A Bayesian Predictive Approach to Go/No-go Decision

K Jiang, C Fan, and Y Zheng

Abstract

Phase II go/no-go decisions are typically based on observed phase II data and statistics like p-values, mean differences, and associated confidence intervals. These statistics, however, can be ambiguous for decision making as they do not inform about the risks of failure or the success probability of the subsequent phase III trials. Probability of success (POS), which has grown in some popularity recently in biostatistics literature, is a more useful and possibly necessary statistics for facilitating a risk-informed decision making process. A Bayesian statistic, POS incorporates both the observed phase II trial data and the design parameters of the planned phase III trials. Jiang (2011) developed a POS function in a closed form for a simple two-parallel-group setting where response variables are normally distributed. In this paper, we extend the results to binary data and derive the POS function for response variables that follow a binomial distribution. Applications are shown in go/no-go decisions and portfolio management.

Key Words: Probability of success, Go/no-go decision, Sample Size, Bayesian, Due diligence, Portfolio management.

Correspondence to: Kaihong Jiang, Sanofi, 55C-315A, 55 Corporate Drive, Bridgewater, NJ 08807, U.S.A. Email: kaihong.jiang@sanofi.com

1. Introduction

In late-stage clinical development of new drugs, small phase II trials, often called proof-of-concept (POC) trial, are conducted first before embarking on phase III trials which are typically large in scale in terms of patient number, clinical operation and development expenditure. The purposes of the phase II trials are mainly for what so called phase II go/no-go decision, in which the drug developer decides, based on the phase II efficacy and safety data, whether to proceed to phase III or to stop and abandon the development. In practice end of phase II go/no-go decisions typically reply on data summary statistics that are observed in the phase II trials, such as p-values, observed effects, and their corresponding confidence intervals, etc. However, these statistics are often ambiguous for decision making as they do not directly inform about the risk of failure or probability of success of the subsequent phase III trials. Proper quantitative assessment of the probability of success (POS) is critical to the risk-informed decision making process.

POS has been studied since as early as 1980s, and has found applications in trial monitoring, designs, sample size determinations and go/no-go decisions. See Whitehead (1986) and Spiegelhalter and Freedman (1986). In a Bayesian framework, probability of success of a trial, P(*Success*), can be expressed as

$$\int_{\theta} P(Success \mid \theta)\pi(\theta)d\theta$$

where $\pi(\theta)$ is the prior distribution of θ - the parameter of interest, and the event "Success" can be defined in various ways, for example, rejection of a hypothesis. O'Hagan, Stevens and Campbell (2005) proposed a similar Bayesian approach based on what was called "assurance" or expected power. The two papers differed in the definition of the success event of interest. Chuang-Stein (2006) provided a numerical example demonstrating that the phase II trial sample sizes may affect the expected power or success probability, hence the sample size, of the phase III trial. Jiang (2011) developed the POS function in a closed form for a simple phase II-III program with normally distributed response variables, and showed its useful applications in go/no-go decisions,

optimal sample size determination for the phase II-III program, and sample size determination for phase II and III trials, respectively. In this paper, we derive the POS function for a binary response variable that follows binomial distribution.

2. *POS* function for normal data – a brief review

For a phase III trial testing the one-sided hypotheses

$$H_0: \theta=0 \text{ versus } H_a: \theta>0,$$

we call the trial a success if H_0 is rejected. Then, probability of success of the trial is simply the unconditional probability of rejecting the null hypothesis $P(Reject\ H_0)$. Since the power of the test is conditional probability $P(Reject\ H_0|\theta)$, if θ follows a prior distribution, we then have following relationship

$$POS = P(Reject\ H_0) = E\big(P(Reject\ H_0 \mid \theta)\big) = E(Power) \qquad (1)$$

where $E(\cdot)$ represents the expectation with respect to the prior distribution. Equation (1) states that POS is expected power. Obviously, power and POS are equivalent to one another only if θ is known with complete certainty which, however, never happens in reality. Let $X \sim N\left(\theta, 2\sigma^2/n\right)$, where θ represents true treatment difference or effect, σ is assumed known. Then, POS has following explicit form

$$POS = \Phi\left(\frac{-z_\alpha + (x_1^{II} - x_2^{II})\sqrt{n/2}/\sigma}{\sqrt{1+n/m}}\right) \qquad (2)$$

where $x_1^{II} - x_2^{II}$ is the observed mean difference between the two treatment groups from the phase II trial, σ^2 is known variance, and *m* and *n* denote the sample size per group for the phase II and III trials, respectively (Jiang 2011). The essence to POS function (2) is that the probability of success of the phase III trial can be evaluated based on the observed phase II data and the planned phase III sample size. As such, it offers a framework for go/no-go decision making in accordance to the evaluated POS: A large POS would suggest a go-decision whereas a small POS should render a no-go. The threshold in POS that divides go and no-go decisions was elaborated in Jiang 2011.

3. POS function for binary data

We consider a simple phase II/III program comprising a phase II exploratory trial and a subsequent phase III confirmatory trial in which a treatment is compared to a control. It is assumed that both trials share the same two-group (experiment and control) design and the same binary response variable, and that they are conducted in the same patient population. The two trials may differ only in sample size, denoted by *m* and *n* per treatment group for the phase II and III trials, respectively. Furthermore, suppose that the hypotheses of interest are

$$H_0 : p_1 - p_2 = 0 \text{ vs. } H_a : p_1 - p_2 > 0,$$

which are subject to significance testing in the phase III trial for which the test statistic is selected to be

$$Z = \frac{Y^{III}}{n} = \frac{X_1^{III} - X_2^{III}}{n}$$

and H_0 is rejected if $Z > z$, where z is some appropriately chosen critical value. In practice, either normal approximation test or exact test may be used for the significance testing. Since phase III sample size *n* is usually large which makes appropriate the use of normal approximation. For convenience, we use the critical value that is determined using normal approximation. Hence the POS function is written as

$$POS = \Pr\left(Y^{III} > z_\alpha \sqrt{n \times \left[p_1(1-p_1) + p_2(1-p_2)\right]}\right). \quad (3)$$

The aim of this section is to derive the POS function given observed phase II data (m, x_1, x_2) and the assumed prior function. The derivations generally follow three steps: First, posterior distributions are derived from the observed phase II data and the assumed prior distributions for the parameters of interest p_i at the phase II stage; Second, by taking the posteriors as the updated priors for the parameters of interest p_i at the phase III stage, i.e., those stipulated in the hypotheses of the phase III trial, one finds the joint distribution of (P, Y^{III}) which paves the way for the derivation of marginal distributions of $Y^{III} = X_1^{III} - X_2^{III}$; Finally, POS function is obtained by (3). Three approaches are taken including two slightly different exact approaches and a normal approximation approach. The two exact approaches differ in what the form of phase II data is used in the

derivation of posterior distribution – one uses the observed difference $x_1^{II} - x_2^{II}$, the other uses individual observation (x_1^{II}, x_2^{II}) without taking a difference.

3.1 Exact method 1

Let

$$X_i^{II} \mid p_i \sim Bin(m, p_i) \text{ and } X_i^{III} \mid p_i \sim Bin(n, p_i), \text{ for } i = 1,2.$$

where $Bin(k, p)$ represents the binomial distribution with sample size *k* and event rate *p*. It is also assumed that, at the phase II stage (prior to observing phase II data), the event rate follows a beta distribution, $P_i \sim Beta(\alpha_i, \beta_i)$, i=1, 2. This class of prior obviously includes the uninformative uniform distribution $U(0,1) = Beta(1,1)$ as a special case.

It is known that, if $X^{II} \mid P = p \sim Bin(m, p)$ and $P \sim Beta(\alpha, \beta)$, then the *posterior* distribution of P given $X^{II} = x^{II}$ is

$$P \mid X^{II} = x^{II} \sim Beta(\alpha + x^{II}, \beta + m - x^{II}). \quad (4)$$

Furthermore, it is also known that, if $X^{III} \mid P' = p' \sim Bin(n, p')$ and $P' \sim Beta(\alpha', \beta')$, then the *compound* distribution of X^{III} is a beta-binomial distribution,

$$\Pr(X^{III} = x^{III} \mid \alpha', \beta') = \binom{n}{x^{III}} \frac{B(\alpha' + x^{III}, \beta' + n - x^{III})}{B(\alpha', \beta')}. \quad (5)$$

Therefore, by replacing $\alpha' = \alpha + x^{II}$ and $\beta' = \beta + m - x^{II}$ in (5), we obtain the distribution of X^{III},

$$\Pr(X^{III} = x^{III} \mid x^{II}, m, \alpha, \beta) = \binom{n}{x^{III}} \frac{B(\alpha + x^{III} + x^{II}, \beta + n - x^{III} + m - x^{II})}{B(\alpha + x^{II}, \beta + m - x^{II})}. \quad (6)$$

Let (x_1, x_2) represent the phase II observed data, and (x, x_3) represent the values of unobserved phase III data (X_1^{III}, X_2^{III}). Notice that x_2 and x_3 represent the outcome values from the same treatment group of the phase II and III trials, respectively. From (6) and the assumed priors, we obtain the distribution of $Y^{III} = X_1^{III} - X_2^{III}$, as follows,

$$\begin{aligned}\Pr(Y^{III} = y^{III}) &= \Pr(X_1^{III} - X_2^{III} = y^{III}) \\ &= \sum_{x_3=0}^{n-y^{III}} \binom{n}{x_3 + y^{III}} \binom{n}{x_3} \frac{1}{B(\alpha_1 + x_1, \beta_1 + m - x_1) B(\alpha_2 + x_2, \beta_2 + m - x_2)} \\ &\quad \times B(\alpha_1 + x_3 + y^{III} + x_1, \beta_1 + n - x_3 - y^{III} + m - x_1) \\ &\quad \times B(\alpha_2 + x_3 + x_2, \beta_2 + n - x_3 + m - x_2). \end{aligned} \quad (7)$$

Finally, the POS function of the phase III trial given observed phase II data is obtained as

$$\begin{aligned}\text{POS} &= \Pr\left(Y^{III} > z_\alpha \sqrt{n \times \{p_1(1-p_1) + p_2(1-p_2)\}}\right) \\ &= \sum_{y=y_z}^{n} \Pr(Y^{III} = y) \end{aligned} \quad (8)$$

where $y_z = \left\lceil z_\alpha \sqrt{np_1(1-p_1) + np_2(1-p_2)} \right\rceil$ with $\lceil \cdot \rceil$ being the ceiling function.

3.2 Exact method 2

An alternative exact approach is to develop the posterior distribution first given the observed phase II data $(m, x_1^{II} - x_2^{II})$, then take it as the updated prior for the phase III trial and form the joint distribution of $Z = (X_1^{III} - X_2^{III})/n$ and the event rate *P*. From the joint distribution one can derive the marginal distribution of *Z*, and finally calculate the success probability $POS = P(Z > z)$. The detailed derivation using this approach is described in the Appendix below.

3.3 Normal approximation method

Using the normal distribution as an approximation of the binomial distribution of the response variables in both phase II and phase III trials, and from (2) above we obtain immediately

$$POS_{\text{Normal}} = \Phi\left(\frac{-z_\alpha + (p_1^{II} - p_2^{II}) \sqrt{n / \left(p_1^{II}(1-p_1^{II}) + p_2^{II}(1-p_2^{II})\right)}}{\sqrt{1 + n/m}} \right) \quad (9)$$

3.4 Comparison of three methods

To compare the three methods, we select four scenarios with p_1 = 0.2, 0.3, 0.4, 0.5 and p_2 = 0.2. Phase III sample size was fixed at n=100 while phase II sample size m varies from 10 to 100. For each combination of m, p_1, and p_2, POS are calculated using functions (8), (9) and (10). The results are summarized in Table 1 and the corresponding plots are shown in Figure 1. Overall, the two exact methods produce similar POS values. The POS values calculated using the normal approximation method are slightly larger than the exact methods when $m \leq 40$, and they can be larger by 9% when m=10.

3. Application

The derived POS functions can be used for Go/No-go decisions and Phase III trial sample size planning. Here we provide an example of practical applications.

Example. A Phase II/III program is planned targeting a 50% reduction of infection rate. For planning purpose, the developer assumes the infection rates are 0.4 and 0.2 for the control and the experimental treatment, respectively. With the assumptions, the development plan calls for a phase II trial with sample size m=75 patients per group (power=70%) and a phase III trial with sample size n=120 patients per group (power=90%). The phase II trial is conducted as planed, and the observed infection rates are 0.32 and 0.20 for the two groups respectively, or $(x_1^{II}, x_2^{II}) = (24,15)$. The p-value is 0.094. Using conventional frequentist approach, one may choose α=0.10 for phase II go/no-go decisions, and it would be a "go" in this case even though the observed reduction rate of 0.375 (=0.12/0.32) is smaller than targeted. The problem with the conventional approach is that one does not know the risk or the POS of the phase III trial, neither how much the phase III sample size n would impact on the risk. We first calculate the planned POS as reference value, POS(m=75, n=120, p_1=0.4, p_2=0.2)=0.82. (All calculations are done using (8) in this example.) With phase II observed data and planned phase III same size, we find POS(75, 120, 0.32, 0.2) = 0.54, which is much smaller than the planned POS of 0.82. The developer would hesitate to move forward. More calculations are done with increased phase III sample size: POS(75, 180, 0.32, 0.2) = 0.64, POS(75, 220, 0.32, 0.2) = 0.68. Clearly, the POS can be increased at the operational

expense of more patients, longer study duration as well larger expenditure. To a large degree, the go/no-go decision boils down to the level of risk one is willing to take, or the smallest POS value that is acceptable to the developer for a go-decision, and its balance to the operational load and considerations. It is noted that the threshold POS value for go/no-go decisions may vary across diseases or drug classes. For CNS and oncology drugs, the threshold value may be smaller than drugs in other disease areas.

Similarly, the proposed method is also applicable to problems encountered in due-diligence evaluations and portfolio management activities. For example, in comparing two or more drugs and deciding on which to license-in or keep in the development portfolio, it is useful to compare their respective success probabilities $POS(\hat{p}_1^{II}, \hat{p}_2^{II}, m, n)$, their expected returns $POS(\hat{p}_1^{II}, \hat{p}_2^{II}, m, n) \times R$ where R represents the financial return should the drug be approved and marketed, or their expected development cost adjusted returns $POS(\hat{p}_1^{II}, \hat{p}_2^{II}, m, n) \times (R - \cos t)$ or $POS(\hat{p}_1^{II}, \hat{p}_2^{II}, m, n) \times R / \cos t$.

4. Discussion

Sound decision making upon phase II data is crucial to drug development and pipeline portfolio management. Elias et al (2006) reported that 42% of 656 phase III trials conducted between 1990 and 2002 by larger pharmaceutical companies for small molecules failed, and that the number one root cause of the failures was “failure to demonstrate significant difference from placebo”. Based on its findings the article concluded that drug developers “should improve their decision making, especially in phase II”. It appears that trial statisticians in the pharmaceutical industry do not normally participate in the go/no-go decision process (which is certainly complex and often beyond the concerned trial data itself). This may be attributed to the misperception that all data and information about the risks of phase III trial failure are conveyed in the p-values, point estimates and confidence intervals – they are indeed not the right statistics to convey the risks in most situations, or the fact that there has not been a well accepted statistical method for the predicative risk assessment as required for decision making. It is

author's hope that the POS based approach will provide a useful tool to facilitate a quantitative risk assessment. It is also recommended that phase II data analyses include an assessment of the predicative probability of success of the planned phase III trial(s).

Appendix – An alternative exact method

A1. Posterior Distribution

First, we derive the posterior distribution of (P_1, P_2) given phase II data Y^{II}, or $\Pr(P_1 = p_1, P_2 = p_2 \mid Y^{II} = y^{II})$. To do so, we start with the derivation of the conditional distribution of Y^{II} given (P_1, P_2).

If $y^{II} \geq 0$,

$$\begin{aligned}
&\Pr(Y^{II} = y^{II} \mid P_1 = p_1, P_2 = p_2) \\
&\quad = \Pr(X_1^{II} - X_2^{II} = y^{II} \mid P_1 = p_1, P_2 = p_2) \\
&\quad = \sum_{x_2=0}^{m-y^{II}} \binom{m}{x_2 + y^{II}} p_1^{x_2+y^{II}} (1-p_1)^{m-x_2-y^{II}} \cdot \binom{m}{x_2} p_2^{x_2} (1-p_2)^{m-x_2}
\end{aligned}$$

Then we have the joint distribution,

$$\begin{aligned}
&\Pr(Y^{II} = y^{II}, P_1 = p_1, P_2 = p_2) \\
&\quad = \Pr(X_1^{II} - X_2^{II} = y^{II} \mid P_1 = p_1, P_2 = p_2) \Pr(P_1 = p_1, P_2 = p_2) \\
&\quad = \sum_{x_2=0}^{m-y^{II}} \binom{m}{x_2 + y^{II}} p_1^{x_2+y^{II}} (1-p_1)^{m-x_2-y^{II}} \cdot \binom{m}{x_2} p_2^{x_2} (1-p_2)^{m-x_2} \\
&\qquad \times \frac{p_1^{\alpha_1-1}(1-p_1)^{\beta_1-1}}{B(\alpha_1,\beta_1)} \cdot \frac{p_2^{\alpha_2-1}(1-p_2)^{\beta_2-1}}{B(\alpha_2,\beta_2)} \\
&\quad = \sum_{x_2=0}^{m-y^{II}} \binom{m}{x_2 + y^{II}} \binom{m}{x_2} \frac{1}{B(\alpha_1,\beta_1)B(\alpha_2,\beta_2)} \\
&\qquad \times p_1^{\alpha_1+x_2+y^{II}-1}(1-p_1)^{\beta_1+m-x_2-y^{II}-1} \cdot p_2^{\alpha_2+x_2-1}(1-p_2)^{\beta_2+m-x_2-1}
\end{aligned}$$

Hence, the marginal distribution is,

$$\begin{aligned}
&\Pr(Y^{II} = y^{II}) \\
&\quad = \int_{p_1=0}^{1} \int_{p_2=0}^{1} \Pr(Y^{II} = y^{II} \mid P_1 = p_1, P_2 = p_2) \Pr(P_1 = p_1, P_2 = p_2) dp_1 dp_2
\end{aligned}$$

$$= \sum_{x_2=0}^{m-y^{II}} \binom{m}{x_2+y^{II}} \binom{m}{x_2} \frac{B(\alpha_1 + x_2 + y^{II}, +\beta_1 + m - x_2 - y^{II}) B(\alpha_2 + x_2, \beta_2 + m - x_2)}{B(\alpha_1, \beta_1) B(\alpha_2, \beta_2)}$$

If $y^{II} < 0$, the lower and upper bound in summation $\sum_{x_2=0}^{m-y^{II}}$ need to be revised to $\sum_{x_2=-y^{II}}^{m}$. It is now straightforward to obtain the posterior distribution,

$$\Pr(P_1 = p_1, P_2 = p_2 \mid Y^{II} = y^{II}) = \frac{\Pr(Y^{II} = y^{II} \mid P_1 = p_1, P_2 = p_2) \Pr(P_1 = p_1, P_2 = p_2)}{\Pr(Y^{II} = y^{II})}$$

A2. Distribution of Y^{III}

Now consider the above posterior distribution as the phase II data updated prior for (P_1, P_2) of the phase III hypotheses. By going through similar derivation steps, we first obtain the joint distribution of (Y^{III}, P_1, P_2), from which we then derive the marginal distribution of Y^{III} by taking expectation over (P_1, P_2).

For $y^{III} \geq 0$,

$$\Pr(Y^{III} = y^{III} \mid P_1 = p_1, P_2 = p_2)$$

$$= \sum_{x_3=0}^{n-y^{III}} \binom{n}{x_3+y^{III}} p_1^{x_3+y^{III}} (1-p_1)^{n-x_3-y^{III}} \cdot \binom{n}{x_3} p_2^{x_3} (1-p_2)^{n-x_3}$$

Then, with the updated prior (9), the joint distribution of (Y^{III}, P_1, P_2) is

$$\Pr(Y^{III} = y^{III}, P_1 = p_1, P_2 = p_2)$$

$$= \frac{1}{\Pr(Y^{II} = y^{II})} \sum_{x_3=0}^{n-y^{III}} \sum_{x_2=0}^{m-y^{II}} \binom{n}{x_3+y^{III}} \binom{n}{x_3} \binom{m}{x_2+y^{II}} \binom{m}{x_2} \frac{1}{B(\alpha_1, \beta_1) B(\alpha_2, \beta_2)}$$
$$\times p_1^{\alpha_1 + x_3 + y^{III} + x_2 + y^{II} - 1} (1-p_1)^{\beta_1 + n - x_3 - y^{III} + m - x_2 - y^{II} - 1} \cdot p_2^{\alpha_2 + x_3 + x_2 - 1} (1-p_2)^{\beta_2 + n - x_3 + m - x_2 - 1}$$

Hence, the marginal distribution of Y^{III} is derived as follows.

For $y^{II} \geq 0$ and $y^{III} \geq 0$,

$$\Pr(Y^{III} = y^{III})$$

$$= \int_{p_1=0}^{1} \int_{p_2=0}^{1} \Pr(Y^{III} = y^{III} \mid P_1 = p_1, P_2 = p_2) \Pr(P_1 = p_1, P_2 = p_2 \mid Y^{II} = y^{II}) dp_1 dp_2$$

$$= \frac{1}{\Pr(Y^{II} = y^{II})} \sum_{x_3=0}^{n-y^{III}} \sum_{x_2=0}^{m-y^{II}} \binom{n}{x_3+y^{III}} \binom{n}{x_3} \binom{m}{x_2+y^{II}} \binom{m}{x_2} \frac{1}{B(\alpha_1, \beta_1) B(\alpha_2, \beta_2)}$$

$$\times B(\alpha_1 + x_3 + y^{III} + x_2 + y^{II}, \beta_1 + n - x_3 - y^{III} + m - x_2 - y^{II})$$
$$\times B(\alpha_2 + x_3 + x_2, \beta_2 + n - x_3 + m - x_2).$$

If $y^{III} < 0$, the lower and upper bound in summation $\sum_{x_3=0}^{n-y^{III}}$ need to be revised to $\sum_{x_3=-y^{III}}^{n}$. If $y^{II} < 0$, the lower and upper bound in summation $\sum_{x_2=0}^{m-y^{II}}$ need to be revised to $\sum_{x_2=-y^{II}}^{m}$.

A3. POS Function

Finally, the POS function of the phase III trial given observed phase II data is obtained as

$$\text{POS} = \Pr\left(Y^{III} > z_\alpha \sqrt{n \times \{p_1(1-p_1) + p_2(1-p_2)\}}\right)$$
$$= \sum_{y=y_z}^{n} \Pr(Y^{III} = y) \qquad (10)$$

where $y_z = \left| z_\alpha \sqrt{np_1(1-p_1) + np_2(1-p_2)} \right|$ with $\lceil \cdot \rceil$ being the integer-ceiling function.

References

1. Whitehead J. (1986), "Sample sizes for phase II and phase III clinical trials: an integrated approach," Statistics in Medicine, 5, 459–464.
2. Spiegelhalter DJ, Freedman LS. (1986) "A predictive approach to selecting the size of a clinical trial, based on subjective clinical opinion," Statistics in Medicine, 5, 1–13.
3. Stallard N, Whitehead J and Cleall S. (2005), "Decision-making in a phase II clinical trial: a new approach combining Bayesian and frequentist concepts. Pharmaceutical Statistics 4: 119–128.
4. O'Hagan A, Stevens JW, Campbell MJ. (2005), "Assurance in clinical trial design," Pharmaceutical Statistics, 4, 187–201.
5. Chuang-Stein C. (2006), "Sample size and the probability of a successful trial," Pharmaceutical Statistics, 5, 305–309.
6. Jiang K. (2011), "Optimal sample sizes and Go/No-go decisions for phase II/III development programs based on probability of success," Statistics in Biopharmaceutical Research, 3, 463-475.

Table 1. A comparison of three POS calculation methods

(Phase III sample size *n*=100)

		$m =$									
(p_1, p_2)		10	20	30	40	50	60	70	80	90	100
(0.5, 0.2)	Normal	0.7944	0.8671	0.9048	0.9274	0.9422	0.9524	0.9598	0.9654	0.9696	0.9730
	Binomial (Sep)	0.7423	0.8360	0.8834	0.9116	0.9299	0.9425	0.9516	0.9585	0.9637	0.9678
	Binomial	0.7546	0.8513	0.8976	0.9240	0.9407	0.9519	0.9599	0.9658	0.9703	0.9738
(0.4, 0.2)	Normal	0.6415	0.6882	0.7182	0.7398	0.7562	0.7692	0.7798	0.7886	0.7960	0.8024
	Binomial (Sep)	0.5901	0.6518	0.6891	0.7151	0.7346	0.7499	0.7622	0.7724	0.7810	0.7883
	Binomial	0.5916	0.6591	0.6991	0.7267	0.7471	0.7630	0.7756	0.7861	0.7948	0.8022
(0.3, 0.2)	Normal	0.4621	0.4487	0.4397	0.4329	0.4276	0.4233	0.4197	0.4166	0.4139	0.4116
	Binomial (Sep)	0.4344	0.4347	0.4330	0.4310	0.4291	0.4274	0.4259	0.4245	0.4233	0.4222
	Binomial	0.4235	0.4250	0.4238	0.4221	0.4204	0.4188	0.4173	0.4160	0.4149	0.4138
(0.2, 0.2)	Normal	0.2773	0.2118	0.1732	0.1474	0.1289	0.1150	0.1043	0.0957	0.0887	0.0829
	Binomial (Sep)	0.2577	0.1972	0.1609	0.1364	0.1189	0.1057	0.0954	0.0873	0.0806	0.0751
	Binomial	0.2406	0.1845	0.1520	0.1305	0.1152	0.1037	0.0948	0.0877	0.0819	0.0771

Normal = Normal approximation method
Binomial (Sep) = Exact method 1
Binomial = Exact method 2

Figure 1: POS calculation using Normal Approximation and Exact methods