

Assessing Therapeutic Equivalence of Three Proportions Using Weighted Likelihood Ratio and Equivalence Cube

D. Carey¹, S. Bae³, R. Shanmugam², A. A. Bartolucci¹, K. P. Singh³

¹Comprehensive Cancer Center and Department of Biostatistics, University of Alabama at Birmingham, Birmingham, AL 35294 - 0022

²Department of Health Services Research, Southwest Texas State University, San Marcos, TX 78666

³Department of Biostatistics, School of Public Health, University of North Texas Health Science Center, Fort Worth, TX 76107-2699

Abstract: A current topic in clinical trials that is capturing the attention and the efforts of researchers is therapeutic equivalence (TE). The drugs are declared to be TE if the confidence intervals about their effectiveness lie within a pre-chosen equivalence range. In this article, we develop a methodology to determine if three treatments are equivalent with respect to their therapeutic effectiveness. Our primary interest is the ratio of their unknown chances of being effective treatments. The natural conjugate beta family of distributions is employed for the prior knowledge. Limiting values of the hyper-parameters of the conjugate family demonstrate that our approach is robust. If TE is not noticed, by allowing the equivalence region to vary, we could figure out the situations under which TE is achievable. For this aim, the weighted likelihood ratio (WLR) and equivalence cube techniques are used for comparing three proportions. Examples are given for illustration.

Keywords: Clinical Trials; Conjugate Beta Family; Equivalence Region; Non-Small-Cell Carcinoma; Lung Cancer

1. INTRODUCTION

Most phase III studies are designed to meet several endpoints in mind. One of these endpoints is the rate or proportion. In clinical trials, often one asks the question which therapy produces the highest proportion of success. The answer depends on the selected criteria in their protocols. These proportions are to depict the percentage of patients in a trial or on a particular treatment with certain characteristics.

Although there are numerous statistical approaches, it is worth mentioning that the Bayesian approach has some advantages. For example, the posterior distribution of the difference of two proportions was effectively used by authors including Hauck and Anderson (1986), Mau (1988), Bartolucci and Singh (1992), Pham-Gia and Turkkan (1993) and Singh (1996). In this article, we extend this idea for comparing three

proportions using the WLR and the 'equivalence cube'.

2. METHODOLOGY OF WEIGHTED LIKELIHOOD RATIO

In Bayesian analysis, multiple comparisons are often analytically intractable due to multiple integrations. A remedy lies in using numerical methods of integration. For this purpose, we need the posterior density. There are challenges in determining the posterior density for three proportions. For more detail, the reader is referred to Carey, Bartolucci, and Singh (2001).

For $H_0: \eta_1 = \eta_2 = 1$ against H_a : at least one distinct, the weighted likelihood ratio (WLR) is given by

$$L_D(H) = \frac{\int l(\xi, \eta_H) g(\xi, \eta_H) d\xi}{\iint \iint l(\xi, \eta) g(\xi, \eta) d\xi d\eta}$$

Let

$$\eta_1 = \frac{p_1}{p_2}, \quad \eta_2 = \frac{p_1}{p_3}, \quad \xi = p_1,$$

Then,

$$p_2 = \frac{\xi}{\eta_1} \text{ and } p_3 = \frac{\xi}{\eta_2}.$$

The absolute value of the Jacobian is

$$|J| = \begin{vmatrix} 0 & -\frac{\xi}{\eta_1^2} & 0 \\ 0 & 0 & -\frac{\xi}{\eta_2^2} \\ 1 & \frac{1}{\eta_1} & \frac{1}{\eta_2} \end{vmatrix} = \frac{\xi^2}{\eta_1^2 \eta_2^2}$$

Then the joint prior becomes

$$g(\xi, \eta_1, \eta_2) = \left(\frac{1}{B(\alpha, \beta)} \right)^3 (\xi)^{\alpha-1} (1-\xi)^{\beta-1} \left(\frac{\xi}{\eta_1} \right)^{\alpha-1} \left(1 - \frac{\xi}{\eta_1} \right)^{\beta-1} \left(\frac{\xi}{\eta_2} \right)^{\alpha-1} \left(1 - \frac{\xi}{\eta_2} \right)^{\beta-1} \frac{\xi^2}{\eta_1^2 \eta_2^2}$$

The joint likelihood function is given as follows:

$$l(\xi, \eta_1, \eta_2) = (\xi)^{y_1} (1-\xi)^{n_1-y_1} \left(\frac{\xi}{\eta_1} \right)^{y_2} \left(1 - \frac{\xi}{\eta_1} \right)^{n_2-y_2} \left(\frac{\xi}{\eta_2} \right)^{y_3} \left(1 - \frac{\xi}{\eta_2} \right)^{n_3-y_3}$$

Note that $g(\xi|\eta_H) = \frac{g(\xi, \eta)}{g(\eta)}$

Substituting in the values of the null gives

$$g(\xi|\eta_H) = \frac{\xi^{3\alpha-1} (1-\xi)^{3\beta-2-1}}{B(3\alpha, 3\beta-2)}$$

and

$$l(\xi, \eta_1, \eta_2) g(\xi|\eta_H) = \left(\frac{1}{B(3\alpha, 3\beta-2)} \right)$$

$$B(3\alpha + y_1 + y_2 + y_3, n_1 - y_1 + n_2 - y_2 + n_3 - y_3 + 3\beta - 2)$$

and

$$\int \int \int l(\xi, \eta_1, \eta_2) g(\xi, \eta_1, \eta_2) d\xi d\eta_1 d\eta_2$$

is equal to the triple integral of the following terms:

$$Q^* = \left(\frac{1}{B(\alpha, \beta)} \right)^3 (\xi)^{\alpha+y_1-1} (1-\xi)^{\beta+n_1-y_1-1} \left(\frac{\xi}{\eta_1} \right)^{\alpha+y_2-1} \left(1 - \frac{\xi}{\eta_1} \right)^{\beta+n_2-y_2-1} \left(\frac{\xi}{\eta_2} \right)^{\alpha+y_3-1} \left(1 - \frac{\xi}{\eta_2} \right)^{\beta+n_3-y_3-1} \frac{\xi^2}{\eta_1^2 \eta_2^2}$$

$$\text{Let } Q = \iiint B(\alpha, \beta)^3 Q^* d\xi d\eta_1 d\eta_2$$

then

$$L_D(H) = B \left(\begin{matrix} 3\alpha + y_1 + y_2 + y_3, \\ n_1 - y_1 + n_2 - y_2 + n_3 - y_3 + 3\beta - 2 \end{matrix} \right) \frac{(B(\alpha, \beta))^3}{B(3\alpha, 3\beta-2)Q}$$

For the hypothesis $H_0: \eta_3 = 1$ against $H_a: \eta_3 \neq 1$

where $\eta_3 = \frac{p_3}{p_2}$,

the WLR is obtained is given as follows:

$$L_D(H) = \frac{B(y_3 + y_2 + 2\alpha, n_2 - y_2 + 2\beta - 1 + n_3 - y_3)}{B(2\alpha, 2\beta - 1)} \bullet \left(\iint \left(\frac{1}{B(\alpha, \beta)} \right)^3 (\xi)^{\alpha+y_2-1} (1-\xi)^{n_2-y_2+\beta-1} (\eta_3 \xi)^{\alpha+y_3-1} (1-\eta_3 \xi)^{n_3-y_3+\beta-1} d\xi d\eta_3 \right)^{-1}$$

For $H_0: \eta_1 = \eta_3 = 1$ against H_a : at least one distinct, the WLR is given as follows:

$$L_D(H) = \frac{B(3\alpha + y_1 + y_2 + y_3, n_1 - y_1 + n_2 - y_2 + n_3 - y_3 + 3\beta - 2)}{B(3\alpha, 3\beta - 2)} \bullet \left(\iiint \left(\frac{1}{B(\alpha, \beta)} \right)^3 (\eta_1 \xi)^{\alpha+y_1-1} (1-\eta_1 \xi)^{n_1-y_1+\beta-1} (\xi)^{\alpha+y_2-1} (1-\xi)^{n_2-y_2+\beta-1} (\eta_3 \xi)^{\alpha+y_3-1} (1-\eta_3 \xi)^{n_3-y_3+\beta-1} \xi^2 d\xi d\eta_1 d\eta_3 \right)^{-1}$$

$$\eta_1 = \frac{p_1}{p_2}, \eta_3 = \frac{p_3}{p_2}, \text{ and } \xi = p_2.$$

For $H_0: \eta_2 = \eta_3 = 1$ against H_a : at least one distinct, the WLR is obtained as follows:

$$L_D(H) = \frac{B(3\alpha + y_1 + y_2 + y_3, n_1 - y_1 + n_2 - y_2 + n_3 - y_3 + 3\beta - 2)}{B(3\alpha, 3\beta - 2)} \bullet \left(\iiint \left(\frac{1}{B(\alpha, \beta)} \right)^3 (\eta_2 \xi)^{\alpha+y_1-1} (1-\eta_2 \xi)^{n_1-y_1+\beta-1} (\xi)^{\alpha+y_3-1} (1-\xi)^{n_3-y_3+\beta-1} \left(\frac{\xi}{\eta_3} \right)^{\alpha+y_2-1} \left(1 - \frac{\xi}{\eta_3} \right)^{n_2-y_2+\beta-1} \left(\frac{\xi}{\eta_3} \right)^2 d\xi d\eta_2 d\eta_3 \right)^{-1}$$

$$\eta_2 = \frac{p_1}{p_3}, \eta_3 = \frac{p_3}{p_2}, \text{ and } \xi = p_3.$$

3. DERIVATION OF EQUIVALENCE CUBE AXES

This section derives expressions for the “equivalence cube” axes. Without losing generality, assume $p_1 > p_2$; then, according to equivalence testing suggested by Blackwelder (1982) and Hauck and Anderson (1986), $p_1 - p_2 \leq \Delta$, where $\Delta = 0.2$. So,

$$\begin{aligned} p_1 - p_2 &\leq 0.2 \\ (p_1 / p_2) - 1 &\leq (0.2 / p_2) \\ (p_1 / p_2) &\leq 1 + (0.2 / p_2) \end{aligned}$$

Hence, we write

$$1 - (0.2 / p_2) \leq (p_1 / p_2) \leq 1 + (0.2 / p_2) \quad (3.1)$$

Similarly, assume $p_1 > p_3$. Thus,

$$\begin{aligned} p_1 - p_3 &\leq 0.2 \\ (p_1 / p_3) - 1 &\leq (0.2 / p_3) \\ (p_1 / p_3) &\leq 1 + (0.2 / p_3) \end{aligned}$$

Now, integrating the results, we note that

$$1 - (0.2 / p_3) \leq (p_1 / p_3) \leq 1 + (0.2 / p_3) \quad (3.2)$$

Moreover, assume $p_3 > p_2$. Thus,

$$\begin{aligned} p_3 - p_2 &\leq 0.2 \\ (p_3 / p_2) - 1 &\leq (0.2 / p_2) \\ (p_3 / p_2) &\leq 1 + (0.2 / p_2) \end{aligned}$$

Hence,

$$1 - (0.2 / p_2) \leq (p_3 / p_2) \leq 1 + (0.2 / p_2) \quad (3.3)$$

4. DATA SET DESCRIPTION

In this example, we illustrate using a real life data set. The patients are randomized to one of three treatments in an advanced non-small-cell carcinoma of the lung trial. The treatments are:

- CAMF (cyclophosphamide, adriamycin, methotrexate with folinic acid),
- CAP (cyclophosphamide, adriamycin, cisplatin), and
- CA (cyclophosphamide, adriamycin).

The total number of observations is 339. The three treatments are to be compared with respect to their ability to achieve a complete response

(CR) or partial response (PR). There are 13 responses out of 98 possibilities for treatment CAMF. The treatment CAP had a response proportion of 9 out of 113. There were 4 responses out of 128 for CA.

The second data set, a test set, consists of three treatments. The three treatments were PA, which had a response of 13 out of 20; CT with 12 out of 20 responses; and ON, which had 11 out of 20 responses.

5. NUMERICAL EXAMPLE OF WEIGHTED LIKELIHOOD RATIO

The Table 1 below shows the results for the weighted likelihood ratio (WLR)

for several values of α and β . Remember that $\eta_1 = p_1/p_2$ and $\eta_2 = p_1/p_3$. The tables give results using the data set consisting of treatments CAMF, CAP, and CA.

Table 1: Weighted Likelihood Ratio Results for $H_0: \eta_1 = \eta_2 = 1$

α	β	WLR
2	3	1.04×10^{-7}
3	2	4.60×10^{-1}

This example shows that this data is not equivalent considering the small values of the weighted likelihood ratio.

Table 2 consists of the numerical results of the second data set.

Table 2: Weighted Likelihood Ratio Results for $H_0: \eta_1 = \eta_2 = 1$

α	β	WLR
2	3	98.72
3	2	35.12

This example shows that this data is equivalent considering the large values of the weighted likelihood ratio.

6. NUMERICAL EXAMPLE FOR EQUIVALENCE CUBE AXES

The equivalence cube assumptions of x-axis $p_1 > p_2$, y-axis $p_1 > p_3$, and z-axis $p_3 > p_2$ are shown in the Figure 1.

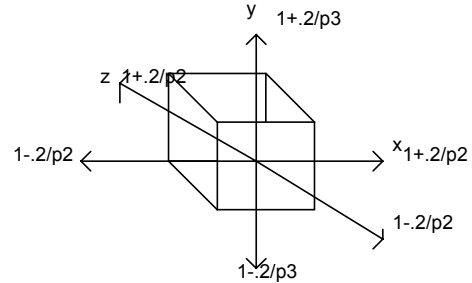


Figure 1: Equivalence cube setting

The 90% equivalence regions using the sample data values from the data set with $\alpha=2$ and $\beta=3$ and treatments, PA, CT, and ON are as follow:

Ratio	Equivalence Region
p_1/p_2	(0.899, 1.260)
p_1/p_3	(1.002, 1.358)
p_3/p_2	(0.703, 1.137)

The endpoints of the equivalence region fall with the limits of the axes for each proportion. That is, (0.899, 1.260) falls within (0.667, 1.333), (1.002, 1.358) falls within (0.636, 1.364), and (0.703, 1.137) falls within (0.667, 1.333). Hence, equivalence is established.

The 90% equivalence regions using the sample data values from the data set with setting $\alpha=3$ and $\beta=2$ and treatments, PA, CT, and ON are as follow:

Ratio	Equivalence Region
p_1/p_2	(0.908, 1.252)
p_1/p_3	(1.127, 1.333)
p_3/p_2	(0.717, 1.123)

The endpoints of the equivalence region fall with the limits of the axes for each proportion. Hence, the equivalence is established.

7. CONCLUSIONS

In this paper, we considered the problem of assessing therapeutic equivalence of three independent proportions using the weighted likelihood ratio and the equivalence cube. This paper assumes that all p_i 's were independent. It would be of great interest to continue this research with the assumption that the p_i 's are not independent. One possible method to be explored for this dependence assumption is the concept expressed in the De Finetti theorem on exchangeable variables (Heath and Sudderth 1976).

This paper presented some issues pertaining to the integration involved in deriving the posterior density for the pair wise comparison of three proportions. There is definitely a need for the development of more methods that would be beneficial in handling multi-dimensional integration problems from a computational perspective. Moreover, the triple integral in this research involved some beta functions with very interesting behavior. It would be of interest to direct attention to the study of the behavior of such complicated functions. The calculations for this research were done using the Monte Carlo method as well as basic integration principles. However, other methods, such as the Gibbs sampling algorithm, need more exploration.

This research would benefit greatly from another viewpoint. For example, though the subject of power is inconsistent in Bayesian framework, it would be of interest to see how it works out in our approach. Hauck and Anderson (1992) present types of bioequivalence and some related issues. Their work has two main areas where further research is needed. First, the statisticians need separate methods for assessing population bioequivalence and methods for individual bioequivalence. Secondly, there is a need for additional methods that are appropriate to measure bioavailability.

The development of other statistical inference methodologies is essential to address the diversity in clinical trials, the amount of available information before, during, and after the trial.

8. REFERENCES

Bartolucci, A. A. and Singh, K. P., Therapeutic equivalence- a Bayesian approach, *Proceedings of the Biopharmaceutical*

Blackwelder, W. C., Proving the null hypothesis in clinical trials. *Controlled Clinical Trials* 3, 345-353, 1982.

Carey, D., Bartolucci, A. A. and Singh, K. P., Assessment of therapeutic equivalence of three proportions using a Bayesian approach, *Proceedings of International Congress on Modeling and Simulation* 4, pp. 2005-2010, 2001.

Good, I. J., *Probability and the Weighing of Evidence*, London: Charles Griffin, 1950.

Hauck, W. W., & Anderson, S., A proposal for interpreting and reporting negative studies, *Statistics in Medicine* 5, 203-209, 1986

Hauck, W. W., & Anderson, S., Types of bioequivalence and related statistical considerations, *International Journal of Clinical Pharmacology, Therapy and Toxicology* 30, 181-187, 1992.

Heath, D., & Sudderth, W., De Finetti's theorem on exchangeable variables, *The American Statistician* 30, 188-189, 1976.

Mau, J., A Statistical Assessment of Clinical Equivalence. *Statistics in Medicine* 7,1267-1277, 1988.

Pham-Gia, T., & Turkkan, N., Bayesian analysis of difference of two proportions, *Communications in Statistics- Theory and Methods* 12, 1755-1771, 1993.

Singh, K. P. Therapeutic Equivalence Using a Rich Family of Prior Distributions *In Lifetime Data: Models in Reliability and Survival Analysis*. Ed. N. P. Jewell, A. C. Kimber, M. T. Lee, A. G. Whitmore. Kluwer Academic Publishers. Boston. pp. 315-322, 1996.