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INTERVAL ESTIMATION OF TREATMENT EFFECTS IN DOUBLE CONSENT RANDOMIZED DESIGN

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Abstract: The double consent randomized design, in which the physician and the patient know exactly what treatment the patient receives, has been proposed to alleviate the concern in carrying out a conventional randomized trial. In the latter, the assignment of patients to treatments after obtaining patients' informed consents depends completely on a chance mechanism. We develop four interval estimators, two using the delta method or the principle of Fieller's Theorem calculated over the pooled samples of eligible patients, and two calculated over the samples excluding patients who have treatment preference. Using Monte Carlo simulation, we evaluate and compare the performance of these estimators in a variety of situations. We note that the estimators using the principle of Fieller's Theorem outperform those derived from the delta method with respect to both coverage probability and average length in almost all situations considered here. We further note that when the expected number of patients who have no treatment preference is moderate or large (say ≥ 25) per treatment, the interval estimator using Fieller's Theorem calculated over the restricted samples is generally more efficient than those calculated over the entire pooled samples without much loss of accuracy as measured by coverage probability. On the other hand, when the expected number of patients who have no treatment preference is small, the coverage probability for the estimators calculated over the restricted samples tends to be less than the desired confidence level, while the coverage probability of the estimator using Fieller's Theorem on the pooled samples may still agree with the desired confidence level.

Key words and phrases: Delta method, Fieller's theorem, interval estimation, randomized consent design.

1. Introduction

In a conventional randomized trial, the assignment of patients to treatments, after obtaining patients' informed consents, depends completely on a chance mechanism. As noted by Zelen (1982, 1990), at the time of consent the physician and the patient do not know which treatment the patient will receive. This can compromise the relationship between the physician and the patient. Furthermore, patients may originally agree to participate in a conventional randomized trial, but have reservation about continuing once the treatment is known. Some patients may even decline the treatment. To alleviate this situation, Zelen (1990)

proposed a double consent randomized design in which patients are randomly assigned to the treatments before their consent is sought. After assigning an eligible patient to a treatment, we approach the patient for consent and discuss all potential risks, benefits, and treatment opinions. We then ask the patient "if he/she prefers to receiving any particular treatment, or he/she simply has no treatment preference". If there is no treatment preference, the patient receives the randomly assigned treatment. Otherwise, the patient receives the treatment of choice. Thus the physician and the patient know which treatment applies. Zelen (1977, 1979, 1990) published a series of papers about the use of the randomized consent design and included a list of projects employing the design. Subsequently, numerous papers have discussed a variety of statistical issues associated with the randomized consent design (Anbar (1983), McHugh (1984), Zelen (1983), Matts and McHugh (1987, 1993), Bernhard and Compagnone (1989)). None of these papers, however, focuses on interval estimation of the treatment effects in the double consent randomized design.

Under the double consent randomized design, we consider four interval estimators: two using the delta method or the principle of Fieller's Theorem (Casella and Berger (1990), Chap.9) calculated over the pooled sample of all eligible patients, and two using calculated over patients who have no treatment preference. On the basis of Monte Carlo simulation, we evaluate and compare the performance of these estimators in a variety of situations.

2. Assumptions and Interval Estimation

Consider the use of a double consent randomized design to compare experimental ($i = 1$) and standard ($i = 2$) treatments. Following Zelen (1990), we assume that a physician will only attempt to register a patient in a clinical trial if the physician has no treatment preference. We assume further that a patient who enters a clinical trial using a randomized consent design will agree to receive the assigned treatment if it coincides with the patient's preference, or if the patient has no treatment preference. Suppose there are N such eligible patients. First we randomly assign these patients to one of the two treatment groups. We then approach patients for consent. The assigned patients have choices to stay with the original assignment or switch to the other treatment group. In other words, a patient will receive the randomly assigned treatment if the patient has no treatment preference. Otherwise, the patient receives the treatment according to whatever he/she chooses. Let Y_j denote the response on the jth patient ($j = 1, \ldots, N$). Furthermore, let S_1 denote the collection of labels j for those subjects who are randomly selected to receive the experimental treatment ($i = 1$). We can then express the random response Y_j on the jth patient as

(Zelen (1990)):

$$Y_j = 1(j \in S_1)\delta_{0j}\mu_1 + 1(j \in S_1)\delta_{1j}\mu_1^\star + 1(j \in S_1)\delta_{2j}\mu_2^\star + [1 - 1(j \in S_1)]\delta_{0j}\mu_2 + [1 - 1(j \in S_1)]\delta_{1j}\mu_1^\star + [1 - 1(j \in S_1)]\delta_{2j}\mu_2^\star + \epsilon_j, \quad (1)$$

where $1(j \in S_1)$ is 1 if $j \in S_1$ and 0 otherwise; $\delta_{0j} = 1$ if the jth patient has no preference and $= 0$ otherwise; $\delta_{1j} = 1$ if the jth patient prefers the experimental treatment and $= 0$ otherwise; $\delta_{2j} = 1$ if the jth patient prefers the standard treatment and $= 0$ otherwise; $\delta_{0j} + \delta_{1j} + \delta_{2j} = 1$, $\mathrm{P}(\delta_{lj} = 1) = \theta_l$ for $l = 0, 1, 2$; μ_i and $\mu_i^\star$, $i = 1, 2$, denote the unknown mean responses for patients who have no treatment preference and for patients who have treatment preference, respectively; ϵ_j denotes the measurement error and independently follows a distribution with $E(\epsilon_j) = 0$ and $\mathrm{Var}\,(\epsilon_j) = \sigma^2$; ϵ_j, δ_{lj}, and $1(j \in S_1)$ are independent. As noted by Zelen (1990), this model allows the mean response to vary between patients who have treatment preference and those who do not, even when they receive the same treatment. Furthermore, given a total sample size N, equal sample allocation between the two treatments is generally optimal for maximizing power. We suppose n patients are assigned to each of the two treatments, $N = 2n$. As does Zelen (1990), we concentrate on interval estimation of the difference in the mean responses between the two treatments among patients who have no treatment preference: $\Delta = \mu_1 - \mu_2$.

On the basis of (1), it follows that the expectation of the difference in the two pooled sample means over all eligible patients who are randomly assigned to treatments, but may actually receive the other treatment according to patients' preference, is

$$E(\bar{Y}_1 - \bar{Y}_2) = \theta_0(\mu_1 - \mu_2), \quad (2)$$

where $\bar{Y}_1 = \sum_j 1(j \in S_1)Y_j/n$, and $\bar{Y}_2 = \sum_j [1 - 1(j \in S_1)]Y_j/n$. Because $\theta_0 \leq 1$, $|E(\bar{Y}_1 - \bar{Y}_2)| \leq |\mu_1 - \mu_2|$. In other words, $\bar{Y}_1 - \bar{Y}_2$ tends to underestimate the absolute magnitude of the difference between the two treatment mean effects. Under (1), after some algebraic manipulations, we find

$$\mathrm{Var}\,(\bar{Y}_1 - \bar{Y}_2) = 4\{\theta_0(1 - \theta_0)[\frac{\mu_1^2 + \mu_2^2}{2}] + (\mu_1^\star)^2\theta_1(1 - \theta_1) + (\mu_2^\star)^2\theta_2(1 - \theta_2) + \sigma^2 - (\mu_1 + \mu_2)\theta_0[\mu_1^\star\theta_1 + \mu_2^\star\theta_2] - 2\mu_1^\star\theta_1\mu_2^\star\theta_2\}/N. \quad (3)$$

Furthermore, we can show that an unbiased estimator of (3) is the traditional sample variance estimator

$$\widehat{\mathrm{Var}}\,(\bar{Y}_1 - \bar{Y}_2) = \frac{2}{N}[S_1^2 + S_2^2], \quad (4)$$

where $S_1^2 = \sum_j 1(j \in S_1)(Y_j - \bar{Y}_1)^2/(n-1)$ and $S_2^2 = \sum_j (1 - 1(j \in S_1))(Y_j - \bar{Y}_2)^2/(n-1)$. This suggests that we can estimate the $\mathrm{Var}\,(\bar{Y}_1 - \bar{Y}_2)$ without

estimating θ_0, θ_1, θ_2, σ^2, μ_1, μ_2, $\mu_1^\star$, and $\mu_2^\star$. By contrast, (4) is biased under a single-consent randomized design (Matts and McHugh (1993)).

Because of (2), a consistent estimator of $\Delta = \mu_1 - \mu_2$ is

$$\hat{\Delta} = (\bar{Y}_1 - \bar{Y}_2)/\hat{\theta}_0, \tag{5}$$

where $\hat{\theta}_0 = \sum_{j=1}^{\mathrm{N}} \delta_{0j}/N$. Note that $\mathrm{Cov}\,(\hat{\theta}_0,\ \bar{Y}_1 - \bar{Y}_2) = (\mu_1 - \mu_2)\theta_0(1-\theta_0)/N$, and hence $\mathrm{Var}\,(\hat{\Delta})$, by the delta method, is

$$\mathrm{Var}\,(\hat{\Delta}) = \mathrm{Var}\,(\bar{Y}_1 - \bar{Y}_2)/\theta_0^2 - (\mu_1 - \mu_2)^2(1-\theta_0)/(N\theta_0). \tag{6}$$

To estimate the $\mathrm{Var}\,(\hat{\Delta})$, we substitute $\hat{\theta}_0$ for θ_0, $\bar{Y}_1 - \bar{Y}_2$ for $\theta_0(\mu_1 - \mu_2)$, and $\widehat{\mathrm{Var}}\,(\bar{Y}_1 - \bar{Y}_2)$ for $\mathrm{Var}\,(\bar{Y}_1 - \bar{Y}_2)$, and hence obtain the variance estimator

$$\widehat{\mathrm{Var}}\,(\hat{\Delta}) = \widehat{\mathrm{Var}}\,(\bar{Y}_1 - \bar{Y}_2)/\hat{\theta}_0^2 - (\bar{Y}_1 - \bar{Y}_2)^2(1-\hat{\theta}_0)/(N\hat{\theta}_0^3). \tag{7}$$

These observations suggest that an asymptotic $100(1-\alpha)\%$ confidence interval of Δ is

$$\left[\hat{\Delta} - Z_{\alpha/2}\sqrt{\widehat{\mathrm{Var}}\,(\hat{\Delta})},\quad \hat{\Delta} + Z_{\alpha/2}\sqrt{\widehat{\mathrm{Var}}\,(\hat{\Delta})}\ \right], \tag{8}$$

where $\widehat{\mathrm{Var}}\,(\hat{\Delta})$ is given by (7). Note that $\hat{\Delta}$ is a ratio and its sampling distribution can be skewed when N is not large. To alleviate this concern, we look to Fieller's Theorem and consider $Z = (\bar{Y}_1 - \bar{Y}_2) - \Delta\hat{\theta}_0$. One has $E(Z) = 0$. Also, since $\mathrm{Cov}\,(\hat{\theta}_0, \bar{Y}_1 - \bar{Y}_2) = (\mu_1 - \mu_2)\theta_0(1-\theta_0)/N$, $\mathrm{Var}\,(Z) = \mathrm{Var}\,(\bar{Y}_1 - \bar{Y}_2) + \Delta^2\mathrm{Var}\,(\hat{\theta}_0) - 2\Delta\,\mathrm{Cov}\,(\hat{\theta}_0, \bar{Y}_1 - \bar{Y}_2) = \mathrm{Var}\,(\bar{Y}_1 - \bar{Y}_2) - \Delta^2\theta_0(1-\theta_0)/N$. Then $Z/\sqrt{\mathrm{Var}\,(\mathrm{Z})}$ is asymptotically standard normal and $P(Z^2/\mathrm{Var}\,(Z) \le Z^2_{\alpha/2}) \doteq 1 - \alpha$ when N is large. This leads us to the quadratic inequality

$$\mathcal{A}\Delta^2 - 2\mathcal{B}\Delta + \mathcal{C} \le 0, \tag{9}$$

where $\mathcal{A} = \hat{\theta}_0^2 + Z^2_{\alpha/2}\hat{\theta}_0(1-\hat{\theta}_0)/\mathrm{N}$, $\mathcal{B} = \hat{\theta}_0(\bar{Y}_1 - \bar{Y}_2)$, and $\mathcal{C} = (\bar{Y}_1 - \bar{Y}_2)^2 - Z^2_{\alpha/2}\widehat{\mathrm{Var}}\,(\bar{Y}_1 - \bar{Y}_2)$. Because $\mathcal{A} > 0$, if $\mathcal{B}^2 - \mathcal{A}\mathcal{C} > 0$, then an asymptotic $100(1-\alpha)\%$ confidence interval for Δ is

$$\left[\frac{\mathcal{B} - \sqrt{\mathcal{B}^2 - \mathcal{A}\mathcal{C}}}{\mathcal{A}},\quad \frac{\mathcal{B} + \sqrt{\mathcal{B}^2 - \mathcal{A}\mathcal{C}}}{\mathcal{A}}\right]. \tag{10}$$

Note that we calculate (8) and (10) on the basis of the pooled samples. Note also that the parameter $\theta_0(\mu_1 - \mu_2)$ represents the difference of the two treatment mean effects over those patients who have no treatment preference. This leads us to consider the statistic $\bar{Y}_1^* - \bar{Y}_2^*$, where $\bar{Y}_1^* = \sum_j 1(j \in S_1)\delta_{0j}Y_j/n$ and

$\bar{Y}_2^* = \sum_j [1 - 1(j \in S_1)]\delta_{0j} Y_j/n$. Under (1), $E(\bar{Y}_1^* - \bar{Y}_2^*)$ equals $\theta_0(\mu_1 - \mu_2)$ as well, and

$$\mathrm{Var}\,(\bar{Y}_1^* - \bar{Y}_2^*) = 4\{\theta_0(1-\theta_0)[\frac{\mu_1^2 + \mu_2^2}{2}] + \theta_0\sigma^2\}/N. \tag{11}$$

Thus, following similar arguments as those leading to (8), an asymptotic $100(1-\alpha)\%$ confidence interval for Δ $(= \mu_1 - \mu_2)$ is

$$\left[\hat{\Delta}^* - Z_{\alpha/2}\sqrt{\widehat{\mathrm{Var}}\,(\hat{\Delta}^*)},\ \ \hat{\Delta}^* + Z_{\alpha/2}\sqrt{\widehat{\mathrm{Var}}\,(\hat{\Delta}^*)}\ \right], \tag{12}$$

where $\hat{\Delta}^* = (\bar{Y}_1^* - \bar{Y}_2^*)/\hat{\theta}_0$, $\widehat{\mathrm{Var}}\,(\hat{\Delta}^*) = \widehat{\mathrm{Var}}\,(\bar{Y}_1^* - \bar{Y}_2^*)/\hat{\theta}_0^2 - (\bar{Y}_1^* - \bar{Y}_2^*)^2(1 - \hat{\theta}_0)/(N\hat{\theta}_0^3)$, $\widehat{\mathrm{Var}}\,(\bar{Y}_1^* - \bar{Y}_2^*) = 2[(S_1^\star)^2 + (S_2^*)^2]/N$, $(S_1^\star)^2 = \sum_j 1(j \in S_1)\delta_{0j}(Y_j - \bar{Y}_1^*)^2/(n-1)$, and $(S_2^\star)^2 = \sum_j (1 - 1(j \in S_1))\delta_{0j}(Y_j - \bar{Y}_2^*)^2/(n-1)$.

Similarly, employing the principle of Fieller's theorem, we consider the quadratic inequality

$$\mathcal{A}^*\Delta^2 - 2\mathcal{B}^*\Delta + \mathcal{C}^* \le 0, \tag{13}$$

where $\mathcal{A}^* = \hat{\theta}_0^2 + Z_{\alpha/2}^2\hat{\theta}_0(1-\hat{\theta}_0)/\mathrm{N}$, $\mathcal{B}^* = \hat{\theta}_0(\bar{Y}_1^* - \bar{Y}_2^*)$, and $\mathcal{C}^* = (\bar{Y}_1^* - \bar{Y}_2^*)^2 - Z_{\alpha/2}^2\widehat{\mathrm{Var}}\ (\bar{Y}_1^* - \bar{Y}_2^*)$. If $(\mathcal{B}^*)^2 - \mathcal{A}^*\mathcal{C}^* > 0$, an asymptotic $100(1-\alpha)\%$ confidence interval for Δ is

$$\left[\frac{\mathcal{B}^* - \sqrt{(\mathcal{B}^*)^2 - \mathcal{A}^*\mathcal{C}^*}}{\mathcal{A}^*},\ \ \frac{\mathcal{B}^* + \sqrt{(\mathcal{B}^*)^2 - \mathcal{A}^*\mathcal{C}^*}}{\mathcal{A}^*}\right]. \tag{14}$$

3. Monte Carlo Simulation

To evaluate the finite sample performance of the interval estimators given at (8), (10), (12), and (14), we use Monte Carlo simulation. Note with Zelen (1990), that when the probability of no treatment preference is smaller than the probability that a physician is willing to enter a patient into a conventional randomized trial, the double consent randomized design will be less efficient than the conventional randomized trial and the former is not recommended for use. The values of θ_0 in five studies using double consent randomized design ranged from 0.28 to 0.78 (Zelen (1990), Table II on page 654). Here, we consider probability vectors of treatment preference $(\theta_0, \theta_1, \theta_2) = (0.5, 0.3, 0.2)$, $(1/3, 1/3, 1/3)$, $(0.2, 0.3, 0.5)$, sample sizes from each treatment of $n = 30, 50, 100$, mean responses for the two treatments of $\mu_1 = 1, 2, 5$ and $\mu_2 = 0$, standard deviations of measurement error at $\sigma = 1, 2, 5$, and nuisance parameters of the mean responses for those patients with self-selected treatments at levels $\mu_1^\star = -2, 2$, $\mu_2^\star = -2, 2$. For each configuration determined by a combination of these parameters, we apply SAS (1990) to generate 10,000 random samples to calculate

the coverage probability and the average length of a 95% confidence interval for the estimators (8), (10), (12), and (14). We generate measurement error ϵ_j from a normal distribution with mean 0 and standard deviation σ. Note that if the estimator $\hat{\theta}_0$ is 0, we cannot use the estimators (8), (10), (12), and (14). Furthermore, if $\mathcal{B}^2 - \mathcal{AC}$ (or $(\mathcal{B}^*)^2 - \mathcal{A}^*\mathcal{C}^* \leq 0$, we cannot use (10) (or (14)). We calculate coverage probability and average length over those samples where estimators exist. For completeness, we also indicate how often a problem arises in a sample.

4. Results

Table 1 gives the estimated coverage probability and average length (in parenthesis) for 95% confidence interval using (8), (10), (12), and (14) in situations where the probability vector of treatment preference is $(\theta_0, \theta_1, \theta_2) = (0.5, 0.3, 0.2)$ or $(0.2, 0.3, 0.5)$, the sample size from each treatment is $n = 30$ or 100, the mean responses for the two treatments are $\mu_1 = 1$ or 5 and $\mu_2 = 0$, the standard deviation of measurement error is $\sigma = 1$ or 5, and the nuisance parameters of the mean responses for those patients with self-selected treatments are $\mu_1^\star = -2$ and $\mu_2^\star = -2$ or 2. Results from other situations generally look similar to those of Table 1, so we do not present them here. These results are available from the authors.

First, note that when n is not large (< 100, say), the coverage probability of (8) and (12) tends to be smaller than 95%, especially when θ_0 is small, while the coverage probability of (10) generally behaves well. Note that (12) and (14), calculated over patients who have no treatment preference, are generally much more efficient than (8) and (10), calculated over pooled samples. For example, consider the case $(\theta_0, \theta_1, \theta_2) = (0.5, 0.3, 0.2)$, $n = 100$, $\mu_1 = 1$, $\sigma = 1$, $\mu_1^\star = -2$, and $\mu_2^\star = -2$. As compared with the estimated average length of the resulting 95% confidence interval using (10) and (14), the estimated coverage probabilities are 0.947 and 0.950, respectively, but the latter is approximately 53% $(= (1.760 - 0.822)/1.760)$ more efficient than the former. Furthermore, when $\theta_0 = 0.5$ and n is large (≥ 100), (14) is generally preferable to (10). Finally, we have found that the probabilities of failing to produce a 95% confidence interval through (8), (10), (12), and (14) are small ($\doteq 0.01$) or even negligible (< 0.001).

5. Discussion

A more systematic and detailed discussion of selection bias due to patients' treatment preference in point estimation of treatment effects using different definitions in a variety of designs, including conventional randomized trials, single-consent randomized trials, and double consent randomized trials, can be found

Table 1. The estimated coverage probability and average length (in parenthesis) of 95% confidence interval by use of interval estimators (8), (10), (12), and (14) for the probability vector of treatment preference $(\theta_0, \theta_1, \theta_2) = (0.5, 0.3, 0.2)$ and $(0.2, 0.3, 0.5)$ in the situations, in which the sample size from each treatment $n = 30$ and 100; the mean responses for the two treatments $\mu_1 = 1$, 5 and $\mu_2 = 0$; the standard deviation of measurement error $\sigma = 1$ and 5; and the mean responses for patients with self-selected treatments $\mu_1^\star = -2$, $\mu_2^\star = -2$, 2.

n	μ_1	σ	$\mu_2^\star$	(8)	(10)	(12)	(14)
				$(\theta_0, \theta_1, \theta_2) = (0.5, 0.3, 0.2)$			
30	1	1	-2	0.934*(3.266)	0.944(3.164)	0.935*(1.509)	0.942(1.467)
			2	0.932*(3.607)	0.941(3.493)	0.936*(1.501)	0.943(1.460)
		5	-2	0.935*(10.48)	0.942(10.14)	0.933*(7.108)	0.941(6.887)
			2	0.937*(10.60)	0.946(10.26)	0.938*(7.086)	0.947(6.864)
	5	1	-2	0.930*(5.015)	0.941(4.897)	0.930*(2.922)	0.943(2.900)
			2	0.929*(4.560)	0.941(4.460)	0.928*(2.924)	0.937*(2.901)
		5	-2	0.935*(11.15)	0.944(10.82)	0.937*(7.537)	0.944(7.327)
			2	0.933*(10.97)	0.943(10.64)	0.940(7.534)	0.947(7.325)
100	1	1	-2	0.945(1.776)	0.947(1.760)	0.948(0.829)	0.950(0.822)
			2	0.943(1.964)	0.945(1.946)	0.948(0.830)	0.950(0.823)
		5	-2	0.949(5.727)	0.951(5.672)	0.949(3.916)	0.951(3.878)
			2	0.944(5.784)	0.945(5.728)	0.945(3.920)	0.947(3.883)
	5	1	-2	0.941(2.738)	0.945(2.718)	0.940(1.597)	0.945(1.593)
			2	0.941(2.490)	0.945(2.473)	0.941(1.594)	0.947(1.590)
		5	-2	0.938*(6.072)	0.940(6.017)	0.946(4.140)	0.945(4.105)
			2	0.947(5.985)	0.948(5.930)	0.945(4.144)	0.948(4.109)
				$(\theta_0, \theta_1, \theta_2) = (0.2, 0.3, 0.5)$			
30	1	1	-2	0.906*(7.224)	0.938*(6.433)	0.904*(2.392)	0.928*(2.180)
			2	0.910*(10.47)	0.945(9.280)	0.914*(2.396)	0.927*(2.181)
		5	-2	0.913*(26.33)	0.944(23.36)	0.915*(10.92)	0.948(9.747)
			2	0.910*(27.72)	0.946(24.55)	0.915*(10.97)	0.951(9.777)
	5	1	-2	0.910*(10.47)	0.933*(9.549)	0.911*(5.514)	0.899*(5.365)
			2	0.912*(11.15)	0.950(10.08)	0.908*(5.492)	0.904*(5.354)
		5	-2	0.912*(27.39)	0.944(24.38)	0.916*(11.95)	0.932*(10.88)
			2	0.915*(27.80)	0.947(24.73)	0.913*(11.97)	0.932*(10.89)
100	1	1	-2	0.935*(3.940)	0.945(3.797)	0.939*(1.350)	0.944(1.309)
			2	0.940(5.619)	0.950(5.410)	0.942(1.347)	0.946(1.306)
		5	-2	0.941(14.28)	0.949(13.74)	0.941(6.167)	0.950(5.942)
			2	0.938*(14.80)	0.948(14.25)	0.942(6.160)	0.951(5.935)
	5	1	-2	0.935*(5.716)	0.946(5.554)	0.934*(3.033)	0.932*(3.013)
			2	0.933*(6.022)	0.947(5.845)	0.938*(3.040)	0.935*(3.019)
		5	-2	0.941(14.85)	0.951(14.31)	0.938*(6.737)	0.943(6.530)
			2	0.939*(14.94)	0.948(14.41)	0.938*(6.730)	0.943(6.524)

$\star$ means the estimated coverage probability $\leq$ the desired 95% confidence level by more than 1%.

elsewhere (Lin and Lui (2002)). We have shown here that one can easily incorporate the effect due to this selection bias into interval estimators for both pooled and restricted samples. Monte Carlo simulations demonstrate that proposed estimators perform reasonably well in situations of the type considered here.

Note that if we have only the information on whether patients accept or reject assigned treatments, the estimators calculated over the restricted sample are not applicable. Still, (8) and (10) remain useful: we can estimate the probability of no treatment preference θ_0 by twice the sample proportion of patients who accept their assigned treatments less 1, this without the need for identifying patients who have no treatment preference (Zelen (1990)).

On the basis of Monte Carlo simulation, we find that (10) and (14) derived by using the principle of Fieller's Theorem outperform (8) and (12) derived by using the delta method. Other applications of this idea can be found in many situations for example (Lui (1996), Lui, Cumberland and Kuo (1996), Lui, Mayer and Eckhardt (2000)).

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