An introduction to the determination of the probability of a successful trial: Frequentist and Bayesian approaches

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Abstract

Determination of posterior probability for go-no-go decision and predictive power are becoming increasingly common for resource optimization in clinical investigation. There are vast published literature on these topics; however, the terminologies are not consistently used across the literature. Further, there is a lack of consolidated presentation of various concepts of the probability of success. We attempted to fill this gap. This paper first provides a detailed derivation of these probability of success measures under the frequentist and Bayesian paradigms in a general setting. Subsequently, we have presented the analytical formula for these probability of success measures for continuous, binary, and time-to-event endpoints separately. This paper can be used as a single point reference to determine the following measures: (a) the conditional power (CP) based on interim results, (b) the predictive power of success (PPoS) based on interim results with or without prior distribution, and (d) the probability of success (PoS) for a prospective trial at the design stage. We have discussed both clinical success and trial success. This paper’s discussion is mostly based on the normal approximation for prior distribution and the estimate of the parameter of interest. Besides, predictive power using the beta prior for the binomial case is also presented. Some examples are given for illustration. R functions to calculate CP and PPoS are available through the LongCART package. An R shiny app is also available at https://ppos.herokuapp.com/.

Keywords: B-value, Beta-Binomial, Clinical success, Conditional power, Normal-normal approximation, Predictive power of success (PPoS), Prior distribution, Probability of success (PoS), Trial success.

1 Introduction

The need to determine the probability of study success may arise at various stages of a clinical trial. For example, the goal of such an exercise could be making go or no go decision based on data from

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the earlier phase. It can also be a useful tool for monitoring a clinical trial for stopping the trial early for futility or make some adaptation (e.g., increase in sample size, drop of an arm). The term “success” or “study success” is often understood in the context of achieving a pre-specified threshold for p-value (e.g., two-sided 0.05 or one-sided 0.025) at the end of the trial. In this paper, we would call it “trial success” to differentiate it from “Clinical success”. “Clinical success” is defined as the observed treatment effect exceeding some threshold value that is often clinically meaningful [1, 2]. This paper focuses on both “trial success” and “clinical success”.

There are multiple statistical tools to measure the probability of success (either “trial success” or “clinical success”) including frequentist tools such as power, conditional power (CP), and Bayesian tools such as the probability of success (PoS) and predictive power of success (PPoS). The power and PoS for a prospective trial are determined at the design stage and thereby do not have any scope of using the interim results. On the contrary, the CP and the PPoS are calculated after observing the interim data; therefore, the uncertainty in the trial data is only limited to the post-interim part. These measures (i.e., power, CP, PoS, and PPoS) are based on some anticipation about $\theta$ where $\theta$ denotes the true treatment effect. The basis of this anticipation about $\theta$ could be either the available interim results, or the results from previous trials (and clinical judgement) or some combination of all these sources, but in general, is not precisely known. In the frequentist approach, the power and CP are calculated using the specified (assumed) value of the $\theta$. However, the power and CP may not give a good indication of overall trial success [3] as it treats the assumed value of $\theta$ as its true value. Therefore, in the Bayesian approach, instead of assuming a specific value of $\theta$, the knowledge about $\theta$ is summarized as distribution of $\theta$ which is then used to calculate PoS or PPoS. This distribution of $\theta$ could be either prior distribution (when no interim results are involved) or predictive distribution (when interim results are involved). For this reason, PoS is also viewed as average ‘power’ over the prior distribution of $\theta$ [4, 5] whereas PPoS is the average CP over the predictive distribution of $\theta$. Note that, in the context of “clinical success”, PoS and PPoS are also known as the probability of clinical success (PoCS) and the predictive power of clinical success (PPoCS), respectively.

Halperin et al. [6] suggested using conditional probability given the current results as a tool for efficacy and futility monitoring in the clinical trial. Use of the B-value to calculate the CP was first presented by Lan and Wittes [7]. The B-value is a function of the Z-value with independent increment property and discussed briefly in this paper in Section 2. Lachin [8] has shown that any formal stopping boundaries based on the CP (along with the type I and II error probabilities) can be expressed using B value in a study with interim futility analysis. Lan, Hu and Proschan [9] have discussed the relationship between the CP and PPoS. Choi, Smith and Becker [10] and Spiegelhalter, Freedman and Blackburn [11] first applied the Bayesian methodology in monitoring clinical trial with binary endpoint where analyses were carried out using conventional frequentist techniques. Such a framework is known as ‘hybrid classical-Bayesian’ [12] and was later applied for the continuous endpoints [13] and the survival endpoints [14] as well. One challenge in decoding all the information available in the literature is the inconsistent use of terminologies in describing these concepts. For example, PPoS has been referred as ‘predictive power’ [1], [3], ‘Bayesian predictive power (BPP)’ [15], ‘predictive probability of statistical significance’ [2], and ‘probability of study success’ [16] in the literature. On the other hand, the PoS in the literature is also referred in the literature as ‘average success probability’ [1, 5], ‘assurance’ [3], and ‘expected power’ [5]. Furthermore, despite the wide popularity of these measures, the current literature still lacks the concise presentation of these concepts with expressions for these measures by type of endpoint for the clinical practitioners to use.
The present work attempts to fill that gap.

In this paper, we first discuss the concept of various probability of success measures before moving on to presenting the analytical formula for continuous, binary and time-to-event endpoints separately with example. Here, we present the following measures: (a) CP based on the interim result, (b) PPoS based on the interim results, and (c) PoS at the design stage of a prospective trial. The PPoS is discussed with or without prior distribution. The discussion in this paper is largely based on the normal-normal approximation; however, we have also discussed the PPoS for the beta-binomial case. R functions to calculate CP and PPoS discussed in this paper are available through LongCART package [17]. An user friendly R shiny app is also available at https://ppos.herokuapp.com/.

2 Notations and preliminaries

We consider the following general form of hypothesis testing in a clinical trial:

$$H_0: \theta = 0 \quad \text{vs.} \quad H_1: \theta > 0$$

where \( \theta \) is a parameter of interest. For example, it could be either mean or proportion in a given population or their difference between two populations or log hazards ratio (HR). We also assume results from the interim analysis performed after the accrual of \( t \) amounts of “information” \( (0 \leq t \leq 1) \) are available. At any given time of analysis, the information \( t \) equals the proportion of evaluable subjects to the maximum number of planned subjects for continuous and binary endpoints or proportion of observed events to the maximum planned events for time to event endpoints. Let’s \( \hat{\theta}(t) \) be the estimate of \( \theta \) at the interim analysis with corresponding standard error (SE) as \( SE[\hat{\theta}(t)] = k \cdot \frac{1}{\sqrt{t}} \).

Note that, \( k \) is the SE of the estimate at the final analysis and does not depend on \( t \). For example, \( k = \sigma/\sqrt{N} \) and \( k \approx 2/\sqrt{D} \) for continuous and survival cases, respectively. With this, for both Z-test and log-rank test, test statistic \( Z(t) \) can be expressed as

$$Z(t) = \frac{\hat{\theta}(t)}{SE[\hat{\theta}(t)]} = \frac{\hat{\theta}(t)}{k} \cdot \sqrt{t}$$

and,

Reject \( H_0 \), if \( Z(t) > c(t) \)

where \( c(t) \) is the rejection boundary. \( c(t) \) must be identified in advance and should be such that it preserves overall type I error of \( \alpha \). In a single look design without any interim analysis, \( c(1) = \Phi(1 - \alpha) \), where \( \Phi(\cdot) \) denotes the cumulative distribution function of a standard normal variate. In a multiple looks design with one or more interim analyses, \( c(1) \) must be determined according to the appropriate alpha spending function (e.g. [18]).

Since, \( E[Z(t)] = (\theta/k) \cdot \sqrt{t} \), the information growth in \( Z(t) \) is proportional to \( \sqrt{t} \). Following Lan and Wittes [2], the B-values are defined as follows:

$$B(t) = Z(t) \cdot \sqrt{t} = \frac{\hat{\theta}(t)}{k} \cdot t \quad \text{(2.1)}$$

with \( B(0) = 0 \) at the trial initiation and \( B(1) = Z(1) \) at the end of the trial. Further,

$$\text{Cov}[B(t), B(s)] = \text{min}(s, t) \quad \text{and} \quad \text{Var}[B(t)] = t \quad \text{(2.2)}$$

3
$B(t)$ has following advantages over $Z(t)$: (a) information growth in $B(t)$ is proportional to $t$ as $E[B(t)] = (\theta/k) \cdot t$, and (b) $B(t)$ has independent increments, implying $B(1) - B(t)$, is independent of the $B(t)$. Because of these two advantages, it is often easier to work with $B(t)$ compared to $Z(t)$.

### 3 Conditional power, Predictive power, Probability of success

With the interim results available at information time $t$, the uncertainty is now restricted to the results from the post-interim data (i.e., data contributing to remaining information of $(1 - t)$). As $B(1) - B(t)$ is independent of $B(t)$, we can decompose $B(1)$ as follows

$$B(1) = B(t) + [B(1) - B(t)]$$

Based on Eq. (2.4), it translates to

$$Z(1) = \sqrt{t} \cdot Z(t) + \sqrt{1 - t} \cdot Z(1 - t) \tag{3.1}$$

where $Z(1-t)$ is the test statistic using the post-interim data only (i.e., data accrued after information $t$) and is defined as follows:

$$Z(1-t) = \frac{\hat{\theta}(1-t)}{SE[\hat{\theta}(1-t)]} = \frac{\hat{\theta}(1-t) \cdot \sqrt{1-t}}{\theta/k}, \tag{3.2}$$

where, $\hat{\theta}(1-t)$ is the estimate of $\theta$ based on post-interim data only. From Eq. (3.1), we have

$$\hat{\theta}(1) = t \cdot \hat{\theta}(t) + (1 - t) \cdot \hat{\theta}(1 - t) \tag{3.3}$$

Clearly, $Z(1-t)$ and $\hat{\theta}(1-t)$ are independent from $Z(t)$ and $\hat{\theta}(t)$. Further, after the interim analysis, $Z(t)$ and $\hat{\theta}(t)$ are fixed and known, but $Z(1-t)$ and $\hat{\theta}(1-t)$ are unknown and random. We call out “Trial success” at the time of final analyses if $Z(1) > c(1)$. Based on Eq. (3.1) and Eq. (3.2), this translates to

**Trial success,** if $\hat{\theta}(1) > \frac{k}{1-t} \cdot [c(1) - \sqrt{t} \cdot Z(t)]$

Further, we call out “clinical success” at the time of final analyses if $\hat{\theta}(1) > \theta_{\text{min}}$. Based on Eq. (3.3), this translates to

**Clinical success,** if $\hat{\theta}(1) > \frac{k}{1-t} \cdot \left[\frac{\theta_{\text{min}}}{k} - \sqrt{t} \cdot Z(t)\right]$

Note the similarity in the definition of the “Trial success” and “Clinical success” criteria. By replacing $c(1)$ with $\frac{\theta_{\text{min}}}{k}$ in the “Trial success” criterion, we can obtain the “Clinical success” criterion. Therefore, we define the general criteria of “success” as follows:

**Success,** if $\hat{\theta}(1-t) > \frac{k}{1-t} \cdot \left[\gamma - \sqrt{t} \cdot Z(t)\right] \tag{3.4}$

where $\gamma = c(1)$ for “Trial success” and $\gamma = \frac{\theta_{\text{min}}}{k}$ for “Clinical success”.


3.1 Conditional power based on interim results

Conditional power (CP) is the conditional probability that a trial success would be observed at the final analysis given the interim results. Assuming the estimate of $\theta$ from the post-interim period to be $\theta'$, the CP is determined based on the following distribution

$$\hat{\theta}(1-t) \sim \text{Normal} \left[ \theta', \frac{k^2}{1-t} \right]$$

Therefore, the CP is

$$CP(t|\theta') = 1 - \Phi \left( \frac{1}{\sqrt{1-t}} \left[ \frac{\hat{\theta}(t)}{k} \left( t + (1-t) \frac{\theta'}{\hat{\theta}(t)} \right) - \gamma \right] \right)$$  (3.5)

It is very intuitive and common to replace $\theta'$ by $\hat{\theta}(t)$ to calculate the CP. In that case, the expression of CP reduces to (e.g., see [4])

$$CP(t|\hat{\theta}(t)) = \Phi \left( \frac{1}{\sqrt{1-t}} \left[ \frac{\hat{\theta}(t)}{k} - \gamma \right] \right) = \Phi \left( \frac{1}{\sqrt{1-t}} \left[ \frac{Z(t)}{\sqrt{t}} - \gamma \right] \right)$$  (3.6)

This is the CP when the post-interim trend expected to be similar to that observed in the interim analysis.

3.2 Predictive power based on interim results

The CP depends on the assumed treatment effect to be observed in the post-interim data, and therefore, calculation of CP can be arbitrary. An alternative is to calculate the probability of success using the predictive distribution of $\hat{\theta}(1-t)$ given the interim results which we refer in this paper as the predictive power of success (PPoS). The PPoS can be viewed as the average of CP($t, \theta$) over the predictive distribution of $\theta$. The Bayesian framework allows us to incorporate the prior distribution of $\theta$ (e.g., based on the historical data or clinicians’ judgements) in the predictive distribution of $\hat{\theta}(1-t)$, although the prior distribution is not mandatory. For the ease of describing, we first determine the expression for PPoS with the prior distribution of $\theta$ and then present the expression without the prior distribution.

Suppose the prior knowledge about $\theta$ can be summarized using the following prior distribution:

$$\theta \sim \text{Normal} \left[ \theta_0, \sigma_0^2 \right]$$  (3.7)

With this prior, the posterior distribution of $\theta$ is

$$\theta|\hat{\theta}(t) \sim \text{Normal} \left[ \psi\hat{\theta}(t) + (1-\psi)\theta_0, \left( \frac{1}{\sigma_0^2} + \frac{t}{k^2} \right)^{-1} \right] \equiv \text{Normal} \left[ \psi\hat{\theta}(t) + (1-\psi)\theta_0, \psi \cdot \frac{k^2}{t} \right]$$

where, $\psi = \frac{\sigma_0^2}{\sigma_0^2 + k^2/t}$ can be viewed as the proportion of the contribution of interim data. Since the $\hat{\theta}(1-t)$ is unknown at information time $t$, we compute the predictive distribution of $\hat{\theta}(1-t)$ as follows:

$$\hat{\theta}(1-t)|\hat{\theta}(t) \sim \text{Normal} \left[ \psi\hat{\theta}(t) + (1-\psi)\theta_0, k^2 \left( \frac{1}{1-t} + \psi \cdot \frac{1}{t} \right) \right]$$
We can now use the predictive distribution of $\hat{\theta}(1-t)$ to derive the PPoS as follows

$$PPoS(t|\hat{\theta}(t), \psi, \theta_0) = 1 - \Phi\left(\frac{k}{\sqrt{1-(1-t)}} \gamma - \sqrt{t \cdot Z(t)} - \psi \hat{\theta}(t) - (1-\psi)\theta_0\right)$$

$$= \Phi\left(\sqrt{\frac{t}{1-t}} \cdot \frac{1}{\sqrt{(1-\psi)t + \psi}} \left[\frac{\hat{\theta}(t)}{k} \{t(1-\psi) + \psi\} + (1-t)(1-\psi)\theta_0 - \gamma\right]\right)$$

(3.8)

This is the PPoS given the interim results and also using the prior distribution. The PPoS is also calculated without the prior distribution (e.g. see [9]). Without the prior distribution, PPoS can be derived as a special case of Eq (3.8) by setting $\psi = 1$ which implies 100% contribution of interim data to the predictive distribution of $\hat{\theta}(1-t)$. Therefore, PPoS given the interim results without prior distribution is obtained as follows (e.g., see [9, 19]):

$$PPoS(t|\hat{\theta}(t)) = \Phi\left(\frac{1}{\sqrt{1-t}} \left[\hat{\theta}(t) - \gamma\right] \cdot \sqrt{t}\right) = \Phi\left(\frac{1}{\sqrt{1-t}} \left[Z(t) - \gamma\right] \cdot \sqrt{t}\right)$$

(3.9)

The expressions of PPoS in Eq. (3.9) and CP in Eq. (3.6) are very similar except the additional $\sqrt{t}$ in the numerator of PPoS. As pointed out by Lan, Hu and Proschan [9], it’s simple consequence is that $CP > PPoS$ for $CP > 0.5$ and $CP < PPoS$ for $CP < 0.5$. In other words, the CP is less extreme than the PPoS. It implies that the stopping rule based on the PPoS will always make it harder to stop a trial than a stopping rule based on the CP.

3.3 Probability of success of a prospective trial at the design stage

The power at the design stage of a clinical trial is calculated assuming some specified treatment effect. An alternative is to calculate the probability of success (PoS) using the prior distribution of $\theta$. The PoS can also be viewed as average power over the prior distribution. The PoS has also been referred to as ‘assurance’ [3], and ‘expected power’ or ‘average success of probability’ [5]. Note that, at the design stage of clinical trial interim results are not available; hence, PoS is entirely based on the prior distribution.

Assuming the prior distribution specified in Eq. (3.7) and expecting the SE in the trial to be $\tilde{k}$, the predictive distribution of $\hat{\theta}(1)$ would be

$$\hat{\theta}(1) | \theta \sim Normal[\theta_0, \sigma_0^2 + var[\hat{\theta}(1)]] \equiv Normal[\theta_0, \sigma_0^2 + \tilde{k}^2]$$

In that case, the PoS given the prior distribution would be

$$POS(\theta_0, \sigma_0) = Pr[Z(1) > \gamma | \theta] = Pr[\hat{\theta}(1) > \tilde{k} \cdot \gamma | \theta] = \Phi\left(\frac{\theta_0 - \tilde{k} \cdot \gamma}{\sqrt{\sigma_0^2 + \tilde{k}^2}}\right)$$

(3.10)

4 Expressions of CP, PPoS and PoS for various endpoints

This section presents the expression of CP, PPoS and PoS to test hypotheses for continuous, binary and survival endpoints separately based on the general expression presented in the previous section.
with normal distribution approximation. However, for the binomial case, we have discussed the PPoS using the beta prior as well. For the two-sample cases, the allocation ratio (treatment arm to control arm) is denoted as \( a : 1 \). We denote \( r^2 = (a + 1)^2 / a \). Note that the expressions for one sample case can be obtained directly from the corresponding expressions from the two-sample case by specifying \( r = 1 \). Intuition for setting \( r = 1 \) is simple: the single arm design can be thought of as \( 1 : 0 \) allocation ratio (instead of \( a : 1 \)) in which case, \( r = (1 + 0) / \sqrt{1} = 1 \). For clarity, we present the expressions for both one sample and two samples scenario separately.

We also would like to remind that here the expressions are presented for general success criteria as presented in Eq. (3.4). One needs to set \( \gamma = c(1) \) for “Trial success” and \( \gamma = \theta_{\min} \) for “Clinical success.”

### 4.1 Continuous endpoint, two samples

We consider study comparing treatment (T) with control (C) with continuous endpoint and corresponding population mean as \( \mu_T \) and \( \mu_C \), respectively. Further, assume the maximum total sample size in the study is \( N \). Here, we test the following hypotheses:

\[
H_0 : \mu_T - \mu_C = \Delta_1 \quad \text{vs.} \quad H_1 : \mu_T - \mu_C > \Delta_1
\]

Here, \( \theta = \mu_T - \mu_C - \Delta_1 \). At interim analysis with total sample size \( n \), the estimate of \( \theta \) is \( \hat{\theta}(t) = \delta_n - \Delta_1 \) where \( \delta_n \) is the difference in the sample means between the two arms at interim. The corresponding test statistic is

\[
Z(t) = \frac{\delta_n - \Delta_1}{r \cdot s_n / \sqrt{n}} = \left( \delta_n - \Delta_1 \right) \sqrt{\frac{n}{N}} \cdot r / s_n
\]

where \( s_n \) is the estimated pooled SD at interim analysis. Further, in this case, \( t = n / N \) and \( k = r \cdot s_n / \sqrt{N} \).

**Conditional power (CP):** The CP with the future trend of difference in the sample means as \( \Delta' \) is

\[
\Phi \left( \frac{1}{r \cdot s_n} \sqrt{\frac{N}{N-n}} \left( \frac{1}{\sqrt{N}} \left[ n(\delta_n - \Delta_1) + (N-n)(\Delta' - \Delta_1) \right] - r \cdot s_n \cdot \gamma \right) \right)
\]

(4.1)

If we assume that the current trend observed through interim analysis continues to hold for the future data as well (i.e., \( \Delta' = \delta_n \)), then the expression for CP is

\[
\Phi \left( \frac{1}{r \cdot s_n} \sqrt{\frac{N}{N-n}} \left( (\delta_n - \Delta_1) \sqrt{N} - r \cdot s_n \cdot \gamma \right) \right)
\]

(4.2)

**Predictive power of success (PPoS):** The expressions of the PPoS are as follows

\[
\text{PPoS, without prior distribution:} \quad \Phi \left( \frac{1}{r \cdot s_n} \sqrt{\frac{n}{N-n}} \left( (\delta_n - \Delta_1) \sqrt{N} - r \cdot s_n \cdot \gamma \right) \right)
\]

(4.3)

\[
\text{PPoS, with assumed prior distribution:}
\]
\[
\Phi \left( \frac{1}{rs_n} \sqrt{\frac{n}{N-n}} \left[ (1-\psi)(n(\delta_n - \Delta_1) + (N-n)(\Delta_0 - \Delta_1)) / \sqrt{N} + \psi(\delta_n - \Delta_1) \sqrt{N} - r \cdot s_n \gamma \right] \right)
\]

(4.4)

where, \( \psi = n\sigma_0^2 / (n\sigma_0^2 + r^2 s_n^2) \).

Probability of success (PoS): The expression of the PoS is as follows

\[
\text{PoS (e.g. see [3]): } \Phi \left( \frac{\sqrt{N} \cdot (\Delta_0 - \Delta_1) - r \cdot \bar{x} \cdot \gamma}{\sqrt{N} \cdot \sigma_0^2 + r^2 \cdot \sigma^2} \right)
\]

(4.5)

where \( \bar{x} \) is the expected pooled SD in the trial. Note that, for the calculation of PPoS with prior distribution in Eq. (4.4) and PoS in Eq. (4.5), following prior of \( \mu_T - \mu_C \) is used

\[
\mu_T - \mu_C \sim \text{Normal} \left[ \Delta_0, \sigma_0^2 \right]
\]

(4.6)

4.2 Continuous endpoint, one sample

Let’s consider a study with a single treatment arm and continuous endpoint. Denote the population mean as \( \mu \) and the maximum sample size in the study is \( N \). We test the following hypotheses:

\[
H_0 : \mu = \mu_1 \quad \text{vs.} \quad H_1 : \mu > \mu_1
\]

Here, \( \theta = \mu - \mu_1 \). At interim analysis with sample size \( n \), the estimate of \( \theta \) is \( \hat{\theta}(t) = \bar{x}_n - \mu_1 \) where \( \bar{x}_n \) is the sample mean at interim. The corresponding test statistic is

\[
Z(t) = \frac{\bar{x}_n - \mu_1}{s_n / \sqrt{n}} = \frac{(\bar{x}_n - \mu_1) \sqrt{n}}{s_n}
\]

where \( s_n \) is the estimated SD at interim analysis. Further, in this case, \( t = n/N \) and \( k = s_n / \sqrt{N} \).

Conditional power (CP): The CP with the future trend of the sample mean as \( \mu' \) is

\[
\Phi \left( \frac{1}{s_n} \sqrt{\frac{N}{N-n}} \left[ \frac{1}{\sqrt{N}} \left( n(\bar{x}_n - \mu_1) + (N-n)(\mu' - \mu_1) \right) - s_n \cdot \gamma \right] \right)
\]

(4.7)

If we assume that the current trend observed through interim analysis continues to hold for future data as well (i.e., \( \mu' = \bar{x}_n \)), then the expression of the CP is

\[
\hat{\theta}(t) = \Phi \left( \frac{1}{s_n} \sqrt{\frac{N}{N-n}} \left( (\bar{x}_n - \mu_1) \sqrt{N} - s_n \cdot \gamma \right) \right)
\]

(4.8)

where, \( \psi = n\sigma_0^2 / (n\sigma_0^2 + s_n^2) \).

Predictive power of success (PPoS): The expressions of the PPoS are as follows

PPoS, without prior distribution:

\[
\Phi \left( \frac{1}{s_n} \sqrt{\frac{n}{N-n}} \left( (\bar{x}_n - \mu_1) \sqrt{N} - s_n \cdot \gamma \right) \right)
\]

(4.9)

PPoS, with assumed prior distribution:
\[
\Phi \left( \frac{1}{\frac{N-n}{n}} \sqrt{n} \left[ \frac{1-\psi}{\sqrt{n-n}} N + \psi (\bar{x}_n - \mu) \sqrt{N-s_n\gamma} \right] \right) \tag{4.10}
\]

**Probability of success (PoS):** The expression of PoS is as follows

\[
\text{PoS: } \Phi \left( \frac{\sqrt{N} \cdot (\mu_0 - \mu_1) - \tilde{\sigma} \cdot \gamma}{\sqrt{N \cdot \sigma^2_0 + \tilde{\sigma}^2}} \right) \tag{4.11}
\]

where \(\tilde{\sigma}\) is the expected SD in the trial. Note that, for the calculation of PPoS with prior distribution in Eq. (4.10) and PoS in Eq. (4.11), following prior for \(\mu\) is used

\[
\mu \sim \text{Normal} \left[ \mu_0, \sigma^2_0 \right] \tag{4.12}
\]

### 4.3 Binary endpoint, two samples

Let’s consider a study comparing treatment (T) with control (C) and binary endpoint. Denote the population proportion as \(\Pi_T\) and \(\Pi_C\), respectively. Further, assume the maximum total sample size in the study is \(N\). The hypotheses of interest are:

\[
H_0: \Pi_T - \Pi_C = \Delta_1 \quad \text{vs.} \quad H_1: \Pi_T - \Pi_C > \Delta_1
\]

Here, \(\theta = \Pi_T - \Pi_C - \Delta_1\). At interim analysis with total sample size \(n\), the estimate of \(\theta\) is \(\hat{\theta}(t) = \delta_n - \Delta_1\) where \(\delta_n = \hat{\pi}_{T,n} - \hat{\pi}_{C,n}\) is the difference in sample proportion between the two arms with \(\hat{\pi}_{T,n}\) and \(\hat{\pi}_{C,n}\) as the estimate of two proportions. Note that,

\[
SE(\delta_n) = \sqrt{\frac{\hat{\pi}_{T,n}(1-\hat{\pi}_{T,n})}{a \cdot n/(1+a)} + \frac{\hat{\pi}_{C,n}(1-\hat{\pi}_{C,n})}{n/(1+a)}} = r \cdot s_n / \sqrt{n}
\]

with \(s^2_n = \frac{a}{a+1} \left\{ \frac{\hat{\pi}_{T,n}(1-\hat{\pi}_{T,n})}{a} + \hat{\pi}_{C,n}(1-\hat{\pi}_{C,n}) \right\}\). Therefore, the corresponding test statistic is

\[
Z(t) = \frac{\delta_n - \Delta_1}{r \cdot s_n / \sqrt{n}} = \frac{(\delta_n - \Delta_1)\sqrt{n}}{r \cdot s_n}
\]

Further, \(t = n/N\) and \(k = r \cdot s_n / \sqrt{N} = SE(\delta_n) \cdot \sqrt{t}\).

**CP, PPoS and PoS with normal approximation:** The expressions of the CP, PPoS and PoS for two sample binary case are similar to the continuous case:

- **Eq. (4.1)** for the CP with the expected difference from post-interim data as \(\Delta’\).
- **Eq. (4.2)** for the CP with the expected difference similar to that observed at interim analysis.
- **Eq. (4.3)** for the PPoS without prior distribution.

Further, assume that the following prior for \(\Pi_T - \Pi_C\) is available to us

\[
\Pi_T - \Pi_C \sim \text{Normal} \left[ \Delta_0, \sigma^2_0 = \sigma^2_0 \right] \tag{4.13}
\]

Using this prior information,
Let \( n \) hypotheses: \( \theta \sim \pi \) with the beta priors

\[
\Pr(\theta|\pi) \propto \theta^{\beta-1} (1-\theta)^{\gamma-1}
\]

where, \( B(\beta, \gamma) \) is the beta distribution. Further, we assume following prior distributions: \( \Pi_T \sim \text{Beta}(a_T, b_T) \) and \( \Pi_C \sim \text{Beta}(a_C, b_C) \). Denote the observed number of response at interim analysis as \( y_T \) based on \( n_T \) subjects in the treatment arm and \( y_C \) based on \( n_C \) subjects in the control arm with \( n_T + n_C = n \). Given the interim result, the posterior distributions of \( \Pi_T \) and \( \Pi_C \) are (e.g., see [2])

\[
\Pi_T | y_T \sim \text{Beta}(x_T + a_T, n_T - x_T + b_T) \\
\Pi_C | x_C \sim \text{Beta}(x_C + a_C, n_C - x_C + b_C)
\]

Let, \( Y_T \) and \( Y_C \) be the observed number of observed response from remaining \( N_T - n_T \) and \( N_C - n_C \) subjects, respectively, with \( N_T + N_C = N \). The predictive distribution of \( Y_T \) and \( Y_C \) are (e.g., see [20])

\[
\Pr(Y_T = y_T | x_T) = \binom{N_T - n_T}{y_T} \frac{B(x_T + y_T + a_T, N_T - x_T - y_T + b_T)}{B(x_T + a_T, n_T - x_T + b_T)} \\
\Pr(Y_C = y_C | x_C) = \binom{N_C - n_C}{y_C} \frac{B(x_C + y_C + a_C, N_C - x_C - y_C + b_C)}{B(x_C + a_C, n_C - x_C + b_C)}
\]

where, \( B(u, v) = \frac{(u-1)!(v-1)!}{(u+v-1)!} \) is the beta function. Thus, the PPoS at the end of the trial is

\[
\sum_{y_T=0}^{N_T-n_T} \sum_{y_C=0}^{N_C-n_C} I(\text{success} | x_T + y_T, x_C + y_C, N_T, N_C) \cdot \Pr(Y_T = y_T | x_T) \cdot \Pr(Y_C = y_C | x_C)
\]

where \( I(\cdot) \) is the indicator function for success criteria which could be either trial success (e.g., based on approximate Z test or Fisher’s exact test) or clinical success indicating the observed difference in proportion exceeds the certain clinical meaningful value.

### 4.4 Binary endpoint, one sample

Let’s consider a study with a single treatment arm and binary endpoint. Let’s \( \Pi \) denotes the population proportion and the maximum sample size in the study is \( N \). We test the following set of hypotheses:

\[
H_0 : \Pi = \Pi_1 \quad \text{vs.} \quad H_1 : \Pi > \Pi_1
\]

Here, \( \theta = \Pi - \Pi_1 \). At interim analysis with sample size \( n \), the estimate of \( \theta \) is \( \hat{\theta}(t) = \hat{\theta}_n - \Delta_1 \) where \( \hat{\theta}_n \) is the sample proportion at interim. The corresponding test statistic is

\[
Z(t) = \frac{\hat{\theta}_n - \Pi_1}{s_n/\sqrt{n}} = \frac{(\hat{\theta}_n - \Pi_1)\sqrt{n}}{s_n}
\]
where, \( s_n = \sqrt{\hat{\pi}_n(1 - \hat{\pi}_n)} \). Further, in this case, \( t = n/N \) and \( k = s_n/\sqrt{N} = \text{SE}(\hat{\pi}_n) \cdot \sqrt{t} \).

CP, PPoS and PoS with normal approximation: The expressions of the CP, PPoS and PoS for one sample binary case are similar to the continuous case:

- Eq. (4.7) (replacing \( \bar{x}_n \) with \( \hat{\pi}_n \), \( \mu_1 \) with \( \Pi_1 \), and \( \mu' \) with \( \Pi' \)) for the CP with the expected difference from post-interim data as \( \Pi' \).
- Eq. (4.8) (replacing \( \bar{x}_n \) with \( \hat{\pi}_n \) and \( \mu_1 \) with \( \Pi_1 \)) for the CP with the expected difference similar to that observed at interim analysis.
- Eq. (4.9) (replacing \( \bar{x}_n \) with \( \hat{\pi}_n \) and \( \mu_1 \) with \( \Pi_1 \)) for the PPoS without prior distribution.

Further, assume that the following prior for \( \Pi \) is available to us:

\[
\Pi \sim \text{Normal} \left[ \Pi_0, \sigma^2_0 = \sigma^2_0 \right] \tag{4.15}
\]

Using this prior information:

- The PPoS with prior distribution can be obtained from Eq. (4.10) (replacing \( \bar{x}_n \) with \( \hat{\pi}_n \), \( \mu_0 \) with \( \Pi_0 \) and \( \mu_1 \) with \( \Pi_1 \)) with \( \psi = n\sigma^2_0/(n\sigma^2_0 + N s^2_n) \).
- The PoS can be obtained from Eq. (4.11) (replacing \( \mu_0 \) with \( \Pi_0 \) and \( \mu_1 \) with \( \Pi_1 \)) with \( \tilde{\sigma} = \sqrt{\hat{\pi}(1 - \hat{\pi})} \) where \( \hat{\pi} \) is the expected proportion in the trial.

PPoS, with the beta prior: Let \( X \) be the observed number of response in the trial which is assumed to follow a binomial distribution with probability of response \( \Pi \). Further, we assume that the prior distribution of \( \Pi \) is Beta(\( a,b \)). Denote the observed number of response as \( x_n \) from \( n \) subjects at interim analyses. Given the interim result, the posterior distribution of \( \Pi \) is

\[
\Pi \mid x_n \sim \text{Beta}(x_n + a, n - x_n + b)
\]

Let, \( Y \) be the number of the observed response from remaining \( N - n \) subjects. The predictive distribution of \( Y \) is (e.g., see [20])

\[
\Pr(Y = y|x_n) = \binom{N - n}{y} \frac{B(x_n + y + a, N - x_n - y + b)}{B(x_n + a, n - x_n + b)} \quad y = 0, 1, \ldots, N - n
\]

Thus, the PPoS would be

\[
\sum_{y=0}^{N-n} I(\text{success}|x_n + y, N) \cdot \Pr(Y = y|x_n) \tag{4.16}
\]

where \( I(\cdot) \) is the indicator function that either trial success criteria is met (e.g., based on approximate Z test or exact binomial test) or clinical success is achieved indicating observed proportion exceeds the certain clinical meaningful value.
4.5 Survival endpoint, two samples

We consider a clinical trial comparing treatment (T) with control (C) with time to event endpoint. Denote the treatment to control hazards ratio as $\lambda$ and the maximum target number of events as $D$. Here, we test the following hypotheses:

$$H_0 : \lambda = \lambda_1 \quad \text{vs.} \quad H_1 : \lambda < \lambda_1$$

Here, $\theta = \log (\lambda_1/\lambda)$. At interim analysis with the total number of events $D_{IA}$, the estimate of $\theta$ is $\hat{\theta}(t) = \log (\lambda_1/\hat{\lambda}_{IA})$ where $\hat{\lambda}_{IA}$ is the estimated HR. The corresponding log-rank statistic for trend test is approximately equivalent to

$$Z(t) = \frac{\log (\lambda_1/\hat{\lambda}_{IA})}{\sqrt{D_{IA}}}$$

Further, in this case, $t = D_{IA}/D$ and $k = r/\sqrt{D}$.

Conditional power (CP): Expression of the CP assuming the estimated HR from the post-interim data as $\lambda'$ is

$$\Phi \left( \frac{1}{r} \sqrt{\frac{D}{D - D_{IA}}} \left[ \frac{D_{IA}}{\sqrt{D}} \log \frac{\lambda_1}{\hat{\lambda}_{IA}} + \frac{D - D_{IA}}{\sqrt{D}} \log \frac{\lambda_1}{\lambda'} - r \cdot \gamma \right] \right)$$

(4.17)

If we assume that the current trend observed at the interim analysis continues to hold for future data as well (i.e., $\lambda' = \hat{\lambda}_{IA}$), then the expression of CP is

$$\Phi \left( \frac{1}{r} \sqrt{\frac{D}{D - D_{IA}}} \left[ \sqrt{D} \cdot \log \frac{\lambda_1}{\hat{\lambda}_{IA}} - r \cdot \gamma \right] \right)$$

(4.18)

Predictive power of success (PPoS): The expressions of the PPoS are as follows:

PPoS, without prior distribution: $\Phi \left( \frac{1}{r} \sqrt{\frac{D_{IA}}{D - D_{IA}}} \left[ \sqrt{D} \cdot \log \frac{\lambda_1}{\hat{\lambda}_{IA}} - r \cdot \gamma \right] \right)$

(4.19)

PPoS, with prior distribution (e.g., see [14]):

$$\Phi \left( \frac{1}{r} \sqrt{\frac{D_{IA}}{D - D_{IA}}} \left[ (1 - \psi) \left\{ \frac{D_{IA}}{\sqrt{D}} \cdot \log \frac{\lambda_1}{\hat{\lambda}_{IA}} + \frac{D - D_{IA}}{\sqrt{D}} \cdot \log \frac{\lambda_1}{\lambda'} \right\} + \psi \cdot \sqrt{D} \cdot \log \frac{\lambda_1}{\hat{\lambda}_{IA}} - r \cdot \gamma \right] \right)$$

(4.20)

where, $\psi = \frac{D_{IA} \cdot \sigma_0^2}{D_{IA} \cdot \sigma_0^2 + r^2}$.

Probability of success (PoS): The expression of the PoS is as follows:

PoS (e.g., see [16]): $\Phi \left( \frac{\sqrt{D} \cdot \log (\lambda_1/\lambda_0) - r \cdot \gamma}{\sqrt{D} \cdot \sigma_0^2 + r^2} \right)$

(4.21)

Note that, for the calculation of the PPoS and PoS with prior distribution, the following prior for $\lambda$ is used

$$\log \lambda \sim \text{Normal} \left[ \log \lambda_0, \sigma_0^2 \right]$$

(4.22)
5 Example

In this section, we illustrate the calculation of CP, PPoS and PoS based on published clinical trial results. We have supplemented these examples with made up prior distribution and interim results for the sole purpose of illustration. Following R functions in LongCART package can be used to calculate these measures: (a) PoS() to calculate PoS at the design stage for all three types of endpoints, (b) succ_ia() to calculate CP and PPoS based on interim results with normal-normal approximation for all three types of endpoints, (c) succ_ia_betabinom_two() to calculate PPoS based on interim results for comparison of two proportions with beta priors, and (d) succ_ia_betabinom_one() to calculate PPoS based on interim results for testing of single proportion with beta prior. An user friendly R shiny app is also available at https://ppos.herokuapp.com/ to calculate these measures.

Example 1: Continuous endpoint

In the pragmatic, nonblinded, non-inferiority CODA trial [21], 1552 subjects (=N) with appendicitis were equally randomized in 1:1 allocation ratio either to receive antibiotics or to undergo appendectomy. The primary outcome was 30-day health status, as assessed with the European Quality of Life–5 Dimensions (EQ-5D) questionnaire (scores range from 0 to 1, with higher scores indicating better health status; non-inferiority margin, 0.05 points). For this illustration, we pretend to have an interim analysis at the sample size of 776 (=n). According to O’Brien alpha spending function, the rejection boundaries for Z test statistic are 2.96 and 1.97 (=c(1)) at interim and final analyses, respectively.

In this case, we are statistically testing the following hypotheses:

\[ H_0: \mu_T - \mu_C \leq -0.05 \] against

\[ H_1: \mu_T - \mu_C > -0.05. \]

Therefore, \( \Delta_1 = -0.05 \). Further, the external information available are translated as following prior distribution of \( \mu_T - \mu_C \):

\[ \mu_T - \mu_C \sim \text{Normal}[\Delta_0 = 0, \sigma_0^2 = (0.02)^2] \]

As the treatment allocation ratio is 1:1, we have \( r^2 = (1 + 1)^2 / 2 = 4 \). Further, the pooled SD was expected to be 0.12 in the study. Therefore, the PoS for trial success (=c(1)) at the design stage is \( \Phi(\frac{\sqrt{1552(0-(-0.05))-2(0.12)(1.97)}}{\sqrt{1552(0.02)^2+4(0.12)^2}}) = 0.965 \) (see Eq. (4.5)).

For the calculation of CP and PPoS, let’s consider following interim results: mean difference, -0.025 (=\( \delta_n \)) points with SD as 0.16 (=\( s_n \)). Here, \( k = (\sqrt{4})(0.16)/\sqrt{1552} = 0.0081 \). Assuming the interim trend to be continued to the remaining part of trial as well, based on Eq. (4.2), the conditional power for trial success (\( \gamma = c(1) = 1.97 \)) is 0.941 and PPoS would be 0.866 (see Eq. (4.4)). Now, expecting -0.030 mean difference from post-interim data (i.e., \( \Delta' = -0.030 \)), the conditional power would be 0.871. Further, the PPoS for trial success given the interim results and prior distribution is 0.944 (see Eq. (4.3)).

Example 2: Binary endpoint

Fenaux et al. [22] reported the trial results of placebo-controlled, phase 3 trial evaluating the effect of Luspatercept in patients with lower-risk myelodysplastic syndromes. The primary endpoint was the proportion of patients with transfusion independence for eight weeks or longer during weeks 1
In this case, we are statistically testing the following hypotheses: $H_0 : \Pi_T - \Pi_C \leq 0$ against $H_1 : \Pi_T - \Pi_C > 0$. Therefore, $\Delta_1 = 0$. We suppose that the elicitation of prior information about the unknown treatment effect $\Pi_T - \Pi_C$ from a relevant expert as follows

$$\Pi_T - \Pi_C \sim \text{Normal} \left[ \Delta_0 = 0.20, \quad \sigma_0^2 = 0.06 \right]$$

As the treatment allocation ratio is 2:1, we have $r^2 = (2 + 1)^2/2 = 4.5$. Further, the SE of $\delta_n$ at the final analysis is expected to be $k = \sqrt{(0.30 \cdot 0.70/140 + 0.10 \cdot 0.90/70)} = 0.053$. Therefore, the PoS for trial success ($\gamma = c(1) = 2.012$) and clinical success ($\gamma = \theta_{\min}/k = 0.15/0.053 = 2.83$) at the design stage are $\Phi \left( \frac{0.20 - (0.053)(2.012)}{\sqrt{0.06 + 0.053}} \right) = 0.645$ and $\Phi \left( \frac{0.20 - (0.053)(2.83)}{\sqrt{0.06 + 0.053}} \right) = 0.578$, respectively (see Eq. (3.2)).

For the calculation of CP and PPoS, let’s consider following interim results: transfusion independence for 8 weeks or longer was observed in 37.9% of the patients in the luspatercept group ($n_T = 105$), as compared with 22.2% of those in the placebo group ($n_C = 53$). Therefore, at interim, $\delta_n = 0.379 - 0.222 = 0.157$ with SE as $\sqrt{0.379 \cdot 0.621/105 + 0.222 \cdot 0.778/53} = 0.074$. Therefore, $s_n = SE \cdot \sqrt{n/r} = (0.074)(\sqrt{158})/\sqrt{4.5} = 0.4385$. Further, $k = 0.074 \cdot \sqrt{0.75} = 0.064$. Assuming the expected difference in proportion from the post interim data to be 0.20 ($=\Delta'$), based on Eq. (4.1), the CP for trial success ($\gamma = c(1) = 2.012$) and clinical success ($\gamma = 0.15/0.064 = 2.34$) are 0.884 and 0.870, respectively. However, if we assume the interim trend to be continued to the remaining part of the trial, based on Eq. (4.2), the CP for trial success and clinical success are 0.804 and 0.587, respectively. Further, the PPoS for trial success and clinical success based on interim results along with prior knowledge are 0.782 and 0.586, respectively (see Eq. (4.3)). However, if we leave out the prior distribution, the PPoS for trial success and clinical success based on interim results only are 0.772 and 0.575, respectively (see Eq. (4.4)).

**Example 3: Binary endpoint with the beta priors**

This example is inspired by the example given in Johns and Andersen [20]. Consider a clinical trial to demonstrate that the relapse rate in patients treated in the experimental treatment arm is less than the control arm’s response rate. It was planned to enrol 340 patients in each arm. The interim analysis was planned after 170 patients in each arm completed treatment. Non-informative uniform priors were assumed for the two relapse rate: $\Pi_T \sim \text{Beta}(a_T = 1, b_T = 1)$ and $\Pi_C \sim \text{Beta}(a_C = 1, b_C = 1)$.

In this case, we are statistically testing the following hypotheses: $H_0 : \Pi_T - \Pi_C \leq 0$ against $H_1 : \Pi_T - \Pi_C > 0$. Suppose we observed following results at interim analysis: (a) in the treatment arm, 155 ($=n_T$) out of 170 patients responded with 13 ($=x_T$) subsequent relapses, and (b) in the control arm, 152 ($=n_C$) out of 169 patients responded with 21 ($=x_C$) subsequent relapses. Subsequently, additional 340 - 170 = 170 patients ($=N_T - n_T$) and 340 - 169 = 171 patients ($=N_C - n_C$) to be
enrolled in the treatment arm and control arm, respectively. With this information, the PPOS for trial success based on a Z test at one sided 0.025 level is 0.536 (see Eq. (4.14)).

Example 4: Time to event endpoint

Lassman et al. [23] recently reported the interim results of INTELLANCE-I trial on glioblastoma patients comparing investigational drug depatuxizumab mafoidotin. Total of 639 subjects (=N) was enrolled in the study with 1:1 allocation ratio. The primary endpoint in the study was overall survival. The target number of events at the final analysis was 441 (=D) and an interim analysis was planned with 332 events. The trial used a weighted log-rank test, however, here we illustrate assuming standard log-rank test. According to O’Brien alpha spending function, the rejection boundaries for the Z test (i.e., trend test) statistic are 2.34 and 2.012 (=c(1)) at interim and final analyses, respectively. For clinical success, we assume the clinically meaningful HR is 0.80 (=λ_{min}) or less.

In this case, we are statistically testing the following hypotheses: $H_0 : HR = 1$ against $H_1 : HR < 1$. Therefore, $λ_1 = 1$. The phase 2 trial of depatuxizumab mafoidotin on recurrent glioblastoma patients [24] reported HR for OS events as 0.71 (=λ_0) with 133 events (i.e., $σ_0 = 2/\sqrt{133} = 0.173$). Therefore, we consider the following prior distribution of $λ$

$$\log λ \sim \text{Normal}[\log 0.71, σ_0^2 = (0.173)^2]$$

As the treatment allocation ratio is 1:1, we have $r^2 = (1 + 1)/2 = 1$. Therefore, the PoS for trial success at the design stage is $Φ(\sqrt{441 \log (1/0.71) - (2)(2.34)} \sqrt{(441)(0.173)^2 + (2)^2}) = 0.728$ (see Eq. (4.21)). Further, the PoS for clinical success ($γ = -\log (0.80)/0.0952 = 2.344$) would be $Φ(\sqrt{441 \log (1/0.71) - (2)(2.344)} \sqrt{(441)(0.173)^2 + (2)^2}) = 0.727$

At the interim, let’s assume the estimated HR was 0.82 (=λ_{IA}) based on 346 events (=D_{IA}). Note that, $k = r/\sqrt{D} = 2/\sqrt{141} = 0.0952$. Assuming the expected HR from the post interim data as 0.75 (=λ') as assumed at the design stage, the conditional power for trial success ($γ = c(1) = 2.012$) and clinical success ($γ = -\log (0.80)/0.0952 = 2.344$) are 0.722 and 0.451, respectively (see Eq. (4.17)). However, if we assume that the interim trend continues to the remaining part of the trial, the conditional powers for trial success and clinical success are 0.561 and 0.288, respectively (see Eq. (4.18)). The PPOS for trial success and clinical success based on interim results only are 0.554 and 0.310, respectively (see Eq. (4.19)). Further, incorporating prior distribution, the PPOS for trial success and clinical success based on interim results are 0.625 and 0.370, respectively (see Eq. (4.20)).

6 Discussion

In this paper expressions for various measures of the probability of success are presented by type of endpoints. The discussion in this paper is restricted to the normal-normal and beta-binomial distributions. For other distributions, the relevant expressions can be obtained using the general framework presented in Section 2 or simulation based methods such as Bayesian clinical trial simulation (BCTS) [2, 16] may be used. Nevertheless, a natural question arises which probability of success measure one should prefer. Often PPOS is preferred over CP for following reasons: (1) these have
better predictive interpretation, (2) unlike frequentist counterpart, the knowledge on \( \theta \) (the parameter of interest) is used as distribution whereas in frequentist calculation we assume that the value of \( \theta \) is known without any uncertainty, and (3) unlike frequentist paradigm, the prior information can be incorporated in the Bayesian paradigm. In general, the CP is more aggressive than the PPoS and hence use of the CP increases the chance of early stopping for futility or efficacy. Lachin [8] has shown that futility termination may markedly decrease the power in direct proportion to the probability of stopping for futility. Therefore, PPoS seems to be more useful while monitoring a trial for early termination.

Effect of sample size on the PPoS compared to the CP was explored by Dallow and Fina [19]. On the other hand, the effect of varying prior distribution of \( \theta \) on predictive power in the context of futility monitoring is discussed by Dmitrienko and Wang [1], and in general by Rufibach, Burger and Abt [15]. In summary, they have proposed to use aggressive prior for futility monitoring as use of non-informative may increase the early termination rate. Tang [14] suggested using the upper limit of PPoS in futility monitoring. The effect of prior on PPoS in the context of the binomial endpoint is discussed by Johns and Andersen [20].

One might consider PPoCS in monitoring for early stopping as well; however, in general, its use should be discouraged. Saville et al. [2] have pointed out that the PPoS (referred as 'predictive probabilities') are naturally appealing for monitoring a clinical trial as (a) the PPoS directly addresses the question whether the study is going to be a success at the end, (b) and the PPoS often changes drastically with the accrual of more data whereas the PPoCS (referred as 'posterior probabilities') may remain nearly identical. Further, we also would like to point out the potential misuse of PPoS for survival endpoints with delayed treatment effects. In that case, the use of futility criteria for early stopping based on PPoS or CP may be misleading. In these cases, the futility criteria, if any, must be determined through exhaustive evaluation of operating characteristics.

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