1 Introduction

One of the most popular measure of effects for continuous data is percent change from baseline \((PC)\) in a clinical trial, however it is said that \(PC\) may skew empirically. Thus, some tests in the framework of nonparametric methodology, such as Wilcoxon rank sum test will be applied for two group comparison. In this paper, we investigate the factors that affect the skewness of two measure of effects, which are \(PC\) and symmetrized percent change \((SPC)\) (Berry, 1989: Berry and Ayers, 2006: Goto et. al, 2007), and also evaluate the factors that affect the power. First, we investigate the relationship between distribution of skewness for two measure of effects and parameters of pre- and post-data based on bivariate power normal distribution \((BPND)\), and identify the factors that affect the distribution of skewness. Second, we evaluate the relationship between the factors and power for two group comparison quantitatively.

In Section 2, we introduce the BPND for pre- and post-data, and define the parameters for evaluation of skewness based on a percentile. In Section 3, we evaluate the relationship between the skewness of \(PC/SPC\) and the parameters of pre- and post-data. In Section 4, we calculate the power for two treatment group comparisons in each shape of distribution based on the simulation and evaluate the relationship between skewness and power. Finally, we summarize our findings in section 5.
2 Bivariate Power Normal Distribution (BPND)

In this section, we introduce the BPND to apply the pre- and post-data and show the identification of parameters for pre- and post-data. In addition, we define the index to evaluate the skewness of measure of effects based on the percentile.

2.1 BPND for pre-and post-data

Let $X_j (j = 1, 2)$ be the positive random variable and power transformation of $X_j$ is defined as,

$$X_j^{(\lambda_j)} = \begin{cases} \frac{X_j^{\lambda_j} - 1}{\lambda_j} & \lambda_j \neq 0 \\ \log X_j & \lambda_j = 0 \end{cases}$$

where $\lambda_j$ is the transforming parameter (Box and Cox, 1964). The ranges for the power transformed variable $X_j^{(\lambda)}$ are $-1/\lambda_j < X_j^{(\lambda)} < +\infty$ for $\lambda_j > 0$ and $-\infty < X_j^{(\lambda)} < -1/\lambda_j$ for $\lambda_j < 0$.

The distribution of $(X_1^{(\lambda_1)}, X_2^{(\lambda_2)})$ is based on the truncated bivariate normal distribution with mean vector $\mu = (\mu_1, \mu_2)^T$ and variance covariance matrix

$$\Sigma = \begin{bmatrix} \sigma_1^2 & \rho \sigma_1 \sigma_2 \\ \rho \sigma_1 \sigma_2 & \sigma_2^2 \end{bmatrix}$$

where $\rho$ is the correlation coefficient between $X_1^{(\lambda_1)}$ and $X_2^{(\lambda_2)}$ (association parameter). Then, two observed values, $(X_1, X_2)$, are based on the bivariate power normal distribution and the joint pff is as (Goto and Hamasaki, 2002),

$$g(x_1, x_2) = \frac{x_1^{\lambda_1 - 1} x_2^{\lambda_2 - 1}}{A(\mathbf{K})} f\left(\left(x_1^{(\lambda_1)}, x_2^{(\lambda_2)}\right)\right), \quad x_1, x_2 > 0$$

where

$$f\left(\left(x_1^{(\lambda_1)}, x_2^{(\lambda_2)}\right)\right) = \frac{1}{2\pi \sigma_1 \sigma_2 \sqrt{1 - \rho^2}} \exp \left\{ -\frac{Q(x_1^{(\lambda_1)}, x_2^{(\lambda_2)})}{2} \right\}$$

and

$$Q(x_1^{(\lambda_1)}, x_2^{(\lambda_2)}) = \frac{1}{1 - \rho^2} \times \left\{ \left(\frac{x_1^{(\lambda_1)} - \mu_1}{\sigma_1}\right)^2 - 2\rho \left(\frac{x_1^{(\lambda_1)} - \mu_1}{\sigma_1}\right) \left(\frac{x_2^{(\lambda_2)} - \mu_2}{\sigma_2}\right) + \left(\frac{x_2^{(\lambda_2)} - \mu_2}{\sigma_2}\right)^2 \right\}.$$ 

$A(\mathbf{K})$ is the probability proportional constant term given by

$$A(\mathbf{K}) = \int_{a_2}^{b_2} \int_{a_1}^{b_1} \phi_2(x_1, x_2 : \rho) \, dx_1 \, dx_2$$

where $\phi_2(x_1, x_2 : \rho)$ is the joint pdf of the BPND and $\mathbf{K}$ is $(k_1, k_2)^T$. When $k_j (j = 1, 2)$ is said to the standardized truncation point and is defined as $k_j = (\lambda_j \mu_j + 1)/(\lambda_j \sigma_j)$, $a_j$ and $b_j$ are given as follows. First, when $\lambda_j > 0$, $a_j = -k_j$ and $b_j = -\infty$. Second, when $\lambda_j = 0$, $a_j = -\infty$ and $b_j = \infty$. And, third, when $\lambda_j < 0$, $a_j = -\infty$ and $b_j = -k_j$.

The BPND is identified by four kind of parameters, which are shape($\lambda_j$), location($\mu_j$), scale($\sigma_j$) and association($\rho$) parameters. Especially, we can obtain various distributions with different shape associated $\lambda_j$. For example, a distribution is the normal, square-root transformed normal and lognormal distributions associated with $\lambda_j$ of 1, 0.5 and 0, correspondingly. The power normal distribution can be fitted to real data including the various shape of distribution, thus we can use the traditional statistical approach based on the normal distribution more easily and widely.
2.2 Identification of parameters for pre- and post-data

It is difficult to interpret the properties of distribution for observed response based on the transformed parameters. Thus, we define the distributions based on the three parameters which are median ($\xi_{0.5}$) and variation of distribution ($\tau$) and $\lambda$ in this paper. $\tau$ is defined as,

$$\tau = \frac{\xi_{0.75} - \xi_{0.25}}{\xi_{0.5}}.$$ 

The 100p percentile ($\xi_p$) of the power normal distribution is given by

$$\xi_p = \begin{cases} 
\{\lambda(\mu + \sigma z_p) + 1\}^{1/\lambda}, & \lambda \neq 0 \\
\exp(\mu + \sigma z_p), & \lambda = 0
\end{cases}$$

where $z_p$ and $z_{p^*}$ are the percentile of 100p and 100$p^*$ for standard normal distribution respectively (Maruo and Goto, 2008). In addition, the combination of three parameters, ($\lambda, \xi_{0.5}, \tau$) is connected with ($\mu, \sigma, K$) by using the grid research and the following two equations, and Maruo and Goto (2008) have called this approach as reparametrization method.

$$\mu = \left(1 + \frac{z_{0.5\sigma}}{K}\right)^{-1} \times \left(\frac{\xi_{0.5\lambda} - 1}{\lambda - z_{0.5\sigma}/(\lambda K)}\right), \quad \sigma = \frac{1 + \lambda\mu}{\lambda K}$$

2.3 Index for evaluation of skewness

In the power normal distribution, some summary statistics such as skewness may not be able to be calculated when $\lambda$ is less than 0, because more than p-ordered moment do not exist. To overcome this problem, we define the variation of skewness ($\eta$) based on the percentile as follows

$$\eta = \frac{\xi_{0.975} - \xi_{0.5}}{\xi_{0.5} - \xi_{0.025}}.$$ 

The distribution of measures of effect is symmetry, when $\eta$ is equal to 1. Thus, the distribution has positively skew (or negatively skew) when $\eta$ is larger (or less) than 1.

3 Statistical Properties for SPC and PC

In this section, we evaluate the skewness of distribution for PC and SPC to use the $\eta$. Pre- ($X_1$) and post-data ($X_2$) are assumed as BPND to evaluate the various distribution. We set the following conditions about parameters of BPND, and identify the distribution based on the combination of parameters.

- We consider that pre- and post-data are positively skewed distribution, and shape parameter ($\lambda_j, j = 1, 2$) set from -1 to 1 by 0.5.
- Shape parameters of pre- and post-data are same ($\lambda = \lambda_1 = \lambda_2$).
- Scale parameters of pre- and post-data are same ($\sigma = \sigma_1 = \sigma_2$).
- Median ($\xi_{0.5}$) of pre-data is 100 and median ($\xi_{0.5}$) of post-data is 10% reduction from pre-value, which is 90.
- Variation of distribution ($\tau_1$) for pre-data is from 0.2 to 0.8 by 0.2.
- Association parameter ($\rho$) between pre- and post-data is 0.4 and 0.8.
After identifying three parameters of pre-data, which are median ($\xi_0$), variation and distribution ($\tau_1$), and shape ($\lambda_1$) parameters, we transformed three parameters, location ($\mu_1$), scale ($\sigma_1$) and $K$ are calculated from these parameters by using reparametrization method. And, we set $\sigma_2$ of post-data, and set the association parameter ($\rho$). Then, we calculate the percentile of $PC$ and $SPC$ by using the Monte-Carlo integration, and also calculate the skewness of distribution ($\eta$).

![Graph](image)

**Figure 1:** Relationship between $\lambda$ of pre-post data and $\eta$ of measure of effects (post-data is 10 percent reduction)

The relationship between $\lambda$ and $\eta$ are shown in Fig. 1 to investigate the shape of distribution for $PC$ and $SPC$. The $\eta$ of $PC$ increased with increasing $\tau_1$ and without depending on $\lambda$ until $\tau_1$ is 0.4. However, the $\eta$ of $PC$ is more increased in -1 or +1 of $\lambda$ when $\tau_1$ is more than 0.4. In addition, $\eta$ of $PC$ increased with $\rho$ decreasing. The reason to skew the distribution is as follows in case that $\tau_1$ increases or $\rho$ decreases, (1) when $\lambda$ is -1, the maximum of observed post-data increases because of positively skewed distribution, and (2) when $\lambda$ is +1, the pre-value near 0 increase because
this distribution is truncated normal distribution. On the other hand, η of SPC is almost 1, and is not depend on λ, ρ and τ₁.

4 Simulation

Objective : Generally, the distribution is assumed as normal, when the statistical tests on the parametric framework are applied. However, real data may differ from normal. In this simulation, the power of PC and SPC are calculated in various shape of distribution based on t-test. The difference of the power normal transformed value for pre- and post-data is approximately normal, and we compare the power between the difference based on the power transformed pre- and post-data and two measure of effects (PC and SPC). Then, we evaluate the loss of information which is impact to power between normal and other distributions. In addition, Wilcoxon rank sum test is included as reference in this simulation.

Design and results : We consider clinical trials with continuous endpoint to compare treatment and reference group. The pre- and post-data are collected, and reduction of post-data means the effect. The distributions of pre- and post-data about treatment and reference groups are assumed as BPND, and λ sets from -1 to +1 by 0.5. The ξ₀.₅ of pre- and post-data for reference group sets as 100. The ξ₀.₅ of pre-data for treatment group set 100, and the ξ₀.₅ of post-data for treatment group sets 90 (10 % reduction from pre-data). The τ of pre-data of both groups sets 0.2, 0.4 and 0.8. Post-data sets same scale parameter (σ) as pre-data. And the ρ sets 0.8. Sample size sets to keep 0.8 of power for t-test about the difference of power normal transformed pre- and post-data. Number of simulation is 50000 times and we calculated the power and type I error, which are defined as the proportion of the number of significance per simulation number, when t-test is applied. Null hypothesis is defined as ”true mean of treatment group is equal to reference group”, and alternative hypothesis is defined as ”true mean of treatment group is not equal to reference group”. Power and type I error are also calculated on Wilcoxon rank sum test.

First, the relationship between λ and type I error were shown in Fig. 2. All simulations kept 0.05 about type I error. Next, the relationship between λ and power were also shown in Fig. 2, and our findings are, (1) the power was almost same in all λ when τ₁=0.2, (2) when τ₁=0.3, power was almost same in all methods from λ= -1 to 0.5, and was Diff(t) = SPC(t) = PC(w) > PC(t) in λ=1. and (3) power was Diff(t) > PC(w) ≈ SPC(t) > PC(t) in all λ, when τ₁=0.8.

5 Conclusion Remarks

We investigated the factors that affect the skewness of two measure of effects (PC and SPC), and also evaluated the factors that affect the power. Then we summarized the findings obtained by our investigations and simulations as follows:

The η of PC increased with increasing τ₁ and without depending on λ until τ became 0.4. However, the η of PC was more increased in -1 or +1 of λ, when τ was more than 0.4. In addition, η of PC increased with ρ decreasing. The reason to skew the distribution is as follows in case that τ₁ increases or ρ decreases. When λ is -1, the maximum value of observed post-data increases because of positively skewed distribution. When λ is +1, the pre-value near 0 increases because this distribution is truncated normal distribution. On the other hand, η of SPC is almost 1, and dose not depend on λ, ρ and τ₁.

The power is almost all the same in all λ when τ₁=0.2. When τ₁=0.4, power is almost the same in all methods from λ= -1 to 0.5, and is Diff(t) = PC(w) ≈ SPC(t) > PC(t) in λ=1. Power is Diff(t) > SPC(t) = PC(w) > PC(t) in all λ, when τ=0.8.
Figure 2: Relationship between $\lambda$ and type I error or between $\lambda$ and Power

References


