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Abstract: Now we extend one method into a sequence of binomial data, propose a stepwise confidence interval method for toxicity study and can identify a minimum effective dose. The first one is based on the well-known conditional confidence intervals for odds ratio, and the other one comes from Santner (1993).″ small-sample confidence intervals for the difference of two success probabilities″, and it produces exact intervals, through employing our method, all the declarations can be guaranteed to be correct with a probability higher than 100(1-α)%. That is, the error rate is properly controlled.

Keywords: Risk Difference, Stepwise Confidence Interval, Practical Equivalence, Dose-Response

0 Introduction We often face the safety evaluation of a new developed drug and finding the minimum effective dose level because regulatory agencies allow a drug to be marketed if it’s manufacturer can demonstrate that its product is safe and can achieve the pre-specified efficacy.

Ago,Hsu and Berger (1999) proposed a stepwise confidence interval method for toxicity studies and for dose-response study under equal variances. But in fact, this is often in doubt.

And, currently, Tao et al. (2002) proposed a new stepwise confidence interval procedure to deal with the variance-free problem as a proper evaluation method. By employing the Stern’s two-stage sampling method, they achieve it. Now we extend one method into a sequence of binomial data, propose a stepwise confidence interval method for toxicity study and can identify a minimum effective dose,

In their article they assume that a random sample $Y_{i1},Y_{i2},Y_{i3}...,Y_{ini}$ is observed from the ith dose level, and considering the following one-way model

$$Y_{ij} = \mu_i + \varepsilon_{ij}, i = 0,1,...k+1; j = 1,2,...ni$$

here μ_0 is the mean response of control group received a placebo and $\mu_1,\mu_2,\ldots,\mu_{k+1}$ are the mean responses to an increasing levels of exposure to a drug, ε_{ij} (i=0,1、…、k+1) are $i.i.d$ normal variables with mean 0 and unknown variances σ_i^2.

To evaluation efficacy for dose of different level, we caring about identification of the minimum effective dose(MED), which means the minimum dose level such that the response probability is significantly better than the response probability of the negative control group. Therefore, we proceed to give proper or improved solutions upon these problems, propose a method for considering the population as binomial distribution which is more believable in practice.

We define the minimum effective dose(MED) as following,

$$MED = \min\{d_i : p_i - p_0 > \delta\}$$

Note: here constant δ used as threshold

In fact, to motivate our stepwise procedure, it is desirable for any test procedure not to declare a lower dose to be efficacious if it does not declare a higher dose level to be efficacious.

This can be achieved by answering the question $p_i - p_0 > \delta$ in a stepwise manner, continuing only when the answer is affirmative, stop at the first M for which the inference is impossible and in following we define our procedure and proved it is reliable in generating simple methods with meaningful guarantee against incorrect decision under the control probability.

Step 0:

If $\Delta_l^k(X) \geq \delta$, then assert

$p_k - p_0 \geq \delta$ Go to step 1,

Else declare $p_k - p_0 \geq \Delta_l^k(X)$, and recommend none dose level as efficacious, then stop the experiment.

Step 1:

If $\Delta_l^{k-1}(X) \geq \delta$, then assert

$p_k - p_0 \geq \delta$, and go to step 2.

Else declare $p_{k-1} - p_0 \geq \Delta_l^{k-1}(X)$、 and the dose level d_k is recommended as the MED.

… …

Step k-1:

If $\Delta_l^1(X) \geq \delta$、then assert

$p_1 - p_0 \geq \delta$ And go to step k.

Else declare $p_1 - p_0 \geq \Delta_l^1(X)$、 then the dose level d_2 is recommended as MED.

Step k:

Declare all the dose level is efficacious and then d_1 is recommended as MED, and stop the experiment.

Suppose the step M is the step at which our stepwise procedure stop and then we have

Theorem 2.1. for all $j=1,2,...,k, \Delta_l^{k-j+1}(X)$ is supposed as a lower confidence bound with confidence level $1-\alpha$ for $p_{k-j+1}-p_0$ 、 then for all $p=(p_0,p_1,p_2,...,p_k)\in\Theta$ we have

$$P_p\left(\bigcap_{j=1}^{M}\{p_{k-j+1}-p_0>\delta\}\bigcap\{p_{k-M}-p_0>\Delta_l^{k-M}(X)\}\right)\geq 1-\alpha\text{、}$$

Where $j=2,...,k+1.$

Proof：Case 1. M =0, it follows immediately from the definition of the low confidence bound.

Case 2, $1\leq M\leq k$ for all $j=1,2,...,k$, we have

(1) $C_j(Y)=\{p_{k-j+1}-p_0>\Delta_l^{k-j+1}(X)$

(2) $\Theta_1=\{p_k-p_0\leq\delta\}$, for all $j=2,...,k+1,$

we define

$$\Theta_j=\bigcap_{l-1}^{j-1}\{p_{k-l+1}-p_0>\delta\}\bigcap\{p_{k-j+1}-p_0\leq\delta\}$$

Then we have

$\Theta_j, j=1,...,k+1$ Partition the whole parameter space Θ, so

$$\bigcup_{j-1}^{k+!}(C_j(Y)\bigcap\Theta_j)$$

is a confidence set for $\theta=(p_0,p_1,p_2,...,p_k)$ with confidence level $1-\alpha$, and when $\theta\in\Theta_j$, we have

$$P_\theta\left\{\theta\in\bigcup_{j-1}^{k+1}(C_j(Y)\bigcap\Theta_j)\right\}=P_\theta\{\theta\in C_j(Y)\}\geq 1-\alpha$$

from the definition of M, we have

1) If $l<M+1,$ then $C_l(Y)\bigcap\Theta_l=\Phi$, because of $\Theta_l\subset\{p_{k-l+1}-p_0\leq\delta\}.$

2) If $l > M+1$, then clearly $\Theta_l \subset \bigcap_{j=1}^{M+1}\{p_{k-j+1} - p_0 > \delta\}$, and we have

3) $\{p_{k-M} - p_0 > \delta\} \subset C_{M+1}(Y)$,

so

$$C(Y) = \bigcup_{i=1}^{k+1}(C_i(Y) \cap \Theta_i)$$

$$= \bigcup_{i=M+1}^{k+1}(C_i(Y) \cap \Theta_i)$$

$$\subset (C_{M+1}(Y) \cap \Theta_{M+1}) \cup \left(\bigcap_{i=1}^{M+1}\{p_{k-i-1} - p_0 > \delta\}\right)$$

$$= (\bigcap_{i=1}^{M-1}\{p_{k-i} - p_0 > \delta\} \cap \{p_{k-M} - p_0 \le \delta\} \cap C_{M+1}(Y)) \cup \left(\bigcap_{i=1}^{M+1}\{p_{k-i+1} - p_0 > \delta\}\right)$$

$$= (\bigcap_{i=1}^{M}\{p_{k-i+1} - p_0 > \delta\} \cap \{p_{k-M} - p_0 \le \delta\} \cap C_{M+1}(Y)) \cup \left(\bigcap_{i=1}^{M+1}\{p_{k-i+1} - p_0 > \delta\} \cap C_{M+!}(Y)\right)$$

$$= \bigcap_{i=1}^{M}\{p_{k-i+!} - p_0 > \delta\} \cap C_{M+1}(Y)$$

and this completes the proof of the theorem.

From the process of our proof, we can find, so long as we can provide a confidence interval with coverage $100(1-\alpha)\%$ for the risk difference of $p_i - p_0, i = 2,3,...,k+1$, then our procedure can perform well, and thus we applied our procedure with much more confidence in practice. So in the next section of the paper, we will review two typical methods of creating the confidence interval for risk difference of $p_i - p_0, i = 2,3,...,k+1$ with confidence level of $100(1-\alpha)\%$.

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