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THREE BAYESIAN TEST INDEXES FOR NORMAL DISTRIBUTIONS

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ABSTRACT

In clinical trials, data that are consistent with a normal distribution are often regarded as candidates for primary evaluation variables. In such cases, t-tests are frequently used to compare different groups of data. However, the repeated use of t-tests leads to problems with multiplicity. This study proposes three new indexes that are based on (Kawasaki and Miyaoka, 2012; 2013). These indexes can be used to evaluate the superiority, non-inferiority and equivalency of population means for normal distributions. These new indexes are constructed based on the Bayesian framework and can be used to prevent multiplicity issues. We apply these three new indexes to actual data in order to demonstrate their usefulness.

Keywords: Bayesian Inference, Normal Distribution, Non-Inferiority, Equivalency, Superiority

1. INTRODUCTION

In clinical trials, evaluation variables that follow the normal distribution have been used frequently to evaluate drug effects and post-operative effects. We are interested in comparisons of population means between two groups. The t-test is a general statistical method (Student, 1908) that uses regression analysis or covariance ratios (Keppel, 1991) to evaluate comparisons between population means for two groups. The usage of these statistical methods is limited by strong statistical suppositions. Additionally, the evaluation of the equivalency requires two one-sided tests. There are also problems with multiplicity. These statistical methods are constructed based on the frequency theory framework.

On the other hand, several evaluation methods have been suggested that are based on the Bayesian framework. For instance, Berry developed a method for using the Bayes' theorem and a method for comparing parameters directly (Berry, 1996). Kawasaki and Miyaoka (2012; 2013) proposed a new evaluation index that can be used to perform direct comparisons between binomial proportions. This index is constructed in the Bayesian framework without considering the issue of multiplicity. This type of index can be used to calculate probabilities and can be easily and intuitively understood. Moreover, these indexes can be used in comparisons that are based on the empirical Bayes method and can be applied to information about previous clinical trials and results. In this study, we propose a new extended index for cases where assessment variables follow the normal distribution. This new index is based on (Kawasaki and Miyaoka, 2012; 2013). Thus, the three new indexes that we suggest can be used to calculate probabilities directly for superiority, non-inferiority and equivalency of population means for normal distributions and can be used to perform comparisons between groups as well.

The remainder of this study is organized as follows. We describe the notations and the three new indexes in section 2, explain them via examples in section 3 and finally, conclude the paper with a brief summary in section 4.

2. MATERIALS AND METHODS

Let $\underline{X}_1 = (X_{11}, X_{12}, X_{13}, , , X_{1n1})$ and $\underline{X}_2 = (X_{21}, X_{22}, X_{23}, , , X_{2n2})$ denote random variables for a normal distribution for trials n_1 and n_2 and parameters (μ_1, σ^2_1) and (μ_2, σ^2_2), respectively. Further, we assume that μ_1

is independent from μ_2.The conjugate prior density for μ_i(i =1, 2) is the normal distribution with parameters $\mu_{i,pre}$ and $\sigma^2_{i,pre}$.

2.1. Bayesian Superiority Index

The Bayesian superiority index θ can be calculated using:

$$\theta = P(\mu_{1,post} > \mu_{2,post} \mid X_1, X_1)$$

$$= P(\mu_{1,post} - \mu_{2,post} > 0 \mid X_1, X_1) = 1 - \Phi\left(\frac{\mu_{1,p} - \mu_{2,p}}{\sqrt{\frac{\sigma^2_{1,p}}{n_1} + \frac{\sigma^2_{2,p}}{n_2}}}\right)$$

where,$\Phi(\bullet)$ is the cumulative distribution function for the standard normal distribution and $\mu_{i,p} = \frac{\frac{n_i \bar{X}_i}{\sigma_i^2} + \frac{\mu_{i,pre}}{\sigma^2_{i,pre}}}{\frac{n_i}{\sigma_i^2} + \frac{1}{\sigma^2_{i,pre}}}$ and $\sigma^2_{i,p} = \frac{1}{\frac{1}{\sigma_i^2} + \frac{1}{\sigma^2_{i,pre}}}$, denotes the posterior mean and variance of μ_i (i = 1, 2).

2.2. Bayesian Non-inferiority Index

The Bayesian non-inferiority index η can be calculated using:

$$\eta = P(\mu_{1,post} < \mu_{2,post} - \Delta_0 \mid X_1, X_1)$$

$$= P(\mu_{1,post} - \mu_{2,post} < -\Delta_0 \mid X_1, X_1) = \Phi\left(\frac{-\Delta_0 - (\mu_{1,p} - \mu_{2,p})}{\sqrt{\frac{\sigma^2_{1,p}}{n_1} + \frac{\sigma^2_{2,p}}{n_2}}}\right)$$

where, Δ_0>0 is the non-inferiority margin.

2.3. Bayesian Equivalency Index

The Bayesian Equivalency index κ can be calculated using:

$$\kappa = P(\mu_{1,post} < \mu_{2,post} - \Delta_0 \mid X_1, X_1)$$

$$= P(-\Delta_0 < \mu_{1,post} - \mu_{2,post} < \Delta_0 \mid X_1, X_1)$$

$$= \Phi\left(\frac{\Delta_0 - (\mu_{1,p} - \mu_{2,p})}{\sqrt{\frac{\sigma^2_{1,p}}{n_1} + \frac{\sigma^2_{2,p}}{n_2}}}\right) - \Phi\left(\frac{-\Delta_0 - (\mu_{1,p} - \mu_{2,p})}{\sqrt{\frac{\sigma^2_{1,p}}{n_1} + \frac{\sigma^2_{2,p}}{n_2}}}\right)$$

where, Δ_0>0 is the equivalency margin.

Table 1. A summary of results for an end point in a clinical trial

Drug	Number	Means	S.D.	Min	Max
New	8	76.63	16.78	44	94
Placebo	8	59.13	12.23	35	75

3. RESULTS

In this section, we show examples from clinical trials (TIT, 2010). The purpose of these trials was to investigate the difference between the means for the active drug group and the placebo group. In **Table 1**, we show a summary of statistics for the active drug group and the placebo group.

3.1. Superiority Test

The purpose of this clinical trial is to find the mean for active drug group and determine whether it is superior to the mean for the placebo group. The primary analysis method in this clinical trial was the t-test and the result was a p-value of 0.0321. Therefore, the result exceeded the one-sided significance level of 0.025 and the null hypothesis could not be rejected. On the other hand, we calculated κ using a non-informative prior and the probability of κ was 0.954.

3.2. Non-Inferiority Test

Next, we show the non-inferior test that indicates that the mean for the active group is not inferior at least 5.0 points than the mean of placebo group. The result from using the t-test is a one-side p-value of 0.0042. On the other hand, η = 0.992.

3.3. Equivalency Test

Finally, we present the equivalency test. This analysis shows that the mean for the active group is within 5.0 points of the mean for the placebo group. The results from using the t-test (e.g., Schuirmann (1987; Phillips, 1990; Diletti *et al*., 1991)) are Two One-Sided Tests (TOST) with a p-value of 0.9444 at a significance level of 5%. Therefore, the results are not equivalent. Additionally, κ = 0.0024.

4. DISCUSSION

We showed the some examples in the results section and obtained some findings.

We calculated κ using a non-informative prior and the probability of κ was 0.954. This result suggests that mean of the active drug group is high, since it has a probability of 95.4%. Next, we calculated η using a non-

informative prior andthe probability of η was 0.954. This result indicates that the mean of the active group is not inferior above 10%, since it has a probability of 99.2%. Finally, we calculated κ using a non-informative prior andthe probability of κ was 0.0024.In this case, the probability of equivalency is 0.2%. Therefore, it is very unlikely that the results are equivalent.

Based upon the foregoing, these new indexes are the indexes that understanding is easy to make intuitively.

5. CONCLUSION

We proposed a new index for superiority, non-inferiority and equivalency for population means from normal distributions that is based on (Kawasaki and Miyaoka, 2012; 2013). These indexes were examined within a Bayesian framework and the problem of multiplicity did not occur. Therefore, this index is an index that can be easily used for clinical trial designs that require adaptive designs or repeated tests. Additionally, the calculation of the index is very easy and does not require special software.

As indicated in the example, the index was easy to understand intuitively because it can be used to calculate probabilities directly. Also, the results from clinical trials are often similar to results from previous clinical trials. We did not mention in this article that information about a previous clinical trial result can be compared to the population mean with the empirical Bayes method. We believe that this will become a great contribution to ethical for patients who participated in clinical trials in the past.

Thus, the three new indexes that were introduced in this study are easy to calculate, are easy to understand intuitively and are useful in clinical trials.

6. ACKNOWLEDGEMENT

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