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THERAPEUTIC EQUIVALENCE ASSESSMENT (TEA) FOR EXPONENTIAL DATA

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Abstract

Active control equivalence trials (ACETs), conducted with the goal of demonstrating therapeutic equivalence, are of growing importance to the pharmaceutical industry, clinical medicine, government, and academia. In this paper, therapeutic equivalence is defined in terms of equivalent clinical outcome (e.g., survival) without regard to assessment of bioequivalence. The likelihood-ratio-based asymptotic fiducial and Bayesian methods for therapeutic equivalence assessment (TEA) are developed in the context of survival analysis, using the exponential

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distribution. The methods are illustrated using leukemia remission data.

1. Introduction

Active control equivalence trials (ACETs) have received much attention in the statistical literature. The reader is referred to Dunnett and Gent [3]; Blackwelder [2]; Patel and Gupta [15]; Hauck and Anderson [10]; Mau [14]; Makuch, Stephens and Escobar [13]; Durrelman and Simon [5]; Fleming [8]; Dunnett and Gent [4]; Ebbutt and Frith [6]; Robins [17]; Weins and Iglewicz [20]. Therapeutic equivalence refers to a new treatment being as efficacious as a standard treatment. Although the FDA has a very strict definition of therapeutic equivalence (FDA [9, p. 2937]) for regulatory purposes, therapeutic equivalence may be considered in a less restrictive context emphasizing "equivalent" efficacy in clinical outcome and therapeutic benefit to the patients. It is in this context, for the purpose of individual clinical decision making, that our methodology is the most beneficial.

Therapeutic equivalence and bioequivalence are two different concepts, despite its controversy. Foremost, the endpoints in therapeutic equivalence and bioequivalence are very different; the endpoint in the former is some measure of clinical outcome, the endpoint in the latter is typically related to blood/plasma levels. Also, assessment of therapeutic equivalence generally requires conduct of a clinical trial(s), whereas bioequivalence is often assessed in a much smaller setting, e.g., bioassays. Durrelman and Simon [5] write, "compared to the biological problem of bioavailability, the therapeutic equivalence of two treatments is a more pragmatic concept. Rather than assessing a theoretical equivalence, which makes little sense when the two treatments can be very different "in principio" (e.g., surgery versus lithotripsy), one is interested in therapeutic decision making." Indeed, in the view of the FDA, bioequivalence is a prerequisite for therapeutic equivalence, clearly establishing a difference between the two concepts.

As a particular example, in the context of breast cancer research, in estrogen-receptive women, consider two drugs, A and B, each for prevention of spread of the cancer. It is hypothesized that spread of the

cancer follows from either (1) increased peptide growth factor (GF) synthesis and subsequent binding of GFs with specific membrane-bound receptors which in turn signal the initiation of a sequence of intracellular actions resulting in cell division, or (2) binding of estrogen to those limited number of cells containing intracellular estrogen receptors; those cells, through a sequence of steps, secrete some of the GFs which then signal the initiation of (1) in nearby cells which otherwise are unresponsive to estrogen. Drug A could be targeted to block the binding of the GFs to their membrane receptors or to block the post-receptor signal transduction. Drug B could be targeted to block the binding of the estrogen to its receptor or to block an event in the estrogen post-receptor signal transduction mechanism. Success with either Drug A or Drug B would prevent spread of the cancer; therefore, the drugs would yield equivalent clinical outcome. However, the active ingredients in the drugs could certainly be different, thereby making assessment of bioequivalence not feasible, despite the therapeutic equivalence. Other examples where bioequivalence is not a relevant concern may be found in hypertension research.

There are a number of classical (non-Bayesian) methods for TEA. Dunnett and Gent [3] present a method of significance testing to compare two binomial samples with data summarized in 2×2 tables. Blackwelder [2] presents a method of hypothesis testing with a dichotomous outcome variable and sample sizes large enough for use of the normal approximation to the binomial. Patel and Gupta [15] present a method of hypothesis testing with a normally distributed response variable. Hauck and Anderson [10] use a confidence interval approach. Mau [14] presents a method of Cox's "confidence distributions" using the normal approximation to the binomial. Fleming [8] presents a method for time to event data, using Cox's proportional hazards regression to estimate the hazard ratio (or relative risk of failure) of the two treatments. The method uses confidence intervals for the hazard ratio to assess either superiority of one treatment or equivalence (for application in "non-inferiority" trials). Dunnett and Gent [4] present a procedure with union-intersection and intersection-union hypothesis testing approaches to test "simultaneously for a positive difference and for equivalence" (Dunnett and Gent [4, p. 1729]).

It is important to note that each of these methods pertains to either normally distributed means or binomially distributed proportions, with the exception of Fleming's [8] method. Recall that his method is based on Cox regression, and therefore, it is nonparametric. Our methodology (as well as the Bayesian methods addressed immediately below) employs parametric modeling in a progressively censored survival analysis setting. Alternatively, some Bayesian methods are available for TEA. Bartolucci and Singh [1] and Singh [18] present a method that is similar to the confidence interval approach above, instead using a Bayesian posterior credibility interval for the ratio of functions of parameters of survival distributions. Their method is developed using the translated exponential in the role of the survival distribution, along with inverted gamma and vague priors.

Recall that therapeutic equivalence can also be considered in a context emphasizing "equivalent" efficacy in clinical outcome and therapeutic benefit to the subjects, where bioequivalence is not a relevant concern. We wish to emphasize a focus on clinical outcome, survival patterns in particular, therefore, we consider TEA based on clinical outcome to be independent of (or, in addition to) any assessments of bioequivalence. Additionally, all of the above-mentioned methods for bioequivalence assessment are based on either means of a normal distribution (the data are usually log transformed first - usually base 10, sometimes base e) or on binomial proportions, i.e., none of the methods make use of survival distributions. In this paper, therapeutic equivalence is defined in terms of equivalent clinical outcome (e.g., survival) without regard to assessment of bioequivalence. The likelihood-ratio-based asymptotic fiducial and Bayesian methods for therapeutic equivalence assessment (TEA) are developed in the context of survival analysis, using the exponential distribution. The methods are illustrated using leukemia remission data.

2. Methodology

We present a likelihood ratio based asymptotic fiducial method for therapeutic equivalence assessment (TEA) for progressively censored survival data. In this paper, we develop the method for the exponential

distributed data. Our method requires an elicitation from a clinical expert to establish the maximum clinically insignificant difference between two treatments. Unlike some other methods, the method does not require a priori specification of the standard and experimental treatments. Our method provides a considerable amount of information for individual clinical decision making, as opposed to merely a hypothesis testing of "reject" or "do not reject" type, or a p-value, or even an often-misinterpreted classical confidence interval. The numerical value of our method is interpretable for individual clinical decision making. Also, for the exponential distributed data, the method is easily implemented in SAS.

The method requires data structure of an ordered pair for each of two treatment groups, (x_{iA}, c_{iA}) for $i = 1$ to n_A and (x_{iB}, c_{iB}) for $i = 1$ to n_B; note that n_A need not equal to n_B. Each x_i is either a time of death (t_i; survival time; uncensored observation) or a time of loss-to-follow-up (t_I^+; a progressively censored observation). Each c_i is either a 0 if the observation is uncensored or a 1 if the observation is censored. Therefore, the number of deaths for either treatment group, r_k, is given by

$$r_k = n_k - \sum_{i=1}^{n_k} c_{ik}, \quad k = A, B. \tag{2.1}$$

The two survival distributions are considered (clinically) equivalent if the distance between them is less than some clinically pre-specified value (note that this discussion is actually relevant for practical consideration). A question then arises: what is a suitable measure of the distance? In the setting of likelihood ratio test of

$$H_0 : f_1(t; \psi) = f_2(t; \psi) \quad \text{versus} \quad H_a : f_1(t; \psi_1) \neq f_2(t; \psi_2), \tag{2.2}$$

where ψ, ψ_1 and ψ_2 are parameter vectors, the likelihood ratio may be transformed into a measure of the distance

$$D = 2[L(\psi_1, \psi_2) - L(\psi)]. \tag{2.3}$$

Although, D is an unknown with respect to the sample space, it is a random variable in parameter space. We now apply the fiducial

arguments: $F_1(\Delta \mid D) = F(D \mid \Delta)$ (Fisher [7]; Quenouille [16]), where Δ is a measure of the distance between the two distributions. The distribution $f(D \mid \Delta)$ is not easy but an asymptotic result provides an alternate approach. Under H_0, D has an asymptotic chi-squared distribution with v degrees of freedom equal to the reduction from the total number of parameters in ψ_1 and ψ_2 to the number of parameters in ψ. Under H_a, D has an asymptotic non-central chi-squared distribution, $f(\chi^2; v, \lambda)$ with v degrees of freedom and non-centrality parameter

$$\lambda = (\theta_r - \theta_{ro})' V_r^{-1} (\theta_r - \theta_{ro}), \tag{2.4}$$

where θ_r and θ_{ro} correspond to a reparameterization of the hypotheses as

$$H_0 : \theta_r = \theta_{ro} \quad \text{versus} \quad H_a : \theta_r \neq \theta_{ro}$$

and, where V_r is the inverse of the Fisher Information matrix with elements

$$(V_{ij}^{-1}) = -E\left(\frac{\partial^2 \ln L}{\partial\theta_i \partial\theta_j}\right) = E\left(\frac{\partial \ln L}{\partial\theta_i}\frac{\partial \ln L}{\partial\theta_j}\right). \tag{2.5}$$

Therefore, although $f(D \mid \Delta)$ is not easily obtained, $f(D \mid \lambda)$ is easily obtained, as $f(x^2; v, \lambda)$. We therefore consider the fiducial distribution of λ given D, $f_f(\lambda \mid D)$, employing the fiducial argument $F_f(\lambda \mid D) = F(D \mid \lambda)$ (Fisher [7]; Quenouille [16]), estimating $F(D \mid \lambda)$ by $F(D \mid \hat{\lambda})$, now subsequent to the demonstration that $\hat{\lambda}$ is a sufficient statistic. The question arises: is λ as a suitable measure of the distance between the two distributions as is Δ?

Both Δ and λ are random variables ranging from 0 to ∞. If $\Delta = 0$, H_0 is true, as that is the only possible way for the numerator and denominator of the likelihood ratio to be equal. If $\lambda = 0$, then H_0 is true, by the definition of λ. As each Δ and λ increases, evidence builds in support of H_a; therefore, each increases as the distributions differ. The

relationship between Δ and λ is implicit, but monotonic. Therefore, asymptotically, λ is as suitable a measure of the distance as is Δ.

To perform the TEA, information must be elicited from a clinical expert in order to establish the maximum clinically insignificant difference between the two distributions. This information, which we will base on median survival times, must then be used to determine a clinically specified value, λ_{expert}. Once λ_{expert} has been established, one simply calculates $P_f(\lambda \le \lambda_{\text{expert}} \mid D) = F_f(\lambda_{\text{expert}} \mid D) \approx F(\lambda_{\text{expert}} \mid \hat{\lambda})$ to obtain the fiducial probability that the two distributions are as close as λ_{expert} or closer. Notably, there is no need to set a significance level a priori; in fact, there is considerable flexibility for individual clinical decision making at this point.

3. Exponential Data

In many survival data it is appropriate to assume that the data come from an exponential population. The likelihood function (Bartolucci and Singh [1]; Singh [18]) is given as follows:

$$e^{L(\beta)} = \left(\frac{1}{\beta}\right)^r e^{-\frac{1}{\beta}\left(\sum_{i=1}^{r} t_i + \sum_{i=r+1}^{n} t_i^+\right)}, \tag{3.1}$$

where t_i denotes an uncensored observation, t_i^+ denotes a censored observation, and $T = \sum_{i=1}^{r} t_i + \sum_{i=r+1}^{n} t_i^+$ denotes the total of all observations. In the setting of likelihood ratio test of

$$H_0 : f_1(t; \beta) = f_2(t; \beta) \quad \text{versus} \quad H_a : f_1(t; \beta_A) \ne f_2(t; \beta_B). \tag{3.2}$$

The estimated likelihood ratio is given by

$$\Lambda = \frac{e^{L(\hat{\beta})}}{e^{L(\hat{\beta}_A, \hat{\beta}_B)}}, \quad 0 < \Lambda < 1, \tag{3.3}$$

where $\hat{\beta} = \frac{T}{r} = \frac{\sum_{i=1}^{r} t_i + \sum_{i=r+1}^{n} t_i^+}{r}$ is the maximum likelihood estimate

(MLE) of β, with corresponding variance estimate

$$\hat{Var}(\hat{\beta}) = \frac{1}{-E\left(\frac{\partial^2 L(\beta)}{\partial \beta^2}\right)\Big|_{\beta=\hat{\beta}}} = \frac{\hat{\beta}^2}{2n-r}.$$

The MLEs and variance estimates in the denominator are obtained analogously.

To determine the non-centrality parameter to define the asymptotic fiducial distribution, we first reparameterize the hypotheses as

$$H_0 : \beta_A - \beta_B = 0 \quad \text{versus} \quad H_a : \beta_A - \beta_B \neq 0. \tag{3.4}$$

The non-centrality parameter is

$$\lambda = (\theta_r - \theta_{ro})' V_r^{-1} (\theta_r - \theta_{r0}); \tag{3.5}$$

whose estimate is

$$\hat{\lambda} = (\hat{\beta}_A - \hat{\beta}_B)' \hat{V}_r^{-1} (\hat{\beta}_A - \hat{\beta}_B). \tag{3.6}$$

Note that V_r^{-1} is simply $Var(\beta_A) + Var(\beta_B)$. We therefore estimate V_r^{-1} by

$$\hat{V}_r^{-1} = \left(\frac{\hat{\beta}_A^2}{2n_A - r_A} + \frac{\hat{\beta}_B^2}{2n_B - r_B}\right)^{-1}, \tag{3.7}$$

and then we obtain $\hat{\lambda}$ as

$$\hat{\lambda} = \frac{(\hat{\beta}_A - \hat{\beta}_B)^2}{\left(\frac{\hat{\beta}_A^2}{2n_A - r_A} + \frac{\hat{\beta}_B^2}{2n_B - r_B}\right)}. \tag{3.8}$$

Having obtained $\hat{\lambda}$, an asymptotic fiducial distribution, $f_f(\lambda \mid D)$, may now be defined according to

$$F_f(\lambda \mid D) = F_f(D \mid \lambda) \approx F(D \mid \hat{\lambda}). \tag{3.9}$$

We propose the required elicitation from a clinical expert to be an

estimate of the maximum clinically insignificant difference in median survival times for the two treatment groups; we shall call the estimate d_{sme}. We first compute $\hat{\beta}_{\text{mid}}$, the midpoint of $\hat{\beta}_A$ and $\hat{\beta}_B$, and $\hat{\text{med}}_{\text{mid}} = \hat{\beta}_{\text{mid}} \times -\ln 0.5 = \hat{\beta}_{\text{mid}} \times 0.69314718$. We then compute

$$\hat{\text{med}}_{\text{Asme}} = \begin{cases} \hat{\text{med}}_{\text{mid}} - \frac{1}{2} d_{\text{sme}}, & \text{if } \hat{\beta}_A < \hat{\beta}_B, \\ \hat{\text{med}}_{\text{mid}} + \frac{1}{2} d_{\text{sme}}, & \text{if } \hat{\beta}_A > \hat{\beta}_B, \end{cases} \tag{3.10}$$

and

$$\hat{\text{med}}_{\text{Bsme}} = \begin{cases} \hat{\text{med}}_{\text{mid}} - \frac{1}{2} d_{\text{sme}}, & \text{if } \hat{\beta}_A > \hat{\beta}_B, \\ \hat{\text{med}}_{\text{mid}} + \frac{1}{2} d_{\text{sme}}, & \text{if } \hat{\beta}_A < \hat{\beta}_B, \end{cases} \tag{3.11}$$

so that

$$|\hat{\text{med}}_{\text{Asme}} - \hat{\text{med}}_{\text{Bsme}}| = d_{\text{sme}}. \tag{3.12}$$

Next, we compute $\hat{\beta}_{\text{Asme}} = \hat{\text{med}}_{\text{Asme}} \div (-\ln 0.5)$ and $\hat{\beta}_{\text{Bsme}} = \hat{\text{med}}_{\text{Bsme}} \div (-\ln 0.5)$. Finally, we compute the implied λ_{expert}, as

$$\lambda_{\text{expert}} = \frac{(\hat{\beta}_{\text{Asme}} - \hat{\beta}_{\text{Bsme}})^2}{\left(\frac{\hat{\beta}^2_{\text{Asme}}}{2n_A - r_A} + \frac{\hat{\beta}^2_{\text{Bsme}}}{2n_B - r_B} \right)}. \tag{3.13}$$

Though, the clinical expert only provides information to estimate the medians with a difference of d_{sme}. We are able to make inferences regarding therapeutic equivalence of the distributions, and not merely therapeutic equivalence of the medians.

4. Applications: Acute Myelogenous Leukemia Data

A phase III trial was performed to compare remission induction in two groups of acute myelogenous leukemia patients (Vogler et al. [19]). The goal of the trial was to demonstrate that the experimental treatment, the anthracycline idarubicin (IDR) in combination with cytarabine (CA), was superior, in remission induction, to a standard treatment, the

anthracycline daunorubicin (DNR) in combination with CA. The trial demonstrated the hypothesized superiority of IDR in remission induction. The only inference made with respect to survival was that no statistically significant difference existed between the two treatment groups, assessed by the log-rank and generalized Wilcoxon rank sum tests. In this section, we demonstrate the likelihood ratio based asymptotic fiducial method for TEA by applying it to this leukemia data, with the goal of demonstrating therapeutically equivalent survival in the two treatment groups. We begin with description of the data structure as well as preliminary descriptive analyses of the data.

Two hundred thirty patients were randomized, 111 to IDR and 119 to DNR. We use 109 and 115 patients, respectively (the exclusions are for incorrect diagnosis, randomized but not treated, or death prior to treatment). There were 104 deaths in the IDR group and 103 deaths in the DNR group, implying 5 and 12 censored observations, respectively. The data are measured in months. For the exponential distribution, MLEs for the IDR group and the DNR group are $\hat{\beta}_e = 16.972$ and $\hat{\beta}_s = 15.725$, respectively. The MLE for the two groups combined is $\hat{\beta}_c = 16.352$. We perform likelihood ratio test for comparing one exponential population with two exponential populations. The likelihood ratio test has a p-value of 0.583, failing to demonstrate evidence for two populations. This result is the desired one as a preliminary for TEA, for if this test demonstrates evidence in favor of two populations, then one treatment is superior to the other in terms of survival. As neither treatment outperforms the other, we may later examine clinically equivalent survival using the exponential distribution.

We examine goodness of fit using the method of Hollander and Proschan [11] and Lee [12, p. 191]. It is noteworthy that this method does lack power, as the test is against a universal alternative. However, a strength of this test is its ability to handle progressive censored data. For IDR and DNR, the test has p-values of 0.7495 and 0.4238, respectively, yielding conclusions that the exponential distribution is appropriate. It is very important that the methodology not be blindly applied in practice. Simply, if a subject matter expert examines the MLEs of the survival

functions and feels that the shapes of the curves for the two treatment groups differ too much to be considered clinically equivalent, then there is no point in performing a statistical TEA. Using the MLEs of the exponential distribution parameters, the Figure gives the survival curves for the acute myelogenous leukemia survival data. The survival curves appear to be very close. Note that at the time of publication by Vogler et al. [19], the authors did feel that the survival curves appear to be clinically equivalent, but no statistical assessment was available to them at that time.

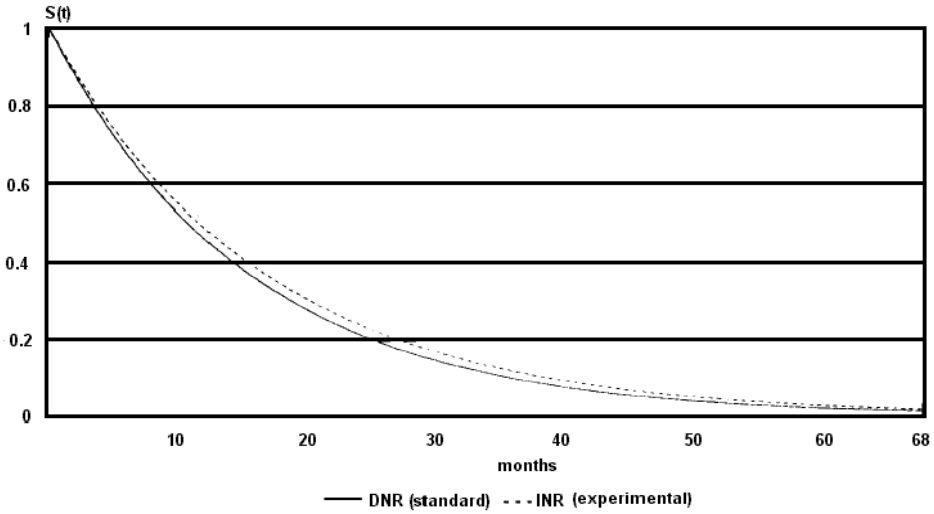

Figure. Exponential ML $S(t)$ for leukemia survival data

The maximum clinically insignificant difference in median survival times for the two treatment groups, d_{sme} has been specified by one of the Vogler et al. [19] authors, Dr. George A. Omura (private communication), to be 3 months. The fiducial probability of therapeutic equivalence with $d_{\text{sme}} = 3$ months is 0.919 and the credibility of therapeutic equivalence is 0.796. The first consideration for a patient is whether or not an approximately 92% or 80% "chance" of "equivalent" survival is acceptable.

The subject matter expert has also specified $3 < d_{\text{sme}} < 6$ to be a clinical "gray area". Therefore, further flexibility for individual clinical decision making is derived by examining the fiducial probability and

credibility through this gray area. For an additional conservative consideration, one may examine the fiducial probability and credibility below the subject expert's specification as well. Results are given in the Table.

Table. Exponential TEA for leukemia survival data

d_{sme}	Fiducial probability	Credibility
2.0	0.75248	0.50549
2.5	0.85300	0.66835
3.0	0.91915	0.79685
3.5	0.95889	0.88628
4.0	0.98068	0.94174
4.5	0.99160	0.97262
5.0	0.99661	0.98815
5.5	0.99873	0.99527

For instance, if an individual is only willing to consider a difference of 2 months in median survival times to be clinically insignificant, then the fiducial approach indicates a 75.3% "chance" of "equivalent" survival, while the Bayesian approach indicates 50.6%. All of this information, in conjunction with all other information regarding the treatments (e.g., quality of life), may be used by an individual patient with his or her physician to make a treatment decision.

Additionally, the subject matter expert has also specified the minimum clinically significant difference in median survival times for the two treatment groups to be 6 months. The probability of a clinically significant difference (here, at least 6 months) may also be calculated from the asymptotic fiducial and Bayesian posterior distributions. These probabilities are essentially fiducial and Bayesian analogs to classical likelihood ratio testing with the exception that these probabilities pertain to both statistically and clinically significant differences, while likelihood ratio testing pertains only to statistically significant difference.

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