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LETTER TO THE EDITOR

Sample Size Determination for the Two One-Sided Tests Procedure in Bioequivalence

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Approximate formulae of sample sizes for Schuirmann's two one-sided tests procedure are derived for bioequivalence studies with the 2×2 crossover design. These formulae are simple enough to be carried out with a pocket calculator.

KEY WORDS: sample size; power; bioequivalence.

Phillips (1) presented a method for power calculation of Schuirmann's two one-sided tests procedure (2) based on the bivariate noncentral *t*-distribution (3). He also provided a table of sample sizes required for the procedure. However, formulas for determination of sample size for the two one-sided tests procedure were not provided.

Ideally, the entire power curve could be used to determine the sample size in a decision-theory context. Practically, formulas are very useful, however, to calculate the sample size for a specific combination of the mean difference in bioavailability and intrasubject variability. Hence, in this letter, we present approximate formulas for calculation of sample sizes for a bioequivalence study with the 2×2 crossover design. These formulas can be carried out easily with a pocket calculator.

First, we define the following quantities required in the formulas:

$$\theta = [(\mu_T - \mu_R)/\mu_R] \times 100$$

$$CV = [(\sqrt{MSE})/\mu_R] \times 100$$

$$\nabla = \text{the bioequivalence limit}$$

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$t(\alpha, v)$ = the upper αth percentile of a t-distribution with v degrees of freedom

where, μ_T, μ_R are the average bioavailability of the test and reference formulations, respectively; MSE is the mean square error from the analysis of variance table for the standard 2×2 crossover design.

Note that θ is the difference in average bioavailability between the two formulations expressed in percentage of the average reference bioavailability while CV stands for the coefficient of variation, which is the intrasubject variability expressed in percentage of the average reference bioavailability. According to the current FDA guidelines, ∇ is usually set to be $\pm 20\%$ of the average reference bioavailability in most bioequivalence studies.

Because the power curves of Schuirmann's two one-sided tests procedure are symmetric about zero (1), we only present the approximate formulas for the case where $\theta \geq 0$ and $\nabla \geq 0$. The number of subjects required to achieve an $1-\beta$ power at the α nominal level is $N = 2n$; where if $\theta = 0$

$$n \geq [t(\alpha, 2n-2) + t(\beta/2, 2n-2)]^2 [CV/\nabla]^2 \tag{1}$$

and if $\theta > 0$

$$n \geq [t(\alpha, 2n-2) + t(\beta, 2n-2)]^2 [CV/(\nabla - \theta)]^2 \tag{2}$$

n is the number of subjects required per sequence. Formula (1) was also derived by Westlake (4) using the confidence interval. Schuirmann (5) has also given an approximate formula for sample size for bioequivalence. But the explicit formula he gives is only for a difference of 10%.

In Formulas (1) and (2), β is the probability of a Type II error concluding bioinequivalence where in fact the two formulations are bioequivalent. θ and CV can usually be obtained from previous studies. However, because the degrees of freedom $(2n-2)$ are usually unknown, the easy way to find the sample size is to enumerate n. A SAS program for calculation of sample sizes based on the proposed approximate formulae is available from the authors upon request.

The following example illustrates the computation of sample size to achieve an 80% power at the 5% nominal level when $\theta = 5\%$ and $\nabla = 20\%$. Suppose from the previous studies the estimated CV is 15.66% and our initial guess of n is 6. Since $t(0.05, 10) = 1.812$ and $t(0.20, 10) = 0.879$, then by Formula (2)

$$n \geq (1.812 + 0.879)^2 [15.66/(20-5)]^2 = 7.9 \approx 8$$

We then use $n=8$ as the initial value for the next enumeration. Because $t(0.05, 14)=1.761$ and $t(0.20, 14)=0.868$, again using Formula (2)

$$n \geq (1.761+0.868)^2[15.66/(20-5)]^2=7.5\approx 8$$

Since the last two enumerations generate the same required sample size per sequence, a total of $2\times 8=16$ subjects would be required to achieve an 80% power at the 5% nominal level, if θ is 5% of the average reference bioavailability. The actual power for 16 subjects, as verified by the SAS program kindly provided by Dr. Phillips, is 81.96%, whereas the power for 14 subjects is 76.12%.

Table I. Sample Sizes for Schuirmann's Two One-sided Tests Procedure at $\nabla=0.2\mu_R$ and the 5% Nominal Level

		$\theta=\mu_T-\mu_R$			
Power	*CV* (%)	0%	5%	10%	15%
80%	10	8	8	16	52
	12	8	10	20	74
	14	10	14	26	100
	16	14	16	34	126
	18	16	20	42	162
	20	20	24	52	200
	22	24	28	62	242
	24	28	34	74	288
	26	32	40	86	336
	28	36	46	100	390
	30	40	52	114	448
	32	46	58	128	508
	34	52	66	146	574
	36	58	74	162	644
	38	64	82	180	716
	40	70	90	200	794
90%	10	10	10	20	70
	12	10	14	28	100
	14	14	18	36	136
	16	16	22	46	178
	18	20	28	58	224
	20	24	32	70	276
	22	28	40	86	334
	24	34	46	100	396
	26	40	54	118	466
	28	44	62	136	540
	30	52	70	156	618
	32	58	80	178	704
	34	66	90	200	794
	36	72	100	224	890
	38	80	112	250	992
	40	90	124	276	1098

Table I presents the required total sample sizes necessary to achieve either an 80 or 90% power for θ from 0 to 15% by increments of 5% as well as *CV*s from 10 to 40% by increments of 2%.

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