

Estimation of Number of Subjects Required for Comparison of Drug versus Control in Adaptive Designs

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Abstract

Introduction: Adaptive designs have often been proposed as a way of using accruing data to affect future allocation scheme in clinical trials. The goal is to assign more patients to the better treatment. To implement clinical trials efficiently, sample size must be estimated in advance. In adaptive design, it is difficult to calculate the required sample size, because the allocation probabilities keep changing during the course of the trials. **Methods:** We focus on the sample size of two-arm (drug versus control) clinical trials. Based on its asymptotic properties, a formula of calculating sample size is derived for the randomised play-the-winner rule. We also compare sample size and power between the randomised play-the-winner rule and equal allocation. Some simulation studies illustrate the operating characteristics of the designs. **Results and Discussion:** The required sample size of the randomised play-the-winner rule is slightly larger than that of the equal allocation design in most cases. The randomised play-the-winner rule is recommended for ethical reasons.

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Introduction

Introduction to Adaptive Designs

Traditional designs for clinical trials make balanced (or 50-50) allocation of patients to treatments. This is done in the past to minimise the variance of different estimators. For example, in a trial to compare experimental therapy (drug) to placebo (control), a standard feature of most designs is to distribute half of the patients to each arm. From a scientific point of view, it may be worthwhile to have a placebo arm equally important in a trial so that the experimental therapy has a reference arm to be compared against. But from an ethical point of view, one may want to reduce the total number of failure outcomes in a trial, and keep the comparability of making a comparison between experimental therapy and placebo as well. Hence, the idea of adaptive designs has been proposed to serve the purpose.

Adaptive designs, an important subdivision of experimental design, are designs in which the probability a treatment is assigned to each patient depends upon the results of the previous patients in the study. The goal is to skew assignment probabilities to favour the treatment performing better thus far in the study.

The following example from Reosenberger¹ motivates the ethical point of adaptive design. Connor et al² reported a clinical trial to evaluate the hypothesis that the antiviral therapy AZT reduces the risk of maternal-to-infant HIV transmission. A standard randomisation scheme was used to obtain equal allocation to both AZT and placebo, resulting in 239 pregnant women receiving AZT and 238 receiving placebo. The endpoint was whether the newborn infant was HIV-negative or HIV-positive. At the conclusion of the trial, 60 newborns were HIV-positive in the placebo group while only 20 newborns were HIV-positive in the AZT group. Three times as many infants on placebo have received the deadly HIV from their mothers. Had they been given AZT, one might say that many more children would have been saved.

There is no doubt that the study of antiviral therapy in maternal-infant HIV transmission is critically important to neonatal public health. The result desired from such a study was best elicited via such a randomised treatment-controlled clinical trial. But facing such serious loss of human lives, it is reasonable to argue the balanced allocation was unethical. It is therefore necessary to develop new clinical trial designs to improve the total success

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rate of the trial while maintaining the comparability among therapy groups.

Randomised Play-the-Winner Rule

The randomised play-the-winner rule is an adaptive randomised design introduced by Wei and Durham,³ which is used occasionally.⁴ The rule particularly applies to clinical trials in which two treatments (drug and control) are tested with dichotomous response of “success” or “failure”. At the start of the clinical trial, an urn contains η_A balls of type A and η_B balls of type B, where η_A and η_B are positive integers. When a patient is recruited, a ball is drawn and replaced. If a type A ball is drawn, the patient is assigned to treatment A (drug); if a type B ball is drawn, the patient is assigned to treatment B (control). When the patient response is observed, the urn is then updated. A success on treatment A or a failure on treatment B generates a type A ball in the urn; a success on treatment B or a failure on treatment A generates a type B ball in the urn. Then the above procedure is executed repeatedly till reaching a point at which the result of comparison of the two treatments comes out under certain criteria. It is easy to find that if A is “working better” in the procedure, the urn composition is skewed to favour treatment A.

In the example of maternal-infant HIV transmission, if the randomised play-the-winner rule is used, then on average about 119 patients will be assigned to the placebo group and 378 patients in the AZT group. At the end of the trial, about 57 of the infants would have been HIV-positive (compared to 80 infants in the actual trial).

The randomised play-the-winner rule has been extensively studied in statistical literature. Its asymptotic properties are reported in references 5, 6 and 7. Rosenberger¹ has discussed logistical and statistical issues of the randomised play-the-winner rule. Some issues on practical implementation were considered by him,⁴ but the problem of sample size has not been considered in the literature.

General Description of Sample Size

In clinical trials, sample size refers to the number of patients who enter the trials receiving experimental or controlled treatment. The aim of sample size calculation is to obtain the smallest sample size required for a study consistent with obtaining the required information from the study at specified levels of confidence. Hence, to conduct a trial, we usually have to calculate the sample size first.

For equal allocation, we usually have a simple formula to estimate the required sample size. It is usually difficult to determine the sample size for adaptive designs. This is because the allocation probabilities change from time to time in the clinical trial. Given a fixed sample size, the number of patients assigned to each treatment is a random

variable. We have to obtain the distribution of the random variable and then determine the sample size based on this distribution.

In this paper, we considered the sample size and test power of the randomised play-the-winner rule. Under the section “Sample Size Calculation”, we derived a simple formula to estimate the required sample size for the randomised play-the-winner rule. One adjusted formula is also given. We also compared the required sample sizes between the 50-50 randomised allocation and the randomised play-the-winner rule for different cases. Power is an important factor to consider in planning a clinical trial. By using the randomised play-the-winner rule, power can be lost relative to equal allocation designs. The power comparison of these two designs is discussed in the section on “Comparison of Power”. All the technical details are in the Appendix.

Sample Size Calculation

We now focus on the sample size calculation in the case of two-arm (experimental and controlled treatments) clinical trials. Let p_E be success probability of experimental treatment and p_C be success probability of controlled treatment. In terms of hypothesis testing, we have:

$$H_0 : p_E = p_C \text{ versus } H_1 : p_E > p_C$$

Let n_E and n_C be the number of patients assigned to the treatment (drug) and the control in a randomised play-the-winner trial, respectively. We also define S_E and S_C as the number of successes on the treatment and the control, respectively. Let $\hat{p}_E = S_E/n_E$ and $\hat{p}_C = S_C/n_C$ be the corresponding estimators.

For a given significant level α , we reject H_0 if

$$\frac{\hat{p}_E - \hat{p}_C}{\sqrt{\hat{p}_E \hat{q}_E / n_E + \hat{p}_C \hat{q}_C / n_C}} > z_{(\alpha)} \quad (1)$$

where $q_E = 1 - p_E$, $q_C = 1 - p_C$ and $z_{(\alpha)}$ is defined as $P(Z > z_{(\alpha)}) = \alpha$. Here Z is a standard normal random variable.

For a given power β , we can derive an estimator of the sample size (see Appendix), n , the smallest integer, which is larger than

$$\frac{(p_E q_E^2 + p_C q_C^2)(q_E + q_C)(z_{(\alpha)} + z_{(1-\beta)})^2}{q_C q_E (p_E - p_C)^2} \quad (2)$$

For the 50-50 allocation rule, the sample size n is estimated as the smallest integer, which is larger than

$$\frac{2(p_E q_E + p_C q_C)(z_{(\alpha)} + z_{(1-\beta)})^2}{(p_E - p_C)^2} \quad (3)$$

For given $\alpha = 0.05$ and $\beta = 0.8$, Table I [based on

TABLE I: COMPARISON OF THEORETICAL SAMPLE SIZE BETWEEN THE RANDOMISED PLAY-THE-WINNER RULE AND EQUAL ALLOCATION WHEN $\alpha = 0.05$ AND $\beta = 0.8$.

P_C		$P_E - P_C$							
		0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
0.2	RPW	1717	456	212	123	81	57	33	22
	50-50	1719	458	213	124	81	57	31	19
0.3	RPW	2164	557	253	145	94	66	39	29
	50-50	2164	557	252	143	91	62	33	19
0.4	RPW	2415	610	273	155	101	72	46	45
	50-50	2412	606	268	149	93	62	31	17
0.5	RPW	2469	615	274	155	103	76	63	
	50-50	2461	606	263	143	87	57	27	
0.6	RPW	2327	574	256	149	105	91		
	50-50	2313	557	235	124	73	46		
0.7	RPW	1993	490	226	149	151			
	50-50	1967	458	186	93	51			
0.8	RPW	1476	381	237					
	50-50	1422	310	115					

The RPW represents the randomised play-the-winner rule and 50-50 represents the equal allocation.

equation 2 and equation 3] shows the required sample sizes for different p_E and p_C values. Overall, the required sample sizes of the two designs are similar. In terms of the sample size, the equal allocation scheme has a slight advantage

TABLE II: ADJUSTED THEORETICAL SAMPLE SIZE OF THE RANDOMISED PLAY-THE-WINNER RULE WHEN $\alpha = 0.05$ AND $\beta = 0.8$

P_C	$P_E - P_C$							
	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
0.2	1718	457	213	124	82	58	34	23
0.3	2165	558	254	146	95	67	40	29
0.4	2416	611	274	156	101	72	46	44
0.5	2470	616	274	156	103	76	61	
0.6	2328	575	256	149	104			
0.7	1994							

TABLE III: SIMULATED SAMPLE SIZE [WITH STANDARD DEVIATION (SD)] OF THE RANDOMISED PLAY-THE-WINNER RULE WHEN $\alpha = 0.05$ AND $\beta = 0.8$

P_C	$P_E - P_C$									
	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5		
0.2 (SD)	1718 (1.4)	4573 (1.4)	213 (1.5)	124 (1.8)	82 (2.2)	58 (2.7)	34 (3.5)	22 (4.8)		
0.3 (SD)	2166 (2.9)	559 (2.9)	255 (3.7)	146 (4.0)	95 (4.9)	67 (5.4)	38 (6.8)	25 (7.9)		
0.4 (SD)	2417 (5.8)	612 (6.5)	275 (7.6)	156 (7.9)	101 (9.0)	72 (10.0)	42 (12.2)	29 (15.7)		
0.5 (SD)	2472 (10.5)	618 (11.9)	276 (13.0)	156 (13.5)	102 (14.9)	72 (16.2)	46 (21.2)			
0.6 (SD)	2331 (18.3)	577 (20.9)	258 (22.1)	146 (22.4)	99 (27.9)	72 (30.1)				
0.7 (SD)	2003 (40.6)	493 (39.2)	224 (41.0)	130 (40.0)	92 (51.0)					
0.8 (SD)	1490 (81.6)	369 (76.4)	175 (81.5)							

SD: standard deviation

over the randomised play-the-winner rule.

Because n_E and n_C are random variables, we should adjust the sample size according to the variation of n_E and n_C . Based on equations 8 and 9 in the Appendix section, adjusted sample sizes were calculated (Table II). We found that differences between the theoretical and adjusted sample sizes to be very small.

Theoretical calculation of sample size is based on the asymptotic distribution of n_E and n_C . It is important to know the finite properties of sample size. Here we use simulation to illustrate. For given p_E, p_C, α and β , simulation is realised in the following way: we start with the urn containing 2 type A balls and 2 type B balls. Let A represent the treatment with success probability p_E and B represent the control with success probability p_C . Then we follow the randomised play-the-winner rule until attaining the significant level α and the power β . Then we record the sample size. Table III shows the average of sample sizes as well as their standard deviations from 1000 simulations for $\alpha = 0.05$ and $\beta = 0.8$. The simulation result supports our theoretical calculation. We have also done simulations in the following cases: ($\alpha = 0.025, \beta = 0.8$); ($\alpha = 0.05, \beta = 0.9$) and ($\alpha = 0.025, \beta = 0.9$). Again, the results are consistent with the theoretical estimation.

For the randomised play-the-winner rule, we can calculate the number of patients in each arm based on the sample size. If the sample size is n , then the $n_E = q_C n / (q_E + q_C)$ and $n_C = q_E n / (q_E + q_C)$. For example, in Table I, the sample size is $n = 155$ for the case $p_C = 0.5$ and $p_E = 0.7$. Then $n_E = 93$ and $n_C = 62$.

Comparison of Power

We have considered the required sample size of the randomised play-the-winner rule for given significant level α and test power β . It is also important to know the test power β for a given sample size n and fixed α . This result tells us how much power we gain or lose, if we use the randomised play-the-winner rule. We used simulation to compare the powers of the randomised play-the-winner rule and the 50-50 allocation.

In the simulation, we used $n = 200$, and $\alpha = 0.025$. For fixed p_C and p_E , the randomised play-the-winner rule starts with the urn as the simulation in the section on “Sample Size Calculation”, and then continues until $n = 200$. Based on the n_E and n_C , $\hat{p}_E$ and $\hat{p}_C$, we reject or accept H_0 . Power is estimated as the proportion of the rejections among all the simulations. For equal allocation, we just allocated 100 patients to the treatment and the control, respectively. Then the power is determined in the same way.

The results in Table IV were based on 1000 simulations. From the results, we noted that the power of the randomised play-the-winner rule is slightly less than that of the 50-50 allocation in most cases. But overall, the difference is very small. It gives some evidence that the randomised play-the-winner rule does not lose much of power besides that it has a better ethical effect.

TABLE IV: COMPARISON OF POWER BETWEEN THE RANDOMISED PLAY-THE-WINNER RULE AND EQUAL ALLOCATION WHEN $n = 200$ AND $\alpha = 0.025$

P_C		$P_E - P_C$							
		0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
0.2	RPW	0.13	0.39	0.69	0.88	0.98	1.00	1.00	1.00
	50-50	0.12	0.42	0.69	0.87	0.97	1.0	1.0	1.0
0.3	RPW	0.13	0.31	0.60	0.82	0.96	1.00	1.00	1.00
	50-50	0.13	0.34	0.59	0.82	0.96	0.99	1.00	1.00
0.4	RPW	0.11	0.33	0.56	0.80	0.94	0.99	1.00	1.00
	50-50	0.13	0.32	0.60	0.84	0.95	0.99	1.00	1.00
0.5	RPW	0.10	0.31	0.57	0.82	0.96	0.99	1.00	
	50-50	0.13	0.33	0.57	0.84	0.95	0.99	1.00	
0.6	RPW	0.11	0.30	0.62	0.84	0.96	1.00		
	50-50	0.11	0.32	0.65	0.88	0.97	1.00		
0.7	RPW	0.14	0.35	0.67	0.94	0.98			
	50-50	0.12	0.38	0.73	0.94	1.00			
0.8	RPW	0.14	0.45	0.85					
	50-50	0.16	0.53	0.93					

The RPW represents the randomised play-the-winner rule and 50-50 represents the equal allocation.

Discussion and Conclusion

From our study, we noted that the required sample size of the randomised play-the-winner rule is usually larger than that of the equal allocation rule, but in most cases, the difference is very small. Also from Table IV, when the sample size is fixed ahead of clinical trials (i.e. $n = 200$), the power of the randomised play-the-winner design is only slightly smaller than that of the equal allocation design. When it is not too difficult (either too expensive or impossible) to get a reasonable sample size, the randomised play-the-winner rule is recommended for ethical reasons.

When p_E is much bigger than p_C , the randomised play-

the-winner rule requires a much larger sample size. In these cases, we may use equal allocation, if we only have a small sample size.

In this paper, we only considered sample size for the randomised play-the-winner rule. We can also derive the sample size formula of other adaptive designs. For multi-arm clinical trials, the sample size calculation becomes more difficult. Some asymptotic results^{7,8} would be useful for further research. We only considered one-sided hypothesis testing throughout this paper. Only some simple modifications are needed for two-sided testing.

APPENDIX: TECHNICAL DETAILS

We derived the formula of calculating the sample size based on asymptotic results.

Asymptotic Normality of the Randomised Play-the-winner Rule

Let n_E and n_C be the number patients assigned to the treatment (drug) and control in a randomised play-the-winner trial, respectively. If we define S_E and S_C as the number of successes on the treatment and the control, respectively, then the likelihood of the data is given by:

$$L \sim p_E^{S_E} q_E^{N_E - S_E} p_C^{S_C} q_C^{N_C - S_C}$$

Athreya and Karlin⁵ showed that

$$\frac{N_E}{N_E + N_C} \rightarrow \frac{q_C}{q_E + q_C} \quad \text{almost surely as } n \rightarrow \infty \quad (4)$$

When $p_E + p_C < 1.5$ (or $q_E + q_C > 0.5$), we have the following asymptotic normality of N_E :

$$\sqrt{n} \left(\frac{N_E}{N_E + N_C} - \frac{q_C}{q_E + q_C} \right) \rightarrow N(0, \sigma^2) \quad (5)$$

in distribution. Where

$$\sigma^2 = \frac{[5 - 2(q_E + q_C)]q_E q_C}{[2(q_E + q_C) - 1](q_E + q_C)^2}$$

The asymptotic normality was first reported by Smythe and Rosenberger.⁶ When $p_E + p_C > 1.5$, the limiting distributions of the proportion of patients assigned to treatment are unknown.

Let $\hat{p}_E = S_E/n_E$ and $\hat{p}_C = S_C/n_C$ be the likelihood estimators. Wei et al⁹ showed that

$$\frac{\hat{p}_E + \hat{p}_C - (p_E + p_C)}{\sqrt{p_E q_E / N_E + p_C q_C / N_C}} \quad (6)$$

is asymptotically $N(0, 1)$ under both H_0 and H_1 .

The Estimation of Sample Size

For given significant level α and test power β , from result in equation 6, we reject H_0 if

$$\frac{\hat{p}_E - \hat{p}_C}{\sqrt{p_E q_E / n_E + p_C q_C / n_C}} > z_{(\alpha)}$$

To achieve the power β , we need the following conditional probability

$$P\left(\frac{\hat{p}_E - \hat{p}_C}{\sqrt{p_E q_E / n_E + p_C q_C / n_C}} > z_{(\alpha)} | H_1\right) > \beta$$

That is

$$P\left(\frac{\hat{p}_E - \hat{p}_C - (p_E - p_C)}{\sqrt{p_E q_E / n_E + p_C q_C / n_C}} > z_{(\alpha)} - \frac{p_E - p_C}{\sqrt{p_E q_E / n_E + p_C q_C / n_C}} | H_1\right) > \beta$$

From equation 6, we have

$$z_{(\alpha)} - \frac{p_E - p_C}{\sqrt{p_E q_E / n_E + p_C q_C / n_C}} < -z_{(1-\beta)}$$

Hence,

$$\frac{p_E - p_C}{\sqrt{p_E q_E / n_E + p_C q_C / n_C}} > z_{(\alpha)} + z_{(1-\beta)}$$

Therefore, the n_E and n_C must satisfy

$$p_E q_E / n_E + p_C q_C / n_C < \left[\frac{p_E - p_C}{z_{(\alpha)} + z_{(1-\beta)}} \right]^2$$

Now from equation 4, on average, we can substitute n_E by $[q_C / (q_E + q_C)]n$ and n_C by $[q_E / (q_E + q_C)]n$. Thus we can estimate the sample size n as

$$n = \frac{(p_E q_E^2 + p_C q_C^2)(q_E + q_C)(z_{(\alpha)} + z_{(1-\beta)})^2}{q_C q_E (p_E - p_C)^2} \quad (7)$$

But both n_E and n_C are random variables, we should consider the variation of n_E and n_C . From equation 5, we have $n_E > [q_C / (q_E + q_C)]n - 1.96\sigma / \sqrt{n}$ and $n_C > [q_E / (q_E + q_C)]n - 1.96\sigma / \sqrt{n}$ with probability 0.95. Now the sample size n is obtained to be the smallest integer, which satisfies

$$\begin{aligned} & \frac{p_E q_E}{[q_C / (q_E + q_C)]n - 1.96\sigma / \sqrt{n}} + \frac{p_C q_C}{[q_E / (q_E + q_C)]n + 1.96\sigma / \sqrt{n}} \\ & < \left[\frac{p_E - p_C}{z_{(\alpha)} + z_{(1-\beta)}} \right]^2 \end{aligned} \quad (8)$$

and

$$\begin{aligned} & \frac{p_E q_E}{[q_C / (q_E + q_C)]n + 1.96\sigma / \sqrt{n}} + \frac{p_C q_C}{[q_E / (q_E + q_C)]n - 1.96\sigma / \sqrt{n}} \\ & < \left[\frac{p_E - p_C}{z_{(\alpha)} + z_{(1-\beta)}} \right]^2 \end{aligned} \quad (9)$$

where σ is given in equation 5.

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