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Comparison of Two One-Sided Test and Confidence Interval Approach in Bioequivalence and Biosimilar Studies

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Abstract

When a drug (biological) product is going off patent protection, a pharmaceutical/biotech company usually files a regulatory submission for generic (biosimilar) approval. For the approval of a generic drug (biosimilar product), the United States Food and Drug Administration (FDA) requires a bioequivalence study (biosimilar studies) to be conducted for bioequivalence (biosimilarity) assessment, demonstrating that the generic drug (biosimilar product) is bioequivalent (biosimilar) to the innovative drug product. For bioequivalence (biosimilarity) assessment, a two one-sided tests (TOST) procedure or a confidence interval (CI) approach is commonly used. However, although TOST is operationally equivalent to the CI approach, TOST is not generally equivalent to the CI approach. For example, when the study endpoint is a binary response, both the sample size estimation procedure and the result of bioequivalence test may be different. In this article, a comparison between the method of TOST and the CI approach in terms of true positive rate and sample size was made theoretically. The confusion matrix is also provided to show that TOST and CI approach may give different result when the outcome variable is binary.

Keywords: Bioequivalence; Biosimilarity; TOST; 90% CI approach; Sample size

Introduction

When a drug or a biological product is going off patent protection, a pharmaceutical or biotech company usually files a regulatory submission for generic or biosimilar approval. For the approval a generic drug or a biosimilar product, the United States Food and Drug Administration (FDA) requires a bioequivalence study or biosimilar study to be conducted for bioequivalence or biosimilarity assessment, which can be used to demonstrate that the generic drug or the biosimilar product is bioequivalent or biosimilar to the innovative reference product, respectively [1,2]. In the regulatory evaluation and approval process for generic or biosimilar product, a two one-sided tests (TOST) procedure or a confidence interval (CI) approach is commonly used [3]. While testing for bioequivalence between the test (e.g., a generic drug or a biosimilar product) and the innovative (reference) product, the following interval hypotheses is usually considered

$$H_0: \text{Not bioequivalent vs.} H_A: \text{Bioequivalent.} \quad (1)$$

Under the above interval hypotheses, many researchers misinterpret that the significance level of TOST is 2α. Thus, it is equivalent to $(1-2\alpha)\times 100\%$ CI. However, Chow and Shao [4] showed that TOST for testing hypotheses (1) is in fact an *α-level* test. Although Chow and Liu [5] indicated that the method of TOST at the 5% significance level at each side is *operationally* equivalent to the 90% CI approach, TOST is not equivalent to the 90% CI in general. A typical example is one that when the study endpoint is a binary response, these two types of procedures are not operationally equivalent. In practice, TOST and CI approach are often mix-up used in bioequivalence/biosimilarity assessment under the assumption that TOST and CI approach are *operationally* identical.

In bioequivalence and/or biosimilar studies, researchers usually start with sample size determination based on TOST procedure but end up drawing conclusion using CI approach. This process is problematic because TOST and CI approach have different statistical meanings, though sometimes may give us the same results. As shown in Table 1, TOST and CI approach are different in terms of hypothesis settings, true positive rate, sample size estimation, and etc.; and they also share some common features.

The purpose of this article is to study the difference between TOST and the CI approach in bioequivalence assessment for generic drugs or biosimilarity assessment for biosimilar products. In the next section, statistical properties of TOST when the study endpoint is either continuous or binary are examined.

Section 3 provides the statistical properties of the CI approach for continuous and binary responses. Section 4 compares TOST and the CI approach in terms of the inconsistencies of true positive rate and required sample size ensuring a desired true positive rate, when concluding bioequivalence or biosimilarity. Some concluding remarks are given in the last section of this article.

Table 1. Comparison of two one-sided test and confidence interval approach testing for bioequivalence.

		Two one-sided test (TOST)	Confidence interval (CI) approach
Difference	Hypothesis (H_A)	μ_T-μ_R is greater/smaller than the pre-determined lower/upper bound (test separately).	The CI of μ_T-μ_R is included of a certain interval.
	Standard error	Make use of pooled proportion, for binary outcome.	Without using pooled proportion, for binary outcome.
	True positive rate	Statistical power.	The probability of the estimated CI within a certain interval, given that the true mean difference is within that interval.
	Sample size calculation	Target on statistical power (Chow et al, 2017).	Target on validity (Jiroutek et al., 2003).
Similarity	TOST and CI approach can be used to test for bioequivalence. (1-2α)% confidence interval is the same as the α level TOST, if the significance level = test size (Chow and Shao, 2002). TOST and CI approach are operationally equivalent for continuous outcome variable (Schuirmann, 1987).		

Two One-Sided Tests (TOST)

For simplicity and illustration purpose, the significance level α of two one-sided tests (TOST) is assumed to be the same as the test size, and the sample size for the test drug group and reference drug group are assumed to be the same, denote as n. In this section, we illustrate the statistical properties of TOST when the outcome variable is either continuous or binary, specifically, the outcome variable is assumed follow normal or Bernoulli distribution.

TOST with Continuous Outcome Variable

Let $X_1^T,...,X_n^T$ denote samples from the test group, following $N(\mu_T,\sigma_T^2)$; and let $X_1^R,\ldots,X_n^R$ denote samples from the reference group, following $N(\mu_R,\sigma_R^2)$. The sample mean of test and reference groups are $\bar{X}_T$ and $\bar{X}_R$; and the sample variance of test and reference groups are S_T^2 and S_R^2. Thus, hypotheses shown in Equation (1) can be written as

$$H_0: \mu_T - \mu_R \le \theta_L \text{ or } \mu_T - \mu_R \ge \theta_U \; vs. H_A: \theta_L < \mu_T - \mu_R < \theta_U, \tag{2}$$

where θ_L and θ_U are the lower and upper bound of equivalence test. To test for bioequivalence between the test and reference drugs, the hypotheses of TOST can be written as [6]

$$H_{01}: \mu_T - \mu_R \le \theta_L \; vs. H_{A1}: \mu_T - \mu_R > \theta_L, \tag{3}$$

and

$$H_{02}: \mu_T - \mu_R \ge \theta_U \; vs. H_{A2}: \mu_T - \mu_R < \theta_U. \tag{4}$$

Since hypotheses testing shown Equation (3) and (4) are typical one-sided test, typical two-sample t test can be used. Assuming the variance of the test and reference group are equal, then the t test statistics for hypothesis tests in Equation (3) and (4) are

$$T_1 = \frac{(\bar{X}_T - \bar{X}_R) - \theta_L}{s_p\sqrt{2/n}} \sim t\big(2(n-1)\big) \text{ and } T_2 = \frac{(\bar{X}_T - \bar{X}_R) - \theta_U}{s_p\sqrt{2/n}} \sim t\big(2(n-1)\big), \tag{5}$$

and

$$s_p^2 = \frac{(n-1)s_T^2 + (n-1)s_R^2}{2(n-1)} = \frac{s_T^2 + s_R^2}{2}.$$

Then we may compare T_1 and T_2 with the critical value of t distribution to determine whether we should reject null hypothesis shown in Equation (3) and (4). We only reject null hypothesis shown in Equation (2), i.e., accept that the test and reference drug are bioequivalence if and only if

$$T_1 > t_{1-\alpha}\big(2(n-1)\big) \text{ and } T_2 < t_\alpha\big(2(n-1)\big). \tag{6}$$

Let p be the power of the TOST, which can be written as

$$\begin{aligned}
p &= P(T_1 > t_{1-\alpha} \text{ and } T_2 < t_\alpha \,|\mu_T - \mu_R = \theta_0) \\
&= P\left(\frac{(\bar{X}_T - \bar{X}_R) - \theta_L}{s_p\sqrt{2/n}} > t_{1-\alpha} \text{ and } \frac{(\bar{X}_T - \bar{X}_R) - \theta_U}{s_p\sqrt{2/n}} < t_\alpha \middle| \mu_T - \mu_R = \theta_0\right) \\
&= P\left(\bar{X}_T - \bar{X}_R > t_{1-\alpha} \times s_p\sqrt{2/n} + \theta_L \text{ and } \bar{X}_T - \bar{X}_R < t_\alpha \times s_p\sqrt{2/n} + \theta_U \middle| \mu_T - \mu_R = \theta_0\right) \\
&= P\left(\frac{\bar{X}_T - \bar{X}_R - \theta_0}{s_p\sqrt{2/n}} > t_{1-\alpha} + \frac{\theta_L - \theta_0}{s_p\sqrt{2/n}} \text{ and } \frac{\bar{X}_T - \bar{X}_R - \theta_0}{s_p\sqrt{2/n}} < t_\alpha + \frac{\theta_U - \theta_0}{s_p\sqrt{2/n}}\right) \\
&= P\left(t_{1-\alpha} + \frac{\theta_L - \theta_0}{s_p\sqrt{2/n}} < \frac{\bar{X}_T - \bar{X}_R - \theta_0}{s_p\sqrt{2/n}} < t_\alpha + \frac{\theta_U - \theta_0}{s_p\sqrt{2/n}}\right) \\
&= P\left(t_{1-\alpha} + \frac{\theta_L - \theta_0}{s_p\sqrt{2/n}} < \frac{\bar{X}_T - \bar{X}_R - \theta_0}{s_p\sqrt{2/n}} < -t_{1-\alpha} + \frac{\theta_U - \theta_0}{s_p\sqrt{2/n}}\right) \\
&:= F_T\left(\frac{\theta_U - \theta_0}{s_p\sqrt{2/n}} - t_{1-\alpha}\right) - F_T\left(\frac{\theta_L - \theta_0}{s_p\sqrt{2/n}} + t_{1-\alpha}\right),
\end{aligned} \tag{7}$$

where θ_0 is the true difference between μ_T and μ_R, $\frac{\bar{X}_T - \bar{X}_R - \theta_0}{s_p\sqrt{2/n}}$ distribution with degree of freedom as $2(n\text{-}1)$, t_q represents the q percentile of t distribution, and $F_T(\cdot)$ is the CDF of t distribution with degree of freedom $2(n\text{-}1)$.

TOST with Binary Outcome Variable

When the outcome variable is binary, assume the test group follows $Bern(p_T)$ and the reference group follows $Bern(p_R)$. The hypotheses for TOST can be written as

$$H_{01}: p_T - p_R \le \theta_L \; vs. H_{A1}: p_T - p_R > \theta_L, \tag{8}$$

and

$$H_{02}: p_T - p_R \ge \theta_U \; vs. H_{A2}: p_T - p_R < \theta_U. \tag{9}$$

Under null hypothesis, assuming $\hat{p}_T$ - $\hat{p}_R$follows approximately normal distribution with mean 0 and variance $\frac{2}{n}p^*(1-p^*)$, where

$$p^* = \frac{n\hat{p}_T + n\hat{p}_R}{2n} = \frac{\hat{p}_T + \hat{p}_R}{2}.$$

Under null hypothesis shown in Equations (8) and (9), typical Z test statistic, using pooled proportion is:

$$Z_1 = \frac{\hat{p}_T - \hat{p}_R - \theta_L}{\sqrt{\frac{2}{n}p^*(1-p^*)}} \sim N(0,1) \text{ and } Z_2 = \frac{\hat{p}_T - \hat{p}_R - \theta_U}{\sqrt{\frac{2}{n}p^*(1-p^*)}} \sim N(0,1). \quad (10)$$

The power of TOST with binary outcome variable is

$$\begin{aligned} p &= P(Z_1 > z_{1-\alpha} \text{ and } Z_2 < z_\alpha \,|p_T - p_R = \theta_0) \\ &= P\left(\frac{\hat{p}_T - \hat{p}_R - \theta_L}{\sqrt{\frac{2}{n}p^*(1-p^*)}} > z_{1-\alpha} \text{ and } \frac{\hat{p}_T - \hat{p}_R - \theta_U}{\sqrt{\frac{2}{n}p^*(1-p^*)}} < z_\alpha \middle| p_T - p_R = \theta_0\right) \\ &= P\left(\hat{p}_T - \hat{p}_R > \theta_L + z_{1-\alpha}\sqrt{\tfrac{2}{n}p^*(1-p^*)} \text{ and } \hat{p}_T - \hat{p}_R < \theta_U + z_\alpha\sqrt{\tfrac{2}{n}p^*(1-p^*)} \middle| p_T - p_R = \theta_0\right) \\ &= P\left(\frac{\theta_L - \theta_0}{\sqrt{\frac{2}{n}p^*(1-p^*)}} + z_{1-\alpha} < \frac{\hat{p}_T - \hat{p}_R - \theta_0}{\sqrt{\frac{2}{n}p^*(1-p^*)}} < \frac{\theta_U - \theta_0}{\sqrt{\frac{2}{n}p^*(1-p^*)}} + z_{1-\alpha}\right) \\ &\coloneqq \Phi\left(\frac{\theta_U - \theta_0}{\sqrt{\frac{2}{n}p^*(1-p^*)}} - z_{1-\alpha}\right) - \Phi\left(\frac{\theta_L - \theta_0}{\sqrt{\frac{2}{n}p^*(1-p^*)}} + z_{1-\alpha}\right). \end{aligned} \quad (11)$$

where $\Phi(\cdot)$ is the CDF of N(0,1), and z_q is the q percentile of $N(0,1)$.

Confidence Interval (CI) Approach

In addition to the two one-sided tests (TOST), another typical approach of bioequivalence test is the confidence interval (CI) approach. Assume θ is the statistic of interest, and its confidence interval is C. Let θ_L and θ_U denote the lower and upper bound of bioequivalence. If $C \cap \Theta_0 = \emptyset$ where Θ_0=Ω-(θ_L, θ_U), then we may conclude bioequivalence [4]. In addition, we should be aware that CI approach is not a hypothesis testing approach, i.e., its sample size estimation approach is different from the one of TOST, and CI approach does not have statistical power, but true positive rate. The true positive rate of CI approach can be derived as

$$p = P(C \cap \Theta_0 = \emptyset \,|\text{true mean difference is } \theta_0 \in (\theta_L, \theta_U)). \quad (12)$$

CI Approach with Continuous Outcome Variable

Let X_i^T and X_i^R (i=1,…,n) denote the samples from test and reference group, following $N(\mu_T, \sigma_T^2)$ and $N(\mu_R, \sigma_R^2)$ Random variable $\frac{\bar{X}_T - \bar{X}_R - (\mu_T - \mu_R)}{s_p\sqrt{2/n}}$ follows t distribution. The (1-2α)% confidence interval for μ_T- μ_R can be written as

$$(\bar{X}_T - \bar{X}_R) \pm t_{1-\alpha} s_p \sqrt{2/n}. \quad (13)$$

The true positive rate of CI approach can be computed as

$$\begin{aligned} p &= P(C \cap \Theta_0 = \emptyset \,|\text{true } \theta \in (\theta_L, \theta_U)) \\ &= P\left((\bar{X}_T - \bar{X}_R) + t_{1-\alpha}s_p\sqrt{2/n} < \theta_U \text{ and } (\bar{X}_T - \bar{X}_R) - t_{1-\alpha}s_p\sqrt{2/n} > \theta_L \middle| \mu_T - \mu_R = \theta_0\right) \\ &= P\left(\bar{X}_T - \bar{X}_R < \theta_U - t_{1-\alpha}s_p\sqrt{2/n} \text{ and } \bar{X}_T - \bar{X}_R > \theta_L + t_{1-\alpha}s_p\sqrt{2/n} \middle| \mu_T - \mu_R = \theta_0\right) \\ &= P\left(\frac{\theta_L - \theta_0}{s_p\sqrt{2/n}} + t_{1-\alpha} < \frac{\bar{X}_T - \bar{X}_R - \theta_0}{s_p\sqrt{2/n}} < \frac{\theta_U - \theta_0}{s_p\sqrt{2/n}} - t_{1-\alpha}\right) \\ &\coloneqq F_T\left(\frac{\theta_U - \theta_0}{s_p\sqrt{2/n}} - t_{1-\alpha}\right) - F_T\left(\frac{\theta_L - \theta_0}{s_p\sqrt{2/n}} + t_{1-\alpha}\right). \end{aligned} \quad (14)$$

CI Approach with Binary Outcome Variable

When the outcome variable is binary, the (1-2α)% confidence interval for p_T-p_R can be written as [7].

$$(\hat{p}_T - \hat{p}_R) \pm z_{1-\alpha}\sqrt{\frac{\hat{p}_T(1-\hat{p}_T)}{n} + \frac{\hat{p}_R(1-\hat{p}_R)}{n}}. \quad (15)$$

And the corresponding true positive for CI approach with binary outcome variable is

$$\begin{aligned} p &= P(C \cap \Theta_0 = \emptyset \,|\text{true } \theta \in (\theta_L, \theta_U)) \\ &= P(\hat{p}_T - \hat{p}_R + z_{1-\alpha}\sqrt{\tfrac{\hat{p}_T(1-\hat{p}_T)}{n} + \tfrac{\hat{p}_R(1-\hat{p}_R)}{n}} < \theta_U \\ &\text{and } \hat{p}_T - \hat{p}_R - z_{1-\alpha}\sqrt{\tfrac{\hat{p}_T(1-\hat{p}_T)}{n} + \tfrac{\hat{p}_R(1-\hat{p}_R)}{n}} > \theta_L \,|p_T - p_R = \theta_0) \\ &= P\left(\theta_L + z_{1-\alpha}\sqrt{\tfrac{\hat{p}_T(1-\hat{p}_T)}{n} + \tfrac{\hat{p}_R(1-\hat{p}_R)}{n}} < \hat{p}_T - \hat{p}_R < \theta_U - z_{1-\alpha}\sqrt{\tfrac{\hat{p}_T(1-\hat{p}_T)}{n} + \tfrac{\hat{p}_R(1-\hat{p}_R)}{n}}\right) \\ &= P\left(\frac{\theta_L - \theta_0}{\sqrt{\frac{\hat{p}_T(1-\hat{p}_T)}{n} + \frac{\hat{p}_R(1-\hat{p}_R)}{n}}} + z_{1-\alpha} < \frac{\hat{p}_T - \hat{p}_R - \theta_0}{\sqrt{\frac{\hat{p}_T(1-\hat{p}_T)}{n} + \frac{\hat{p}_R(1-\hat{p}_R)}{n}}}\right. \\ &\qquad \left. < \frac{\theta_U - \theta_0}{\sqrt{\frac{\hat{p}_T(1-\hat{p}_T)}{n} + \frac{\hat{p}_R(1-\hat{p}_R)}{n}}} - z_{1-\alpha}\right) \\ &\coloneqq \Phi\left(\frac{\theta_U - \theta_0}{\sqrt{\frac{\hat{p}_T(1-\hat{p}_T)}{n} + \frac{\hat{p}_R(1-\hat{p}_R)}{n}}} - z_{1-\alpha}\right) - \Phi\left(\frac{\theta_L - \theta_0}{\sqrt{\frac{\hat{p}_T(1-\hat{p}_T)}{n} + \frac{\hat{p}_R(1-\hat{p}_R)}{n}}} + z_{1-\alpha}\right). \end{aligned} \quad (16)$$

Comparison between TOST and CI Approach

In this section, we aim to compare the performance of TOST and CI approach in testing bioequivalence, in terms of true positive rate and sample size. Specifically, when the same sample size is fixed, the true positive rates for two approaches are compared; when the true positive rate is fixed, the sample size required for two approaches are compared. Additionally, the probabilities of consistence and inconsistence for TOST and CI approach are also computed. When the outcome variable is continuous, from Equation (7) and (14), we know that the true positive rates for bioequivalent best for TOST and CI approach are the same. Thus, in this section, we mainly focus on situation with binary outcome variable.

Fixed Sample Size Comparison

When the outcome variable is binary, the process of derive true positive rate is different in TOST and CI approach. Specifically, as shown in Equation (11) and (16), TOST uses pool proportion to compute the standard error of proportion difference, whereas CI approach does not. Using these two equations, the true positive rate difference of TOST and CI approach can be computed as

$$\begin{aligned} \Delta_p &= \Phi\left(\frac{\theta_U - \theta_0}{\sqrt{\frac{2}{n}p^*(1-p^*)}} - z_{1-\alpha}\right) - \Phi\left(\frac{\theta_L - \theta_0}{\sqrt{\frac{2}{n}p^*(1-p^*)}} + z_{1-\alpha}\right) - \Phi\left(\frac{\theta_U - \theta_0}{\sqrt{\frac{\hat{p}_T(1-\hat{p}_T)}{n} + \frac{\hat{p}_R(1-\hat{p}_R)}{n}}} - z_{1-\alpha}\right) \\ &\quad + \Phi\left(\frac{\theta_L - \theta_0}{\sqrt{\frac{\hat{p}_T(1-\hat{p}_T)}{n} + \frac{\hat{p}_R(1-\hat{p}_R)}{n}}} + z_{1-\alpha}\right) \\ &= \Phi\left(\frac{\theta_U - \theta_0}{se_{TOST}} - z_{1-\alpha}\right) - \Phi\left(\frac{\theta_L - \theta_0}{se_{TOST}} + z_{1-\alpha}\right) - \Phi\left(\frac{\theta_U - \theta_0}{se_{TOST} - \Delta_{se}} - z_{1-\alpha}\right) + \Phi\left(\frac{\theta_L - \theta_0}{se_{TOST} - \Delta_{se}} + z_{1-\alpha}\right) \\ &= \int_{-\infty}^{\frac{\theta_U - \theta_0}{se_{TOST}} - z_{1-\alpha}} \phi(x)\,dx - \int_{-\infty}^{\frac{\theta_L - \theta_0}{se_{TOST}} + z_{1-\alpha}} \phi(x)\,dx - \int_{-\infty}^{\frac{\theta_U - \theta_0}{se_{TOST} - \Delta_{se}} - z_{1-\alpha}} \phi(x)\,dx + \int_{-\infty}^{\frac{\theta_L - \theta_0}{se_{TOST} - \Delta_{se}} + z_{1-\alpha}} \phi(x)\,dx \\ &= \int_{\frac{\theta_L - \theta_0}{se_{TOST}} + z_{1-\alpha}}^{\frac{\theta_U - \theta_0}{se_{TOST}} - z_{1-\alpha}} \phi(x)\,dx - \int_{\frac{\theta_L - \theta_0}{se_{TOST} - \Delta_{se}} + z_{1-\alpha}}^{\frac{\theta_U - \theta_0}{se_{TOST} - \Delta_{se}} - z_{1-\alpha}} \phi(x)\,dx, \end{aligned} \quad (17)$$

where $\phi(x)$ is the PDF of standard normal distribution,

$$se_{TOST} = \sqrt{\frac{2p^*(1-p^*)}{n}},$$

and Δ_{se} represent the difference of the standard error of $\hat{p}_T - \hat{p}_R$ between TOST and CI approach, i.e., $se_{CI}=se_{TOST} - \Delta_{se}$. Δ_{se} can be computed as

$$\frac{2p^*(1-p^*)}{n} = \frac{2\frac{\hat{p}_T+\hat{p}_R}{2}(1-\frac{\hat{p}_T+\hat{p}_R}{2})}{n} = \frac{(\hat{p}_T+\hat{p}_R)\left(\frac{2-(\hat{p}_T+\hat{p}_R)}{2}\right)}{n} = \frac{(\hat{p}_T+\hat{p}_R)(2-(\hat{p}_T+\hat{p}_R))}{2n},$$

$$\frac{\hat{p}_T(1-\hat{p}_T)}{n}+\frac{\hat{p}_R(1-\hat{p}_R)}{n} = \frac{\hat{p}_T-\hat{p}_T^2+\hat{p}_R-\hat{p}_R^2}{n} = \frac{(\hat{p}_T+\hat{p}_R)-(\hat{p}_T^2+\hat{p}_R^2)}{n}$$
$$= \frac{(\hat{p}_T+\hat{p}_R)-(\hat{p}_T+\hat{p}_R)^2+2\hat{p}_T\hat{p}_R}{n} = \frac{(\hat{p}_T+\hat{p}_R)(1-(\hat{p}_T+\hat{p}_R))+2\hat{p}_T\hat{p}_R}{n}$$
$$= \frac{2(\hat{p}_T+\hat{p}_R)(1-(\hat{p}_T+\hat{p}_R))}{2n}+\frac{2\hat{p}_T\hat{p}_R}{n},$$

$$\Delta_{se} = \frac{2p^*(1-p^*)}{n} - \left(\frac{\hat{p}_T(1-\hat{p}_T)}{n}+\frac{\hat{p}_R(1-\hat{p}_R)}{n}\right)$$
$$= \frac{(\hat{p}_T+\hat{p}_R)(2-(\hat{p}_T+\hat{p}_R))}{2n} - \frac{2(\hat{p}_T+\hat{p}_R)(1-(\hat{p}_T+\hat{p}_R))}{2n} - \frac{2\hat{p}_T\hat{p}_R}{n}$$
$$= \frac{(\hat{p}_T+\hat{p}_R)(2-(\hat{p}_T+\hat{p}_R))}{2n} - \frac{(\hat{p}_T+\hat{p}_R)(2-2(\hat{p}_T+\hat{p}_R))}{2n} - \frac{2\hat{p}_T\hat{p}_R}{n}$$
$$= \frac{(\hat{p}_T+\hat{p}_R)\left(2-(\hat{p}_T+\hat{p}_R)-2+2(\hat{p}_T+\hat{p}_R)\right)}{2n} - \frac{2\hat{p}_T\hat{p}_R}{n}$$
$$= \frac{(\hat{p}_T+\hat{p}_R)(\hat{p}_T+\hat{p}_R)-4\hat{p}_T\hat{p}_R}{2n} = \frac{(\hat{p}_T-\hat{p}_R)^2}{2n} \quad (18)$$

Using Taylor expansion, the CDF of $N(0,1)$ can be written as

$$\Phi(x) = \frac{1}{\sqrt{2\pi}}\sum_{i=0}^{n}\frac{(-1)^n}{n!\,2^n(2n+1)}x^{2n+1}+\frac{1}{2}. \quad (19)$$

If we only keep the first term of Taylor expansion in Equation (19), then $\Phi(x_1) - \Phi(x_2)$ can be simplified as

$$\Phi(x_1)-\Phi(x_2) = \frac{1}{\sqrt{2\pi}}\left(\sum_{i=0}^{n}\frac{(-1)^n}{n!\,2^n(2n+1)}x_1^{2n+1} - \sum_{i=0}^{n}\frac{(-1)^n}{n!\,2^n(2n+1)}x_2^{2n+1}\right)$$
$$= \frac{1}{\sqrt{2\pi}}\sum_{i=0}^{n}\frac{(-1)^n}{n!\,2^n(2n+1)}(x_1^{2n+1}-x_2^{2n+1}) \approx \frac{1}{\sqrt{2\pi}}(x_1-x_2). \quad (20)$$

Then Equation (17) can be simplified as

$$\Delta_p \approx \frac{1}{\sqrt{2\pi}}\left(\frac{\theta_U-\theta_0}{se_{TOST}}-z_{1-\alpha}-\frac{\theta_L-\theta_0}{se_{TOST}}-z_{1-\alpha}\right) - \frac{1}{\sqrt{2\pi}}\left(\frac{\theta_U-\theta_0}{se_{TOST}-\Delta_{se}}-z_{1-\alpha}-\frac{\theta_L-\theta_0}{se_{TOST}-\Delta_{se}}-z_{1-\alpha}\right)$$
$$= \frac{1}{\sqrt{2\pi}}\left(\frac{\theta_U-\theta_L}{se_{TOST}}-\frac{\theta_U-\theta_L}{se_{TOST}-\Delta_{se}}\right) = \frac{\theta_U-\theta_L}{\sqrt{2\pi}}\left(\frac{1}{se_{TOST}}-\frac{1}{se_{TOST}-\Delta_{se}}\right). \quad (21)$$

From Equation (18), we have

$$\Delta_{se} = \frac{(\hat{p}_T-\hat{p}_R)^2}{2n} \geq 0. \quad (22)$$

Thus, $\Delta_p \leq 0$, i.e., the true positive rate of TOST is smaller or equal to the true positive rate of CI approach, when the sample size is the same.

Fixed True Positive Rate Comparison

When the desired true positive rate for TOST and CI approach are the same, let n_1 denote the sample size required for TOST, and n_2 denote the sample size required for CI approach. Since the target population is the same, we assume the estimated proportion of test and reference group are the same, i.e., $\hat{p}_T=\hat{p}_R$. Again, using Taylor expansion, the true positive rate of TOST and CI approach are

$$p_b^{TOST} = \Phi\left(\frac{\theta_U-\theta_0}{\sqrt{\frac{2}{n_1}p^*(1-p^*)}}-z_{1-\alpha}\right) - \Phi\left(\frac{\theta_L-\theta_0}{\sqrt{\frac{2}{n_1}p^*(1-p^*)}}+z_{1-\alpha}\right)$$
$$\approx \frac{1}{\sqrt{2\pi}}\left(\frac{\theta_U-\theta_0}{\sqrt{\frac{2}{n_1}p^*(1-p^*)}}-z_{1-\alpha}-\frac{\theta_L-\theta_0}{\sqrt{\frac{2}{n_1}p^*(1-p^*)}}-z_{1-\alpha}\right)$$
$$= \frac{1}{\sqrt{2\pi}}\left(\frac{\theta_U-\theta_L}{\sqrt{\frac{2}{n_1}p^*(1-p^*)}}-2z_{1-\alpha}\right), \quad (23)$$

$$p_b^{CI} = \Phi\left(\frac{\theta_U-\theta_0}{\sqrt{\frac{\hat{p}_T(1-\hat{p}_T)}{n_2}+\frac{\hat{p}_R(1-\hat{p}_R)}{n_2}}}-z_{1-\alpha}\right) - \Phi\left(\frac{\theta_L-\theta_0}{\sqrt{\frac{\hat{p}_T(1-\hat{p}_T)}{n_2}+\frac{\hat{p}_R(1-\hat{p}_R)}{n_2}}}+z_{1-\alpha}\right)$$
$$\approx \frac{1}{\sqrt{2\pi}}\left(\frac{\theta_U-\theta_L}{\sqrt{\frac{\hat{p}_T(1-\hat{p}_T)}{n_2}+\frac{\hat{p}_R(1-\hat{p}_R)}{n_2}}}-2z_{1-\alpha}\right). \quad (24)$$

When the true positive rates are the same, we have

$$\frac{1}{\sqrt{2\pi}}\left(\frac{\theta_U-\theta_L}{\sqrt{\frac{2}{n_1}p^*(1-p^*)}}-2z_{1-\alpha}\right) = \frac{1}{\sqrt{2\pi}}\left(\frac{\theta_U-\theta_L}{\sqrt{\frac{\hat{p}_T(1-\hat{p}_T)}{n_2}+\frac{\hat{p}_R(1-\hat{p}_R)}{n_2}}}-2z_{1-\alpha}\right)$$
$$\Leftrightarrow \frac{2}{n_1}p^*(1-p^*) = \frac{\hat{p}_T(1-\hat{p}_T)}{n_2}+\frac{\hat{p}_R(1-\hat{p}_R)}{n_2}$$
$$\Leftrightarrow \frac{2}{n_1}\cdot\frac{\hat{p}_T+\hat{p}_R}{2}\cdot\left(1-\frac{\hat{p}_T+\hat{p}_R}{2}\right) = \frac{\hat{p}_T(1-\hat{p}_T)}{n_2}+\frac{\hat{p}_R(1-\hat{p}_R)}{n_2}$$
$$\Leftrightarrow \frac{1}{n_1}\cdot\frac{\hat{p}_T+\hat{p}_R}{1}\cdot\left(\frac{2-\hat{p}_T-\hat{p}_R}{2}\right) = \frac{\hat{p}_T(1-\hat{p}_T)}{n_2}+\frac{\hat{p}_R(1-\hat{p}_R)}{n_2}$$
$$\Leftrightarrow n_2(\hat{p}_T+\hat{p}_R)(2-\hat{p}_T-\hat{p}_R) = 2n_1[\hat{p}_T(1-\hat{p}_T)+\hat{p}_R(1-\hat{p}_R)]$$

$$\Leftrightarrow \frac{n_2}{n_1} = \frac{2[\hat{p}_T(1-\hat{p}_T)+\hat{p}_R(1-\hat{p}_R)]}{(\hat{p}_T+\hat{p}_R)(2-\hat{p}_T-\hat{p}_R)} = \frac{2[\hat{p}_T+\hat{p}_R-\hat{p}_T^2-\hat{p}_R^2-2\hat{p}_T\hat{p}_R+2\hat{p}_T\hat{p}_R]}{(\hat{p}_T+\hat{p}_R)(2-\hat{p}_T-\hat{p}_R)} = \frac{2[\hat{p}_T+\hat{p}_R-(\hat{p}_T+\hat{p}_R)^2+2\hat{p}_T\hat{p}_R]}{(\hat{p}_T+\hat{p}_R)(2-\hat{p}_T-\hat{p}_R)}$$
$$= \frac{2(\hat{p}_T+\hat{p}_R)(1-(\hat{p}_T+\hat{p}_R))}{(\hat{p}_T+\hat{p}_R)(2-\hat{p}_T-\hat{p}_R)} + \frac{4\hat{p}_T\hat{p}_R}{(\hat{p}_T+\hat{p}_R)(2-\hat{p}_T-\hat{p}_R)}$$
$$= \frac{2-2(\hat{p}_T+\hat{p}_R)+\frac{4\hat{p}_T\hat{p}_R}{\hat{p}_T+\hat{p}_R}}{2-(\hat{p}_T+\hat{p}_R)}. \quad (25)$$

Next, we compare $\hat{p}_T+\hat{p}_R$ and $\frac{4\hat{p}_T\hat{p}_R}{\hat{p}_T+\hat{p}_R}$:

$$\hat{p}_T+\hat{p}_R - \frac{4\hat{p}_T\hat{p}_R}{\hat{p}_T+\hat{p}_R} = \frac{(\hat{p}_T+\hat{p}_R)^2-4\hat{p}_T\hat{p}_R}{\hat{p}_T+\hat{p}_R} = \frac{(\hat{p}_T-\hat{p}_R)^2}{\hat{p}_T+\hat{p}_R} \geq 0, \quad (26)$$

suggesting $\hat{p}_T+\hat{p}_R \geq \frac{4\hat{p}_T\hat{p}_R}{\hat{p}_T+\hat{p}_R}$. In other words,

$$2-2(\hat{p}_T+\hat{p}_R)+\frac{4\hat{p}_T\hat{p}_R}{\hat{p}_T+\hat{p}_R} \leq 2-2(\hat{p}_T+\hat{p}_R)+\hat{p}_T+\hat{p}_R = 2-(\hat{p}_T+\hat{p}_R)$$
$$\Leftrightarrow \frac{2-2(\hat{p}_T+\hat{p}_R)+\frac{4\hat{p}_T\hat{p}_R}{\hat{p}_T+\hat{p}_R}}{2-(\hat{p}_T+\hat{p}_R)} \leq 1$$
$$\Leftrightarrow \frac{n_2}{n_1} \leq 1. \quad (27)$$

Therefore, when the desired true positive rates are the same, for binary outcome variable, the sample size for CI approach is smaller or equal to the one for TOST approach.

Confusion Point

Let assume the sample size for TOST and CI approach is the same, i.e., conduct TOST and CI approach to test for bioequivalence using the same data set. Assume the true proportion difference is p_0 and the variance is $\frac{p_0(1-p_0)}{n}$ Thus,

$$\frac{\hat{p}_T-\hat{p}_R-p_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} \sim N(0,1).$$

The conditional probability of TOST claiming bioequivalent, given CI approach claiming bioequivalent is

$$P(TOST\ bioequivalent\ |CI\ bioequivalent) = P(Z_1 > z_{1-\alpha}\ and\ Z_2 < z_\alpha | C \in (\theta_L,\theta_U))$$
$$= P(\theta_L + z_{1-\alpha}\sqrt{\frac{2}{n}p^*(1-p^*)} < \hat{p}_T-\hat{p}_R$$
$$< \theta_U + z_\alpha\sqrt{\frac{2}{n}p^*(1-p^*)} | \theta_L + z_{1-\alpha}\sqrt{\frac{\hat{p}_T(1-\hat{p}_T)}{n}+\frac{\hat{p}_R(1-\hat{p}_R)}{n}} < \hat{p}_T-\hat{p}_R$$
$$< \theta_U - z_{1-\alpha}\sqrt{\frac{\hat{p}_T(1-\hat{p}_T)}{n}+\frac{\hat{p}_R(1-\hat{p}_R)}{n}}). \quad (28)$$

When the test and reference drug are equivalent, the lower and upper bound of $\hat{p}_T$- $\hat{p}_R$ in TOST are

$$LB_{TOST} = \theta_L + z_{1-\alpha}\sqrt{\frac{2}{n}p^*(1-p^*)} \text{ and } UB_{TOST} = \theta_U - z_{1-\alpha}\sqrt{\frac{2}{n}p^*(1-p^*)}. \quad (29)$$

When the test and reference drug are equivalent, the lower and upper bound of $\hat{p}_T$- $\hat{p}_R$ in CI approach are

$$LB_{CI} = \theta_L + z_{1-\alpha}\sqrt{\frac{\hat{p}_T(1-\hat{p}_T)}{n}+\frac{\hat{p}_R(1-\hat{p}_R)}{n}} \text{ and } UB_{CI} = \theta_U - z_{1-\alpha}\sqrt{\frac{\hat{p}_T(1-\hat{p}_T)}{n}+\frac{\hat{p}_R(1-\hat{p}_R)}{n}}. \quad (30)$$

From Equation (22), we know $\sqrt{\frac{2}{n}p^*(1-p^*)} \geq \sqrt{\frac{\hat{p}_T(1-\hat{p}_T)}{n}+\frac{\hat{p}_R(1-\hat{p}_R)}{n}}$ Thus,

$$LB_{TOST} \geq LB_{CI} \text{ and } UB_{TOST} \leq UB_{CI} \quad (31)$$

The relationship between the lower and upper bound of TOST and CI approach are shown in Figure 1.

Figure 1. Relationship among boundaries of TOST and CI approaches.

Then the conditional probability shown in Equation (27) can be written as

$$\begin{aligned}
&P(TOST\ bioequivalent\ |CI\ bioequivalent) = P\left(Z_1 > z_{1-\alpha}\ and\ Z_2 < z_{\alpha|C\in(\theta_L,\theta_U))}\right)\\
&= P(LB_{TOST} < \hat{p}_T - \hat{p}_R < UB_{TOST}|LB_{CI} < \hat{p}_T - \hat{p}_R < UB_{CI})\\
&= \frac{P(LB_{TOST} < \hat{p}_T - \hat{p}_R < UB_{TOST})}{P(LB_{CI} < \hat{p}_T - \hat{p}_R < UB_{CI})}\\
&= \frac{P\left(\frac{LB_{TOST}-p_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} < \frac{\hat{p}_T-\hat{p}_R-p_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} < \frac{UB_{TOST}-p_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right)}{P\left(\frac{LB_{CI}-p_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} < \frac{\hat{p}_T-\hat{p}_R-p_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} < \frac{UB_{CI}-p_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right)}\\
&= \frac{\Phi\left(\frac{UB_{TOST}-p_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right) - \Phi\left(\frac{LB_{TOST}-p_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right)}{\Phi\left(\frac{UB_{CI}-p_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right) - \Phi\left(\frac{LB_{CI}-p_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right)} = \frac{\frac{UB_{TOST}-p_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} - \frac{LB_{TOST}-p_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}}{\frac{UB_{CI}-p_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} - \frac{LB_{CI}-p_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}}\\
&= \frac{UB_{TOST}-LB_{TOST}}{UB_{CI}-LB_{CI}}. \quad (32)
\end{aligned}$$

The conditional probability of TOST claiming not bioequivalent, given CI approach claiming bioequivalent is

$$\begin{aligned}
&P(TOST\ not\ bioequivalent\ |CI\ bioequivalent) = P\left(Z_1 < z_{1-\alpha}\ or\ Z_2 > z_\alpha | C \in (\theta_L,\theta_U)\right)\\
&= P(\hat{p}_T - \hat{p}_R < LB_{TOST}\ or\ \hat{p}_T - \hat{p}_R > UB_{TOST}|LB_{CI} < \hat{p}_T - \hat{p}_R < UB_{CI})\\
&= \frac{P(LB_{CI} < \hat{p}_T - \hat{p}_R < LB_{TOST}\ or\ UB_{TOST} < \hat{p}_T - \hat{p}_R < UB_{CI})}{P(LB_{CI} < \hat{p}_T - \hat{p}_R < UB_{CI})}\\
&= \frac{P(LB_{CI} < \hat{p}_T - \hat{p}_R < LB_{TOST}) + P(UB_{TOST} < \hat{p}_T - \hat{p}_R < UB_{CI})}{P(LB_{CI} < \hat{p}_T - \hat{p}_R < UB_{CI})}\\
&= \frac{P\left(\frac{LB_{CI}-\hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} < \frac{\hat{p}_T-\hat{p}_R-\hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} < \frac{LB_{TOST}-\hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right) + P\left(\frac{UB_{TOST}-\hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} < \frac{\hat{p}_T-\hat{p}_R-\hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} < \frac{UB_{CI}-\hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right)}{P\left(\frac{LB_{CI}-p_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} < \frac{\hat{p}_T-\hat{p}_R-p_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} < \frac{UB_{CI}-p_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right)}\\
&= \frac{\Phi\left(\frac{LB_{TOST}-\hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right) - \Phi\left(\frac{LB_{CI}-\hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right) + \Phi\left(\frac{UB_{CI}-\hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right) - \Phi\left(\frac{UB_{TOST}-\hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right)}{\Phi\left(\frac{UB_{CI}-p_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right) - \Phi\left(\frac{LB_{CI}-p_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right)}\\
&= \frac{\frac{1}{\sqrt{2\pi}}\left(\frac{LB_{TOST}-\hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} - \frac{LB_{CI}-\hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right) + \frac{1}{\sqrt{2\pi}}\left(\frac{UB_{CI}-\hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} - \frac{UB_{TOST}-\hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right)}{\frac{1}{\sqrt{2\pi}}\left(\frac{UB_{CI}-p_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} - \frac{LB_{CI}-p_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right)}\\
&= \frac{LB_{TOST}-LB_{CI}+UB_{CI}-UB_{TOST}}{UB_{CI}-LB_{CI}}. \quad (33)
\end{aligned}$$

The conditional probability of TOST claiming bioequivalent, given CI approach claiming not bioequivalent is

$$\begin{aligned}
&P(TOST\ bioequivalent\ |CI\ not\ bioequivalent)\\
&= P\left(Z_1 > z_{1-\alpha}\ and\ Z_2 < z_\alpha | C \notin (\theta_L,\theta_U)\right)\\
&= P(LB_{TOST} < \hat{p}_T - \hat{p}_R < UB_{TOST}|\hat{p}_T - \hat{p}_R < LB_{CI}\ or\ \hat{p}_T - \hat{p}_R > UB_{CI}) = 0. \quad (34)
\end{aligned}$$

The conditional probability of TOST claiming not bioequivalent, given CI approach claiming not bioequivalent is

$$\begin{aligned}
&P(TOST\ not\ bioequivalent\ |CI\ not\ bioequivalent)\\
&= P\left(Z_1 < z_{1-\alpha}\ or\ Z_2 > z_\alpha | C \notin (\theta_L,\theta_U)\right)\\
&= P(\hat{p}_T - \hat{p}_R < LB_{TOST}\ or\ \hat{p}_T - \hat{p}_R > UB_{TOST}|\hat{p}_T - \hat{p}_R < LB_{CI}\ or\ \hat{p}_T - \hat{p}_R > UB_{CI})\\
&= \frac{P(\hat{p}_T - \hat{p}_R < LB_{CI}\ or\ \hat{p}_T - \hat{p}_R > UB_{CI})}{P(\hat{p}_T - \hat{p}_R < LB_{CI}\ or\ \hat{p}_T - \hat{p}_R > UB_{CI})} = 1. \quad (35)
\end{aligned}$$

Therefore, from Equation (32) to (35), the confusion matrix of TOST result conditional on CI approach result is shown in Table 2.

Table 2. Confusion matrix of TOST result conditional on CI approach.

	Conditional on CI approach	
TOST	Bioequivalence	Not bioequivalence
Bioequivalent	$\frac{UB_{TOST}-LB_{TOST}}{UB_{CI}-LB_{CI}}$	0
Not bioequivalent	$\frac{LB_{TOST}-LB_{CI}+UB_{CI}-UB_{TOST}}{UB_{CI}-LB_{CI}}$	1

Similarly, we may also derive the confusion matrix of CI approach conditional on TOST approach. The conditional probability of CI approach claiming bioequivalent conditional on TOST claiming bioequivalent is

$$\begin{aligned}
&P(CI\ bioequivalent|TOST\ bioequivalent) = P(C \in (\theta_L,\theta_U)|Z_1 > z_{1-\alpha}\ and\ Z_2 < z_\alpha)\\
&= P(LB_{CI} < \hat{p}_T - \hat{p}_R < UB_{CI}|LB_{TOST} < \hat{p}_T - \hat{p}_R < UB_{TOST})\\
&= \frac{P(LB_{TOST} < \hat{p}_T - \hat{p}_R < UB_{TOST})}{P(LB_{TOST} < \hat{p}_T - \hat{p}_R < UB_{TOST})} = 1. \quad (36)
\end{aligned}$$

The conditional probability of CI approach claiming not bioequivalent conditional on TOST claiming bioequivalent is

$$\begin{aligned}
&P(CI\ not\ bioequivalent|TOST\ bioequivalent) = P(C \notin (\theta_L,\theta_U)|Z_1 > z_{1-\alpha}\ and\ Z_2 < z_\alpha)\\
&= P(\hat{p}_T - \hat{p}_R < LB_{CI}\ or\ \hat{p}_T - \hat{p}_R > UB_{CI}|LB_{TOST} < \hat{p}_T - \hat{p}_R < UB_{TOST}) = 0. \quad (37)
\end{aligned}$$

The conditional probability of CI approach claiming bioequivalent conditional on TOST claiming not bioequivalent is

$$\begin{aligned}
&P(CI\ bioequivalent|TOST\ not\ bioequivalent) = P(C \in (\theta_L,\theta_U)|Z_1 < z_{1-\alpha}\ or\ Z_2 > z_\alpha)\\
&= P(LB_{CI} < \hat{p}_T - \hat{p}_R < UB_{CI}|\hat{p}_T - \hat{p}_R < LB_{TOST}\ or\ \hat{p}_T - \hat{p}_R > UB_{TOST})\\
&= \frac{P(LB_{CI} < \hat{p}_T - \hat{p}_R < LB_{TOST}\ or\ UB_{TOST} < \hat{p}_T - \hat{p}_R < UB_{CI})}{P(\hat{p}_T - \hat{p}_R < LB_{TOST}\ or\ \hat{p}_T - \hat{p}_R > UB_{TOST})}\\
&= \frac{P(LB_{CI} < \hat{p}_T - \hat{p}_R < LB_{TOST}) + P(UB_{TOST} < \hat{p}_T - \hat{p}_R < UB_{CI})}{P(\hat{p}_T - \hat{p}_R < LB_{TOST}) + 1 - P(\hat{p}_T - \hat{p}_R < UB_{TOST})}\\
&= \frac{P\left(\frac{LB_{CI}-\hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} < \frac{\hat{p}_T-\hat{p}_R-\hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} < \frac{LB_{TOST}-\hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right) + P\left(\frac{UB_{TOST}-\hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} < \frac{\hat{p}_T-\hat{p}_R-\hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} < \frac{UB_{CI}-\hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right)}{P\left(\frac{\hat{p}_T-\hat{p}_R-\hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} < \frac{LB_{TOST}-\hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right) + 1 - P\left(\frac{\hat{p}_T-\hat{p}_R-\hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} < \frac{UB_{TOST}-\hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right)}
\end{aligned}$$

$$= \frac{\Phi\left(\frac{LB_{TOST} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right) - \Phi\left(\frac{LB_{CI} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right) + \Phi\left(\frac{UB_{CI} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right) - \Phi\left(\frac{UB_{TOST} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right)}{\Phi\left(\frac{LB_{TOST} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right) + 1 - \Phi\left(\frac{UB_{TOST} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right)}$$

$$= \frac{\frac{1}{\sqrt{2\pi}}\left(\frac{LB_{TOST} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} - \frac{LB_{CI} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right) + \frac{1}{\sqrt{2\pi}}\left(\frac{UB_{CI} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} - \frac{UB_{TOST} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right)}{\frac{1}{\sqrt{2\pi}}\left(\frac{LB_{TOST} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} - \frac{UB_{TOST} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right) + 1}$$

$$= \frac{\frac{LB_{TOST} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} - \frac{LB_{CI} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} + \frac{UB_{CI} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} - \frac{UB_{TOST} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}}{\frac{LB_{TOST} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} - \frac{UB_{TOST} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} + \sqrt{2\pi}}$$

$$= \frac{LB_{TOST} - \hat{p}_0 - (LB_{CI} - \hat{p}_0) + UB_{CI} - \hat{p}_0 - (UB_{TOST} - \hat{p}_0)}{(LB_{TOST} - \hat{p}_0) - (UB_{TOST} - \hat{p}_0) + \sqrt{2\pi}\sqrt{\frac{p_0(1-p_0)}{n}}}$$

$$= \frac{LB_{TOST} - LB_{CI} + UB_{CI} - UB_{TOST}}{LB_{TOST} - UB_{TOST} + \sqrt{\frac{2\pi p_0(1-p_0)}{n}}}. \quad (38)$$

The conditional probability of CI approach claiming not bioequivalent conditional on TOST claiming not bioequivalent is

$$P(CI\ not\ bioequivalent | TOST\ not\ bioequivalent)$$
$$= P(C \notin (\theta_L, \theta_U) | Z_1 < z_{1-\alpha}\ or\ Z_2 > z_\alpha)$$
$$= P(\hat{p}_T - \hat{p}_R < LB_{CI}\ or\ \hat{p}_T - \hat{p}_R > UB_{CI} | \hat{p}_T - \hat{p}_R < LB_{TOST}\ \ or\ \ \hat{p}_T - \hat{p}_R > UB_{TOST})$$
$$= \frac{P(\hat{p}_T - \hat{p}_R < LB_{CI}\ or\ \hat{p}_T - \hat{p}_R > UB_{CI})}{P(\hat{p}_T - \hat{p}_R < LB_{TOST}\ \ or\ \ \hat{p}_T - \hat{p}_R > UB_{TOST})}$$
$$= \frac{P(\hat{p}_T - \hat{p}_R < LB_{CI}) + 1 - P(\hat{p}_T - \hat{p}_R < UB_{CI})}{P(\hat{p}_T - \hat{p}_R < LB_{TOST}) + 1 - P(\hat{p}_T - \hat{p}_R < UB_{TOST})}$$
$$= \frac{\Phi\left(\frac{LB_{CI} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right) + 1 - \Phi\left(\frac{UB_{CI} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right)}{\Phi\left(\frac{LB_{TOST} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right) + 1 - \Phi\left(\frac{UB_{TOST} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}\right)}$$
$$= \frac{\frac{1}{\sqrt{2\pi}} \times \frac{LB_{CI} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} + 1 - \frac{1}{\sqrt{2\pi}} \times \frac{UB_{CI} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}}{\frac{1}{\sqrt{2\pi}} \times \frac{LB_{TOST} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}} + 1 - \frac{1}{\sqrt{2\pi}} \times \frac{UB_{TOST} - \hat{p}_0}{\sqrt{\frac{p_0(1-p_0)}{n}}}}$$
$$= \frac{LB_{TOST} - UB_{TOST} + \sqrt{\frac{2\pi p_0(1-p_0)}{n}}}{LB_{CI} - UB_{CI} + \sqrt{\frac{2\pi p_0(1-p_0)}{n}}}. \quad (39)$$

Therefore, from Equation (36) to (39), the confusion matrix of CI approach result conditional on TOST approach result is shown in Table 3.

Table 3. Confusion matrix of TOST result conditional on CI approach.

	Conditional on TOST approach	
CI approach	Bioequivalence	Not bioequivalence
Bioequivalent	1	$\frac{LB_{TOST} - LB_{CI} + UB_{CI} - UB_{TOST}}{LB_{TOST} - UB_{TOST} + \sqrt{\frac{2\pi p_0(1-p_0)}{n}}}$
Not bioequivalent	0	$\frac{LB_{TOST} - UB_{TOST} + \sqrt{\frac{2\pi p_0(1-p_0)}{n}}}{LB_{CI} - UB_{CI} + \sqrt{\frac{2\pi p_0(1-p_0)}{n}}}$

Concluding Remarks

In assessing the bioequivalence of a generic drug or a biosimilar product to the innovative drug product, two one-sided tests (TOST) or confidence interval (CI) approach are the most commonly used approaches in bioequivalent tests. However, TOST and CI approach are often mixed-up by researchers. Though Chow and Shao [4] have proved the *operationally* equivalence between TOST and CI approach, this results only hold under special circumstances. In other words, this is not a general conclusion. When the outcome variable is continuous, 5% level TOST is equivalent to 90% CI approach; when the outcome variables is binary, this conclusion is invalid. In this paper, we compared the difference between TOST and CI approach and illustrated their difference in true positive rate and sample size. The confusion matrices of these two approaches for binary outcomes were also shown in Table 2 and 3. When CI approach concludes "bioequivalence", TOST may give a different conclusion; when CI approach concludes "not bioequivalence", TOST tends to always give "not bioequivalence". When TOST concludes "bioequivalence", CI approach tends to always give "bioequivalence"; when TOST concludes "not bioequivalence", CI approach may give different conclusions. Thus, we have shown that, when outcome variable is binary, TOST and CI approach do not always give the same conclusion about bioequivalence. Due to the fundamental difference between TOST and CI approach, to avoid making mistake, we strongly recommend researchers not mix up the results of these two approaches.

References

[1] Agresti, A., and Caffo, B. (2000). Simple and effective confidence intervals for proportions and differences of proportions result from adding two successes and two failures. The American Statistician, 54(4), 280-288.

[2] Berger, R. L., & Hsu, J. C. (1996). Bioequivalence trials, intersection-union tests and equivalence confidence sets. Statistical Science, 11(4), 283-319.

[3] Chow, S.C. and Liu, J.P. (2008). Design and Analysis of Bioavailability and Bioequivalence Studies, Third Edition, Taylor & Francis, New York, New York.

[4] Chow, S. C., and Shao, J. (2002). A note on statistical methods for assessing therapeutic equivalence. Controlled Clinical Trials, 23(5), 515-520.

[5] Chow, S. C., Shao, J., Wang, H., and Lokhnygina, Y. (2017). Sample size calculations in clinical research. Chapman and Hall/CRC.

[6] FDA (2003). Bioavaiability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations. The United States Food and Drug Administration, Rockville, Maryland.

[7] FDA (2015). Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. The United States Food and Drug Administration, Silver Spring, Maryland.

[8] Jiroutek, M. R., Muller, K. E., Kupper, L. L., and Stewart, P. W. (2003). A new method for choosing sample size for confidence interval–based inferences. Biometrics, 59(3), 580-590.

[9] Schuirmann, D. J. (1987). A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. Journal of pharmacokinetics and biopharmaceutics, 15(6), 657-680.