ADAPTIVE DESIGNS FOR PHASE III STUDIES : A BRIEF INTRODUCTION

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1. Introduction

An *adaptive design* is a clinical study design that uses accumulating data to decide on how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial (Chow & Chang, 2011). Such methodology is available for phase I (e.g.: continual reassessment method for dose-finding clinical trials), phase II (e.g.: Simon's two-stage design), phase II/III (e.g.: adaptive seamless phase II/III designs) and phase III designs (e.g.: group sequential methods). The aim of this report is to present an overview of adaptive designs in clinical trials with a focus on phase III adaptive designs.

2. Definition, Rationale and allowed modifications

2.1. Definition

An *adaptive design* is a clinical study design that uses accumulating data to decide how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial. The goal of adaptive designs is to learn from the accumulating data and to apply what is learned as quickly as possible. In such trials, changes are made "by design," and not on an ad hoc basis; therefore, adaptation is a *design feature* aimed to enhance the trial, not a remedy for inadequate planning (Galo et al., 2006).

2.2. Rationale

Adaptive designs allow also to change the study hypotheses, such as (1) switching for superiority to non-inferiority; (2) switch from a single hypothesis to a multiple hypothesis or a combined outcome; (3) changing hypotheses due to the switch in study endpoints; (4) dropping ineffective treatment arms; (5) interchange between the null and the alternative hypothesis; (6) stop the trial earlier for futility or efficacy (Chow & Chang, 2011). Indeed, at the beginning of the clinical trial, the investigator may not have adequate information about the effect size of the treatment, and rather than to continue to conduct an inappropriate powered trial, the sponsor may wish to modify the sample size or stop the clinical trial when there is enough convincing evidence of benefit (=efficacy) or harm (=futility) (Friedman, Fureberg & DeMets, 2010). Moreover, adaptive designs are well suited for economical purposes: they allow an earlier termination of the trial. If the results are positive, the compound/treatment may be exploited sooner and if the results are negative, the resources are not wasted (Chow & Chang, 2011).

2.3. Most common modifications

Adaptations or modifications of on-going clinical trials that are commonly made to trial procedures include eligibility criteria, study dose or regimen, treatment duration, study endpoints, laboratory testing procedures, diagnostic procedures, criteria for evaluability, assessment of clinical responses, deletion/addition of treatment groups, and safety parameters. In practice, during the conduct of the clinical trial, statistical procedures including randomization procedure in treatment allocation, study objectives/hypotheses, sample size reassessment, study design, data monitoring and interim analysis procedure, statistical analysis plan, and/or methods for data analysis are often adjusted in order to increase the probability of success of the trial by controlling the pre-specified type I error.

3. Basics of Group Sequential Design Theory

3.1. Alpha, Beta and Power

The remaining of the report will use notions of Type I error (= alpha), Type-II error (beta) and power. It is therefore time to formally define these concepts. We define H_0 as the null hypothesis of no treatment differences between two treatments groups on a proportion, continuous variables or time to event.

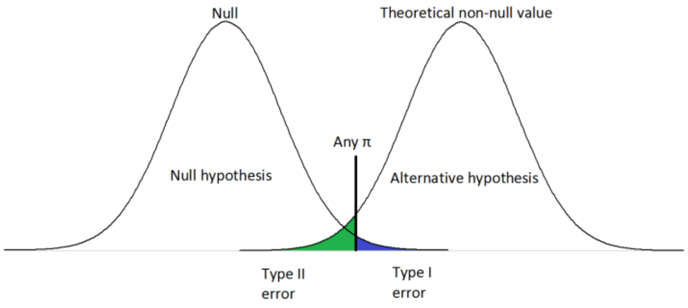
	H_0 true	H_0 false
Reject H_0	Type I error (α) False positive	Correct outcome True positive
Fail to reject H_0	Correct outcome True negative	Type II error (β) False negative

Based on the above table, we define (on the left) and depict graphically (on the right) the concepts of alpha, beta and power as:

α: rejection of H_0 when it is true

β: accept H_0 when H_0 is false

power ($1-\beta$): Probability to reject H_0 when H_0 is false



3.2. Distributional assumptions

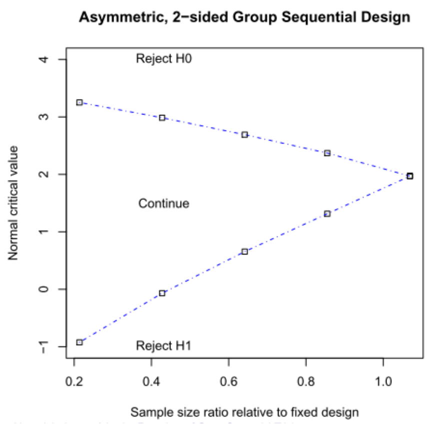
Mathematically, group sequential design is defined as such: let X_1, X_2,… be independent and identically distributed random variables with mean θ and variance 1. For some positive integer, let $n_1 < n_{2\ldots}\ n_k$ represent fixed sample size where data will be analysed and inference surrounding $\theta = (\bar{x}_{Ai} - \bar{x}_{Bi})$ will be examined. The first k-1 analyses are the interim analyses and the k^{th} analysis corresponds to the final analysis. For i=1,2,…,k, consider the following statistics:

$$Z_i = (\bar{x}_{Ai} - \bar{x}_{Bi}) * (n_i/2\sigma^2)$$

3.3. Hypotheses testing, alpha, beta and theta: example of a superiority trial

We take example of a superiority trial. The primary hypothesis is:

- H_0: $\theta \leq 0$ vs H_1: $\theta > 0$
- α=0.025; β=0.10 at a fixed θ
- Upper bounds stop the trial for efficacy
- Lower bounds stop the trial for futility



The figure on the right identifies for a given θ the critical values at which, for each interim analyses (here 4) and final analysis the null hypothesis of no difference on the primary outcome between the treatment groups.

4. Choices to be made for the design of the adaptive trial

4.1. Non-inferiority or superiority

Group sequential methods are available to test non-inferiority or superiority (=equality) hypotheses. Moreover, as already indicated, switch between superiority and non-inferiority during the trial is possible (Chow & Chang, 2011; Lai, Shih & Zhu, 2004) but the choice of the non-inferiority margin is crucial in this context (Chow & Chang, 2011).

4.2. Number of interim analyses

The number of interim analyses has to be determined by the sponsor and the statistical tests are performed based on accrued data at some pre-specified interval rather than after every new observation is obtained. The higher the number of interim analyses, the higher the final sample size. However, there is little advantage to plan a large number of interim analyses (the sample sizes are small, certainly at the beginning of the trial, and the variability of the data high, making decision based on only a few interim data extremely difficult). As a general rule of thumb, Pocock (1988) recommends never to plan more than 5 interim analysis but at least 1, in order to warrant scientific and ethical validity of the trial.

4.3. Stopping boundaries

Stopping boundaries consist of a set of critical values that the test statistics calculated from actual data will be compared with to determine whether the trial should be terminated or continue. In other words, if the observed sample mean at a given stage falls outside the boundaries, we will terminate the trial; otherwise the trial continues.

4.4. Early Boundary

Four commonly used boundary scales are used to construct the stopping boundaries: the standardized z-statistic (presented in 3.2), the sample-mean scale, the error-spending scale and the sum-mean scale. The z-statistics is commonly used by statistical programs such as the gsDesign R Package (Anderson, 2011).

4.5. Stopping rules – sample size

Several stopping rules have been developed. We present four of them, appearing the most in the statistical and medical literature on group sequential designs: the Peto, Pocock, O'Brien & Fleming and Wang & Tsiatis test.

4.5.1. Haybittle-Peto test

The test developed by Haybittle (1971) and Peto et al. (1976) uses a very large critical value to stop the clinical trial earlier: stop if an interim analysis indicates probability of 0.001 (=Type I error) that the treatment are different.

The Haybittle-Peto's test may be expressed as:

1) After group $k=1,\dots,K-1$,
   a. If $|Z_k| > 3$ then stop, reject H_0;
   b. Otherwise continue to group $k+1$.
2) After group K,
   a. If $|Z_K| > C_{HP}(K,\alpha)$ then stop, reject H_0;
   b. Otherwise stop, accept H_0.

4.5.2. Pocock's test

The test developed by Pocock (1977) is done at a same nominal level of alpha over the course of the clinical trial. If $C_P(K,\alpha)$ denotes the critical value for having an overall type I error of rate α, the Pocock's test may be expressed as:

1) After group $k=1,\dots,K-1$,
   a. If $|Z_k| > C_P(K,\alpha)$ then stop, reject H_0;
   b. Otherwise continue to group $k+1$.
2) After group K,
   a. If $|Z_K| > C_P(K,\alpha)$ then stop, reject H_0;
   b. Otherwise stop, accept H_0.

The critical value $C_P(K,\alpha)$ depends only of the pre-specified type I error (α) and the number of interim analyses. The power of the above test procedure can be determined by the number of planned interim analyses (K), the type I error (α), the type II error (β) and the proportion between σ^2 and δ^2 (i.e., σ^2/δ^2), where δ is $|\mu_1 - \mu_2|$.

4.5.3. O'Brien and Fleming test

If the Pocock's test is straightforward and simple, it is performed at a constant nominal level. O'Brien and Fleming (1979) proposed a test, also based on the standardized statistics Z_k, where it is more difficult to reject the null H_0 at earlier stages of the analysis. This test increases the nominal significance for rejecting H_0 at each analysis as the study progresses and is defined as:

1) After group $k=1,\dots,K-1$,
   a. If $|Z_k| > C_B(K,\alpha)\sqrt{K/k}$ then stop, reject H_0;
   b. Otherwise continue to group $k+1$.
2) After group K,
   a. If $|Z_K| > C_B(K,\alpha)$ then stop, reject H_0;
   b. Otherwise stop, accept H_0.

The value of $C_B(K,\alpha)$ is chosen to ensure that the over type I error is α.

4.5.4. Wang and Tsiatis test

Wang and Tsiatis's test includes the Pocock and O'Brien and Fleming as special cases. The procedure may be summarized as follows:

1) After group $k=1,\dots,K-1$,
   a. If $|Z_k| > C_W(K,\alpha,\Delta)(k/K)^{\Delta-1/2}$ then stop, reject H_0;
   b. Otherwise continue to group $k+1$.
2) After group K,
   a. If $|Z_K| > C_W(K,\alpha,\Delta)$ then stop, reject H_0;
   b. Otherwise stop, accept H_0.

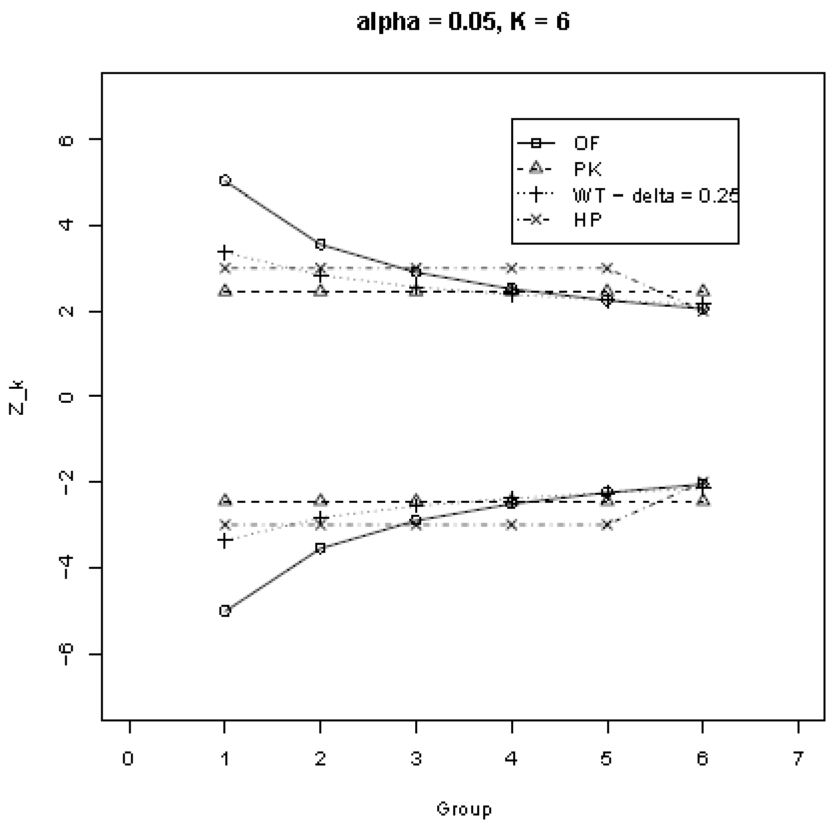
The Wang-Tsiatis's test reduces to Pocock's test when $\Delta=0.5$ and to the O'Brien and Fleming test when $\Delta=0$.

4.5.1. Which test to choose?

Here is a comparison table presenting the advantages and disadvantage of each design seen in the above section (Wang and Tsiatis is between O'Brien & Fleming and Pocock)

	Advantages	Disadvantages
Haybittle-Peto	1) Simple to use 2) Results in final critical values close to critical values for fixed-sample test	1) Impossible to find C_{HP} achieving the desired Type-I error rate for some combinations of α and K (when α is small and K large)
O'Brien & Fleming	1) Final critical value is close to critical value for a fixed-sample design 2) More powerful than Pocock, requiring then a smaller maximum sample size	1) Less likely to stop early than Pocock boundaries, which implies a larger expected sample size
Pocock	1) Simple to use 2) Lower probability to stop early, which implies a smaller expected sample size	1) Substantial reduction in power

The O'Brien and Fleming test is unlikely to lead to stop for efficacy in early stages of the clinical trial. Later on, it leads to a higher chance of stopping for efficacy than the other two designs. The O'Brien and Fleming boundaries avoid the awkward situation of accepting the null hypothesis when the observed statistic at the end of the clinical trial is much larger than the conventional critical value (i.e., 1.96 for a two-sided 5% significance level). As seen earlier, the large critical value for the O'Brien and Fleming boundary can be adjusted to a lower value (e.g., 3.5) by means of the Wang-Tsiatis boundary without noticeably changing the critical values used later on, including the final value. Last, the O'Brien and Fleming design requires the lower sample size. The next graph presents the N and upper bounds for a fictitious clinical trial for a same nominal level of type I error (α) and 5 interim analyses and a final analysis.



In conclusion, the O’Brien and Fleming test is often chosen for conservative reasons: it allows higher critical values at the earlier stages of the clinical trial. Additionally, monitoring committees are likely to choose for a conservative approach given that a few additional events can alter the results substantially of a clinical trial, certainly at an earlier stage of the trial, when only a fraction of the total expected sample size is enrolled.

Last, a combination The O’Brien-Fleming sequential boundary might be used for monitoring beneficial effects, while a Pocock-type sequential boundary could provide guidance for safety monitoring

4.6. Alpha and Beta Spending Functions

4.6.1. Alpha Spending Functions (efficacy)

A major disadvantage of group sequential methods is that they are designed for a fixed number of equally spaced interim analyses. However, in practice, it is common to plan interim analyses based on calendar and, as a consequence, interim analyses may not be equally spaced. Therefore, the overall type I error (α) may be far away from the target value.

To overcome this problem, Lan & DeMets (1983; 1995) proposed to distribute (or spend) the total probability of false positive risk (= type I error = α) as a continuous function of the information time in group sequential procedures for interim analyses. If the total information scheduled to accumulate over the maximum duration T is known, the boundaries can be computed as a continuous function of the information time, which is referred as the alpha spending function, denoted by $\alpha(s)$. The alpha spending function is an increasing function of information time: it equals 0 when information time is 0 and it equals the overall significance level when information time is 1. In other words, $\alpha(0)=0$ and $\alpha(1)=\alpha$. Let s_1 and s_2 be two information times, $0< s_1< s_2 \leq 1$ and denote $\alpha(s_1)$ and $\alpha(s_2)$ be their corresponding value of alpha spending function at information time s_1 and s_2. Then, $0< \alpha(s_1)< \alpha(s_2) \leq 1$ is the probability of type I error (alpha) one wishes to spend at information time s_1.

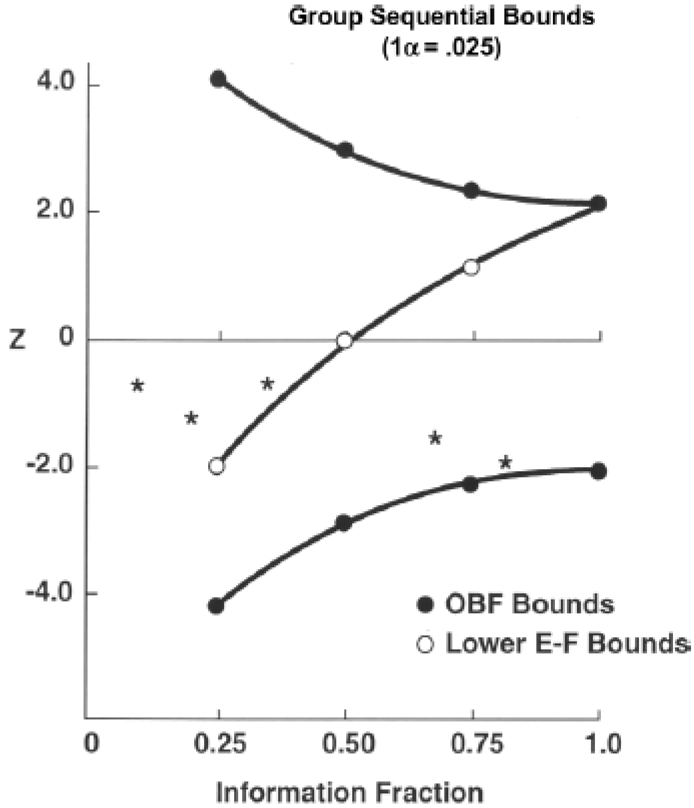
Here are the alpha spending functions proposed by Lan & DeMets (1983)

$\alpha_1(s) = 2\{1-\Phi(z_{\alpha/2}/\sqrt{2})\}$	O'Brien-Fleming
$\alpha_2(s) = \alpha \log[1+(e-1)s]$	Pocock
$\alpha_3(s) = \alpha s^{\rho}$, $\rho>0$	Lan-DeMets-Kim
$\alpha_4(s) = \alpha[(1-e^{\zeta s})/(1-e^{\zeta})]$, $\zeta\neq 0$	Hwang-Shih

Sample size calculation for Lan-DeMets's alpha spending function are also available and , although alpha spending function does not require a fixed maximum number and equally spaced interim analyses, it is necessary to make those assumptions in order to calculate the sample size under the alternative hypothesis.

4.6.2. Beta Spending Functions (futility)

The beta spending function allows a Data Monitoring Committee to stop the trial for futility reasons, meaning that data are convincing enough that the new proposed treatment is harmful for patients and that is therefore unethical to continue the clinical trial. The beta spending function method is similar to the alpha spending function but has the goal of ruling out a treatment effect of a pre-specified size. In other words, beta spending functions control the type II (or β) error. The resulting sequential group design may have symmetric or asymmetric boundaries. The next graph, reprinted form DeMets (2006), indicates that conclusions change whether the lower bound is symmetric or asymmetric (=triangular) to the alpha-spending function. As indicated, when the lower-bound is symmetric to the upper-bound (OBF bounds in the graph bellow), the fictitious clinical trial is never stopped for futility reasons. On the contrary, when the lower-bound is asymmetric (lower E-F Bounds in the graph below), the fictitious clinical trial is stopped after information fraction 0.5 (= after having analysed half of the total planned number of recruited subjects for the clinical trial). Another way to deal with the lower bound is simply to ignore it and never stop a clinical trial for futility reasons.



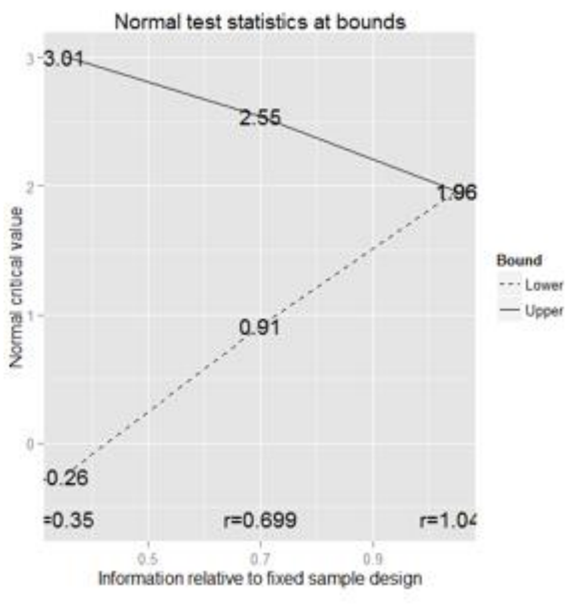
OBF = O'Brien–Fleming Bounds [12].
E-F = Emerson–Fleming Bounds [26].

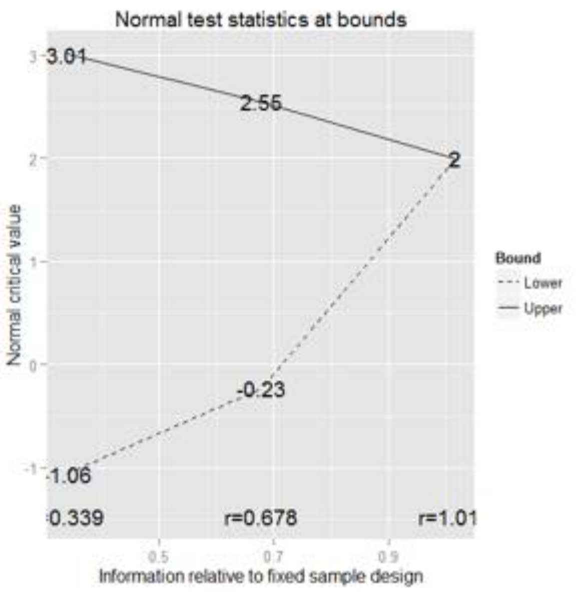
Figure 3 Vesnarinone trial (VEST) group sequential bounds

Therefore, 6 possibilities exist to cross the alpha and beta spending boundaries:

1) A one-sided design: this design ignores the lower-bound
2) A two-sided, symmetric design: this design has symmetric upper and lower bounds
3) A two-sided, asymmetric, beta-spending with bending lower bound
4) A two-sided, asymmetric, beta-spending with non-bending lower bound
5) A two-sided, asymmetric, lower bound spending under the null hypothesis with bending lower bound
6) A two-sided, asymmetric, lower bound spending under the null hypothesis with non-bending lower bound

The beta-spending function controls the incremental amount of the Type-II error at each analysis. Under the null hypothesis, the lower bounds are lower, allowing a larger indecision region. The left graph presents a beta-spending lower bound and the right one depicts a lower bound under the null hypothesis.





For possibilities 1, 2 and 5, boundaries can be computed in a single step just by knowing the cumulative proportion of the final planned statistical information (sample size/number of events) at each analysis that is specified using the timing input variable. For possibility 6, the upper and lower boundaries are computed separately and independently using these same methods. For possibilities 1, 2, 5 or 6 the total sample size is then set to obtain the desired power under the alternative hypothesis by using a root finding algorithm.

For possibilities 3 and 4 sample size and bounds are set simultaneously using an iterative algorithm which makes the computation slightly more complex than the above.

5. During the adaptive trial: at interim analysis

5.1. Recalculate the sample size

Recalculation of the sample size at interim analyses is desirable in order to determine whether the selected sample size is justifiable based on clinical data accumulated up to the time point of interim analysis. Note that the FDA will not accept to decrease the sample size in the course of the trial for safety data reasons (CDER, 2010). Unblinding the treatment codes for sample size re-estimation may introduce bias in the clinical trial. Shih (1993) and Shih & Zhao (1997) proposed a methodology without unblinding the treatment codes for interim data where at least 50% of the planned sample size complete the trial for double-blind clinical trials with binary outcomes. The procedure is in X steps:

1) Within each center, assign randomly each subject to a dummy stratum (e.g.: A or B), and the randomization is not done on baseline characteristics of subjects
2) Subjects within each stratum are the randomly assigned to a treatment group with a probability π or to the control group with the probability 1- π (π Є (0, 0.5).
3) Based on the pooled event rates, evaluate p_1 and p_2 without unblinding the treatment codes

5.2. Conditional/Predictive power

Conditional/Predictive power at an interim analysis – the first is frequentist and the second Bayesian - is defined as the power of rejecting the null hypothesis at the end of the trial conditional on the observed data accumulated up to the time point of the planned interim analysis. Indeed, if the data at interim analysis indicate a strong evidence of futility, it is unethical to continue the trial and therefore, the trial may be stopped under the null hypothesis. Most repeated significance tests (Pocock, O'Brien and Fleming and Wang and Tsiatis) are designed for early stop under the alternative hypothesis, and, for them, the analysis of conditional power can be used as a quantitative method for determining whether the trial should be terminated prematurely.

5.3. Switch between superiority/non-inferiority

In order to increase the probability of success of the trial, it is not uncommon to switch from superiority to non-inferiority (Chow & Chang, 2011) and one of the major consideration is therefore the choice of the non-inferiority margin which should be based on sound clinical reasoning and statistical judgment (ICH E10 guideline). As indicated in Chow & Chang, 2011, pp. 78-79:

"*According to the ICH E10 Guideline, a non-inferiority margin may be selected based on past experience in placebo control trials with valid design under conditions similar to those planned for the new trial, and the determination of a non-inferiority margin should not only reflect uncertainties in the evidence on which the choice is based, but also be suitably conservative. Furthermore, as a basic frequentist statistical principle, the hypothesis of non-inferiority should be formulated with population parameters, not estimates from historical trials. Along these lines, Chow and Shao (2006) proposed a method of selecting non-inferiority margins with some statistical justification. Chow and Shao proposed non-inferiority margin depends on population parameters including parameters related to the placebo control if it were not replaced by the active control. Unless a fixed (constant) non-inferiority margin can be chosen based on clinical judgment, a fixed non-inferiority margin not depending on population parameters is rarely suitable. Intuitively, the non-inferiority margin should be small when the effect of the active control agent relative to placebo is small or the variation in the population under investigation is large. Chow and Shao's approach ensures that the efficacy of the test therapy is superior to placebo when non-inferiority is concluded. When it is necessary/desired, their approach can produce a non-inferiority margin that ensures that the efficacy of the test therapy relative to placebo can be established with great confidence.*"

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