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RESEARCH ARTICLE

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Predicting study duration in clinical trials with a time-to-event endpoint

Ryunosuke Machida[1,2] | **Yosuke Fujii**[3] | **Takashi Sozu**[4]

[1]Department of Information and Computer Technology, Tokyo University of Science Graduate School of Engineering, Tokyo, Japan

[2]Biostatistics Division, Center for Research Administration and Support, National Cancer Center, Tokyo, Japan

[3]Biometrics & Data Management, Pfizer R&D Japan G.K., Tokyo, Japan

[4]Department of Information and Computer Technology, Faculty of Engineering, Tokyo University of Science, Tokyo, Japan

Correspondence
Ryunosuke Machida, 5-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan.
Email: rmachida@ncc.go.jp

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In event-driven clinical trials comparing the survival functions of two groups, the number of events required to achieve the desired power is usually calculated using the Freedman formula or the Schoenfeld formula. Then, the sample size and the study duration derived from the required number of events are considered; however, their combination is not uniquely determined. In practice, various combinations are examined considering the enrollment speed, study duration, and the cost of enrollment. However, effective methods for visually representing their relationships and evaluating the uncertainty in study duration are insufficient. We developed a graphical approach for examining the relationship between sample size and study duration. To evaluate the uncertainty in study duration under a given sample size, we also derived the probability density function of the study duration and a method for updating the probability density function according to the observed number of events (ie, information time). The proposed methods are expected to improve the operation and management of clinical trials with a time-to-event endpoint.

KEYWORDS
clinical trial, prediction, sample size, study duration, time-to-event

1 | INTRODUCTION

In clinical trials with time-to-event outcomes as the primary endpoint, such as overall survival or progression-free survival, the planned number of participants and study duration are usually determined based on statistical power for demonstrating a difference between treatment and control groups.[1-3] When calculating the planned number of participants, the number of events that achieves the desired power is usually calculated.[4,5] Then, the planned number of participants and the study duration derived from the required number of events are considered; however, their combination is not uniquely determined. In practice, various combinations are examined considering the enrollment speed, study duration, and costs of participant enrollment and follow-up.

Assuming exponentially distributed time-to-event data, methods for evaluating the planned number of participants and statistical power have been developed considering the enrollment period (or follow-up period), censoring, and drop-out.[6-8] Schoenfeld and Richter[9] proposed nomograms for determining the planned number of participants given an enrollment period and follow-up period. However, to examine the combination of "the planned number of participants" and mean "study duration" easily, it is necessary to derive their relationships for representing the durations of enrollment period and follow-up period and subsequently develop methods for visually representing the relationships between these durations. In event-driven clinical trials, the study duration involves uncertainty, that is, there is variation in the time point at which the required number of events is obtained. Review papers[10,11] have highlighted the predictions for the

number of enrolled participants and duration of enrollment, and the number of events in the future. Bagiella and Heitjan[12] proposed the simulation-based methods for predicting the time point of interim and/or final analyses with Bayesian prediction intervals. Anisimov[13] assumed multicenter clinical trials and developed the analytic statistical technique for the mean and bound for the number of events at certain time points in the future. Anisimov's method[13] also allows the evaluation of the mean and predictive bounds for the time to reach a given number of events for any duration of the enrollment stage; however, it does not discuss the probability density function of the study duration. The methods for evaluating the effect of the planned number of participants on the uncertainty of study duration are not sufficiently developed. Thus, we develop a graphical approach for conveniently examining the relationship between the planned number of participants and mean study duration or enrollment period, for several scenarios of treatment effects, enrollment speed, and drop-out proportion. We also derive the probability density function (PDF) of the study duration with a closed form assuming single center clinical trials and a fixed enrollment speed. Moreover, we develop the method for updating the PDF according to the observed number of events and drop-out at a certain time point after the beginning of a study.

In Section 2, we define the statistical settings and provide the probability of event occurrence, the PDF of the study duration, and the method for updating the PDF according to the observed number of events. In Section 3, we illustrate numerical examples for the relationship between the planned number of participants and study duration or enrollment period, the PDF of study duration, and the updating the PDF of study duration. Finally, in Section 4, we present our concluding remarks.

2 | PROBABILITY DENSITY FUNCTION OF THE STUDY DURATION

2.1 | Statistical settings

Consider a randomized clinical trial comparing the efficacy of the treatment group ($i = 1$) to that of the control group ($i = 2$) with a total of n enrolled and randomized participants.[14] Suppose that $\kappa_1 n$ participants are assigned to the treatment group and $\kappa_2 n = (1 - \kappa_1)n$ participants to the control group. The time-to-event outcome is evaluated as the primary endpoint where the outcomes follow the exponential distribution with constant hazard rates λ_1 and λ_2 for the treatment and control groups. We are interested in testing the hypothesis on the hazard ratio to demonstrate a reduction in the occurrence of events over time, that is, $H_0 : \lambda_1/\lambda_2 \geq 1$ vs $H_1 : \lambda_1/\lambda_2 < 1$. The log-rank test at a significance level of α is used to test the hypothesis H_0. Thus, the required number of total events d is calculated using the Schoenfeld formula[4] as follows:

$$d = \frac{(z_\alpha + z_\beta)^2}{\kappa_1 \cdot \kappa_2 (\log(\lambda_1/\lambda_2))^2},$$

where z_α and z_β are the $(1 - \alpha)$ and $(1 - \beta)$ quantiles of the standard normal distribution and $1 - \beta$ is the desired power. The study is completed when the required number of events is obtained. The study duration is defined as the time from the beginning of the study to its end.

Assume that a planned number of participants (sample size) n is enrolled during a specified enrollment period a of the study. We define the planned number of participants as the sample size in the following sections, that is, the planned number of events does not denote the sample size. The enrollment speed m (constant value) is defined as the mean number of participants per unit time ($m = n/a$), which is a different framework of the Poisson enrollment model.[15,16] In the enrollment period, the random variable U is the time point at which a participant is enrolled in the study, and it follows uniform distribution within $[0, a]$. Note that the enrollment does not follow the Poisson process assumed in the previously proposed methods.[12,13] Anisimov[13] uses the advanced enrollment model, that is, the Poisson-gamma model,[15,16] in which participants are enrolled in each center according to the different enrollment rates that are regarded as a sample from a gamma distribution in Poisson processes. This model allows us to assume that center initiation delays and closing or opening of some centers in the future.

2.2 | Probability of event occurrence

A participant enrolled at time point U is followed until event, drop-out, or the end of study. The time to occurrence of event V and the time of drop-out W are defined counterfactually, and distributed independently as a certain distribution with probability density function $f_i(v)$ and $g_i(w)$, respectively, where i refers to the treatment group. The random variable Z

denotes the time from the beginning of the study until the occurrence of an event or a drop-out for each participant without considering the end time of study, $Z = min(V, W) + U$. For each participant in group i, the probability of occurrence of an event without censoring is as follows:

$$\Pr[V \le v, W > V] = \int_0^v \int_v^\infty g_i(x) f_i(y) dxdy = \Psi_i(v), \tag{1}$$

where $Z = V + U$ (or $V = Z - U$) under the condition: $W > V$. Thereafter, the mean probability of occurrence of an event without censoring for group i is obtained as the expected value of $\Psi_i(v)$ for U (marginalization for U) as follows:

$$\Pi_i(z) = \frac{1}{a} \int_0^a \int_0^{z-u} \int_v^\infty g_i(x) f_i(y) dxdydu = \frac{1}{a} \int_0^a \Psi_i(z-u) du.$$

From Simpson's rule[6] (a method for approximating the integral), the equation is given by

$$\Pi_i(z) = \frac{1}{a} \int_0^a \Psi_i(z-u) du \approx \frac{1}{6} \left(\Psi_i(z-a) + 4\Psi_i(z-0.5a) + \Psi_i(z) \right). \tag{2}$$

If the approximation is not adequate because of large enrollment period, the accuracy can be improved by dividing the enrollment period into several intervals and applying Simpson's rule to each interval. If $f_i(v)$ and $g_i(w)$ are exponential distributions with a hazard of λ_i and γ_i; this probability is simply expressed (without using Simpson's rule) as

$$\Pi_i(z) = \frac{1}{a} \int_0^a \int_0^{z-u} \int_v^\infty \gamma_i \exp(-\gamma_i x) \cdot \lambda_i \exp(-\lambda_i y) dxdydu = \frac{\lambda_i}{\lambda_i + \gamma_i} \left(1 - \frac{\exp(-(\lambda_i + \gamma_i)z)}{a(\lambda_i + \gamma_i)} \left(\exp((\lambda_i + \gamma_i)a) - 1 \right) \right).$$

Although this formula is similar to that in Rubinstein et al.,[8] and is derived under fixed enrollment and follow-up periods, we have redefined it as Z is a random variable. The result for the case where $f_i(v)$ is the Weibull distribution is shown in the appendix. The probability of occurrence of an event for whole participants (merging groups) is $\Pi(z) = \kappa_1 \Pi_1(z) + \kappa_2 \Pi_2(z)$. Under the given enrollment period a and enrollment speed m, the sample size is ma. Then, the expected number of events is $ma \cdot \Pi(z) = ma\,(\kappa_1 \Pi_1(z) + \kappa_2 \Pi_2(z))$. This means that the combination of the enrollment period a and study duration z is arbitrary and has to be determined by the solution of $d = ma \cdot \Pi(z)$. This equation can be solved by the Newton-Raphson method. We do not consider the situation in which the study is completed during the enrollment period in the following sections ($Z \ge a$), however, the previously proposed methods[12,13] are not limited in this situation.

2.3 | Derivation of the probability density function of study duration

We derive the probability density function (PDF) of the study duration to evaluate the uncertainty in study duration under a given sample size n. The times from the beginning of the study until the occurrence of an event for each participant are $Z_1, Z_2, \ldots, Z_n$ and they are assumed to be independently distributed as $\Pi(z)$. This is a strong assumption since the probability of the occurrence of an event for each participant depends on the time point of their enrollment, as expressed in Equation (1). Our simulation study, however, revealed that this assumption did not affect the evaluation of the uncertainty of study duration. The derivative of $\Pi(z)$ with respect to z is

$$\pi(z) = \frac{d}{dz} \Pi(z) = \sum_{i=1,2} \kappa_i \frac{\lambda_i \exp(-(\lambda_i + \gamma_i)z)}{a(\lambda_i + \gamma_i)} \left(\exp((\lambda_i + \gamma_i)a) - 1 \right).$$

We define $Z_{(1)} \le Z_{(2)} \le \ldots \le Z_{(n)}$ as the order statistics of $Z_1, Z_2, \ldots, Z_n$. The PDF of study duration is the same as that of $Z_{(d)}$, since the study is completed when the required number of events d is obtained. The cumulative distribution function (CDF) of study duration is given by

$$\Pi_d(z) = \Pr[Z_{(d)} \le z] = \sum_{d_o=d}^{n} \frac{n!}{d_o!(n-d_o)!} \Pi(z)^{d_o} (1 - \Pi(z))^{n-d_o}. \tag{3}$$

Finally, the PDF of study duration is given by

$$\pi_d(z) = \frac{d}{dz}\Pi_d(z) = \frac{n!}{(d-1)!(n-d)!}\Pi(z)^{d-1}(1-\Pi(z))^{n-d}\pi(z). \tag{4}$$

By using Equations (3) and (4), we can also evaluate the uncertainty for the time point at which the arbitrary number of events is obtained. The R code to illustrate the CDF and PDF of study duration is shown in Supplementary Material.

2.4 | Updating the PDF of study duration

We develop a method for updating the PDF according to the observed number of events. In practice, the PDF can be updated at the time points for regular monitoring or interim analyses when the data are accumulated. The prespecified conditions, including the hazard λ_i and drop-out proportion γ_i, can be easily updated using the maximum likelihood estimation as reported in Bagiella and Heitjan.[12] If these conditions are modified during the study, the updated PDF of study duration is obtained by substituting the modified values into Equation (4). We update the PDF of study duration using "actual time $l_j(>a)$ at j-th update" and "the observed number of events and drop-out at l_j".

When the observed number of events and drop-out by time point l_j are d_j and c_j, the participants exposed to the occurrence of an event (ie, participants at risk) are expressed as $r_j = n - d_j - c_j$ and the remaining number of events required for the analysis is $d - d_j$. The probability of occurrence of an event under the condition $Z > l_j$ among r_j participants is given by

$$\Pi^{(j)}(z) = \Pi(z|Z > l_j) = \int_{l_j}^{z} \pi(z)dz\left(\sum_{i=1,2}\kappa_i\frac{1}{a}\int_0^a (1-F_i(l_j-u))(1-G_i(l_j-u))du\right)^{-1}, \tag{5}$$

where $F_i(v)$ and $G_i(w)$ are the CDFs of $f_i(v)$ and $g_i(w)$, respectively. The derivative of $\Pi^{(j)}(z)$ with respect to Z is given by

$$\pi^{(j)}(z) = \frac{d}{dz}\Pi^{(j)}(z) = \pi(z)\left(\sum_{i=1,2}\kappa_i\frac{1}{a}\int_0^a (1-F_i(l_j-u))(1-G_i(l_j-u))du\right)^{-1}.$$

We again consider the order statistics among the participants at risk at l_j, that is, the times from the beginning of the study until the occurrence of an event for r_j are given as follows: $Z_1^{(j)}, Z_2^{(j)}, \ldots, Z_{r_j}^{(j)}$, which are assumed to be independently distributed as $\Pi^{(j)}(z)$, and their order statistics can be expressed as follows: $Z_{(1)}^{(j)} \le Z_{(2)}^{(j)} \le \ldots \le Z_{(r_j)}^{(j)}$. Since the study is completed when $d - d_j$ events out of r_j are obtained, the updated CDF using the order statistics is given by

$$\Pi_d^{(j)}(z) = \Pr[Z_{(d-d_j)}^{(j)} \le z] = \sum_{d_o^{(j)}=d-d_j}^{r_j} \frac{r_j!}{d_o^{(j)}!(r_j-d_o^{(j)})!}\left(\Pi^{(j)}(z)\right)^{d_o^{(j)}}\left(1-\Pi^{(j)}(z)\right)^{r_j-d_o^{(j)}}. \tag{6}$$

Finally, the updated PDF is given by

$$\pi_d^{(j)}(z) = \frac{d}{dz}\Pi_d^{(j)}(z) = \frac{r_j!}{(d-d_j-1)!(r_j-d+d_j)!}\left(\Pi^{(j)}(z)\right)^{d-d_j-1}\left(1-\Pi^{(j)}(z)\right)^{r_j-d+d_j}\pi^{(j)}(z). \tag{7}$$

3 | NUMERICAL EXAMPLES

3.1 | Settings for median survival time, enrollment speed, and drop-out proportion

We illustrate the relationship between sample size and study duration, the PDF of study duration, and updating the PDF of study duration for clinical trials as shown in Section 2.1. As the basic assumptions, the significance level α is 0.025 (one-sided), the desired power $1-\beta$ is 0.9, and the allocation ratio is $\kappa_1 = \kappa_2 = 0.5$ (ie, equal sample sizes in each group).

We evaluate the effect of median survival time (MST), enrollment speed, and drop-out proportion on the study duration under the eight scenarios shown in Table 1. These scenarios were virtual settings based on trials, assuming large

TABLE 1 Scenarios for MST, enrollment speed, and drop-out proportion

Scenarios	MST (months)		HR	Enrollment speed	*d*	Drop-out proportion at 24 months (%)
	Treatment group	Control group				
1	20	10	0.50	10	88	0
2	20	11	0.55	10	118	0
3	19	10	0.53	10	103	0
4	19	11	0.58	10	141	0
5	20	10	0.50	6	88	0
6	20	10	0.50	14	88	0
7	20	10	0.50	10	88	10
8	20	10	0.50	10	88	20

Note: Enrollment speed: number of participants enrolled per month (participants/month). *d*: required number of events to achieve the desired power of 0.9 at the one-sided significance level of 0.025.
Abbreviations: HR: hazard ratio for the treatment group against the control group; MST, median survival time.

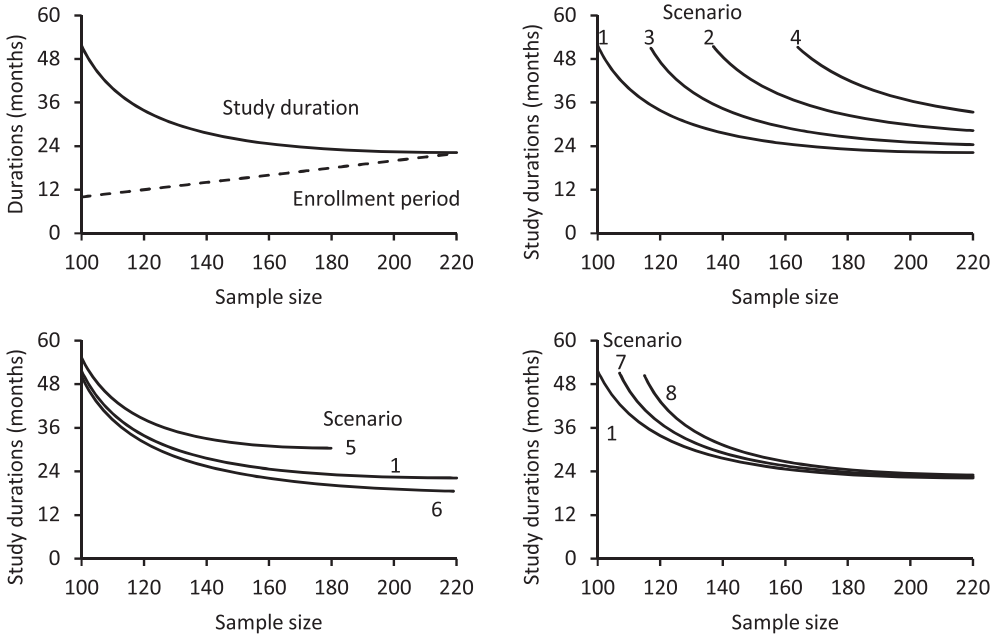

FIGURE 1 Relationship between sample size and study duration or enrollment period for Scenario 1 (top left figure), Scenarios 1 and 2 to 4 (top right figure), Scenarios 1, 5, and 6 (bottom left figure), and Scenario 1, 7, and 6 (bottom right figure)

treatment effects in patients with advanced cancer.[17,18] Although the target hazard ratio of 0.5 was assumed in Scenario 1, we confirmed that the results did not change in other settings.

The first scenario is the basic case in the numerical examples. In Scenarios 2 to 4, the MSTs are changed in the treatment and/or control groups. In Scenarios 5 and 6, the enrollment speeds are changed. In Scenarios 7 and 8, the drop-out proportions are changed, where drop-out proportions of 10% and 20% for each group at 24 months are considered. Thus, $\gamma_1 = \gamma_2 = -\log(1-0.1)/24$ in Scenario 7, and $\gamma_1 = \gamma_2 = -\log(1-0.2)/24$ in Scenario 8. All calculations are performed with SAS 9.4 (SAS Institute, Inc., Cary, NC, USA).

3.2 | Relationship between sample size and study duration

Graphs representing the relationship between sample size and study duration for each scenario are shown in Figure 1. These relationships are considered for average characteristics, and the randomness in the enrollment and event occurrence is not considered.

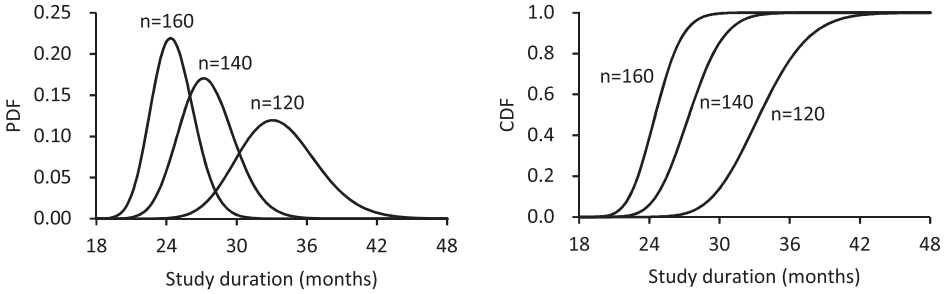

FIGURE 2 Probability density functions (left figure) and cumulative distribution functions (right figure) for sample sizes of 120, 140, and 160 under Scenario 1

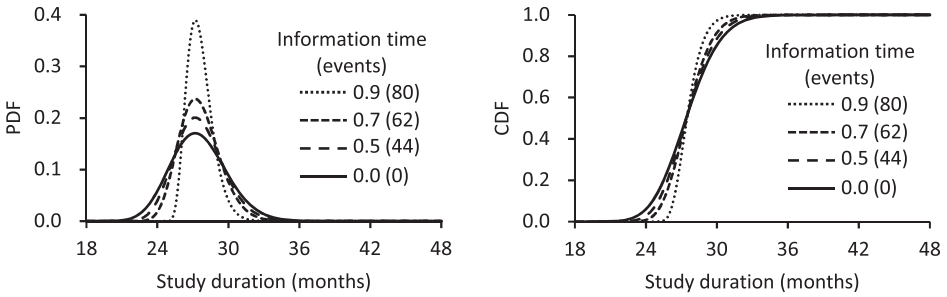

FIGURE 3 Probability density functions (left figure) and cumulative distribution functions (right figure) after updating at information times of 0.5, 0.7, and 0.9 with a sample size of 140

The enrollment period increases linearly as the sample size increases because the mean enrollment speed is constant (top left figure). The study duration decreases exponentially as the sample size increases. These graphs enable us to visually and easily determine their combinations. For example, if a study duration of 36 months (3 years) is fixed at the planning stage of the study, a sample size of 116 and an enrollment period of 11.6 months are obtained in Scenario 1 (basic scenario). If the study duration has to be shortened to 24 months (2 years) from 36 months (3 years), the sample size increases to 168 from 116. In Scenarios 2 to 4, since the differences in MST between the two groups are smaller than that in Scenario 1, the required number of events increases. Thus, these scenarios require larger sample sizes under the fixed study duration. For example, if the study duration of 36 months is fixed, the sample size increases to 165 in Scenario 2 from 116 in Scenario 1. In Scenario 5, since the enrollment speed is lower than that in Scenario 1, a larger sample size is necessary under the fixed study duration. For example, if the study duration of 36 months is fixed, the sample size increases to 127 in Scenario 5 from 116 in Scenario 1. In Scenario 6, since the enrollment speed is greater than that in Scenario 1, a smaller sample size is sufficient under the fixed study duration. In Scenarios 7 and 8, since drop-out of the participants is assumed, a larger sample size is necessary under the fixed study duration. However, the effect of drop-out on the study duration decreases as the sample size increases.

3.3 | The PDF of study duration

The PDFs of study duration for sample sizes of 120, 140, and 160 in Scenario 1 are shown in Figure 2.

The variability in the study duration decreases (ie, the slope of the cumulative distribution function increases), as the sample size increases. The probability that the study is completed within a certain period is easily obtained from the cumulative distribution function. For example, when the sample size is 140, the probability that the study is completed within 30 months is 85.3%. Using the PDF of study duration, we can easily evaluate the uncertainty in study duration.

3.4 | Updating the PDF of study duration

We illustrate the process of updating the PDF of study duration at information times (numbers of events) of 0.5 (44), 0.7 (62), and 0.9 (80) for the study with a sample size of 140 in Scenario 1. When the number of events is obtained as expected, the corresponding actual times are 14.9, 19.1, and 24.6 months, respectively. Under these situations, the updated PDFs of study duration based on the observed number of events are shown in Figure 3.

The variability in study duration decreases as the information time increases, since a greater number of events d_j is obtained. For example, when the sample size is 140 in Scenario 1, the median study durations [interquartile ranges]

are 27.4 [3.2], 27.4 [2.7], and 27.5 [1.4] months at information times of 0, 0.5, and 0.9, respectively. Using the proposed method, we can easily improve the uncertainty in study duration.

4 | CONCLUDING REMARKS

The graphical relationship between the planned number of participants (sample size) and study duration enables us to visually and easily evaluate their combinations based on their "expected values." For example, if it is necessary to complete the study as early as possible owing to pressure from competing drug companies or researchers, the study duration can be shortened by increasing the sample size. However, in clinical trials, it is not possible to unconditionally increase the sample size from an ethical point of view. Further, if a short study duration is planned, the effort and costs associated with enrollment increase because the enrollment period increases. Thus, this strategy depends on the conditions of clinical trials. Under practical conditions, it is critical to determine the sample size considering the study duration and development cost.

Considering and updating the PDF of study duration enables us to evaluate the uncertainty in study duration. Bagiella and Heitjan[12] proposed the methods for predicting the time point of interim and/or final analyses with Bayesian prediction intervals; (a) at the beginning of the trial, (b) during the enrollment period, and (c) after the enrollment period. On the other hand, we derived the exact distribution of study duration by limiting to the simple situation of (a) and (c). This is useful for the operation and management of clinical trials. The study duration and its variability decreases as the sample size increases. Further, updating the PDF during the study improves the uncertainty in study duration, resulting in the more accurate management of clinical trials.

When updating the PDF of study duration, it would be better to update the allocation ratio of κ using the number of participants at risk in each group. Under the alternative hypothesis, the expected number of events in the control group is larger than that in the treatment group. Thus, the number of participants at risk at a certain time point is not equal between the two groups, even if the allocation ratio is even, that is, $\kappa_1 = \kappa_2$. Therefore, Equation (5) overestimates the actual probability because the weight for the probability of the control group is greater than the true value when calculating the average probability of occurrence of events in two groups. For this reason, the allocation ratio should be updated with the ratio of "participants at risk" in each group, if possible. However, the number of participants for each group cannot be determined from regular monitoring in blinded clinical trials because we usually observe only the total number of events in two groups. Therefore, we derived Equation (5) without updating κ_i. Further, the bias in the updated PDF is negligible.

In many clinical trials, the enrollment speed may not be constant because clinical sites often commence enrollment at different times. The proposed methods can be easily applied to this situation by the following extensions. One method involves the assumption of another distribution of enrollment U other than uniform. When calculating the probability of occurrence of an event $\Pi_i(z)$ for group i, the simultaneous probability of $\Psi_i(v)$ and the newly assumed distribution of enrollment is needed to integrate with the range $[0, a]$ corresponding to enrollment period. This can be derived numerically by using Simpson's rule. Another method involves dividing the enrollment period into several periods with different enrollment speeds and considering the probability of occurrence of an event for each period. Thereafter, the probability for group i can be calculated as a weighted average of the number of participants registered in each period.

Future directions include the clarification of the relationship between the proposed method and the approach proposed by Anisimov[13] assuming multicenter clinical trials. The proposed method uses order statistics to derive the PDF of study duration. On the contrary, Anisimov[13] proved that the number of events for the new participants to be enrolled into the trial at any time point in the future can be represented as a mixed Poisson process with a random parameter. We have not discussed the effect of the difference in these settings on the PDF of study duration. We therefore need to extend the proposed method to include the uncertainty in enrollment.

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ORCID

Ryunosuke Machida https://orcid.org/0000-0002-3734-6203

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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APPENDIX A. PDF OF STUDY DURATION (WEIBULL DISTRIBUTION)

If $f_i(v)$ is a Weibull distribution with the shape parameter θ_i and scale parameter η_i, the mean probability of occurrence of an event without censoring for group i is given by

$$\Pi_i(z) \approx 1 - \frac{1}{6}\left(\exp(-\eta_i(z-a)^{\theta_i}) + 4\exp(-\eta_i(z-0.5a)^{\theta_i}) + \exp(-\eta_i z^{\theta_i})\right) \tag{A1}$$

using Equation (2), where we do not assume that drop-out occurs. The probability of occurrence of an event for whole participants (merging groups) is $\Pi(z) = \kappa_1\Pi_1(z) + \kappa_2\Pi_2(z)$. The derivative of $\Pi(z)$ with respect to z is given by

$$\begin{aligned}\pi(z) = \frac{d}{dz}\Pi(z) = \sum_{i=1,2}\kappa_i\frac{1}{6}(&\eta_i\theta_i(z-a)^{\theta_i-1}\exp(-\eta_i(z-a)^{\theta_i}) \\ &+ 4\eta_i\theta_i(z-0.5a)^{\theta_i-1}\exp(-\eta_i(z-0.5a)^{\theta_i}) + \eta_i\theta_i z^{\theta_i-1}\exp(-\eta_i z^{\theta_i})).\end{aligned} \tag{A2}$$

Substituting Equations (A1) and (A2) into (3) or (4) gives the CDF or PDF of study duration (using the order statistic shown in Section 2.3). These enable us to evaluate the effect of the shape parameter (or scale parameter) in the Weibull distribution on the probability distribution of the study duration.

When the observed number of events by time point l_j is d_j, the participants exposed to the occurrence of an event (ie, participants at risk) are expressed as $r_j = n - d_j$ and the remaining number of events required for the analysis is $d - d_j$. The probability of occurrence of an event under condition $Z > l_j$ among r_j is given by

$$\begin{aligned}\Pi^{(j)}(z) &= \Pi(z|Z > l_j) = \frac{1}{1-\Pi(l_j)}\int_{l_j}^{z}\pi(z)dz \\ &= \frac{1}{1-\Pi(l_j)}\sum_{i=1,2}\kappa_i\frac{1}{6}((\exp(-\eta_i(z-a)^{\theta_i}) + 4\exp(-\eta_i(z-0.5a)^{\theta_i}) + \exp(-\eta_i z^{\theta_i}) \\ &\quad - (\exp(-\eta_i(l_j-a)^{\theta_i}) + 4\exp(-\eta_i(l_j-0.5a)^{\theta_i}) + \exp(-\eta_i l_j^{\theta_i})).\end{aligned} \tag{A3}$$

The derivative of $\Pi^{(j)}(z)$ with respect to Z is given by

$$\pi^{(j)}(z) = \frac{d}{dz}\Pi^{(j)}(z) = \frac{\pi(z)}{1-\Pi(l_j)}. \tag{A4}$$

Substituting Equations (A3) and (A4) into (6) or (7) give the updated CDF or PDF of study duration.