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Sample Sizes for Survival Analysis Based on the Conditional Score Test for Person-time Observations

Tosiya Sato

Department of Epidemiology and Biostatistics,
Kyoto University School of Public Health
Kyoto 606-8501, Japan
e-mail: shun@pbh.med.kyoto-u.ac.jp

In the design of clinical trials in which the primary endpoint is time to occurrence of a clinical event, sample size calculation should be based on the subsequent survival analysis. This paper gives sample size formulas based on the conditional score test for the hazard ratio, which is equivalent to the normal approximation of the Cox F test. The proposed method is adopted to uniform patient entry, loss to follow-up, and treatment switching. In cancer clinical trials, it is sometimes required to show that the two treatments have equivalent survival benefit when the new treatment has apparent advantages on toxicity. Application of the proposed sample size formula to the equivalence test of two treatments is also given.

Key words: Conditional score test, Person-time, Sample size, Survival analysis.

1. Introduction

In many clinical trials, the primary endpoint is time to clinical events, such as recurrence, complication, or death. Sample size calculation in these trials should be based on the context of survival analysis. Several sample size methods were proposed when the survival time distribution is assumed to be exponential (George and Desu, 1974; Rubinstein et al., 1981; Lachin, 1981), and when only the constant hazard ratio is assumed (Schoenfeld, 1981; Freedman, 1982). These methods have been extended to more complex yet realistic situations such as staggered patient entry, loss to follow-up, noncompliance, and non-proportionality of the hazard ratio mainly because of the treatment switching (Lachin and Foulkes, 1986; Lakatos, 1988).

In this paper, new sample size formulas are provided which are based on the fixed person-time Poisson observations. The proposed formula for the significance test of the two treatment groups is adopted to uniform accrual rates, uniform loss to follow-up rates, and uniform treatment switching rates. The assumptions used are identical to those of the exponential survival time. However, the conditional score test of two independent Poisson observations, which is the normal approximation of the Cox F test (Cox, 1964), allows us to handle continuous treatment switching

scenario.

In cancer clinical trials, it is sometimes important to study the efficacy of a newly developed less toxic therapy. Compared to the standard therapy, the new therapy should have less toxic adverse events, yet it should have the same survival benefit as the standard therapy. The primary endpoint should still be time to the clinical event. In this case, one will prove two survival distributions are equivalent. The sample size formula for equivalence tests is given which is adopted to uniform accrual rate and uniform loss to follow-up rates.

In the next section, a brief description of the sample size calculations based on the conditional score test of the person-time Poisson observations is presented. Then calculations of expected person-time and the proposed sample size formula are given. These are extended to the equivalence test situation.

2. Poisson Conditional Score Test

Consider two independent Poisson observations x and y of clinical events with fixed person-time denominators m_T and m_C over the study period. The number of clinical events x in the test treatment assigned group consists of two independent Poisson observations (x_1, x_0) with fixed person-time denominators (m_{T1}, m_{T0}) and means $(m_{T1}d_1, m_{T0}d_0)$, where m_{T1} is the total person-times that the test treatment assigned participants have been correctly given the test treatment, m_{T0} that the test assigned participants have been incorrectly given the control treatment, and (d_1, d_0) are the hazards of the test and the control treatments constant over the study period. In the control treatment assigned group, y also consists of two independent Poisson observations (y_1, y_0) with fixed person-time denominators (m_{C1}, m_{C0}) and means $(m_{C1}d_1, m_{C0}d_0)$, where m_{C1} is the total person-times that the control assigned participants have been incorrectly given the test treatment and m_{C0} that the control assigned participants have been correctly given the control treatment.

Under the null hypothesis that $d_1 = d_0$, the conditional distribution of x given the total clinical events, $t = x + y$, is binomial with size t and probability $m_T/(m_T + m_C)$. The intention-to-treat test statistic under the null hypothesis is derived as the Poisson conditional score test;

$$Z = \frac{x - \frac{m_T}{m_T + m_C}t}{\sqrt{\frac{m_T m_C t}{(m_T + m_C)^2}}},$$

which will have an asymptotically standard normal distribution. It is equivalent to the normal approximation of the Cox F test (Cox, 1964). Under the alternative hypothesis that $d_1 \neq d_0$, the conditional distribution of x given t is also binomial with size t but probability $(m_{T1}d_1 + m_{T0}d_0)/[(m_{T1} + m_{C1})d_1 + (m_{T0} + m_{C0})d_0]$. When the test of the null hypothesis is conducted at one-sided level α with required power $1 - \beta$, again using the normal approximation under the

alternative hypothesis, the required person-times will be obtained by the following equation:

$$\begin{aligned} & z_\alpha [(m_{T1} + m_{C1})d_1 + (m_{T0} + m_{C0})d_0] \sqrt{m_T m_C} \\ & - (m_{T1} m_{C0} - m_{T0} m_{C1})(d_1 - d_0) \sqrt{(m_{T1} + m_{C1})d_1 + (m_{T0} + m_{C0})d_0} \\ & = -z_\beta (m_T + m_C) \sqrt{(m_{T1} d_1 + m_{T0} d_0)(m_{C1} d_1 + m_{C0} d_0)} \end{aligned} \quad (1)$$

where z_α and z_β are the standard normal deviates at levels α and β .

3. Expected Person-Times and Sample Size Formula

Suppose a clinical trial in which patients are to be recruited over an enrollment period of T_0 years and to be followed until T_1 years. Here T_1 denotes the total study period and thus $T_0 < T_1$. The test treatment is randomly assigned to n study participants and the control treatment to kn participants. As defined in the previous section, the constant event rate (hazard) of the test treatment is denoted by d_1 and that of the control treatment by d_0 . We assume that participant accrual rate, loss to follow-up rates, and treatment switching rates are constant in each group. Let l_T and l_C be the loss to follow-up rates in the test and the control assigned groups, e_T be the rate of switch from the test to the control treatment, and e_C the rate of switch from the control to the test treatment. We further assume that a test assigned participant's hazard is changed from d_1 to d_0 immediately after the control treatment is given, and vice versa. The expected person-times, $E(m.) = M.$, are given by

$$M_{T1} = nA_T, M_{T0} = ne_TB_T, M_{C0} = knA_C, \text{ and } M_{C1} = kne_CB_C,$$

where

$$\begin{aligned} A_T &= \frac{r_{T1}T_0 + e^{-r_{T1}T_1} - e^{-r_{T1}(T_1-T_0)}}{r_{T1}^2 T_0}, \\ B_T &= \frac{r_{T1}r_{T0}(r_{T1} - r_{T0})T_0 + r_{T0}^2 \left[e^{-r_{T1}T_1} - e^{-r_{T1}(T_1-T_0)} \right] - r_{T1}^2 \left[e^{-r_{T0}T_1} - e^{-r_{T0}(T_1-T_0)} \right]}{r_{T1}^2 r_{T0}^2 (r_{T0} - r_{T1})T_0}, \\ A_C &= \frac{r_{C0}T_0 + e^{-r_{C0}T_1} - e^{-r_{C0}(T_1-T_0)}}{r_{C0}^2 T_0}, \\ B_C &= \frac{r_{C0}r_{C1}(r_{C1} - r_{C0})T_0 + r_{C1}^2 \left[e^{-r_{C0}T_1} - e^{-r_{C0}(T_1-T_0)} \right] - r_{C0}^2 \left[e^{-r_{C1}T_1} - e^{-r_{C1}(T_1-T_0)} \right]}{r_{C0}^2 r_{C1}^2 (r_{C1} - r_{C0})T_0}, \end{aligned}$$

$r_{T1} = d_1 + l_T + e_T$, $r_{T0} = d_0 + l_T$, $r_{C0} = d_0 + l_C + e_C$, and $r_{C1} = d_1 + l_C$. Derivations of the above expectations appear in Appendix.

Substitute these expected person-times into expression (1) and solve it on n , we obtain the required sample size for the test assigned group:

$$n = \frac{\left[z_\alpha D \sqrt{EF} + z_\beta (E + kF) \sqrt{(A_T d_1 + e_T B_T d_0)(A_C d_0 + e_C B_C d_1)} \right]^2}{kD(d_1 - d_0)^2 (A_T A_C - e_T e_C B_T B_C)^2} \quad (2)$$

where $D = (A_T + k e_C B_C) d_1 + (k A_C + e_T B_T) d_0$, $E = A_T + e_T B_T$, and $F = A_C + e_C B_C$, and kn for the control assigned group. When no treatment switching occurs, the required sample size is reduced to

$$n = \frac{[z_\alpha(A_T d_1 + k A_C d_0) + z_\beta(A_T + k A_C) \sqrt{d_1 d_0}]^2}{k(d_1 - d_0)^2 A_T A_C (A_T d_1 + k A_C d_0)}.$$

Based on this expression, Table 1 shows total sample sizes where $T_0 = 3$ years, $T_1 = 5$ years, the one-sided $\alpha = 0.05$, $1 - \beta = 0.9$, $d_1 = 0.20$ per year, $d_0 = 0.30$ per year, and $k = 1$ with varying l_T and l_C . The settings in Table 1 are the same as those in Table 3b in Lachin and Foulkes (1986). Compared to these sample sizes, the ratio of Lachin and Foulkes' sample size to expression (2) is uniformly greater than 1 on the order of 1.01-1.04. As noted by Lachin and Foulkes (1986), sample sizes are roughly proportional to $l_T + l_C$. In Table 2, both l_T and l_C are fixed at 0.05 per year, the treatment switching rates are varied. The required sample size is nearly four times when $e_T = e_C = 0.2$ per year.

Table 1. Total sample sizes with varying loss to follow-up l_T and l_C (per one person-year) in groups T and C: $T_0 = 3$, $T_1 = 5$, one-sided $\alpha = 0.05$, $1 - \beta = 0.9$, $d_1 = 0.2$, $d_0 = 0.3$, $k = 1$

l_T	l_C				
	0	0.05	0.10	0.15	0.20
0	368	382	398	412	428
0.05	382	396	412	426	442
0.10	396	410	426	442	456
0.15	412	426	442	456	472
0.20	428	442	456	472	488

Table 2. Total sample sizes with varying treatment exchange e_T and e_C (per one person-year) in groups T and C: $T_0 = 3$, $T_1 = 5$, one-sided $\alpha = 0.05$, $1 - \beta = 0.9$, $d_1 = 0.2$, $d_0 = 0.3$, $k = 1$, $l_T = l_C = 0.05$

e_T	e_C				
	0	0.05	0.10	0.15	0.20
0	396	454	520	590	668
0.05	462	536	620	714	816
0.10	Combinations not available				
0.15	616	734	870	1028	1210
0.20	706	850	1022	1224	1466

4. Sample Size for Equivalence Trials

First, we consider the general case to show that the hazard ratio of two treatments is HR_0 . We will adopt two simultaneous one-sided tests (Hauck and Anderson, 1986). That is, we conclude that $d_1/d_0 = HR_0$ only if we reject both of the null hypotheses of the following two tests at the one-sided α level:

A) $H_0: d_1/d_0 \geq HR_A$, $H_1: d_1/d_0 < HR_A$, and

B) $H_0: d_1/d_0 \leq HR_B$, $H_1: d_1/d_0 > HR_B$,

where HR_A and HR_B are prespecified tolerance hazard ratios which satisfy $HR_A > HR_0 > HR_B$. Using the same arguments in the significance test and under the null hypothesis of the test A, the conditional score test statistic is given by

$$Z_A = \frac{x - \frac{m_T HR_A}{m_T HR_A + m_C} t}{\sqrt{\frac{m_T m_C HR_A t}{(m_T HR_A + m_C)^2}}},$$

which will have an asymptotically standard normal distribution. When the required power of the test is set to $1 - \beta$ and using the normal approximation at the alternative hypothesis, the required person-times are given by

$$\begin{aligned} z_\alpha(m_T d_1 + m_C d_0) \sqrt{HR_A} + (HR_A d_0 - d_1) \sqrt{m_T m_C (m_T d_1 + m_C d_0)} \\ = -z_{\beta/2} (m_T HR_A + m_C) \sqrt{d_1 d_0}. \end{aligned}$$

In many (not most) clinical trials, the only one of the two one-sided tests is required, which means the non-inferiority test. In that case, $z_{\beta/2}$ should be z_β .

Similar to the previous section, the following trial settings are adopted: the participant enrollment period T_0 , study period T_1 , n test treatment assigned participants, kn control treatment assigned participants, constant event rates, constant accrual rates, and constant loss to follow-up rates. In the design of equivalence trials, we should not consider attenuation caused by treatment switching. Unlike the significance test, such an intention-to-treat approach does not give a valid α -level test of null hypotheses (ICH E9 Expert Working Group, 1999). The expected person-times are $M_T = nA_T$ and $M_C = knA_C$. Substitute them into the above equation and solve it on n , we have the sample size for the test treatment group:

$$n_A = \frac{[z_\alpha(A_T d_1 + kA_C d_0) \sqrt{HR_A} + z_\beta(A_T HR_A + kA_C) \sqrt{d_1 d_0}]^2}{k(HR_A d_0 - d_1)^2 A_T A_C (A_T d_1 + kA_C d_0)} \quad (3)$$

and kn_A for the control treatment group. For the test B, HR_A is changed to HR_B in the sample size calculation. The required sample size is then the larger of the two sample sizes, n_A or n_B .

In the typical equivalence trial, the alternative hypothesis is that $HR_0 = 1$ ($d_1 = d_0$). In this case, the sample size formula is simplified to

$$n_i = \frac{[z_\alpha(A'_T + kA'_C) \sqrt{HR_i} + z_\beta(A'_T HR_i + kA'_C)]^2}{k(HR_i - 1)^2 d_0 A'_T A'_C (A'_T + kA'_C)}, \quad i = \{A, B\} \quad (4)$$

where

$$A'_j = \frac{(d_0 + l_j)T_0 + e^{-(d_0 + l_j)T_1} - e^{-(d_0 + l_j)(T_1 - T_0)}}{(d_0 + l_j)^2 T_0}, \quad j = \{T, C\}$$

Based on the sample size formula (4), Table 3 shows total sample sizes to show that $HR_0 = 1$ where $T_0 = 3$ years, $T_1 = 5$ years, one-sided $\alpha = 0.05$, $1 - \beta = 0.8$, $d_1 = d_0 = 0.20$ per year, and Jpn J Biomet Vol. 23, No. 1, 2002

Table 3. Total sample sizes for equivalence trials with varying loss to follow-up l_T and l_C (per one person-year) in groups T and C: $T_0 = 3$, $T_1 = 5$, $\alpha = 0.05$, $1 - \beta = 0.8$, $d_1 = d_0 = 0.2$, $HR_A = 1.2$, $k = 1$

l_T	l_C				
	0	0.05	0.10	0.15	0.20
0	2080	2172	2266	2366	2466
0.05	2158	2250	2344	2442	2544
0.10	2240	2330	2426	2524	2624
0.15	2324	2414	2510	2608	2708
0.20	2410	2500	2596	2694	2794

$k = 1$ with varying l_T and l_C . Here we set the tolerance hazard ratios as $HR_A = 1.2$ and $HR_B = 0.8$. In these tolerance values, n_A is uniformly larger than n_B , and only $2n_A$ is given in Table 3. The loss to follow-up in the control assigned group had slightly larger effect to sample sizes than that in the test assigned group.

5. Discussion

The basic assumption for the proposed sample size formulas is the exponential survival time distribution. Using the same distributional assumption, George and Desu (1974) proposed the sample size formula based on the Wald test of the log hazard ratio, $\ln d_1/d_0$; Lachin (1981) proposed the formula based on the Wald test of the hazard difference, $d_1 - d_0$. We have computed sample sizes using George and Desu's, Lachin's, and expression (2) over a range of likely values for d_1 , d_0 , T_0 , and T_1 (no loss to follow-up and no treatment switching). For one-sided $\alpha = 0.05$ and $1 - \beta = 0.9$, the ratio of George and Desu's formula to formula (2) is on the order of 1.0-1.03, and the ratio of Lachin's formula to formula (2) is 1.0-1.1. When loss to follow-up is taken into consideration (as shown in Table 2), the ratio of Lachin's formula to formula (2) were small, and so these approaches and Rubinstein et al.'s (1981) seems to be equivalent (since Rubinstein et al.'s is an approximation of George and Desu's).

Lakatos and Lan (1992) have pointed out that, although they are robust for non-exponential but proportional hazards, the sample size methods based on the exponential survival time are not robust for non-proportional hazards. One example of non-proportional hazards given by Lakatos and Lan (1992) was noncompliance (continuous treatment switching). For example, when the effect of smoking cessation on time to death or myocardial infarction was investigated in the Multiple Risk Factor Intervention Trial, only 30% of the smoking cessation group complied by quitting smoking and 80% of the continuing smoking group complied by continuing to smoke (Mark and Robins, 1993).

Previously proposed sample sizes with noncompliance assumed that the treatment switching occurs only at the start of the treatment (Lachin and Foulkes, 1986) or at the start of the prespecified discrete period (Lakatos, 1988). The proposed formula (2) allows continuous treat-

ment switching over the study period, so that it can well handle this kind of non-proportionality. When the extreme non-proportionality other than the treatment switching is expected from the external information, one can use Lakatos' method (1988). (A SAS macro for Lakatos' method is available (Shih, 1995).)

One of the two referees has pointed out that the extension of expressions (2) and (3) to the case when the stratified randomization is planned would be important. Using arguments that parallel those given in Section 6 of Lachin and Foulkes (1986), one can extend the proposed sample size formulas to the case of stratified randomization. In that case, one should use the test statistic derived by Shore, Pasternack, and Curnen (1976), which is based on the conditional score test for the stratified data.

In the analysis of trials to show equivalence, the use of the intention-to-treat principle has been criticized (Senn, 1991; Sato, 1994). As a result, we did not consider the effect of treatment switch in the sample size formula (4). However, in the conduct of the equivalence trial, treatment switch or noncompliance will occur. In that case, Sato (1994) has recommended the use of the confidence interval based on the randomized analysis proposed by Mark and Robins (1993). The survival time model used in the randomized analysis is the accelerated failure time model (Cox and Oakes, 1984), not the model of the hazard itself. However, in the randomized analysis, not the attenuated parameter by the intention-to-treat analysis but the true effect parameter can be estimated, and the acceleration parameter is simply the inverse of the hazard ratio under the exponential (or Weibull) survival assumption.

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Appendix

We will give the expected person-times for the test treatment assigned group. Let $n_{T1}(t)$ be the expected number at risk who are correctly given the test treatment at time t , and $n_{T0}(t)$ be the expected number at risk who are incorrectly given the control treatment at time t . Since we assume the constant accrual rate, the expected numbers at risk from the onset of the trial to the end of enrollment period T_0 are defined by the following set of differential equations:

$$\begin{aligned}\frac{d}{dt}n_{T1}(t) &= \frac{n}{T_0} - r_{T1}n_{T1}(t), \text{ and} \\ \frac{d}{dt}n_{T0}(t) &= e_{T1}n_{T1}(t) - r_{T0}n_{T0}(t),\end{aligned}$$

where $r_{T1} = d_1 + l_T + e_T$ and $r_{T0} = d_0 + l_T$. Solving them, we have

$$n_{T1}(t) = \frac{n(1 - e^{-r_{T1}t})}{r_{T1}T_0},$$

$$n_{T0}(t) = \frac{ne_T[r_{T0}(1 - e^{-r_{T1}t}) - r_{T1}(1 - e^{-r_{T0}t})]}{r_{T1}r_{T0}(r_{T0} - r_{T1})T_0},$$

and the expected person-times are given by

$$M_{T1}(0, T_0) = \int_0^{T_0} n_{T1}(t)dt = \frac{n(r_{T1}T_0 + e^{-r_{T1}T_0} - 1)}{r_{T1}^2T_0}, \text{ and}$$

$$M_{T0}(0, T_0) = \int_0^{T_0} n_{T0}(t)dt = \frac{ne_T[r_{T1}r_{T0}(r_{T0} - r_{T1})T_0 + r_{T0}^2(e^{-r_{T1}T_0} - 1) - r_{T1}^2(e^{-r_{T0}T_0} - 1)]}{r_{T1}^2r_{T0}^2(r_{T0} - r_{T1})T_0}.$$

From the end of enrollment period T_0 to the end of study T_1 , only the increment of $n_{T1}(t)$ changes to $-r_{T1}n_{T1}(t)$. Hence we obtain

$$n_{T1}(t) = \frac{n(1 - e^{-r_{T1}T_0})e^{-r_{T1}(t-T_0)}}{r_{T1}T_0},$$

$$n_{T0}(t) = \frac{ne_T[r_{T0}(1 - e^{-r_{T1}T_0})e^{-r_{T1}(t-T_0)} - r_{T1}(1 - e^{-r_{T0}T_0})e^{-r_{T0}(t-T_0)}]}{r_{T1}r_{T0}(r_{T0} - r_{T1})T_0},$$

and

$$M_{T1}(T_0, T_1) = \frac{n[1 - e^{-r_{T1}(T_1-T_0)} + e^{-r_{T1}T_1} - e^{-r_{T1}T_0}]}{r_{T1}^2T_0},$$

$$M_{T0}(T_0, T_1) = \frac{ne_T[r_{T0}^2\{1 - e^{-r_{T1}(T_1-T_0)} + e^{-r_{T1}T_1} - e^{-r_{T1}T_0}\} - r_{T1}^2\{1 - e^{-r_{T0}(T_1-T_0)} + e^{-r_{T0}T_1} - e^{-r_{T0}T_0}\}]}{r_{T1}^2r_{T0}^2(r_{T0} - r_{T1})T_0}.$$

Then the total person-times for the entire study period are given by

$$M_{T1} = M_{T1}(0, T_0) + M_{T1}(T_0, T_1) = \frac{n[r_{T1}T_0 + e^{-r_{T1}T_0} - e^{-r_{T1}(T_1-T_0)}]}{r_{T1}^2T_0},$$

$$M_{T0} = M_{T0}(0, T_0) + M_{T0}(T_0, T_1)$$

$$= \frac{ne_T[r_{T1}r_{T0}(r_{T0} - r_{T1})T_0 + r_{T0}^2\{e^{-r_{T1}T_0} - e^{-r_{T1}(T_1-T_0)}\} - r_{T1}^2\{e^{-r_{T0}T_0} - e^{-r_{T0}(T_1-T_0)}\}]}{r_{T1}^2r_{T0}^2(r_{T0} - r_{T1})T_0} \quad (A.1)$$

The same arguments apply to the control treatment assigned group, and give the total person-times as shown in the text.