in the interim analysis will lead to an inflated overall type-I error since there are derived under the opposite hypothesis. On the contrary, too large conditional power, saying $CP \geq 0.9$, will lead to the termination of the trials by efficacy. Thus, at interim. However, applying multiple tests in one clinical trial might inflate the overall type-I error. Chen, Lan and DeMets have showed that the overall type-I error will not be inflated if the sample size is modified only when the interim analysis is promising using conventional Wald test. Rather than using weighted test which has been shown by [4], using adjusted critical value in conventional test is also applicable. To find the explicit form of adjusted critical value and other variables, the connection between variable of interest and normal distribution must be constructed. The most feasible way is to use the properties of stochastic process and Brownian motion which is also the validation of using the promising zone in clinical trial. In this article, the problem of selecting an appropriate

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the sample size can only be increased when the conditional power is promising which means CP should fall in a certain interval. The detailed definition of promising zone design will be given next.

Definition of promising zone design

The collection of interim analysis test statistics W_1 and corresponding conditional power $CP_\delta(W_1,n_2)$ will be divided into three intervals. Within each interval, the way to modify sample size are different.

Unfavorable Zone

For the unfavorable zone which is defined by $n^*_2(CP_{\max})$ where $CP_{\min}$ should be specified before

the beginning of the trial, conditional power in this interval is too low to meet the request of power. Continuing the trial might even lead to failure since the final power might be lower than the requirement by increasing the sample size from n_1 to n_2. The trial could be terminated early for futility.

Favorable Zone

For the favorable zone which is defined by $CP_\delta(W_1,n_2)>CP_{max}$ where CP_{max} usually defined as $1-\beta$, the conditional power in this interval indicates the contemporary trial result is so good that to meet the power

request and there is no need to increase the sample size to the planned n_2. The trial could proceed with the current sample size n_1 or be terminated for efficacy.

Promising zone

For the promising zone which is defined by $CP_{\min}<CP_\delta(W_1,n_2)<CP_{max}$, the conditional power in this interval cannot lead to neither early futility termination nor efficacy termination of the trial. The trial needs to proceed to large sample size to detect sufficient evidence. However, with the conditional power and statistic derived in the interim analysis, the increased sample size could be adjusted to a new value $n^*_2(n^*_2<n_{\max})$ rather than n_2 to avoid the futility or exceeding the budget. Since $CP_{\max}$ usually defined by the overall power requirement $1-\beta$, it is more important to determine the lower bound of the interval. In this article, the works are mainly focus on determine the lower bound.

Construction of Brownian Motion

To get the explicit formula of conditional power, adjusted critical value and adjusted sample size, the hypothesis tests in promising zone design need to be justified to follow the properties of Brownian Motion. To construct the Brownian Motion, the concept of information will be introduced. This section is mainly developed from [5]. Statistically speaking, the progressing of clinical trial is measured better by the accumulated information rather than the participants enrolled. Considering the estimation of treatment effect in each stage $\hat{\delta}_J=\overline{D_J}$, the information of $\overline{D_J}$ define as $I\left(\overline{D_J}=1/\left(\overline{D_J}\right)\right)$. Next, the construction of Brownian Motion will be demonstrated. Considering in a clinical trial with k stages, then there will be k estimations of treatment effect $(\overline{D_1},\overline{D_2},\ldots\overline{D_k})$. It can be shown that the sequence of $\overline{D_i}$ satisfies three properties of stochastics process:

$$(P1)\,E(\overline{D_I})=\delta_0$$

$$(P2)\,\mathrm{var}(\overline{D_I})=\frac{2\sigma^2}{n_i}$$

$$(P3)\,\mathrm{cov}(\overline{D_J},\overline{D_I})=\min\left\{\overline{D_J},\overline{D_I}\right\}$$

and the result of Central [5] Limit Theorem (when k is large enought), the sequence of estimations $(\overline{D_1},\overline{D_2},\ldots\overline{D_k})$ can be approximate by Brownian Motion. Applying the general statement in the two-stage scenario, the mean treatment difference between two group, $\widetilde{D}=\overline{D_2}-\overline{D_1}$ and $\widetilde{D^*}=\overline{D_2^*}-\overline{D_1}$ are two components of a sequence of Brownian Motion, where $\overline{D_2^*}$ is the treatment difference detected with a modified sample size n_2^* [6] The variance here takes the fisher information that leads to $\widetilde{D}\sim N\left(0,\sqrt{\frac{2\sigma^2}{n_1}-\frac{2\sigma^2}{n_2}}\right)$ and $\widetilde{D^*}\sim N\left(0,\sqrt{\frac{2\sigma^2}{n_1}-\frac{2\sigma^2}{n_2^*}}\right)$ can be easily justified by using the properties of Brownian Motion. On the contrary, under the alternative hypothesis, $H_A:\delta>0$, it gives $E(\overline{D_1})=E(\overline{D_2})=\delta\neq 0$. However, since $D_i\sim\delta\sim N\left(0,\frac{2\sigma^2}{n_i}\right)$, the difference of these two variables still has the Markov Properties, $\widetilde{D}\sim N\left(0,\sqrt{\frac{2\sigma^2}{n_1}-\frac{2\sigma^2}{n_2}}\right)$ and $\widetilde{D^*}\sim N\left(0,\sqrt{\frac{2\sigma^2}{n_1}-\frac{2\sigma^2}{n_2^*}}\right)$. The two different construction of variables following Brownian Properties will be used to separately derive the formula of type-I error and conditional power.

Proposed Method

Determine the Promising Zone by Controlling the Type-I Error Rate.

To preserve the overall type one error, the critical value of final analysis needs to be adjusted [6], the adjusted type-I error can be derived as follows,

$$\Pr_{\delta_0}\left(W_2>Z_\alpha\,|\,W_1\right)=\Pr_{\delta_0}\left(W^*_2>Z^*_\alpha\,|\,W_1\right)$$

Where δ_0 is the treatment effect under the null hypothesis, W^*_2 is the statistic in the final analysis with adjusted sample size n^*_2 and the adjusted critical value Z^*_α. More specifically, the left-hand side of the equation is

$$\Pr\left(W_2^*>Z^*_\alpha\,|\right)$$

$$=\Pr_\delta\left(D_2>Z_\alpha\sqrt{\frac{2\sigma}{n_2}}\,|\,W_1\right)$$

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$$= \Pr_{\delta_0}\left(D_2 - D_1 > Z_\alpha\sqrt{\frac{2\sigma^2}{n_2}} - D_1 \mid W_1 \right)$$

$$= \Pr_{\delta_0}\left(\frac{D_2 - D_1}{\sqrt{\frac{2\sigma^2}{n_1} - \frac{2\sigma^2}{n_2}}} > \frac{Z_\alpha\sqrt{\frac{2\sigma^2}{n_2}} - D_1}{\sqrt{\frac{2\sigma^2}{n_1} - \frac{2\sigma^2}{n_2}}} \mid W_1 \right)$$

By the null hypothesis, $\delta = 0$, by the assumption of Brownian Motion, W_1

$$= 1 - \phi\left(\frac{Z_\alpha\sqrt{\frac{2\sigma^2}{n_2}} - W_1\sqrt{\frac{2\sigma^2}{n_1}}}{\sqrt{\frac{2\sigma^2}{n_1} - \frac{2\sigma^2}{n_2}}} \right)$$

$$= \phi\left(\frac{W_1\sqrt{\frac{1}{n_1}} - Z_\alpha\sqrt{\frac{1}{n_2}}}{\sqrt{\frac{n_2 - n_1}{n_2 n_1}}} \right)$$

By the similar calculation,

$$\Pr\left(W^*_2 \geq Z^*_\alpha \mid W_1\right) = 1 - \phi\left(\frac{Z^*_\alpha\sqrt{\frac{2\sigma^2}{n^*_2}} - W\sqrt{\frac{2\sigma^2}{n_1}}}{\sqrt{\frac{2\sigma^2}{n_1} - \frac{2\sigma^2}{n^*_2}}} \right) = \phi\left(\frac{W_1\sqrt{\frac{1}{n_1}} - Z^*_\alpha\sqrt{\frac{1}{n^*_2}}}{\sqrt{\frac{n^*_2 - n_1}{n^*_2 n_1}}} \right)$$

By the identity of these two type-I error, the adjusted critical value can be derived as

$$Z^*_\alpha = Z_\alpha\sqrt{\frac{n^*_2 - n_1}{n_2 - n_1}} + \sqrt{\frac{n^*_2}{n_1}}W_1 - \sqrt{\frac{n_2(n^*_2 - n_1)}{n_1(n_2 - n_1)}}W_1$$

By the properties of Brownian Motion under the alternative hypothesis, the conditional power can be presented as

$$\Pr_{\hat{\delta}}\left(W_2 > Z_\alpha \mid W_1\right) = 1 - \phi\left(\frac{Z_\alpha\sqrt{n_1} - W_1\sqrt{n_2}}{\sqrt{n_2 + n_1}} \right) = \phi\left(\frac{W_1\sqrt{n_2} - Z_\alpha\sqrt{n_1}}{\sqrt{n_2 + n_1}} \right)$$

By the similar calculation, the conditional power with adjusted sample size can be derived as follows:

$$\Pr_{\hat{\delta}}\left(W^*_2 > Z^*_\alpha \mid W_1\right) = 1 - \phi\left(\frac{Z_\alpha\sqrt{n_1} - W_1\sqrt{n^*_2}}{\sqrt{n^*_2 + n_1}} \right) = \phi\left(\frac{W_1\sqrt{n^*_2} - Z_\alpha\sqrt{n_1}}{\sqrt{n^*_2 + n_1}} \right)$$

Substituting the adjusted critical value in the formula of conditional power, the formula can be simplified as:

$$\Pr_{\hat{\delta}}\left(W^*_2 > Z^*_\alpha \mid W_1\right) = 1 - \phi\left(\sqrt{\frac{n^*_2}{n_2 - n_1}}W_1 - \sqrt{\frac{n_2}{n_2 - n_1}}Z_\alpha \right)$$

Set the conditional power with modified sample size n_2^* equals to 1-β, the modified sample size can be derived. It can be shown as

$$\phi\left(\sqrt{\frac{n_2}{n_2 - n_1}}W_1 - \sqrt{\frac{n_2}{n_2 - n_1}}Z_\alpha \right) = 1 - \beta$$

and

$$n^*_2 = (n_2 - n_1)\frac{\left(\sqrt{\frac{n_1}{n_2 - n_1}}Z_{alpha} - Z_\beta\right)}{W^2_1}$$

Moreover, the budget limit of the trial also needs to be considered in the design stage. Define the finally modified sample size with consideration of $n_{\max}$ as n'_2 where $n'_2(W_1) = \min\left(n_{\max}, n^*_2\right)$

Determine the promising zone by constraints

Proposed one [2] new method to determine the promising zone of the conditional power. This method is like the method of controlling type-I error but easier to be conducted by investigators. The algorithm is given as following.

$$Maximize\left\{CP_\delta\left(W_1, n^*_2\right)\right\}$$

$$s.t. n_1 \leq n^* \leq n_{\max}$$

$$CP_{\min} \leq CP_\delta\left(W_1, n^*_2\right) \leq CP_{\max}$$

By maximizing the objective function, an interval of interim analysis can be derived denoted as $\left[W^L_1, W^U_1\right]$. Furthermore, considering the scenario when $n^*(W_1, \delta, CP_{\min}) = \begin{cases} n_1 \text{ if } W_1 < W^L_1 \\ n_{\max} \text{ if } W_1 \in \left[W^L_1, W^U_1\right] \\ n^*(W_1) \end{cases}$, since CP is determined by both W_1 and n_2. In this case, there is need to increase the sample size anymore due to the consideration of trial budget limitation. With the increment of W_1, to remain $CP = CP_{\max}$, the sample size should be reduced. Define the smallest interim analysis statistic $W^0_1 = \min\left\{W_1 \mid CP_\delta\left(W_1, n^*_2\right) = CP_{\max}\right\}$. And the algorithm for sample size is defined as following:

$$n^*(W_1, \delta, CP_{\min}) = \begin{cases} n_1 \text{ if } W_1 < W^L_1 \\ n_{\max} \text{ if } W_1 \in \left[W^L_1, W^U_1\right] \\ n^*(W_1) \end{cases}$$ By the formula of sample size and conditional power

Simulated Study

In this section, two simulated studies with parameters from real clinical trial protocol will be introduced. The first examples utilize parameters of a clinical trial of pancreatic cancer introduced by Hsiao [2]. The trial is a two-group placebo-control design. Participants were randomly assigned to treatment group using a recombinant human hyaluronidase and a concurrent placebo control group. The primary endpoint progression-free survival. Several literatures have shown that with the consideration of the uncertainty of parameters, the trial had to show desired power of hazard ratio in the range of [0,67,0.75]. Here, the simulated study will focus on the minimal treatment different $\delta_{\min} = ln(0.75) = 0.29$. By the requirement of sponsor, the $n_{\max} = 420$, $n_{\max} = 420$, $n_1 = 140$, $n_2 = 280$, $CP_{\max} = 0.9$, $CP_{\min} = 0.8$ and $\alpha = 0.025$. In the simulated study, the relationship of modified sample size, modified power, original power, power increment, the probability of falling in the promising zone will be analyzed to evaluate the feasible and effect of promising zone design.

By method 1, determining the promising zone by preserving type-I error, the interim test statistic $W_1 \sim N(1.72,1)$ and the promising zone is $W_1 \in [1.27, 2.02]$. With such distribution and promising zone, the probability of falling in the promising zone is $P \approx 0.29$. And the table with 5 randomly selected levels of the promising

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zone is shown in (Table 1) below. By the method 2, the promising zone in this example is $W \in [1.187, 2, 338]$. The table with 5 randomly picked W_1 presenting relationships between sample size, W_1 and CP is shown in (Table 2) below. The second example comes from a phase 3 Schizophrenia trial. By [7], participants with negative symptoms schizophrenia are randomized into two groups, one with the test drug and one with an active control. The primary endpoint is the increment of standardized score in the Negative Symptoms Assessment from the baseline to week 26. The planned trial size, $n_2 = 442$, was calculated based on 80% power to detect a mean score difference δ=2 with a one-sided level-0.025 test, assuming a score standard deviation σ = 7.5 in each treatment group. $n_{\max} = 884$ and the interim analysis will be conducted after 208 participants have been treated.

Table 1: Randomly picked 5 simulated unit with method 1 in example 1.

W_1	Modified Sample Size	Modified Power	Original Power	Power Increment
1.285	420	0.987	0.929	0.059
1.493	420	0.987	0.929	0.059
1.514	420	0.987	0.929	0.059
1.845	340.377	0.965	0.929	0.037
1.947	303.939	0.946	0.929	0.018

Table 2: Randomly picked 5 simulated unit with method 2 in example 1.

W_1	Modified Sample Size	Modified Power	Original Power	Power Increment
1.646	415.642	0.987	0.929	0.058
1.776	386.676	0.981	0.929	0.052
1.808	379.793	0.979	0.929	0.05
1.92	356.467	0.972	0.929	0.043
1.925	355.454	0.971	0.929	0.043

By the method 1, the promising zone is $W_1 = [1.17, 1.76]$. And a table with randomly picked 5 values are shown in (Table 3). In this example, the probability of falling in promising zone based on different values of δ are shown in the (Table 4). By the CPZ Design method, the promising zone is $W_1 \in [-19.585, -9.230]$. And the table with 10 randomly selected W_1 and corresponding sample size, power is shown in the (Table 5).

Table 3: Randomly picked 5 simulated unit with method 1 in example 2.

	Modified Sample Size	Modified Power	Original Power	Power Increment
1.212	884	0.994	0.886	0.108
1.387	744.406	0.984	0.886	0.098
1.477	645.353	0.969	0.886	0.083
1.517	608.718	0.961	0.886	0.074
1.54	589.068	0.955	0.886	0.069

Table 4: Probability of falling in the promising zone based on different values of δ

δ	Probability
1.6	0.234
1.7	0.232
1.8	0.227
1.9	0.221
2	0.212

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Table 5: Randomly picked 10 simulated unit with method 2 in example 2.

	Modified Sample Size	Modified Power	Original Power	Power Increment
-18.4	884	0.994	0.886	0.108
-18.151	874.173	0.994	0.886	0.107
-17.239	819.846	0.991	0.886	0.104
-16.877	798.923	0.989	0.886	0.103
-15.351	714.722	0.981	0.886	0.094
-13.675	629.699	0.966	0.886	0.079
-13.117	603.123	0.959	0.886	0.073
-11.544	532.861	0.936	0.886	0.049
-11.353	524.798	0.932	0.886	0.046
-9.612	455.969	0.896	0.886	0.009

Discussion

Feasibility of promising zone design

From the two examples of [8] simulated studies, we can see that the power increment in the first example is relatively small. And with the increase of interim analysis, the power increment drops. Furthermore, the probability of falling into the promising zone remains lower than 30%. Whether it is necessary to conduct an extra interim analysis remains to be discussed. And it needs to be treated separately by different trials and different parameters.

Drawbacks of Promising Zone Design

As with all designs with early determination, promising zone lost chances to detect further information. The most one among all information is the potential adverse events. Since promising zone design is aiming to increase the probability of success of the trial at phase III and toxicity [9] analysis is usually applied at phase I, it is not an obstacle that hardly stops investigators from using promising zone design.

Particularly for the method of determining the promising zone by preserving the type-I error, the formula gives identity conditional power regardless of the treatment effect. This identity is caused by the construction of the Brownian Motion. However, whether it will still show this identity when using different tests and constructing the Brownian Motion by other methods remains discussion. In terms of the constraint optimization method, there is no modification in critical values which means there is no constraint for type-I error. The type-I error might not be preserved under some circumstances. Further research could focus on the combination of the two methods above.

References

1. Mehta Cyrus, Pocock Stuart (2011) Adaptive Increase in Sample Size When Interim Results are Promising: A Practical Guide with Examples. Statistics in med 30(28): 3267-3284.
2. Hsiao S T, Liu L, Mehta C R (2019) Optimal promising zone designs. Biometrical journal. Bio Zeitschrift 61(5): 1175-1186.
3. Chow S C, Shao J, Wang H, Lokhnygina Y (2017) Sample Size Calculation in Clinical Research. Third Edition, Taylor & Francis, New York, USA.
4. Cui L, Hung H J, Wang S J (1999) Modification of sample size in group sequential clinical trials. Biometrics 55(3): 853-857.
5. Lan K G, Zucker D M (1993) Sequential monitoring of clinical trials: the role of information and Brownian motion. Stat in Med 12(8): 753-765.
6. Mörters P, Peres Y (2010) Brownian motion (Vol 30) Cambridge University Press UK.
7. Gao P, Ware J H, Mehta C (2008) Sample size re-estimation for adaptive sequential design in clinical trials. J Bio Stat 18(6): 1184-1196.
8. Jennison C, Turnbull B W (1999) Group sequential methods with applications to clinical trials CRC Press USA.
9. Whitehead J (1997) The design and analysis of sequential clinical trials. John Wiley & Sons, USA.

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