## Boundary Scales in RCTdesign

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#### Abstract

Many authors make distinctions between clinical trial designs derived using "group sequential designs" (e.g., O'Brien-Fleming or Pocock designs), "error spending functions" (e.g., Lan & DeMets or Hwang, Shih, & DeCani), "stochastic curtailment" (e.g., conditional power or Bayesian predictive power), and "Bayesian designs" based on posterior probabilities. However, in RCTdesign we regard these as "distinctions without differences". In fact, every sequential stopping rule can be expressed in each of those boundary scales. In this tutorial, we demonstrate the way the various boundary scales are specified in RCTdesign, in order that the user can evaluate the appropriateness of a particular sequential sampling scheme on the scales that are of greatest interest in a particular application. Alternative tutorials discuss the relative merits of particular boundary scales in greater detail.

## 1 Introduction

Group sequential designs have been described in the literature for a variety of test statistics:

- The normalized Z statistic was used as the basis for defining group sequential rules by multiple authors.
  - Pocock (1977) explored the robustness of normal distribution based stopping rules in the context of stopping rules that were constant for a Z statistic.
  - O'Brien and Fleming (1979) considered "conservative early" designs defined for a Z statistic.
  - Wang and Tsiatis (1987) described a family of designs on the Z statistic scale that smoothly varied from the Pocock to the O'Brien-Fleming boundaries.
  - Pampallona and Tsiatis (1994) extended the Wang and Tsiatis family to one-sided designs and four boundary designs defined according to both type I error and power.
- Owing to the computational formula for the sampling distribution of the group sequential test statistic, the partial sum of the observations was used as the basis for group sequential designs by some authors.
  - Whitehead and Stratton (1983) defined the triangular designs on the basis of the score statistic on the partial sum scale.
  - Emerson and Fleming (1989) defined the symmetric one- and two-sided tests on the basis of the partial sum scale.
- Some authors have defined tests on the scale of the estimated treatment effect.
  - Kittelson and Emerson (1999) used the "sample mean scale" to define the unified family of designs, that includes the Pocock, O'Brien & Fleming, Whitehead & Stratton, Wang & Tsiatis, Emerson & Fleming, Pampallona & Tsiatis, Xiong's SCPRT, and predictive power families as special cases.

• A number of authors have described group sequential designs on the basis of "error spending functions".

- Lan and DeMets (1983) first described the error spending approach.
- Kim and DeMets (1987) described the power family of error spending functions.
- Hwang, Shih, and DeCani (1990) described an alternative family of error spending functions.
- Anderson and Clark (2009) explored several families of two parameter error spending functions.
- A number of authors have considered the use of stochastic curtailment in stopping rules.
  - Lan, Simon, and Halperin (1982) suggested the use of conditional power as a basis for stopping a study.
  - Spiegelhalter, Freedman, and Blackburn (1986) suggested the use of a Bayesian prior to calculate the predictive power.
  - Xiong (1995) defined the sequential conditional probability ratio test based on the conditional probability of a reversed decision were the trial to continue.
- And some authors have proposed a pure Bayesian approach that considers the posterior probability of an effective treatment.
  - Berry (1985) compared the classical frequentist approach to the Bayesian viewpoint.
  - Freedman and Spiegelhalter (1989) and (1991) also provide discussion contrasting the frequentist and Bayesian approaches.
  - Spiegelhalter, Freedman, and Parmar (1994) presented a paper to the Royal Statistical Society that was published with discussion.

In RCTdesign, we regard that these approaches are largely "distinctions without differences". It is largely immaterial how a stopping rule is derived and for what statistic it is defined, because we can always transform the boundary on a different scale. In the next section we illustrate the 1:1 correspondence between stopping rules on one of the above scales and stopping rules on any of the others. In section 3 we discuss how the various scales are specified using seqScale() in RCTdesign, and the illustrate their use with a few examples in section 4. (It should be noted that this document focuses primarily on the way to specify the various scales. Additional tutorials on both the Software and the Learning webpages provide additional detail on the advantages and disadvantages of particular boundary scales in the evaluation of a candidate clinical trial design.)

We initialize RCTdesign by typing

> library(RCTdesign)

## 2 Correspondence Among Boundary Scales

In this section we demonstrate the 1:1 correspondence between the boundary scales using a one-sample "mean" probability model for illustration.

Notationally, we can without loss of generality consider that we have data  $X_i \sim (\theta, \sigma^2)$  for i = 1, ..., N, where the individual measurement  $X_i$  might represent a contrast across individuals (e.g., difference in measurements) or some other transformation of observations (e.g., the *i*th subject's contribution to the score or partial score function), and  $\sigma^2$  represents the variability of each sampling unit (or, more generally, is related to the statistical information contributed by each observation). We are interested in testing the null hypothesis  $H_0: \theta = \theta_0$ , and we assume  $\sigma^2$  is known. Our sequential sampling scheme involves performing

analyses after accrual of  $N_1, N_2, \ldots, N_J = N$  observations, and comparing some statistic  $T_j$  that tends to be larger for large values of  $\theta$  to stopping boundaries  $a_j \leq b_j \leq c_j \leq d_j$ . The group sequential test statistic (M, T) is defined as

- $M = \min\{1 \le j \le J : T_i \notin (a_i, b_i) \cup (c_i, d_i)\}$ , and
- $T = T_M$ .

Note that because the Jth analysis is the last analysis, we must have  $a_J = b_J$  and  $c_J = d_J$ . For convenience, we assume that for  $j \neq J$ ,  $(a_j, b_j) \cup (c_j, d_j)$  is a nonempty proper subset of  $(-\infty, \infty)$ . (It truly poses no theoretical difficulty on derivation of the group sequential sampling distribution if this last assumption is violated.)

If  $T_j$  is a minimal sufficient statistic in the fixed sample setting (no interim analysis), then  $(N_M, T)$  is a minimal sufficient statistic in the sequential sampling setting.

In this section, we will discuss the various choices for the statistic  $T_j$ .

#### 2.1 Normalized Z Statistic

As  $\theta$  is a mean, it is typical that the test statistic would be the normalized Z statistic

$$Z_j = \sqrt{N_j} \frac{\overline{X}_j - \theta_0}{\sigma}$$

where

$$\overline{X}_j = \frac{1}{N_j} \sum_{i=1}^{N_j} X_i.$$

Owing to the central limit theorem, in moderate to large samples, and in the absence of a sequential sampling scheme (i.e., J=1),  $Z_j$  has an approximate normal distribution. Under the null hypothesis in that setting  $Z_j \sim \mathcal{N}(0,1)$ , and a test would be performed by comparing  $Z_j$  to quantiles of the standard normal distribution. For instance, in a level  $\alpha/2$  one-sided test of the null hypothesis against a greater alternative  $H_1: \theta > \theta_0$ , the test decision would be

reject 
$$H_0 \iff Z_j \geq z_{1-\alpha/2}$$
,

where  $\Phi(z_{\alpha}) = \alpha$  with  $\Phi(\cdot)$  the cumulative distribution function for the standard normal distribution.

A sequential sampling plan having  $J \neq 1$  will instead compare  $Z_j$  to boundaries  $a_j^{(Z)} \leq b_j^{(Z)} \leq c_j^{(Z)} \leq d_j^{(Z)}$ , where the superscript is added to highlight that these are the boundaries corresponding to a normalized Z statistic. (In the tutorial on design families we discuss approaches to defining such critical values.)

## 2.2 (Maximum Likelihood) Estimate

As  $\theta$  is a mean, we can use the sample mean  $\overline{X}_j$  as a distribution free estimate  $\hat{\theta}_j = \overline{X}_j$  of  $\theta$ . In many parametric models (e.g., normal, binomial, Poisson, exponential),  $\hat{\theta}_j$  can be shown to be the maximum likelihood estimate of  $\theta$ , even in the sequential sampling setting.

The estimate  $\overline{X}_j$  is of course easily related to the normalized Z statistic by

$$\overline{X}_j = \frac{\sigma}{\sqrt{N_j}} Z_j + \theta_0.$$

Hence, because that relationship is an "order preserving" transformation, we have

$$Z_j \le a_j^{(Z)} \qquad \Longleftrightarrow \qquad \overline{X}_j \le \frac{\sigma}{\sqrt{N_j}} a_j^{(Z)} + \theta_0 \equiv a_j^{(X)},$$

where we use the subscript "X" to denote boundaries appropriate for the estimate of the treatment effect  $\theta$ .

(We note that in some probability models, a multiplicative scale, rather than an additive scale, is used as the measure of treatment effect (e.g., the geometric mean ratio, the odds ratio, the rate ratio, and the hazard ratio are typically used for comparisons across study arms, rather than differences between distribution parameters as are commonly used with means and proportions). In those models, we tend to analyze our data using a logarithmic transformation of the more scientific measure of treatment effect. In RCTdesign, we allow, for example, a user to use either the hazard ratio as the "X" scale or the log hazard ratio as the "X" scale according to whether log.transform=FALSE or log.transform=TRUE, respectively.)

## 2.3 Fixed Sample P Value Statistic

It is common to express group sequential boundaries by transforming them to the p value that would be appropriate for the fixed sample setting. When testing the null hypothesis against a one-sided greater alternative, we would compute

$$P_j = 1 - \Phi(Z_j) = 1 - \int_{-\infty}^{Z_j} \frac{1}{\sqrt{2\pi}} e^{-u^2/2} du.$$

Though this value would only truly be a p value in the fixed sample (J = 1) setting, this scale is at times useful for implementing group sequential sampling schemes (see the tutorial on the relative advantages and disadvantages of particular boundary scales for a more detailed discussion).

Obviously, the fixed sample p value  $P_j$  is directly related to the normalized Z statistic  $Z_j$ , and as this relationship is "order preserving" (though it reverses orders) we note

$$Z_j \le a_j^{(Z)} \iff P_j \ge 1 - \Phi(a_j^{(Z)}) \equiv a_j^{(P)},$$

where we use the subscript "P" to denote the boundaries appropriate for comparisons to the fixed sample p value. Note that for this boundary scale, we will have  $a_j^{(P)} \ge b_j^{(P)} \ge c_j^{(P)} \ge d_j^{(P)}$ .

#### 2.4 Partial Sum Statistic

Computationally, it is generally easier to describe the sampling density for the group sequential statistic on the partial sum scale

$$S_j = \sum_{i=1}^{N_j} X_i.$$

The partial sum scale also relates naturally to the score function in maximum likelihood, as well as having a natural interpretation in the setting of a one arm study with a binary endpoint: it is the total number of events seen so far in the study.

The partial sum statistic  $S_i$  is easily related to the normalized Z statistic  $Z_i$  by

$$S_j = \sqrt{N_j} \, \sigma Z_j + N_j \theta_0.$$

Again, we have an order preserving transformation, and

$$Z_j \le a_j^{(Z)} \iff S_j \le \sqrt{N_j} \, \sigma a_j^{(Z)} + N_j \theta_0 \equiv a_j^{(S)},$$

where we use the subscript "S" to denote boundaries appropriate for the partial sum statistic.

## 2.5 Error Spending Statistic

Using the methods of Armitage, McPherson, and Rowe (1969), the sampling density for group sequential test statistic (M, T) can be derived. As noted above, this is most easily expressed on the partial sum scale, but it is also easily expressed on the estimate or normalized Z statistic scales. We can then describe a boundary threshold according to the probability under a particular value of  $\theta$  of exceeding that threshold at or before a particular analysis.

It should be stressed that for greatest interpretability, the error spending statistic for a particular boundary at the jth analysis depends not only on the value of theta used to calculate the probability, but also on all other stopping boundaries prior to the jth analysis. Hence, we might define some theta<sub>a</sub> and define the error spending statistic  $E_{aj}^*$  for some observed  $Z_j = z_j \leq a_j^{(Z)}$  as

$$E_{aj}^*(z_j) = Pr[Z_j \le z_j \mid \forall k < j \ Z_k \in (a_k^{(Z)}, b_k^{(Z)}) \cup (c_k^{(Z)}, d_k^{(Z)})] + \sum_{k=1}^{j-1} Pr[Z_k \le a_k^{(Z)} \mid \forall \ell < k \ Z_\ell \in (a_\ell^{(Z)}, b_\ell^{(Z)}) \cup (c_\ell^{(Z)}, d_\ell^{(Z)})].$$

(Note that while it is possible to define  $E_{aj}(z_j)$  for values of  $z_j > a^{(Z)}$ ), it is not generally of interest under the error spending framework.)

In RCTdesign, the error spending scale is actually displayed as the proportion of error spent at the jth analysis relative to the total error spent by the Jth analysis:

$$E_{aj}(z_j) = E_{aj}^*(z_j) / E_{aJ}^*(a_J^{(Z)}).$$

Again, we have an order preserving transformation, and we can relate a threshold on this error spending function scale to the boundary on the normalized Z statistic scale:

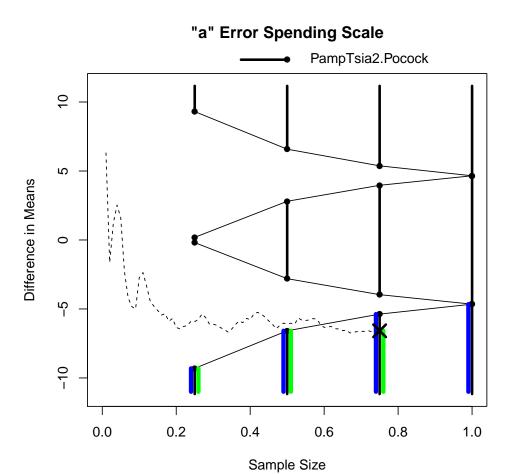
$$Z_j \le a_j^{(Z)} \iff E_{aj}(Z_j) \le E_{aj}(a_j^{(Z)}) \equiv a_j^{(E_a)}.$$

Though the idea behind error spending functions is straightforward, the notation for error spending functions is quite complicated and graphs provide greater understanding of the ways that error spending scales are used with multiple stopping boundaries.

Error spending statistic scales are defined the "a", "b", "c", and "d" boundaries based on treatment effects  $\theta_a$ ,  $\theta_b$ ,  $\theta_c$ , and  $\theta_d$ . Using a two-sided Pampallona and Tsiatis (1994) design having four Pocock stopping boundaries displayed on the estimate scale using information time on the x axis, the following figures display for each of the four error spending scales

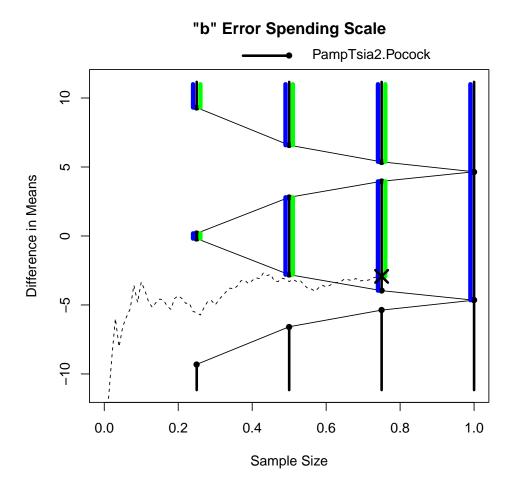
- the region for which the corresponding scale is typically defined marked in blue,
- a simulated RCT's sample path marking how the estimated treatment effect varied as the data accrued,
- the final group sequential statistic  $(M, \overline{X})$  (marked by "X") for the simulated RCT, and
- the region over which the cumulative error spending probability would be computed for the corresponding error spending scale (marked in green) for the observation marked by "X".

The  $E_{aj}$  scale is typically defined for values of  $Z_j \leq a_j^{(Z)}$ , computing cumulative probabilities of being below the "a" boundary.



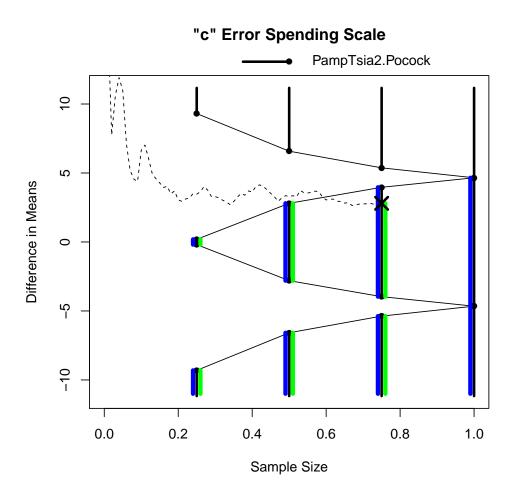
- In a two-sided hypothesis test,  $\theta_a$  is usually defined as null hypothesis  $\theta_a = \theta_0$ , and the boundaries defined by a lower type I error spending function.
- In a one-sided hypothesis test of a lesser alternative,  $\theta_a$  is usually defined as null hypothesis  $\theta_a = \theta_0$ , and the boundaries defined by the type I error spending function.
- In a one-sided hypothesis test of a greater alternative,  $\theta_a$  is usually defined as the design alternative hypothesis  $\theta_a = \theta_1$ , and the boundaries defined by a type II error spending function.

The  $E_{bj}$  scale is typically defined for values of  $Z_j \geq b_j^{(Z)}$ , computing cumulative probabilities of being above the "b" boundary.



- In a two-sided hypothesis test,  $\theta_b$  is usually defined as a lower alternative hypothesis  $\theta_b = \theta_-$ , and the boundaries defined by a type I| error spending function for the lower alternative.
- In a one-sided hypothesis test the "b" boundary is not generally of interest and is not displayed in routine output. (In detailed RCTdesign output, the "b" boundary is synonymous with the "d" boundary in one-sided designs.)

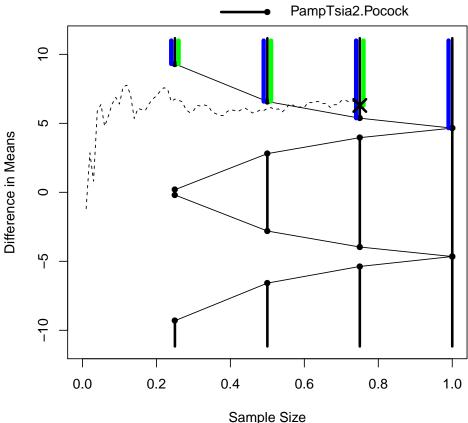
The  $E_{cj}$  scale is typically defined for values of  $Z_j \leq c_j^{(Z)}$ , computing cumulative probabilities of being below the "c" boundary.



- In a two-sided hypothesis test,  $\theta_c$  is usually defined as an upper alternative hypothesis  $\theta_b = \theta_+$ , and the boundaries defined by a type I| error spending function for the upper alternative.
- In a one-sided hypothesis test the "c" boundary is not generally of interest and is not displayed in routine output. (In detailed RCTdesign output, the "c" boundary is synonymous with the "a" boundary in one-sided designs.)

The  $E_{dj}$  scale is typically defined for values of  $Z_j \geq d_j^{(Z)}$ , computing cumulative probabilities of being





above the "d" boundary.

- In a two-sided hypothesis test,  $\theta_d$  is usually defined as null hypothesis  $\theta_a = \theta_0$ , and the boundaries defined by a lower type I error spending function.
- In a one-sided hypothesis test of a greater alternative,  $\theta_d$  is usually defined as null hypothesis  $\theta_d = \theta_0$ , and the boundaries defined by the type I error spending function.
- In a one-sided hypothesis test of a lesser alternative,  $\theta_d$  is usually defined as the design alternative hypothesis  $\theta_d = \theta_1$ , and the boundaries defined by a type II error spending function.

(The above graphs defining error spending functions are very closely related to the "stagewise" or "analysis time" ordering of the outcome space that is used by some authors to compute confidence intervals, p values, and point estimates.)

## 2.6 Bayesian Statistics

In a Bayesian setting, we are interested in statistics based on the posterior distribution of  $\theta$ , which is based on the observed data and some prespecified prior distribution of the mean parameter. Usually the posterior distribution of  $\theta$  is conditioned on the observations  $X_1, \ldots, X_{N_j}$ , and it is computed under some parametric distribution for the data. In our setting, however, we have not assumed some parametric distribution for our observations. Instead we have only characterized the mean  $\theta$  and variance  $\sigma^2$ . In this setting we therefore rely on the sample mean  $\overline{X}_j$  as the "distribution-free sufficient statistic" for the mean  $\theta$ . Owing to the central limit theorem, we can base our Bayesian inference using a multivariate normal distribution for  $(\overline{X}_1, \overline{X}_2, \ldots, \overline{X}_J)^T$  as an approximation for the likelihood of the data. This then becomes a distribution-free approach to Bayesian inference using the same general probability space as is used for our distribution-free frequentist inference.

For convenience, we will consider only the conjugate prior distribution for a normally distributed observation. Thus, we will assume a prior distribution  $\theta \sim \mathcal{N}(\zeta, \tau^2)$ . The posterior distribution for  $\theta$  conditional on observation  $\overline{X}_i$  is thus approximated by

$$\theta \mid \overline{X}_j = \overline{x}_j) \sim \mathcal{N}\left(\frac{N_j \tau^2 \overline{x}_j + \sigma^2 \zeta}{N_j \tau^2 + \sigma^2}, \frac{\sigma^2 \tau^2}{N_j \tau^2 + \sigma^2}\right).$$

Statistics of interest might include the posterior probabilities that the mean  $\theta$  is greater than the null hypothesis  $\theta_0$  or prespecified alternative hypotheses  $\theta_+$  and  $\theta_-$ . In general, then, we can define a statistic for the posterior probability that the mean  $\theta$  is greater than some hypothesized value  $\theta_*$ . We define statistics

$$B_{j}(\zeta, \tau^{2}, \mu_{*}) = Pr(\theta \geq \theta_{*} \mid \overline{X}_{j})$$

$$= 1 - \Phi\left(\frac{\theta_{*}[N_{j}\tau^{2} + \sigma^{2}] - N_{j}\tau^{2}\overline{X}_{j} - \sigma^{2}\zeta}{\sigma\tau\sqrt{N_{j}\tau^{2} + \sigma^{2}}}\right)$$

A special case that is of occasional interest is the noninformative (improper) prior corresponding to the limit as  $\tau^2 \to \infty$ . In this setting, the Bayesian posterior probability reduces to

$$B_j(\zeta, \tau^2 = \infty, \theta_*) = Pr(\theta \ge \theta_* \mid \overline{X}_j) = 1 - \Phi\left(\sqrt{N_j} \frac{\theta_* - \overline{X}_j}{\sigma}\right)$$

which is similar in form (but not interpretation) to the fixed sample P value.

These Bayesian statistics are equivalent to the frequentist normalized Z statistic for the purposes of defining a stopping rule, because the Bayesian posterior statistic  $B_j$  is merely a transformation of  $Z_j$  that reverses ordering. So we have

$$Z_j \le a_j^{(Z)} \qquad \Longleftrightarrow \qquad B_j \ge 1 - 1 - \Phi\left(\frac{\theta_*[N_j\tau^2 + \sigma^2] - N_j\tau^2a_j^{(X)} - \sigma^2\zeta}{\sigma\tau\sqrt{N_j\tau^2 + \sigma^2}}\right) equiva_j^{(B)}.,$$

where  $a_j^{(X)} = \frac{\sigma}{\sqrt{N_j}} a_j^{(Z)} + \theta_0$  as above and we use the subscript "B" to denote the boundaries appropriate for comparisons to the Bayesian posterior probability (for the specified  $\theta_*$  and the specified prior distribution). Note that for this boundary scale, we will have  $a_j^{(B)} \geq b_j^{(B)} \geq c_j^{(B)} \geq d_j^{(B)}$ .

A special note needs to be made about the interpretation of the prior distribution in multiplicative models such as the geometric mean, odds, rate, and hazards. In these models, the actual analysis is performed on the scale of the log geometric mean, log odds, log rate, or log hazard ratio. However, RCTdesign encourages

the use of the more "human" scale for input and output. Hence, in these multiplicative models, we are really using prior distribution  $\log(\theta) \sim \mathcal{N}(\zeta, \tau^2)$ , but the user will be able to specify  $e^{\zeta}$  as the median of the prior distribution for  $\theta$ . Because the mean and median of a normal distribution are equal to each other, this terminology as the median of the prior distribution will hold in the additive models as well. In all cases,  $\tau^2$  will be referred to as the "variation parameter of the prior distribution", but it will only be the variance of  $\theta$  in an additive model.

## 2.7 Measures of Futility: Conditional and Predictive Power

In the setting of group sequential trials, it is often of interest to consider various measures of the futility of continuing the study. A common goal of such measures is estimating the probability that the test statistic at the Jth analysis might exceed some threshold, where the calculation of the probability is conditioned on the observation at the jth analysis. The use of the word "futility" arises out of the use of these conditional power and predictive power statistics to decide when the data are so unpromising that there is very little probability of attaining a statistically significant effect even if the study does continue.

In what follows, we consider the use of  $\overline{X}_j$  as the test statistic and define  $t_{\overline{x}J}$  as the threshold of interest for that test statistic at the Jth analysis. Most often,  $t_{\overline{x}J} = a_J^{(X)}$  or  $t_{\overline{x}J} = d_J^{(X)}$ , the boundaries of the stopping rule when the maximal sample size is accrued.

Using the independence of the individual observations, and in the absence of early stopping, the conditional distribution of the estimate  $\overline{X}_J$  at the final analysis given the estimate  $\overline{X}_j$  at the jth analysis is found to be

$$\overline{X}_J \mid \overline{X}_j \sim \mathcal{N}\left(\theta + \frac{N_j}{N_J}[\overline{X}_j - \theta], \ \frac{[N_J - N_j]}{N_J} \frac{\sigma^2}{N_J}\right).$$

Computing probabilities based on the above distribution will not result in a statistic, as the distribution depends on the unknown parameter  $\theta$ . We can, however, compute the probabilities under hypothesized values for  $\theta$ . Obvious candidates for such computations might be the null hypothesis  $\theta_0$ , either of the alternative hypotheses  $\theta_+$  or  $\theta_-$ , the maximum likelihood estimate  $\hat{\theta} = \overline{X}_j$  of  $\theta$  at the jth analysis, bounds of the naive confidence interval for  $\theta$  at the jth analysis, etc. We can then define statistics for a specified threshold  $t_{\overline{X}j}$  and specified value of  $\theta = \theta_*$ :

$$C_j(t_{\overline{X}J}, \theta_*) \equiv Pr(\overline{X}_J > t_{\overline{X}J} \mid \overline{X}_j; \theta = \theta_*) = 1 - \Phi\left(\frac{N_J[t_{\overline{X}J} - \theta_*] - N_j[\overline{X}_j - \theta_*]}{\sigma\sqrt{N_J - N_j}}\right)$$

Note that when the conditional probabilities are computed using the observed maximum likelihood estimate  $\overline{X}_j$  for  $\theta$ , we obtain

$$\begin{split} C_{j}(t_{\overline{X}J}, \theta_{*} = \overline{X}_{j}) & \equiv Pr(\overline{X}_{J} > t_{\overline{X}J} \mid \overline{X}_{j}; \theta = \overline{X}_{j}) \\ & = 1 - \Phi\left(\frac{N_{J}[t_{\overline{X}J} - \overline{X}_{j}]}{\sigma\sqrt{N_{J} - N_{j}}}\right) \end{split}$$

An alternative approach is to use a Bayesian prior distribution for  $\theta$  to compute its posterior distribution based on the observation of  $\overline{X}_j$ , and then to compute a predictive probability by averaging the conditional probabilities of exceeding the threshold as  $\theta$  ranges over that posterior distribution. Using this approach with a normal prior distribution  $\theta \sim \mathcal{N}(\zeta, \tau^2)$  yields a posterior distribution  $\lambda(\theta|\overline{X}_j)$  that is normal as given above. We then compute the marginal conditional distribution of  $\overline{X}_J$  given  $\overline{X}_j$  as a normal distribution having mean

 $\{[N_J\tau^2+\sigma^2]N_j\overline{X}_j+[N_J-N_j]\sigma^2\zeta\}/\{N_j[N_j\tau^2+\sigma^2]\} \text{ and variance } \sigma^2[N_J-N_j][N_J\tau^2+\sigma^2]/\{N_J^2[N_j\tau^2+\sigma^2]\} \text{ and survival function}$ 

$$\begin{split} H_{j}(t_{\overline{X}J},\zeta,\tau^{2}) & \equiv \int Pr(\overline{X}_{J} > t_{\overline{X}J} \,|\, \overline{X}_{j},\theta) \,\lambda(\theta \,|\, \overline{X}_{j}) \,d\theta \\ & = 1 - \Phi\left(\frac{N_{J}[N_{J}\tau^{2} + \sigma^{2}][t_{\overline{X}J} - \overline{X}_{j}] + \sigma^{2}[N_{J} - N_{j}][\overline{X}_{j} - \zeta]}{\sigma\sqrt{[N_{J} - N_{j}][N_{J}\tau^{2} + \sigma^{2}][N_{J}\tau^{2} + \sigma^{2}]}}\right) \end{split}$$

When we consider a point mass prior having  $\tau^2 = 0$ , the Bayesian predictive probability becomes the conditional power based on assuming  $\theta = \zeta$ .

When we consider a noninformative prior distribution  $(\theta \sim \mathcal{N}(\zeta, \tau^2))$  and taking the limit as  $\tau^2 \to \infty$ , the posterior distribution  $\lambda(\theta|\overline{X}_j)$  is normal with mean  $\overline{X}_j$  and variance  $\sigma^2/N_j$ . we then compute the marginal conditional distribution of  $\overline{X}_J$  given  $\overline{X}_j$  as having survival function

$$H_j(t_{\overline{X}J}, \zeta, \tau^2 = \infty) = 1 - \Phi\left(\frac{N_J[t_{\overline{X}J} - \overline{X}_j]}{\sigma\sqrt{\frac{N_J}{N_j}[N_J - N_j]}}\right)$$

## 3 Specification of Boundary Scales in RCTdesign using seqScale()

Stopping boundaries and group sequential test statistics can be expressed on any of 9 different scale types, some of which involve multiple parameters. In this section we first describe the use of seqScale(), which creates "seqScale" objects representing a particular scale type.

#### 3.1 Overview of seqScale()

A "seqScale" object consists of a code for a scale type, along with any parameters required to clarify the exact scale desired. The RCTdesign function seqScale() is used to create a "seqScale" object using one or more of the following arguments.

- scaleType is a character string that is either
  - a shorthand (usually single letter) code that is one of "X", "Z", "P", "S", "E", "B", "H", or "C"
  - alternatively, this may be character string that matches one of "sample.mean", "z.value", "p.value", "partial.sum", "error.spend", "bayesian", "predictive", "conditional", or "standardized", where each element in the latter set is equivalent to the corresponding element in the shorthand set. Only enough of the longer term to uniquely identify a scale need be supplied.
- optional parameters that indicate those additional quantities necessary to clarify the exact scale desired (note that the "X", "Z", "P", and "S" scales do not ever need any additional parameters):
  - hypTheta is used by the "C" (conditional power) scale to indicate the presumed treatment effect to be used for the distribution of future observations.
  - priorTheta is used by the "B" (Bayesian posterior) and "H" (Bayesian predictive power) scales to
    indicate the prior beliefs (before gathering any data) about the mean or median of the probability
    distribution for the treatment effect parameter.
  - priorVariation is used by the "B" (Bayesian posterior) and "H" (Bayesian predictive power) scales to indicate the prior beliefs (before gathering any data) about the variability of the probability distribution for the treatment effect parameter.

- pessimism is an alternative method used by the "B" (Bayesian posterior) and "H" (Bayesian predictive power) scales to indicate the prior beliefs (before gathering any data) about the mean or median of the probability distribution for the treatment effect parameter.

- threshold is used by the "C", "B", and "H" scales to indicate the threshold for computing conditional, posterior, or predictive probabilities, respectively.
- boundaryNumber is used by the "E" (error spending) scale to indicate which of the four error spending scales to be used.
- scaleParameters is used to specify arbitrary alternatives to be used on the "E" (error spending)
   scale, as well as by advanced users to specify any of the above parameters in a less transparent manner.

It should be noted that there are slight nuances to the use of boundary scales depending upon whether

- the interest is in displaying the entire stopping boundary on a particular scale, or
- the interest in converting a particular observed test statistic (an observation that is not likely equal to a boundary) on a particular scale.

In the following subsections we illustrate the use of seqScale() and its arguments to specify each of the above scales in each of those settings.

# 3.2 Specification of the (Maximum Likelihood) Estimate Boundary Scale: Scale Type "X"

The estimate boundary scale does not require any additional parameters. Hence, a "seqScale" object denoting the estimate scale can be created (and stored as a variable Xscale by the command:

```
> Xscale <- seqScale("X")
> Xscale
```

Sample Mean scale

Note that the print method for a seqScale object just prints the wording used to describe the scale when printing boundaries.

Because the estimate scale does not require any additional parameters, any RCTdesign function that requires the specification of a scale will also accept the character "X" to mean the estimate scale. That is, the RCTdesign function will automatically convert the character to a "seqScale" object.

## 3.3 Specification of the Normalized Z Boundary Scale: Scale Type "Z"

The normalized Z statistic boundary scale does not require any additional parameters. Hence, a "seqScale" object denoting the normalized Z statistic scale can be created (and stored as a variable Zscale by the command:

```
> Zscale <- seqScale("Z")
> Zscale
```

Normalized Z-value scale

Note that the print method for a seqScale object just prints the wording used to describe the scale when printing boundaries.

Because the normalized Z statistic scale does not require any additional parameters, any RCTdesign function that requires the specification of a scale will also accept the character "Z" to mean the normalized Z statistic scale. That is, the RCTdesign function will automatically convert the character to a "seqScale" object.

## 3.4 Specification of the Fixed Sample P Value Boundary Scale: Scale Type "P"

The fixed sample P value boundary scale does not require any additional parameters. Hence, a "seqScale" object denoting the fixed sample P value scale can be created (and stored as a variable Pscale by the command:

```
> Pscale <- seqScale("P")
> Pscale
```

Fixed Sample P-value scale

Note that the print method for a seqScale object just prints the wording used to describe the scale when printing boundaries.

Because the fixed sample P value scale does not require any additional parameters, any RCTdesign function that requires the specification of a scale will also accept the character "P" to mean the fixed sample P value scale. That is, the RCTdesign function will automatically convert the character to a "seqScale" object.

#### 3.5 Specification of the Partial Sum Statistic Boundary Scale: Scale Type "S"

The partial sum statistic boundary scale does not require any additional parameters. Hence, a "seqScale" object denoting the partial sum statistic scale can be created (and stored as a variable Sscale by the command:

```
> Sscale <- seqScale("S")
> Sscale
```

Cumulative Sum scale

Note that the print method for a seqScale object just prints the wording used to describe the scale when printing boundaries.

Because the partial sum statistic scale does not require any additional parameters, any RCTdesign function that requires the specification of a scale will also accept the character "S" to mean the partial sum statistic scale. (That is, the RCTdesign function will automatically convert the character to a "seqScale" object.

## 3.6 Specification of the Error Spending Boundary Scale: Scale Type "E"

In its most general form, an error spending scale can be defined for each boundary and for arbitrary values of  $\theta$ . Hence, a completely arbitrary error spending scale might be specified using

- boundaryNumber as one of "a", "b", "c", or "d", and
- hypTheta as a numeric value of  $\theta$

For instance, the upper type I error spending scale for a setting testing the hypotheses  $H_0: \theta = 0$  versus  $H_1: \theta > 0$  might be created (and stored as a variable Escale by the command:

When printing an entire boundary, however, we most often would want to see each boundary displayed according to the type I or type II error spending function for the value of  $\theta$  that is rejected by that boundary. Hence, RCTdesign allows a used to specify a "seqScale" object having scaleType= "E", but with no other parameters specified. This will then cause a stopping boundary for a two-sided test to be displayed on four different error spending scales:

- the upper outer ("d") boundary (perhaps corresponding to "superiority") will be displayed as the upper type I error spending scale relative to the null hypothesis (which is the hypothesis rejected by that boundary),
- the upper inner ("c") boundary (perhaps corresponding to the "futility of demonstrating superiority") will be displayed as the upper type II error spending scale relative to the upper alternative hypothesis that is the hypothesis rejected by that boundary,
- the lower inner ("b") boundary (perhaps corresponding to the "futility of demonstrating inferiority") will be displayed as the lower type II error spending scale relative to the lower alternative hypothesis that is the hypothesis rejected by that boundary,
- the lower outer ("a") boundary (perhaps corresponding to "inferiority") will be displayed as the lower type I error spending scale relative to the null hypothesis (which is the hypothesis rejected by that boundary).

For a stopping boundary appropriate for a one-sided test of a greater alternative, the boundary will be displayed on two different error spending scales:

- the upper ("d") boundary (corresponding to "efficacy") will be displayed as the type I error spending scale relative to the null hypothesis (which is the hypothesis rejected by that boundary),
- the lower ("a") boundary (perhaps corresponding to "futility of demonstrating efficacy") will be displayed as the type II error spending scale relative to the alternative hypothesis that is the hypothesis rejected by that boundary.

For a stopping boundary appropriate for a one-sided test of a lesser alternative, the boundary will be displayed on two different error spending scales:

• the upper ("d") boundary (perhaps corresponding to "futility of demonstrating efficacy") will be displayed as the type II error spending scale relative to the alternative hypothesis that is the hypothesis rejected by that boundary.

• the lower ("a") boundary (corresponding to "efficacy") will be displayed as the type I error spending scale relative to the null hypothesis (which is the hypothesis rejected by that boundary).

In this default setting, then, the user can specify that the error spending functions are to be displayed by instead creating a "seqScale" object (again named Escale) using the R code

```
> Escale <- seqScale("E")
> Escale
```

Error Spending Function scale

Note that the print method for a seqScale object just prints the wording used to describe the scale when printing boundaries.

Because this default error spending scale does not require any additional parameters, any RCTdesign function that requires the specification of a scale suitable for display of boundaries will also accept the character "E" to mean this scale. That is, the RCTdesign function will automatically convert the character to a "seqScale" object. It should be noted, however, that this default error spending seqScale object cannot be used for display of a single statistic, because there are actually 2 - 4 different error spending scales represented.

## 3.7 Specification of the Bayesian Posterior Boundary Scale: Scale Type "B"

In its most general form, a Bayesian posterior probability scale can be defined for an arbitrary threshold and for arbitrary values of the mean (or median) and variance of the prior distribution. Hence, a completely arbitrary error spending scale might be specified using

- priorTheta as a numeric value representing the median of the prior distribution for  $\theta$ ,
- priorVariation as a positive numeric value represent the variation in the prior distribution for  $\theta$  (the default is infinity  $(\infty)$ ), and
- threshold as a numeric value of the  $\theta$  to be used as the limit for computing the cumulative posterior probability.

For instance, in a setting testing the hypotheses  $H_0: \theta = \theta_0 = 0$  versus  $H_1: \theta = \theta_1 = 10$  we might presume a prior distribution centered at  $zeta = (\theta_1 + \theta_0)/2 = 5$  with variation described by  $\tau = \theta_1 - \theta_0 = 10$ . A Bayesian posterior probability scale to display the posterior probability  $Pr(\theta > \theta_0 | \hat{\theta}, \zeta, \tau^2)$  could be created (and stored as a variable Bscale by the command:

When printing an entire boundary, however, we most often would want to see each boundary displayed according to the posterior probability that the decision to reject the corresponding hypothesis is correct. Hence, RCTdesign allows a used to specify a "seqScale" object having scaleType= "B" without specifying a value for threshold. This will then cause a stopping boundary for a two-sided test to be displayed on four different posterior probability scales:

• the upper outer ("d") boundary (perhaps corresponding to "superiority") will be displayed as the posterior probability that the null hypothesis (or lower) is false,

- the upper inner ("c") boundary (perhaps corresponding to the "futility of demonstrating superiority") will be displayed as the posterior probability that the upper alternative hypothesis that is the hypothesis rejected by that boundary is false,
- the lower inner ("b") boundary (perhaps corresponding to the "futility of demonstrating inferiority") will be displayed as the posterior probability that the lower alternative hypothesis that is the hypothesis rejected by that boundary is false,
- the lower outer ("a") boundary (perhaps corresponding to "inferiority") will be displayed as the posterior probability that the null hypothesis (or higher) is false.

For a stopping boundary appropriate for a one-sided test of a greater alternative, the boundary will be displayed on two different error spending scales:

- the upper ("d") boundary (corresponding to "efficacy") will be displayed as the posterior probability that the null hypothesis is false,
- the lower ("a") boundary (perhaps corresponding to "futility of demonstrating efficacy") will be displayed as the posterior probability that the alternative hypothesis that is the hypothesis rejected by that boundary is false.

For a stopping boundary appropriate for a one-sided test of a lesser alternative, the boundary will be displayed on two different error spending scales:

- the upper ("d") boundary (perhaps corresponding to "futility of demonstrating efficacy") will be displayed as the posterior probability that the alternative hypothesis that is the hypothesis rejected by that boundary is false.
- the lower ("a") boundary (corresponding to "efficacy") will be displayed as the probability that the null hypothesis is false.

In this default setting, then, the user can specify that the posterior probabilities are displayed by creating a "seqScale" object (again named Bscale) using the R code that does not provide a threshold

Note that the print method for a seqScale object just prints the wording used to describe the scale when printing boundaries.

Because the default posterior probability scale does not require any additional parameters, any RCT-design function that requires the specification of a scale suitable for display of boundaries will also accept the character "B" to mean a prior distribution with the default noninformative (flat) prior. That is, the RCTdesign function will automatically convert the character to a "seqScale" object. It should be noted, however, that this default error spending seqScale object cannot be used for display of a single statistic, because there are actually 2 - 4 different Bayesian poeterior probability scales represented.

# 3.8 Specification of the Conditional Power and Bayesian Predictive Power Boundary Scales: Scale Types "C" and "H"

In their most general form, the conditional power and Bayesian predictive power scales can be defined for an arbitrary threshold at the final analysis and for arbitrary values of the hypothesized value of  $\theta$  (for the conditional power scale) or arbitrary values of the mean (or median) and variance of the prior distribution (for the Bayesian predictive power scale). Hence, a completely arbitrary error spending scale might be specified using

- hypTheta as a numeric value representing a hypothesized value of  $\theta$  to be used in calculating the probability distribution for future observations,
- priorTheta as a numeric value representing the median of the prior distribution for  $\theta$ ,
- priorVariation as a positive numeric value represent the variation in the prior distribution for  $\theta$  (the default is infinity  $(\infty)$ ), and
- threshold as a numeric value of the  $\theta$  to be used as the limit for computing the cumulative posterior probability.

Looking first at the conditional power scale, in a setting testing the hypotheses  $H_0: \theta = \theta_0 = 0$  versus  $H_1: \theta = \theta_1 = 10$  we might presume a distribution for future dat based on  $\theta = (\theta_1 + \theta_0)/2 = 5$ . At some interim analysis we might be interested in the probability that a statistically significant result will be observed at the final analysis. In a one-sided symmetric test, this would correspond to  $\overline{X}_J \geq d_J^{(X)} = 5$ . A conditional power scale to display the conditional probability  $Pr(\overline{X}_J \geq d_J^{(X)} | \theta = 5, \overline{X}_j)$  could be created (and stored as a variable Cscale by the command:

Alternatively, we could choose to model our uncertainty in the true value of  $\theta$  by using a Bayesian prior instead of a single hypothesized value of  $\theta$ . For instance, in a setting testing the hypotheses  $H_0: \theta = \theta_0 = 0$  versus  $H_1: \theta = \theta_1 = 10$  we might presume a prior distribution centered at  $\zeta = (\theta_1 + \theta_0)/2 = 5$  with variation described by  $\tau = \theta_1 - \theta_0 = 10$ . In a one-sided symmetric test, a Bayesian predictive power scale to display the predictive probability  $Pr(\overline{X}_J \geq d_J^{(X)} = 5|\zeta, \tau^2, \overline{X}_j)$  could be created (and stored as a variable Hscale by the command:

We emphasize that the conditional power ("C") scale is presuming that you know the value of  $\theta$  for all future observations, while the predictive power ("H") scale is modeling prior uncertainty in the value of  $\theta$ , and updating that prior with the observed data. Because choosing priorVariation=0 also indicates certainty in the value of  $\theta$ , the following two specifications are equivalent ways to obtain the exact same conditional power function, though RCTdesign will use different descriptions of the scales.

When printing an entire boundary, however, we might be most interested in seeing the probability of a "reversed" decision if the trial continued. Hence, at an interim analysis boundary that corresponds to a failure to reject the null, we might want to see the probability of rejecting the null hypothesis at the final analysis if the trial continued. Similarly, at an interim analysis that corresponds to rejection of the null hypothesis, we might want to see the probability of not rejecting the null hypothesis at the final analysis. Hence, RCTdesign allows a used to specify a "seqScale" object having scaleType= "C" or scaleType= "H" without specifying a value for threshold. This will then cause a stopping boundary for a two-sided test to be displayed on four different conditional or predictive probability scales:

- the upper outer ("d") boundary (perhaps corresponding to "superiority") will be displayed as the predictive (conditional) probability that the null hypothesis would not be rejected at the final analysis,
- the upper inner ("c") boundary (perhaps corresponding to the "futility of demonstrating superiority") will be displayed as the predictive (conditional) probability that the null hypothesis would be rejected in favor of a greater alternative at the final analysis,
- the lower inner ("b") boundary (perhaps corresponding to the "futility of demonstrating inferiority") will be displayed as the predictive (conditional) probability that the null hypothesis would be rejected in favor of a lesser alternative at the final analysis,
- the lower outer ("a") boundary (perhaps corresponding to "inferiority") will be displayed as the predictive (conditional) probability that the null hypothesis would not be rejected at the final analysis.

For a stopping boundary appropriate for a one-sided test of a greater alternative, the boundary will be displayed on two different error spending scales:

• the upper ("d") boundary (corresponding to "efficacy") will be displayed as the predictive (conditional) probability that the null hypothesis would not be rejected at the final analysis,

• the lower ("a") boundary (perhaps corresponding to "futility of demonstrating efficacy") will be displayed as the predictive (conditional) probability that the null hypothesis would be rejected in favor of a greater alternative at the final analysis.

For a stopping boundary appropriate for a one-sided test of a lesser alternative, the boundary will be displayed on two different error spending scales:

- the upper ("d") boundary (perhaps corresponding to "futility of demonstrating efficacy") will be displayed as the predictive (conditional) probability that the null hypothesis would be rejected in favor of a lesser alternative at the final analysis.
- the lower ("a") boundary (corresponding to "efficacy") will be displayed as the predictive (conditional) probability that the null hypothesis would not be rejected at the final analysis.

In this default setting, then, the user can specify that the posterior probabilities are displayed by creating a "seqScale" object (again named Hscale) using the R code that does not provide a threshold

```
> Hscale <- seqScale("H", priorTheta = 5, priorVariation= 10^2)
> Hscale
```

#### Predictive Probability scale

(Predictive probability that estimated treatment effect at the last analysis would correspond to an opposite decision based on prior distribution having median 5 and variation parameter 100)

```
> Cscale <- seqScale("H", priorTheta = 5, priorVariation= 0)
> Cscale
```

#### Predictive Probability scale

(Predictive probability that estimated treatment effect at the last analysis would correspond to an opposite decision based on prior distribution having median 5 and variation parameter 0)

Note that the print method for a seqScale object just prints the wording used to describe the scale when printing boundaries.

Because the default posterior probability scale does not require any additional parameters, any RCTdesign function that requires the specification of a scale suitable for display of boundaries will also accept the character "H" to mean a predictive probability distribution with the default noninformative (flat) prior. That is, the RCTdesign function will automatically convert the character to a "seqScale" object. It should be noted, however, that this default error spending seqScale object cannot be used for display of a single statistic, because there are actually 2 - 4 different predictive (conditional) power scales represented.

There are, in addition, two display options for conditional power functions that can be used for boundaries (but not individual statistics). A conditional power ("C") scale with hypTheta="hypothesis" or hypTheta="estimate" will use a different hypothesized value of  $\theta$  for each boundary.

In the case of hypTheta="design", the hypothesized value of  $\theta$  will be that value that is being rejected by the corresponding boundary. Hence, for a stopping boundary for a two-sided test to be displayed on four different conditional or predictive probability scales:

• the upper outer ("d") boundary (perhaps corresponding to "superiority") will be displayed as the predictive (conditional) probability that the null hypothesis would not be rejected at the final analysis computed under the assumption that the upper alternative hypothesis is true,

- the upper inner ("c") boundary (perhaps corresponding to the "futility of demonstrating superiority") will be displayed as the predictive (conditional) probability that the null hypothesis would be rejected in favor of a greater alternative at the final analysis computed under the assumption that the null hypothesis is true,
- the lower inner ("b") boundary (perhaps corresponding to the "futility of demonstrating inferiority") will be displayed as the predictive (conditional) probability that the null hypothesis would be rejected in favor of a lesser alternative at the final analysis computed under the assumption that the null hypothesis is true,
- the lower outer ("a") boundary (perhaps corresponding to "inferiority") will be displayed as the predictive (conditional) probability that the null hypothesis would not be rejected at the final analysis computed under the assumption that the lower alternative hypothesis is true.

For a stopping boundary appropriate for a one-sided test of a greater alternative, the boundary will be displayed on two different error spending scales:

- the upper ("d") boundary (corresponding to "efficacy") will be displayed as the predictive (conditional) probability that the null hypothesis would not be rejected at the final analysis computed under the assumption that the upper alternative hypothesis is true,
- the lower ("a") boundary (perhaps corresponding to "futility of demonstrating efficacy") will be displayed as the predictive (conditional) probability that the null hypothesis would be rejected in favor of a greater alternative at the final analysis computed under the assumption that the null hypothesis is true.

For a stopping boundary appropriate for a one-sided test of a lesser alternative, the boundary will be displayed on two different error spending scales:

- the upper ("d") boundary (perhaps corresponding to "futility of demonstrating efficacy") will be displayed as the predictive (conditional) probability that the null hypothesis would be rejected in favor of a lesser alternative at the final analysis computed under the assumption that the null hypothesis is true.
- the lower ("a") boundary (corresponding to "efficacy") will be displayed as the predictive (conditional) probability that the null hypothesis would not be rejected at the final analysis computed under the assumption that the lower alternative hypothesis is true.

```
> Cscale <- seqScale("C", hypTheta ="design")
> Cscale
```

#### Conditional Probability scale

(Conditional probability that estimated treatment effect at the last analysis would correspond to an opposite decision computed using hypothesized true treatment equal to hypotheses being rejected)

Because the default conditional probability scale corresponds to the choice hypTheta="design', any RCT-design function that requires the specification of a scale suitable for display of boundaries will also accept the character "C" to mean that conditional probability scale.

In the case of hypTheta="estimate", the hypothesized value of  $\theta$  will be equal to the current (maximum likelihood) estimate of the treatment effect parameter. Hence, when displaying a stopping boundary on such a conditional power scale, each stopping threshold on each boundary is computed using a different hypothesized value of  $\theta$ .

```
> Cscale <- seqScale("C", hypTheta ="estimate")
> Cscale
```

Conditional Probability scale

(Conditional probability that estimated treatment effect at the last analysis would correspond to an opposite decision computed using hypothesized true treatment equal to maximum likelihood estimate)

## 4 Using Scales in RCTdesign

The boundary scale is used when

- specifying a family of stopping boundary shape functions,
- specifying the scale for tabulation of stopping boundaries, and
- specifying the scale for graphical display of stopping boundaries.

The following subsections provide more detail regarding these uses of "seqScale" objects.

### 4.1 Specifying Design Families in seqDesign()

Families of sequential stopping boundaries each define a functional relationship between stopping boundaries at successive analyses. (See the tutorial on stopping boundaries for additional detail.) The various stopping boundary families differ according to the scale used to define the boundary relationship function and the parameterization of that function.

The seqDesign() argument design.family can take a single character argument to indicate a boundary scale. Permissible values include:

- seqDesign(..., design.family="X", ...) is used to define stopping boundaries for the unified family of Kittelson and Emerson (1999), which includes the Pocock (1977), O'Brien and Fleming (1979), Whitehead and Stratton (1983), Wang and Tsiatis (1987), Emerson and Fleming (1989), Pampallona and Tsiatis (1994), and Xiong (1995) families as special cases. The values of boundary shape function parameters P, R, and A will further characterize the exact family desired.
  - A level 0.025 one-sided symmetric design (Emerson and Fleming, 1989) with O'Brien-Fleming boundary relationships testing the difference of means for a two arm study can be obtained by the following code, which takes advantage of the default values of the prob. model="mean", arms=2, test.type="greater", null.hypothesis=0, size= 0.025, design.family= "X", P=1 (for the unified family of designs), R=0, A=0, and display.scale="X".

```
> obfX <- seqDesign("mean", nbr.analyses=4, alt.hypothesis= 8, sd= 20, power=0.90)
  > obfX
  Call:
  seqDesign(prob.model = "mean", alt.hypothesis = 8, sd = 20, nbr.analyses = 4,
      power = 0.9)
  PROBABILITY MODEL and HYPOTHESES:
     Theta is difference in means (Treatment - Comparison)
     One-sided hypothesis test of a greater alternative:
             Null hypothesis : Theta <= 0</pre>
                                                (size = 0.025)
      Alternative hypothesis : Theta >= 8
                                                (power = 0.900)
     (Emerson & Fleming (1989) symmetric test)
  STOPPING BOUNDARIES: Sample Mean scale
                          Futility Efficacy
      Time 1 (N= 68.50) -9.6812 19.3624
      Time 2 (N = 137.01)
                            0.0000
                                     9.6812
      Time 3 (N = 205.51)
                            3.2271
                                      6.4541
      Time 4 (N = 274.02)
                            4.8406
                                      4.8406
- A level 0.025 one-sided symmetric design (Emerson and Fleming, 1989) with Pocock boundary
  relationships testing the difference of means for a two arm study can be obtained by the fol-
  lowing code, which takes advantage of the default values of the prob. model="mean", arms=2,
  test.type="greater", null.hypothesis=0, size= 0.025, design.family= "X", R=0, A=0, and
  display.scale="X".
  > pocX <- seqDesign("mean", nbr.analyses=4, alt.hypothesis= 8, sd= 20, power=0.90, P=0.5)
  > pocX
  Call:
  seqDesign(prob.model = "mean", alt.hypothesis = 8, sd = 20, nbr.analyses = 4,
      power = 0.9, P = 0.5)
  PROBABILITY MODEL and HYPOTHESES:
     Theta is difference in means (Treatment - Comparison)
     One-sided hypothesis test of a greater alternative:
             Null hypothesis : Theta <= 0
                                                (size = 0.025)
      Alternative hypothesis : Theta >= 8
                                                (power = 0.900)
     (Emerson & Fleming (1989) symmetric test)
  STOPPING BOUNDARIES: Sample Mean scale
                          Futility Efficacy
      Time 1 (N = 90.36)
                            0.0000
                                      9.7735
      Time 2 (N = 180.71)
                            2.8626
                                      6.9109
      Time 3 (N = 271.07)
                            4.1308
                                      5.6427
      Time 4 (N = 361.42)
                            4.8868
                                      4.8868
- A level 0.025 one-sided triangular design (Whitehead and Stratton, 1983) testing the difference of
  means for a two arm study can be obtained by the following code, which takes advantage of the de-
  fault values of the prob. model="mean", arms=2, test.type="greater", null.hypothesis=0,
  size 0.025, design.family= "X", P=1 (for the unified family of designs), R=0, and display.scale="X".
  > triX <- seqDesign("mean", nbr.analyses=4, alt.hypothesis= 8, sd= 20, power=0.90, A=1)
  > triX
```

```
Call:
  seqDesign(prob.model = "mean", alt.hypothesis = 8, sd = 20, nbr.analyses = 4,
      power = 0.9, A = 1)
  PROBABILITY MODEL and HYPOTHESES:
     Theta is difference in means (Treatment - Comparison)
     One-sided hypothesis test of a greater alternative:
             Null hypothesis : Theta <= 0
                                               (size = 0.025)
      Alternative hypothesis : Theta >= 8
                                                (power = 0.900)
     (Triangular test (Whitehead & Stratton, 1983))
  STOPPING BOUNDARIES: Sample Mean scale
                          Futility Efficacy
      Time 1 (N = 80.55)
                           -2.4299 12.1493
      Time 2 (N = 161.09)
                            2.4299
                                      7.2896
      Time 3 (N = 241.64)
                            4.0498
                                      5.6697
      Time 4 (N = 322.19)
                            4.8597
                                      4.8597
- A level 0.025 one-sided design from the Pampallona and Tsiatis (1984) group sequential design
  family having O'Brien-Fleming boundary relationships and testing the difference of means for a
  two arm study can be obtained by the following code, which takes advantage of the default values of
  the prob. model="mean", arms=2, test.type="greater", null.hypothesis=0, size= 0.025,
  design.family= "X", P=1, R=0, A=0, and display.scale="X". In this example, we choose a
  "futility" boundary based on rejection of the alternative for which we have 90% power.
  > ptX <- seqDesign("mean", nbr.analyses=4, alt.hypothesis= 8, sd= 20, power=0.90,
            alpha=c(0.1,0.025),beta=c(0.975,0.9))
  > ptX
  Call:
  seqDesign(prob.model = "mean", alt.hypothesis = 8, sd = 20, nbr.analyses = 4,
      power = 0.9, alpha = c(0.1, 0.025), beta = c(0.975, 0.9))
  PROBABILITY MODEL and HYPOTHESES:
     Theta is difference in means (Treatment - Comparison)
     One-sided hypothesis test of a greater alternative:
             Null hypothesis : Theta <= 0</pre>
                                               (size = 0.025)
      Alternative hypothesis : Theta >= 8
                                               (power = 0.900)
  STOPPING BOUNDARIES: Sample Mean scale
                          Futility Efficacy
      Time 1 (N = 70.71)
                          -5.1783 18.8217
      Time 2 (N = 141.42)
                            1.4109
                                      9.4109
      Time 3 (N = 212.13)
                                      6.2739
                            3.6072
```

• seqDesign(..., design.family="E", ...) is used to define stopping boundaries on the error spending scale. The values of boundary shape function parameters P, R, and A will further characterize the exact family desired including the unified error spending function family (which includes the Kim and DeMets (1987) family), the Hwang, Shih, and DeCani (1990) error spending function family, and the Anderson and Clark (2009) error spending function family based on the logistic distribution.

4.7054

4.7054

Time 4 (N = 282.84)

 A level 0.025 one-sided design with O'Brien-Fleming type boundary relationships within the Kim and DeMets (1987) error spending family testing the difference of means for a two arm study

```
can be obtained by the following code, which takes advantage of the default values of the prob.
  model="mean", arms=2, test.type="greater", null.hypothesis=0, size= 0.025, P=-3.25 (for
  the error spending design family), R=0, A=0, and display.scale="X".
  > obfE1 <- seqDesign("mean", nbr.analyses=4, alt.hypothesis= 8, sd= 20, power=0.90,
            design.family="E")
  > obfE1
  Call:
  seqDesign(prob.model = "mean", alt.hypothesis = 8, sd = 20, nbr.analyses = 4,
      power = 0.9, design.family = "E")
  PROBABILITY MODEL and HYPOTHESES:
     Theta is difference in means (Treatment - Comparison)
     One-sided hypothesis test of a greater alternative:
             Null hypothesis : Theta <= 0</pre>
                                               (size = 0.025)
      Alternative hypothesis : Theta >= 8
                                               (power = 0.900)
  STOPPING BOUNDARIES: Sample Mean scale
                          Futility Efficacy
      Time 1 (N= 68.02) -7.0711 16.7521
      Time 2 (N = 136.03)
                            0.0367
                                      9.6443
      Time 3 (N = 204.05)
                            3.0208
                                      6.6602
      Time 4 (N = 272.07)
                            4.8405
                                      4.8405
- A level 0.025 one-sided design with Pocock type boundary relationships within the Kim and
  DeMets (1987) error spending family testing the difference of means for a two arm study can
  be obtained by the following code, which takes advantage of the default values of the prob.
  model="mean", arms=2, test.type="greater", null.hypothesis=0, size= 0.025, R=0, A=0,
  and display.scale="X".
  > pocE <- seqDesign("mean", nbr.analyses=4, alt.hypothesis= 8, sd= 20, power=0.90,
            design.family="E", P=-1)
  > pocE
  Call:
  seqDesign(prob.model = "mean", alt.hypothesis = 8, sd = 20, nbr.analyses = 4,
      power = 0.9, design.family = "E", P = -1)
  PROBABILITY MODEL and HYPOTHESES:
     Theta is difference in means (Treatment - Comparison)
     One-sided hypothesis test of a greater alternative:
             Null hypothesis : Theta <= 0</pre>
                                               (size = 0.025)
      Alternative hypothesis : Theta >= 8
                                               (power = 0.900)
  STOPPING BOUNDARIES: Sample Mean scale
                          Futility Efficacy
      Time 1 (N= 78.80) -1.5198 11.2545
      Time 2 (N = 157.61)
                            2.0663
                                     7.6685
      Time 3 (N = 236.41)
                            3.7199
                                      6.0149
      Time 4 (N = 315.22)
                            4.8674
                                      4.8674
```

- A level 0.025 one-sided design with O'Brien-Fleming type boundary relationships within the Hwang, Shih, and DeCani (1990) error spending family testing the difference of means for a two arm study can be obtained by the following code, which takes advantage of the default val-

```
ues of the prob. model="mean", arms=2, test.type="greater", null.hypothesis=0, size=
0.025, R=0, and display.scale="X".
> obfE2 <- seqDesign("mean", nbr.analyses=4, alt.hypothesis= 8, sd= 20, power=0.90,
          design.family="E", P=-5, A=1)
> obfE2
Call:
seqDesign(prob.model = "mean", alt.hypothesis = 8, sd = 20, nbr.analyses = 4,
   power = 0.9, design.family = "E", P = -5, A = 1)
PROBABILITY MODEL and HYPOTHESES:
   Theta is difference in means (Treatment - Comparison)
   One-sided hypothesis test of a greater alternative:
           Null hypothesis : Theta <= 0</pre>
                                           (size = 0.025)
   Alternative hypothesis : Theta >= 8
                                            (power = 0.900)
STOPPING BOUNDARIES: Sample Mean scale
                       Futility Efficacy
   Time 1 (N = 67.00) -6.6317 16.3104
   Time 2 (N= 134.01) -0.5100 10.1887
   Time 3 (N = 201.01)
                         2.6118
                                 7.0669
   Time 4 (N = 268.01)
                         4.8393
                                  4.8393
```

• seqDesign(..., design.family="Z", ...) and seqDesign(..., design.family="S", ...) are also allowed, though they are merely straightforward transformations of the unified family defined for the estimate scale. There is little reason to use these families.

## 4.2 Specifying Display Scales in seqDesign()

Irrespective of the boundary scale that might be used to define the boundary shape functions for a particular sequential design, the user may specify a boundary scale to be used in the routine display of the boundaries. Such is effected using the display.scale argument to seqDesign(). The display.scale argument can take any valid "seqScale" argument, or it can take a single character that is interpretable as a default boundary scale.

Using the one-sided symmetric design obfX as an example, we could obtain:

• Boundaries displayed on the normalized statistics ("Z") scale by initially defining

```
(Emerson & Fleming (1989) symmetric test)
 STOPPING BOUNDARIES: Normalized Z-value scale
                         Futility Efficacy
      Time 1 (N = 68.50) -2.0032 4.0065
      Time 2 (N = 137.01) 0.0000
                                    2.8330
      Time 3 (N= 205.51) 1.1566 2.3131
      Time 4 (N= 274.02) 2.0032 2.0032
• Boundaries displayed on the normalized statistics ("Z") scale by updating the original design
 > obfX.Z <- update(obfX, display.scale="Z")</pre>
 > obfX.Z
 seqDesign(prob.model = "mean", alt.hypothesis = 8, sd = 20, nbr.analyses = 4,
     power = 0.9, display.scale = "Z")
 PROBABILITY MODEL and HYPOTHESES:
     Theta is difference in means (Treatment - Comparison)
     One-sided hypothesis test of a greater alternative:
            Null hypothesis : Theta <= 0</pre>
                                           (size = 0.025)
     Alternative hypothesis : Theta >= 8
                                             (power = 0.900)
     (Emerson & Fleming (1989) symmetric test)
 STOPPING BOUNDARIES: Normalized Z-value scale
                         Futility Efficacy
      Time 1 (N = 68.50) -2.0032
                                    4.0065
      Time 2 (N= 137.01) 0.0000
                                    2.8330
      Time 3 (N= 205.51) 1.1566 2.3131
      Time 4 (N = 274.02)
                           2.0032 2.0032
• Boundaries displayed on the conditional power ("C") scale that presumes the original design hypotheses
 are true for future observations
 > obfX.Ch <- update(obfX, display.scale="C")
 > obfX.Ch
 seqDesign(prob.model = "mean", alt.hypothesis = 8, sd = 20, nbr.analyses = 4,
     power = 0.9, display.scale = "C")
 PROBABILITY MODEL and HYPOTHESES:
     Theta is difference in means (Treatment - Comparison)
     One-sided hypothesis test of a greater alternative:
             Null hypothesis : Theta <= 0</pre>
                                           (size = 0.025)
      Alternative hypothesis : Theta >= 8
                                             (power = 0.900)
     (Emerson & Fleming (1989) symmetric test)
 STOPPING BOUNDARIES: Conditional Probability scale
           (Conditional probability that estimated treatment effect
            at the last analysis would correspond to an opposite
            decision computed using hypothesized true treatment
```

```
equal to hypotheses being rejected) Futility Efficacy Time 1 (N= 68.50) 0.5 0.5 Time 2 (N= 137.01) 0.5 0.5 Time 3 (N= 205.51) 0.5 0.5 Time 4 (N= 274.02) 0.5 0.5
```

• Boundaries displayed on the conditional power ("C") scale that presumes the current estimates of treatment effect are true for future observations

```
> obfX.Ce <- update(obfX, display.scale=seqScale("C",hypTheta="estimate"))
> obfX.Ce
Call:
seqDesign(prob.model = "mean", alt.hypothesis = 8, sd = 20, nbr.analyses = 4,
   power = 0.9, display.scale = seqScale("C", hypTheta = "estimate"))
PROBABILITY MODEL and HYPOTHESES:
   Theta is difference in means (Treatment - Comparison)
   One-sided hypothesis test of a greater alternative:
          Null hypothesis : Theta <= 0</pre>
                                        (size = 0.025)
    Alternative hypothesis : Theta >= 8
                                           (power = 0.900)
   (Emerson & Fleming (1989) symmetric test)
STOPPING BOUNDARIES: Conditional Probability scale
        (Conditional probability that estimated treatment effect
         at the last analysis would correspond to an opposite
        decision computed using hypothesized true treatment
         equal to maximum likelihood estimate)
                      Futility Efficacy
    Time 1 (N= 68.50) 0.0000 0.0000
    Time 2 (N = 137.01)
                        0.0023
                                 0.0023
    Time 3 (N=205.51)
                        0.0909 0.0909
    Time 4 (N = 274.02)
                        0.5000
                                 0.5000
```

• Boundaries displayed on the Bayesian posterior probability ("B") scale using a non informative prior

STOPPING BOUNDARIES: Bayesian scale

```
(Posterior probability of hypotheses based on prior
           distribution having median 0
           and variation parameter Inf)
                         Futility Efficacy
     Time 1 (N = 68.50)
                           1.0000
                                    1.0000
     Time 2 (N = 137.01)
                           0.9977
                                    0.9977
      Time 3 (N=205.51)
                           0.9896
                                    0.9896
      Time 4 (N = 274.02)
                           0.9774
                                    0.9774
• Boundaries on the error spending ("E") scale
 > obfX.E <- update(obfX, display.scale="E")</pre>
 > obfX.E
 Call:
 seqDesign(prob.model = "mean", alt.hypothesis = 8, sd = 20, nbr.analyses = 4,
      power = 0.9, display.scale = "E")
 PROBABILITY MODEL and HYPOTHESES:
     Theta is difference in means (Treatment - Comparison)
     One-sided hypothesis test of a greater alternative:
             Null hypothesis : Theta <= 0</pre>
                                            (size = 0.025)
      Alternative hypothesis : Theta >= 8
                                              (power = 0.900)
     (Emerson & Fleming (1989) symmetric test)
 STOPPING BOUNDARIES: Error Spending Function scale
                         Futility Efficacy
      Time 1 (N = 68.50)
                           0.0012
                                    0.0012
      Time 2 (N=137.01)
                           0.0927
                                    0.0927
     Time 3 (N=205.51) 0.4470
                                   0.4470
      Time 4 (N = 274.02)
                         1.0000
                                    1.0000
```

### 4.3 Transforming Boundaries to Alternative Scales using seqBoundary()

In RCTdesign, the display scale specified with display.scale when defining the boundary is truly just a default value for tabulating or plotting the boundaries. Using the RCTdesign function seqBoundary(), a user can extract a stopping boundary on an arbitrary scale as specified by its second argument, scale. (It should be emphasized that seqBoundary() returns only the boundary, and no other aspects of the group sequential design.)

Using the one-sided symmetric design obfX as an example, we could print the stopping boundaries using arbitrary scales as follows:

• Boundaries displayed on the normalized statistics ("Z") scale by executing

> seqBoundary (obfX, scale="Z")

```
Time 3 (N= 205.51) 1.1566 2.3131
Time 4 (N= 274.02) 2.0032 2.0032
```

• Because the scale argument is the second, we do not have to name the argument supplied to the call to seqBoundary(): boundaries are also displayed on the normalized statistics ("Z") scale by executing

```
> seqBoundary (obfX, "Z")
```

```
STOPPING BOUNDARIES: Normalized Z-value scale Futility Efficacy Time 1 (N= 68.50) -2.0032 4.0065 Time 2 (N= 137.01) 0.0000 2.8330 Time 3 (N= 205.51) 1.1566 2.3131 Time 4 (N= 274.02) 2.0032 2.0032
```

• Boundaries displayed on the conditional power ("C") scale that presumes the original design hypotheses are true for future observations

```
> seqBoundary(obfX, "C")
```

Time 4 (N = 274.02)

```
STOPPING BOUNDARIES: Conditional Probability scale

(Conditional probability that estimated treatment effect at the last analysis would correspond to an opposite decision computed using hypothesized true treatment equal to hypotheses being rejected)

Futility Efficacy
```

```
Time 1 (N= 68.50) 0.5 0.5

Time 2 (N= 137.01) 0.5 0.5

Time 3 (N= 205.51) 0.5 0.5

Time 4 (N= 274.02) 0.5 0.5
```

• Boundaries displayed on the conditional power ("C") scale that presumes the current estimates of treatment effect are true for future observations

```
> seqBoundary(obfX, seqScale("C",hypTheta="estimate"))
```

```
STOPPING BOUNDARIES: Conditional Probability scale

(Conditional probability that estimated treatment effect at the last analysis would correspond to an opposite decision computed using hypothesized true treatment equal to maximum likelihood estimate)

Futility Efficacy

Time 1 (N= 68.50) 0.0000 0.0000

Time 2 (N= 137.01) 0.0023 0.0023

Time 3 (N= 205.51) 0.0909 0.0909
```

• Boundaries displayed on the Bayesian posterior probability ("B") scale using a non informative prior

0.5000

```
> seqBoundary(obfX, seqScale("B", priorTheta=0, priorVariation=Inf))
```

```
STOPPING BOUNDARIES: Bayesian scale
(Posterior probability of hypotheses based on prior distribution having median 0
```

0.5000

```
and variation parameter Inf) Futility Efficacy Time 1 (N= 68.50) 1.0000 1.0000 Time 2 (N= 137.01) 0.9977 0.9977 Time 3 (N= 205.51) 0.9896 0.9896 Time 4 (N= 274.02) 0.9774 0.9774
```

• Boundaries on the error spending ("E") scale

```
> segBoundary(obfX, "E")
```

```
STOPPING BOUNDARIES: Error Spending Function scale Futility Efficacy Time 1 (N= 68.50) 0.0012 0.0012 Time 2 (N= 137.01) 0.0927 0.0927 Time 3 (N= 205.51) 0.4470 0.4470 Time 4 (N= 274.02) 1.0000 1.0000
```

## 4.4 Transforming Boundaries to Alternative Scales using changeSeqScale()

The RCTdesign function changeSeqScale() can also be used to obtain the stopping boundaries on arbitrary scales. (Unlike seqBoundary(), changeSeqScale() can also be used to transform individual observations of the group sequential test statistic.)

Using the one-sided symmetric design obfX as an example, we could print the stopping boundaries using arbitrary scales as follows:

• Boundaries displayed on the normalized statistics ("Z") scale by executing

• Because the outScale argument is the second, we do not have to name the argument supplied to the call to seqBoundary(): boundaries are also displayed on the normalized statistics ("Z") scale by executing

```
> changeSeqScale (obfX, "Z")
```

```
STOPPING BOUNDARIES: Normalized Z-value scale

a d

Time 1 (N= 68.50) -2.0032 4.0065

Time 2 (N= 137.01) 0.0000 2.8330

Time 3 (N= 205.51) 1.1566 2.3131

Time 4 (N= 274.02) 2.0032 2.0032
```

• Boundaries displayed on the conditional power ("C") scale that presumes the current estimates of treatment effect are true for future observations

```
> changeSeqScale(obfX, seqScale("C",hypTheta="estimate"))
 STOPPING BOUNDARIES: Conditional Probability scale
          (Conditional probability that estimated treatment effect
           at the last analysis would correspond to an opposite
           decision computed using hypothesized true treatment
           equal to maximum likelihood estimate)
      Time 1 (N = 68.50) 0.0000 0.0000
      Time 2 (N = 137.01) 0.0023 0.0023
      Time 3 (N = 205.51) 0.0909 0.0909
      Time 4 (N = 274.02) 0.5000 0.5000
• Boundaries displayed on the Bayesian posterior probability ("B") scale using a non informative prior
 > changeSeqScale(obfX, seqScale("B", priorTheta=0, priorVariation=Inf))
 STOPPING BOUNDARIES: Bayesian scale
          (Posterior probability of hypotheses based on prior
           distribution having median 0
           and variation parameter Inf)
     Time 1 (N = 68.50) 1.0000 1.0000
      Time 2 (N= 137.01) 0.9977 0.9977
      Time 3 (N = 205.51) 0.9896 0.9896
      Time 4 (N = 274.02) 0.9774 0.9774
• Boundaries on the error spending ("E") scale
 > changeSeqScale(obfX, "E")
 STOPPING BOUNDARIES: Error Spending Function scale
      Time 1 (N= 68.50) 0.0012 0.0012
```

# 4.5 Displaying Boundaries on Alternative Scales using seqEvaluate() or Plotting Functions

Time 2 (N= 137.01) 0.0927 0.0927 Time 3 (N= 205.51) 0.4470 0.4470 Time 4 (N= 274.02) 1.0000 1.0000

Most RCTdesign functions that are used to evaluate stopping boundaries can also accept "seqScale" objects as an argument.

The RCTdesign function seqEvaluate will produce a boundary table that displays stopping boundaries on a variety of specified scales using arguments XScale, ZScale, PScale, EbndScale, EaltScale, Chyp-Scale, CestScale, CaltScale, CnullScale, CHypTheta, HPriorTheta, HPriorVariation, and HPriorNames. (See the tutorials and help files on seqEvaluate() for more information.)

For instance, we can tabulate the boundaries for obfX using the following code, which takes advantage of the default values that specify the display of the estimate ("X"), normalized "Z" statistic, fixed sample "P" value, and noninformative prior based Bayesian posterior probability ("B") scales:

```
> obfXeval <- seqEvaluate(obfX, EbndScale=TRUE, ChypScale=TRUE,
```

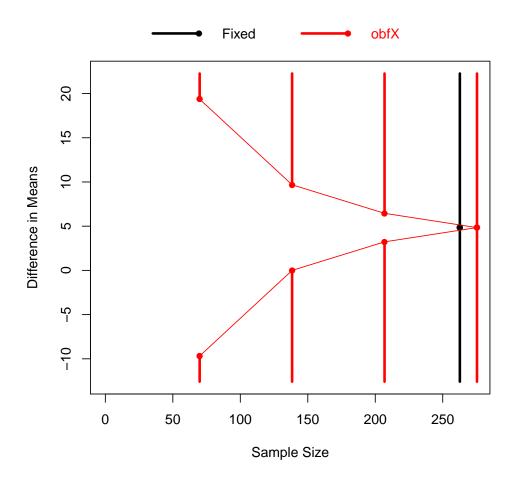
+ CestScale=TRUE)

> obfXeval\$bndTable

```
Anlys SampSize
                        CrudeEst
                                             Z
                                                                    Ebnd Chyp
                                                       FxdP
       1 68.50492 -9.681215e+00 -2.003230e+00 9.774237e-01 3.081788e-05
Fut
       2 137.00984 -3.787070e-10 -1.108203e-10 5.000000e-01 2.318459e-03 0.5
Fut
Fut
       3 205.51475 3.227072e+00 1.156565e+00 1.237250e-01 1.117585e-02 0.5
       4 274.01967 4.840607e+00 2.003230e+00 2.257632e-02 2.500000e-02
Eff
       1 68.50492 1.936243e+01 4.006459e+00 3.081788e-05 3.081788e-05 0.5
       2 137.00984 9.681215e+00 2.832994e+00 2.305709e-03 2.318459e-03
Eff
                                                                          0.5
Eff
       3 205.51475 6.454143e+00 2.313130e+00 1.035774e-02 1.117585e-02 0.5
        4 274.01967 4.840607e+00 2.003230e+00 2.257632e-02 2.500000e-02
Eff
                                                                           NA
           Cest
                     Hnoninf
Fut 1.968981e-12 0.0002605244
Fut 2.305709e-03 0.0225763247
Fut 9.085860e-02 0.1237250334
Fut
             NA
Eff 1.000000e+00 0.9997394756
Eff 9.976943e-01 0.9774236753
Eff 9.091414e-01 0.8762749666
Eff
             NA
                          NA
```

Similarly, when displaying the boundaries graphically, we can use the display scale used when creating the design

## > plot(obfX)



Alternatively, we can decide to display the boundary on some other scale, e.g., the normalized Z statistic scale

## > plot(obfX,display.scale="Z")

