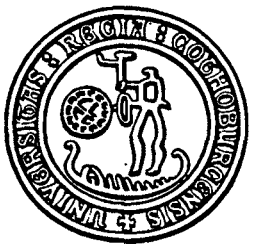

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SEQUENTIAL ANALYSIS OF SIMPLE HYPOTHESES WHEN USING PLAY-THE-WINNER ALLOCATION

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SEQUENTIAL ANALYSIS OF SIMPLE HYPOTHESES WHEN USING PLAY-THE-WINNER ALLOCATIONS.

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ABSTRACT

Play-the-winner allocations aim to place more subjects on the better treatment. The subjects enter the study sequentially. In this paper, a method for analyzing a dichotomous response, when using the randomized play-the-winner allocation and the modified play-the-winner allocation, is studied. The method is based on Wald's sequential probability ratio test. The properties of the method and of the allocation rules are studied for the case of simple hypotheses. The expected sample sizes and the expected numbers of subjects assigned to the inferior treatment are estimated by simulation.

Keywords: Play-the-winner randomization, response dependent allocation, sequential probability ratio test, restricted randomization, sequential medical trials.

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1 Introduction

Consider an experiment where two treatments, say T_1 and T_2, are compared. The response to the treatment is dichotomous, namely success or failure. Patients arrive sequentially at the experimental site and have to be treated immediately. The question arises how to allocate patients to the two treatments.

A simple allocation rule is to choose randomly a treatment for each patient. To fulfill ethical requirements Play-the-winner allocations have been suggested, first by Zelen (1969). Characteristic for the Play-the-winner allocations is that the probability for a treatment increases as the number of successes for the treatment increases. Therefore, we can assume that less patients are allocated to the inferior treatment than to the superior one.

For a sequential analysis of the experiments we can use Wald's sequential probability ratio test, SPRT, for simple hypotheses,

$$H_0: p_{T_1} = p_{T_2} = p_{T_10} = p_{T_20} \quad \text{versus} \quad H_1: p_{T_1} = p_{T_11},\ p_{T_2} = p_{T_21} \quad .$$

It will be assumed that

$$p_{T_10} \neq p_{T_11} \text{ and } p_{T_20} \neq p_{T_21} \quad .$$

Wald's SPRT is originally presented in the case of independent and identically distributed random variables. If a play-the-winner allocation is used the variables are not independent and identically distributed: the treatment of the current patient depends on the treatment, and the response to treatment, of one or more of the previous patients. Therefore, the original Wald's SPRT can be used for sequential analysis. We will present a generalization of the test that is suitable for this more complicated situation. We will assume immediate responses, to simplify the calculations.

The paper is organized as follows. Three Play-the-Winner allocation rules, Play-the-winner (PW) allocation, modified Play-the-winner (MPW) allocation and randomized Play-the-winner (RPW) allocation, are summarized in Section 2. In Section 3 we recall Wald's SPRT and some of its basic properties, and in Section 4, the test is generalized to our experimental situation, where the random variables are not independent and identically distributed. As main result we show that the error probabilities are bounded, for inference based on Wald's SPRT, when the RPW allocation rule is used

in the experimental setting of allocating patients to the two treatments. In Section 5 we compare two Play-the-Winner allocation rules, the RPW and the MPW, and total randomization (TR), when using the SPRT, by means of expected sample size and expected number of patients allocated to the inferior treatment. TR assigns treatment T_1 with probability ½ and treatment T_2 with probability ½, each time a patient arrives. Hence, TR represents an allocation rule for which the random variables are independent and identically distributed. Note that, in the case of immediate responses, the PW and the MPW are identical (see Section 2). The expectations are calculated through simulations.

2 Play-the-winner allocation rules

The first Play-the-winner allocation was introduced by Zelen (1969). Zelen's allocation, denoted by PW, is best described by an urn. In the urn we for each success of a treatment put a ball representing the treatment, and for each failure put a ball representing the other treatment. When a patient is to be allocated to a treatment we draw a ball from the urn, without replacement. If the urn is empty, as it is at the start, each treatment has probability ½. This method allows the responses to be delayed, but if many responses are delayed for substantial time treatments will mostly be assigned with probability ½ each.

In the same paper Zelen introduced another allocation rule, where the responses were assumed to be immediate. When allocating the first patient, the treatments have probability ½ each to be assigned to the patient. For the following allocations one keeps on assigning the same treatment until it gives a failure, then switches to the other treatment and keeps on assigning this one until it gives a failure. The allocation is continued in this manner until the experiment is stopped. This allocation rule is denoted by MPW, modified play-the-winner. Note that, with immediate responses the MPW allocation is identical to the PW allocation.

Later, a randomized Play-the-winner allocation was introduced by Wei and Durham (1978). Now we can think of an urn in which we, at the start, have ω_1 balls representing treatment T_1 and ω_2 balls representing treatment T_2. When a patient is to be allocated to a treatment a ball is drawn from the urn, with replacement. If the response "success" is received, from a patient allocated to treatment T_1 (or T_2 respectively), we add ρ T_1-balls to the urn. If the response is a "failure" we add ρ T_2-balls to the urn. Note that here, the history of successes and failures will affect every allocation, even if the responses are delayed. This last allocation rule is denoted by RPW(ω_1,ω_2,ρ). A special case of the RPW(ω_1,ω_2,ρ) is when $\omega_1 = \omega_2$, which is denoted by RPW(ω,ρ).

The statistical analysis of results from experiments where RPW(ω,ρ) allocation rules have been used has been discussed by several authors. Wei and Durham (1978) suggested an inverse stopping rule for deciding which one of the two treatments is the

better one. They also compared the RPW(0,1) with the PW, with respect to, the expected number of patients treated by the inferior treatment, the average sample size and the estimated probabilities of correct selection of the inferior treatment. The comparison of the average sample sizes was done when the inverse stopping rule was used. Wei and Durham concluded that the RPW(0,1) seemed to be approximately equal to the PW for practical use.

Wei (1988) used the inverse stopping rule to stop the experiment, and proposed a fixed sample permutation test for the analysis. For comments on the work of Wei (1988), and general comments on difficulties with the inference after using the RPW(ω,ρ) allocation, the discussion introduced by Begg (1990) is recommended. In Wei, Smythe, Lin and Park (1990) exact conditional, exact unconditional and approximate confidence intervals were studied. One of their conclusions were that the design should not be ignored in the analysis. However, the suggested analysis ignores the stopping rule and therefore ignores part of the design.

3 Wald's Sequential Probability Ratio Test

In this section Wald's sequential probability ratio test and some of its basic properties, are described. The theory below follows unpublished lecture notes, Holm (1990). A good introduction to the theory of sequential analysis can be found, for example, in Govindarajulu (1981) or Siegmund (1985).

3.1 The test

We are interested in discriminating between two simple hypotheses

$$H_0: \theta = \theta_0,\ H_1: \theta = \theta_1 \quad , \text{ where } \theta_0 \neq \theta_1,$$

with a sequential probability ratio test, with desired significance level α and desired power in the alternative $1-\beta$, and the test is constructed as follows.

Assume that $X_1,\ldots,X_n$ are independent identically distributed random variables with probability distribution function $f_\theta(\cdot)$, and with joint probability distribution function $f_{n,\theta}(\cdot)$. Then the likelihood ratio λ_n can be written as

$$\lambda_n = \frac{f_{n,\theta_1}(\mathbf{x}_n)}{f_{n,\theta_0}(\mathbf{x}_n)} \ .$$

Let A and B be absorbing barriers. Then we have three possibilities:

$$\begin{aligned} B < \lambda_n < A &\quad \text{continue with an additional observation} \\ \lambda_n \leq B &\quad \text{stop the experiment and accept } H_0 \\ \lambda_n \geq A &\quad \text{stop the experiment and reject } H_0 \end{aligned} \ .$$

Often it is more practical to work with the log likelihood ratio, $\ln\lambda_n$, a=lnA and b=lnB.

In the following we will use the notation $\{\mathbf{X}\}_1^i = \{X_1,\ldots,X_i\}$.

3.2 Some important properties

The following results enable us to choose the bounds A and B, so that the true significance level, α *, and the true power under the alternative, $1-\beta$ *, will be close to the desired ones. Equations 3.2.1 and 3.2.2 give us the bounds of the true α * and $1-\beta$ *, while α and $1-\beta$ are desired.

The proofs of the propositions below are included to illustrate that the proof of Proposition 3.2 is the only one that requires the assumption of independent and identically distributed random variables.

Proposition 3.1 : Assume that $P(N < \infty) = 1$. Then for given A and B

$$A \le \frac{1-\beta^*}{\alpha^*} \quad \text{and} \quad B \ge \frac{\beta^*}{1-\alpha^*} \ ,$$

where α^* and β^* are the true type-I and type-II errors.

Proof : Let

$$R_n = \left\{ \{x\}_1^n \ ; \ N = n, \ \lambda_N \ge T_1 \right\} \ .$$

Therefore, the R_n's are mutually disjoint. Now we can write

$$\alpha^* = P_{\theta_0}\left(\lambda_N \ge T_1\right) = \sum_{n=1}^{\infty} P_{\theta_0}(R_n) = \sum_{n=1}^{\infty} \int_{R_n} f_{n,\theta_0}(x_n)dx_n \ .$$

Remembering that

$$\frac{f_{n,\theta_1}}{f_{n,\theta_0}} \ge T_1$$

on R_n we obtain

$$\alpha^* = \sum_{n=1}^{\infty} \int_{R_n} f_{n,\theta_0}(x_n)dx_n \le \frac{1}{T_1} \sum_{n=1}^{\infty} \int_{R_n} f_{n,\theta_1}(x_n)dx_n = \frac{1}{T_1} P_{\theta_1}\left(\lambda_N \ge T_1\right) = \frac{1}{T_1}(1-\beta^*) \ .$$

Hence,

$$T_1 \le \frac{1-\beta^*}{\alpha^*} \ .$$

Similarly we can show that

$$T_2 \ge \frac{\beta^*}{1-\alpha^*} \ .$$

■

Proposition 3.2 : If $X_1,...,X_n$ are independent and identically distributed random variables and

$$P\left(\ln \frac{f_{\theta_1}(X_i)}{f_{\theta_0}(X_i)} = 0 \right) < 1 \quad \forall\, i \ ,$$

then

$$P(N < \infty) = 1 \ .$$

Proof: Let $\Delta > 0$. Then

$$P\left(\ln \frac{f_{\theta_1}(X_i)}{f_{\theta_0}(X_i)} = 0 \right) = \lim_{\Delta \to 0} P\left(-\Delta \le \ln \frac{f_{\theta_1}(X_i)}{f_{\theta_0}(X_i)} \le \Delta \right) < 1 \qquad \forall\, i$$

implies that

$$\exists\, \Delta \ ; \ P\left(\left| \ln \frac{f_{\theta_1}(X_i)}{f_{\theta_0}(X_i)} \right| \le \Delta \right) = \gamma < 1 \ \text{ for some } \gamma > 0, \ \forall\, i.$$

Furthermore,

$$P\left(\left| \ln \frac{f_{\theta_1}(X_i)}{f_{\theta_0}(X_i)} \right| > \Delta \right) = P\left(\ln \frac{f_{\theta_1}(X_i)}{f_{\theta_0}(X_i)} < -\Delta \right) + P\left(\ln \frac{f_{\theta_1}(X_i)}{f_{\theta_0}(X_i)} > \Delta \right)$$

$$\le 2 \max\left\{ P\left(\ln \frac{f_{\theta_1}(X_i)}{f_{\theta_0}(X_i)} < -\Delta \right), P\left(\ln \frac{f_{\theta_1}(X_i)}{f_{\theta_0}(X_i)} > \Delta \right) \right\} \quad , \forall\, i,$$

and hence,

$$\max\left\{ P\left(\ln \frac{f_{\theta_1}(X_i)}{f_{\theta_0}(X_i)} < -\Delta \right), P\left(\ln \frac{f_{\theta_1}(X_i)}{f_{\theta_0}(X_i)} > \Delta \right) \right\} \ge \frac{1-\gamma}{2} \quad , \forall\, i.$$

Let

$$n_0 = \left[\frac{a-b}{\Delta} \right] + 1 \ .$$

Then

$$P\left(\sum_{i=1}^{n_0}\ln\frac{f_{\theta_1}(X_i)}{f_{\theta_0}(X_i)}\notin(b,a)\right)\geq P\left(\ln\frac{f_{\theta_1}(X_i)}{f_{\theta_0}(X_i)}<-\Delta\ ,\ \forall i\right)+P\left(\ln\frac{f_{\theta_1}(X_i)}{f_{\theta_0}(X_i)}>\Delta\ ,\ \forall i\right)$$

$$=\prod_{i=1}^{n_0}P\left(\ln\frac{f_{\theta_1}(X_i)}{f_{\theta_0}(X_i)}<-\Delta\right)+\prod_{i=1}^{n_0}P\left(\ln\frac{f_{\theta_1}(X_i)}{f_{\theta_0}(X_i)}>\Delta\right)$$

$$=\left(P\left(\ln\frac{f_{\theta_1}(X_i)}{f_{\theta_0}(X_i)}<-\Delta\right)\right)^{n_0}+\left(P\left(\ln\frac{f_{\theta_1}(X_i)}{f_{\theta_0}(X_i)}>\Delta\right)\right)^{n_0}$$

$$\geq\left(\max\left\{P\left(\ln\frac{f_{\theta_1}(X_i)}{f_{\theta_0}(X_i)}<-\Delta\right),P\left(\ln\frac{f_{\theta_1}(X_i)}{f_{\theta_0}(X_i)}>\Delta\right)\right\}\right)^{n_0}\geq\left(\frac{1-\gamma}{2}\right)^{n_0}>0\ .$$

Furthermore, let us denote

$$\varepsilon=\left(\frac{1-\gamma}{2}\right)^{n_0}\ .$$

We now have that

$$P(N>kn_0)\leq(1-\varepsilon)^k\ ,$$

that implies

$$\lim_{k\to\infty}P(N>kn_0)=0\ .$$

Therefore

$$P(N<\infty)=1\ .$$

■

Proposition 3.3 : Assume that $P(N<\infty)=1$. If A and B are chosen to be

$$A=\frac{1-\beta}{\alpha}\ \text{ and }\ B=\frac{\beta}{1-\alpha}\ ,$$

where α and β are the desired levels of the error probabilities, then the true level of significance, α^*, and the true power under the alternative, $1-\beta^*$, satisfy

$$\alpha^*+\beta^*\leq\alpha+\beta\ .$$

Proof: As $P(N < \infty) = 1$ is assumed, the requirement of Proposition 3.1 is satisfied. Hence,

$$\begin{cases} A\alpha^* \le 1-\beta^* \\ \beta^* \le B(1-\alpha^*) \end{cases}.$$

Now it follows that

$$\begin{cases} \dfrac{1-\beta}{\alpha}\alpha^* \le 1-\beta^* \\ \beta^* \le \dfrac{\beta}{1-\alpha}(1-\alpha^*) \end{cases},$$

which implies that

$$\begin{cases} \alpha^*(1-\beta) \le \alpha(1-\beta^*) \\ \beta^*(1-\alpha) \le \beta(1-\alpha^*) \end{cases}.$$

Furthermore,

$$\alpha^*(1-\beta)+\beta^*(1-\alpha) \le \alpha(1-\beta^*)+\beta(1-\alpha^*)$$

and finally

$$\alpha^* + \beta^* \le \alpha + \beta \ .$$

■

Note that Proposition 3.2 implies Proposition 3.1, which implies Proposition 3.3.

The allocation rule TR, where the two treatments are allocated with probability ½ each, satisfy the requirements for Propositions 3.1 - 3.3, as the random variables in this case are independent and identically distributed.

By using Propositions 3.1 and 3.3 we obtain

$$\frac{1-B}{A^+ - B} \le \alpha^* \le \frac{1-B^-}{A-B^-} \qquad (3.2.1)$$

and

$$A^+\frac{1-B}{A^+ - B} \le 1-\beta^* \le A\frac{1-B^-}{A-B^-} \ , \qquad (3.2.2)$$

where A^+ is the maximum value of the likelihood ratio, when stopping and rejecting H_0, and B^- is the minimum value of the likelihood ratio, when stopping and accepting H_0.

4 SPRT for a response dependent allocation

We investigate allocation rules that create dependence between the random variables. Therefore we need to generalize the theory of Wald's SPRT to this situation. We do this for our specific experimental setting, where we want to compare two treatments that both have two possible responses, success and failure.

In Section 4.1 we derive the log likelihood ratio, $\ln\lambda_n$, and in Section 4.2 we show that the properties, discussed in Section 3.2, are true also for the generalized SPRT. These properties enable us to construct a generalized test in the same way as the ordinary Wald's SPRT is constructed.

4.1 The log likelihood ratio

To simplify the calculations immediate responses are assumed.

From now on we use the following notations :

p_T = the success probability of treatment T

$S_{T(i-1)}$ = number of successes of treatment T among the i - 1 first patients

$F_{T(i-1)}$ = number of failure of treatment T among the i - 1 first patients

where T is either T_1 or T_2.

Furthermore, it is assumed that $0 < p_{T_1} < 1$, $0 < p_{T_2} < 1$ and that $p_{T_2} \le p_{T_1}$.

Simple hypothesis of the following kind are considered

$$H_0: p_{T_1} = p_{T_2} = p_{T_10} = p_{T_20} \quad \text{versus} \quad H_1: p_{T_1} = p_{T_11},\ p_{T_2} = p_{T_21}$$

It is assumed that

$$p_{T_10} \neq p_{T_11} \text{ and } p_{T_20} \neq p_{T_21}\ .$$

Our response variables are

$$Y_i = \begin{cases} 1 \text{ if patient i was allocated to treatment } T_1 \\ 0 \text{ if patient i was allocated to treatment } T_2 \end{cases}$$

$$X_i = \begin{cases} 1 \text{ if the treatment on patient i was a success} \\ 0 \text{ if the treatment on patient i was a failure} \end{cases}$$

The likelihood function can be determined as

$$L_N = P(Y_1 = y_1, X_1 = x_1) * \prod_{i=2}^{N} \left\{ P\left(Y_i = y_i \middle| \{Y\}_1^{i-1} = \{y\}_1^{i-1}, \{X\}_1^{i-1} = \{x\}_1^{i-1}\right) P(X_i = x_i | Y_i = y_i) \right\}$$

$$= P(Y_1 = y_1)\prod_{i=1}^{N} p_{T_1}^{y_i x_i}\left(1-p_{T_1}\right)^{y_i(1-x_i)} p_{T_2}^{(1-y_i)x_i}\left(1-p_{T_2}\right)^{(1-y_i)(1-x_i)}$$

$$* P\left(Y_i = 1 \middle| \{Y\}_1^{i-1} = \{y\}_1^{i-1}, \{X\}_1^{i-1} = \{x\}_1^{i-1}\right)^{y_i}\left(1 - P\left(Y_i = 1 \middle| \{Y\}_1^{i-1} = \{y\}_1^{i-1}, \{X\}_1^{i-1} = \{x\}_1^{i-1}\right)\right)^{(1-y_i)} .$$

Hence, the likelihood ratio is

$$\lambda_N = \prod_{i=1}^{N}\left(\frac{p_{T_1 1}}{p_{T_1 0}}\right)^{y_i x_i}\left(\frac{1-p_{T_1 1}}{1-p_{T_1 0}}\right)^{y_i(1-x_i)}\left(\frac{p_{T_2 1}}{p_{T_2 0}}\right)^{(1-y_i)x_i}\left(\frac{1-p_{T_2 1}}{1-p_{T_2 0}}\right)^{(1-y_i)(1-x_i)} .$$

The test statistic we use is the log likelihood ratio, the same as in Wald's SPRT. It can be written as

$\ln \lambda_N$

$$= \sum_{i=1}^{N}\left[y_i x_i \ln\left(\frac{p_{T_1 1}}{p_{T_1 0}}\right) + y_i(1-x_i)\ln\left(\frac{1-p_{T_1 1}}{1-p_{T_1 0}}\right) + (1-y_i)x_i \ln\left(\frac{p_{T_2 1}}{p_{T_2 0}}\right) + (1-y_i)(1-x_i)\ln\left(\frac{1-p_{T_2 1}}{1-p_{T_2 0}}\right)\right]$$

$$= S_{T_1(N)} \ln\left(\frac{p_{T_1 1}}{p_{T_1 0}}\right) + F_{T_1(N)} \ln\left(\frac{1-p_{T_1 1}}{1-p_{T_1 0}}\right) + S_{T_2(N)} \ln\left(\frac{p_{T_2 1}}{p_{T_2 0}}\right) + F_{T_2(N)} \ln\left(\frac{1-p_{T_2 1}}{1-p_{T_2 0}}\right).$$

4.2 Some properties

Assuming that Condition 1 below holds we will show Proposition 4.1, the correspondence for Proposition 3.2. This implies Proposition 3.1, which implies Proposition 3.3.

Condition 1:

$$P(Y_{i+1} = 1 | N > i) \le P(Y_{i+2} = 1 | N > i, Y_{i+1} = 1, X_{i+1} = 1) \le ..$$
$$\le P(Y_{i+m} = 1 | N > i, \{Y\}_{i+1}^{i+m-1} = \{1\}_{i+1}^{i+m-1}, \{X\}_{i+1}^{i+m-1} = \{1\}_{i+1}^{i+m-1})$$

and

$$P(Y_{i+1} = 0 | N > i) \le P(Y_{i+2} = 0 | N > i, Y_{i+1} = 0, X_{i+1} = 1) \le ..$$
$$\le P(Y_{i+m} = 0 | N > i, \{Y\}_{i+1}^{i+m-1} = \{0\}_{i+1}^{i+m-1}, \{X\}_{i+1}^{i+m-1} = \{1\}_{i+1}^{i+m-1})$$

$$, \forall m$$

Proposition 4.1 : If Condition 1 is satisfied, then $P(N<\infty)=1$.

Proof : The following is true for all values of i.

Let $m=\left\lceil \frac{a-b}{t} \right\rceil+1$, where $t=\min\left\lceil \begin{matrix}\text{the absolute values of the possible}\\ \text{increases of log likelihood, in one step}\end{matrix} \right\rceil$.

By assumptions $p_{T_1 0}\neq p_{T_1 1}$ and $p_{T_2 0}\neq p_{T_2 1}$, we have that

$$t=\min\left[\left|\ln\left(\frac{p_{T_1 1}}{p_{T_1 0}}\right)\right|,\left|\ln\left(\frac{1-p_{T_1 1}}{1-p_{T_1 0}}\right)\right|,\left|\ln\left(\frac{p_{T_2 1}}{p_{T_2 0}}\right)\right|,\left|\ln\left(\frac{1-p_{T_2 1}}{1-p_{T_2 0}}\right)\right|\right]>0.$$

Let us denote

$$C_{T_1,i+1}=\left\{\left(Y_{i+1}=1,X_{i+1}=1\right),\ldots,\left(Y_{i+m}=1,X_{i+m}=1\right)\right\}$$

and

$$C_{T_2,i+1}=\left\{\left(Y_{i+1}=0,X_{i+1}=1\right),\ldots,\left(Y_{i+m}=0,X_{i+m}=1\right)\right\}.$$

Therefore

$$\begin{aligned}P\left(C_{T_1,i+1}\cup C_{T_2,i+1}\middle|N>i\right)&=P\left(C_{T_1,i+1}\middle|N>i\right)+P\left(C_{T_2,i+1}\middle|N>i\right)\\&=P\left(Y_{i+1}=1\middle|N>i\right)P\left(X_{i+1}=1\middle|Y_{i+1}=1\right)\\&\quad*\prod_{j=2}^{m}P\left(Y_{i+j}=1\middle|N>i,\{Y\}_{i+1}^{i+j-1}=\{1\}_{i+1}^{i+j-1},\{X\}_{i+1}^{i+j-1}=\{1\}_{i+1}^{i+j-1}\right)P\left(X_{i+j}=1\middle|Y_{i+j}=1\right)\\&\quad+P\left(Y_{i+1}=0\middle|N>i\right)P\left(X_{i+j}=1\middle|Y_{i+1}=0\right)\\&\quad*\prod_{j=2}^{m}P\left(Y_{i+j}=0\middle|N>i,\{Y\}_{i+1}^{i+j-1}=\{0\}_{i+1}^{i+j-1},\{X\}_{i+1}^{i+j-1}=\{1\}_{i+1}^{i+j-1}\right)P\left(X_{i+j}=1\middle|Y_{i+j}=0\right).\end{aligned}$$

As a result of Condition 1 we obtain

$$P\left(C_{T_1,i+1}\cup C_{T_2,i+1}\middle|N>i\right)\geq\begin{cases}\left(\frac{1}{2}p_{T_1}\right)^m & \text{if } P\left(Y_{i+1}=1\middle|N>i\right)\geq\frac{1}{2}\\ \left(\frac{1}{2}p_{T_2}\right)^m & \text{if } P\left(Y_{i+1}=0\middle|N>i\right)\geq\frac{1}{2}\end{cases}$$

and furthermore

$$P\left(C_{T_1,i+1}\cup C_{T_2,i+1}\middle|N>i\right)\geq\min\left(\left(\tfrac{1}{2}p_{T_1}\right)^m,\left(\tfrac{1}{2}p_{T_2}\right)^m\right).$$

Note that the events $C_{T_1,i+1}$ and $C_{T_2,i+1}$ are two possible events, but not the only ones, for hitting a boundary in m steps.

Hence,

$$P(N=\infty) \le P(N > n_0+m, N > n_0+2m, \ldots) = \lim_{r\to\infty} P(N > n_0+m) \prod_{j=2}^{r} P\left(N > n_0+jm \middle| N > n_0+(j-1)m\right)$$

$$= \lim_{r\to\infty} \left(1-P(N \le n_0+m)\right) \prod_{j=2}^{r} \left(1-P\left(N \le n_0+jm \middle| N > n_0+(j-1)m\right)\right)$$

$$\le \lim_{r\to\infty} \prod_{j=2}^{r} \left(1-P\left(C_{A,n_0+(j-1)m+1} \cup C_{B,n_0+(j-1)m+1} \middle| N > n_0+(j-1)m\right)\right)$$

$$\le \lim_{r\to\infty} \left(1-\min\left[\left(\tfrac{1}{2}p_A\right)^m, \left(\tfrac{1}{2}p_B\right)^m\right]\right)^{r-1} = 0.$$

We then have that

$$P(N=\infty) \le 0 \ ,$$

and hence

$$P(N<\infty) = 1 \ .$$

■

Above it was proved that $P(N<\infty)=1$, under Condition 1. This implies Proposition 3.1. We can now construct the SPRT in the same way as the original Wald's SPRT.

4.3 Properties when using RPW and MPW

In the subsections, 4.3.1 and 4.3.2, we show that Condition 1 is satisfied for RPW and MPW, and for PW which is identical to MPW in the case of immediate responses.

4.3.1 RPW

At the start of the experiment we have ω balls representing each treatment in the urn. When receiving a response ρ balls are added to the urn : balls of type T_1 if we received a success for treatment T_1 or a failure for treatment T_2 and balls of type T_2 if we received a failure for treatment T_1 or a success for treatment T_2.

In the RPW case the probability of allocating a patient to treatment T_1 is

$$P(Y_i = 1) = \frac{\omega + \rho\left(S_{T_1(i-1)} + F_{T_2(i-1)}\right)}{2\omega + \rho(i-1)} \ .$$

To see that Condition 1 is satisfied for the RPW allocation we need to check both inequalities. To show that the first one holds we first write

$$P(Y_{i+1}=1|N>i)=\frac{P(Y_{i+1}=1|N>i)(2\omega+\rho i)+\rho P(Y_{i+1}=1|N>i)}{(2\omega+\rho(i+1))}$$
$$\leq \frac{P(Y_{i+1}=1|N>i)(2\omega+\rho i)+\rho}{(2\omega+\rho(i+1))}$$
$$=P(Y_{i+2}=1|N>i,Y_{i+1}=1,X_{i+1}=1)\ ,$$

and, for j = 2,3,... ,

$$P(Y_{i+j}=1|N>i,\{Y\}_{i+j-1}^{i+m-1}=\{1\}_{i+j-1}^{i+m-1},\{X\}_{i+j-1}^{i+m-1}=\{1\}_{i+j-1}^{i+m-1})=$$
$$\frac{P(Y_{i+j}=1|N>i,\{Y\}_{i+1}^{i+j-1}=\{1\}_{i+j}^{i+j-1},\{X\}_{i+1}^{i+j-1}=\{1\}_{i+1}^{i+j-1})(2\omega+\rho(i+j))}{(2\omega+\rho(i+j))}$$
$$\leq \frac{P(Y_{i+j}=1|N>i,\{Y\}_{i+1}^{i+j-1}=\{1\}_{i+j}^{i+j-1},\{X\}_{i+1}^{i+j-1}=\{1\}_{i+1}^{i+j-1})(2\omega+\rho(i+j-1))+\rho}{(2\omega+\rho(i+j))}$$
$$=P(Y_{i+j+1}=1|N>i,\{Y\}_{i+1}^{i+j}=\{1\}_{i+j}^{i+j},\{X\}_{i+1}^{i+j}=\{1\}_{i+1}^{i+j})\ .$$

Hence,

$$P(Y_{i+1}=1|N>i)\leq P(Y_{i+2}=1|N>i,Y_{i+1}=1,X_{i+1}=1)\leq\ldots$$
$$\leq P(Y_{i+m}=1|N>i,\{Y\}_{i+1}^{i+m-1}=\{1\}_{i+1}^{i+m-1},\{X\}_{i+1}^{i+m-1}=\{1\}_{i+1}^{i+m-1})\ .$$

Now, to see the second part of Condition 1, we can write

$$P(Y_{i+1}=0|N>i)\leq P(Y_{i+2}=0|N>i,Y_{i+1}=0,X_{i+1}=1)\leq\ldots$$
$$\leq P(Y_{i+m}=0|N>i,\{Y\}_{i+1}^{i+m-1}=\{0\}_{i+1}^{i+m-1},\{X\}_{i+1}^{i+m-1}=\{1\}_{i+1}^{i+m-1})\ .$$

The above inequality is equivalent to

$$1-P(Y_{i+1}=1|N>i)\leq 1-P(Y_{i+2}=1|N>i,Y_{i+1}=0,X_{i+1}=1)\leq\ldots$$
$$\leq 1-P(Y_{i+m}=1|N>i,\{Y\}_{i+1}^{i+m-1}=\{0\}_{i+1}^{i+m-1},\{X\}_{i+1}^{i+m-1}=\{1\}_{i+1}^{i+m-1})\ .$$

Note that

$$P(Y_{i+1}=1|N>i)=\frac{P(Y_{i+1}=1|N>i)(2\omega+\rho i)+\rho P(Y_{i+1}=1|N>i)}{(2\omega+\rho(i+1))}$$
$$\geq \frac{P(Y_{i+1}=1|N>i)(2\omega+\rho i)}{(2\omega+\rho(i+1))}$$
$$=P(Y_{i+2}=1|N>i,Y_{i+1}=0,X_{i+1}=1)\ .$$

Furthermore, for j = 2,3,... , we have

$$P\left(Y_{i+j}=1\middle|N>i,\{Y\}_{i+j-1}^{i+m-1}=\{0\}_{i+j-1}^{i+m-1},\{X\}_{i+j-1}^{i+m-1}=\{1\}_{i+j-1}^{i+m-1}\right)$$

$$=\frac{P\left(Y_{i+j}=1\middle|N>i,\{Y\}_{i+1}^{i+j-1}=\{0\}_{i+j}^{i+j-1},\{X\}_{i+1}^{i+j-1}=\{1\}_{i+1}^{i+j-1}\right)\left(2\omega+\rho\left(i+j\right)\right)}{\left(2\omega+\rho\left(i+j\right)\right)}$$

$$\geq\frac{P\left(Y_{i+j}=1\middle|N>i,\{Y\}_{i+1}^{i+j-1}=\{0\}_{i+j}^{i+j-1},\{X\}_{i+1}^{i+j-1}=\{1\}_{i+1}^{i+j-1}\right)\left(2\omega+\rho\left(i+j-1\right)\right)}{\left(2\omega+\rho\left(i+j\right)\right)}$$

$$=P\left(Y_{i+j+1}=1\middle|N>i,\{Y\}_{i+1}^{i+j}=\{0\}_{i+j}^{i+j},\{X\}_{i+1}^{i+j}=\{1\}_{i+1}^{i+j}\right).$$

and hence,

$$P\left(Y_{i+1}=0\middle|N>i\right)\leq P\left(Y_{i+2}=0\middle|N>i,Y_{i+1}=0,X_{i+1}=1\right)\leq\ldots$$

$$\leq P\left(Y_{i+m}=0\middle|N>i,\{Y\}_{i+1}^{i+m-1}=\{0\}_{i+1}^{i+m-1},\{X\}_{i+1}^{i+m-1}=\{1\}_{i+1}^{i+m-1}\right).$$

Hence, it is proved that Condition 1, and therefore Propositions 4.1, 3.1 and 3.3, are satisfied for the RPW allocation.

4.3.2 MPW

In the MPW case the probability of allocating a patient to treatment T_1 equals 1 given that the previous treatment was T_1 and the response a success or if the previous treatment was T_2 and the response a failure, and for the probability of allocating a patient to treatment T_2, respectively. Therefore it is easy to see that the MPW, and therefore also the PW, satisfies Condition 1, as shown below.

To show that the first inequality of Condition 1 is satisfied we write

$$P\left(Y_{i+1}=1\middle|N>i\right)\leq 1=P\left(Y_{i+2}=1\middle|N>i,Y_{i+1}=1,X_{i+1}=1\right)$$

and, for j = 2,3,... ,

$$P\left(Y_{i+j}=1\middle|N>i,\{Y\}_{i+j-1}^{i+m-1}=\{1\}_{i+j-1}^{i+m-1},\{X\}_{i+j-1}^{i+m-1}=\{1\}_{i+j-1}^{i+m-1}\right)$$

$$=P\left(Y_{i+j}=1\middle|N>i,Y_{i+j-1}=1,X_{i+j-1}=1\right)=1.$$

Hence,

$$P\left(Y_{i+1}=1\middle|N>i\right)\leq P\left(Y_{i+2}=1\middle|N>i,Y_{i+1}=1,X_{i+1}=1\right)\leq\ldots$$

$$\leq P\left(Y_{i+m}=1\middle|N>i,\{Y\}_{i+1}^{i+m-1}=\{1\}_{i+1}^{i+m-1},\{X\}_{i+1}^{i+m-1}=\{1\}_{i+1}^{i+m-1}\right).$$

To show that the second part of Condition 1 holds, we note that

$$P\left(Y_{i+1}=0\middle|N>i\right)\le 1=P\left(Y_{i+2}=0\middle|N>i,Y_{i+1}=0,X_{i+1}=1\right)$$

and, for j = 2,3,... ,

$$P\left(Y_{i+j}=0\middle|N>i,\{Y\}_{i+j-1}^{i+m-1}=\{0\}_{i+j-1}^{i+m-1},\{X\}_{i+j-1}^{i+m-1}=\{1\}_{i+j-1}^{i+m-1}\right)$$
$$=P\left(Y_{i+j}=0\middle|N>i,Y_{i+j-1}=0,X_{i+j-1}=1\right)=1\ .$$

Hence,

$$P\left(Y_{i+1}=0\middle|N>i\right)\le P\left(Y_{i+2}=0\middle|N>i,Y_{i+1}=0,X_{i+1}=1\right)\le\ldots$$
$$\le P\left(Y_{i+m}=0\middle|N>i,\{Y\}_{i+1}^{i+m-1}=\{0\}_{i+1}^{i+m-1},\{X\}_{i+1}^{i+m-1}=\{1\}_{i+1}^{i+m-1}\right)\ .$$

Therefore, Condition 1 is satisfied also for the MPW allocation rule.

5 Comparison of three allocation rules

We know that the RPW(ω,ρ) allocates more patients to the treatment that, during the experiment, seems to be better. We would also like to know if the RPW(ω,ρ) allocates fewer patients to the inferior treatment, than to the treatment superior in reality.
Each allocation to the treatment inferior in reality can be viewed as a loss. It is therefore of interest to minimize the number of patients allocated to that treatment.
Another important question is how the expected sample size behaves when one uses an RPW(ω,ρ) allocation, compared to other allocation rules.
We compare the RPW(ω,ρ) with the MPW and with total randomization, TR. TR is the simplest randomized allocation rule used and it satisfies the requirements for Wald's SPRT (independent identical distributed random variables). MPW, on the other hand, is one of the simplest play-the-winner allocation rules, but given that the response from the previous patient is known, the next allocation is deterministic. RPW(ω,ρ) is response dependent, but not deterministic.
We study the differences between the allocation rules by means of the expected sample size, E[N], and the expected number of patients allocated to the inferior treatment, $E[N_B]$. These expectations are complicated to compute for the MPW and RPW, since we do not have independent and identically distributed random variables. The probability that patient i is allocated to treatment T_1 depends on all the earlier allocations and responses. Simulations were therefore conducted to investigate the behavior of the expected values E[N] and $E[N_B]$.

5.1 Description of the simulation study

The RPW was simulated with five different combinations of the parameters ω and ρ, namely RPW(100.000,1), RPW(10,1), RPW(1,1), RPW(1,10) and RPW(1,100.000).
At the start of the experiment the allocation probability is ½ for each treatment, for every value on ω and ρ. The larger the ratio $\frac{\rho}{\omega}$ is, the faster the response affects the allocation probability.

Large response dependency, in the early states of the experiment, could be hard to get accepted when the allocation rule is used in a real practical setting, but to get a good understanding of how the RPW allocation behaves, extreme response dependency is included.

As ω increases the RPW gets closer to total randomization. High values of ω let the play-the-winner quality come slower into the experiment. Correspondingly for ρ, the RPW gets closer to the MPW as ρ increases.

For each of the three allocation rules two different hypothesis cases were tested, namely

$$1.\ H_0: p_{T_1} = p_{T_2} = 0.7 \quad \text{versus} \quad H_1: p_{T_1} = 0.8,\ p_{T_2} = 0.6$$

and

$$2.\ H_0: p_{T_1} = p_{T_2} = 0.6 \quad \text{versus} \quad H_1: p_{T_1} = 0.8,\ p_{T_2} = 0.4\ .$$

Hypothesis case 1. represents a small treatment difference while 2. represents a larger treatment difference. Simulations were done in these two cases both under the assumption that H_0 is false and H_1 is true and under the assumption that H_0 is true and H_1 is false.

We used Wald's sequential probability ratio test, with significance level α=0.05 and power under the alternative 1-β=0.95.

The true significance level α^* and the true power under the alternative $1-\beta^*$ are bounded as below (see equation 3.2.1 and equation 3.2.2).

Hypothesis case 1 :

$$0.0375 \approx \frac{54}{1441} \le \alpha^* \le \frac{55}{1081} \approx 0.0509$$

$$0.9493 \approx \frac{4104}{4323} \le 1-\beta^* \le \frac{1045}{1081} \approx 0.9667$$

Hypothesis case 2 :

$$0.0333 \approx \frac{36}{1081} \le \alpha^* \le \frac{37}{721} \approx 0.0513$$

$$0.9491 \approx \frac{1026}{1081} \le 1-\beta^* \le \frac{703}{721} \approx 0.9750$$

For each of the four cases, two hypothesis under two different assumptions, 500.000 independent experiments were simulated.

5.2 Results of the simulations

For Hypothesis case 1. (see figure 1), the sample sizes were about the same for total randomization and RPW(100.000,1). The sample size seems to decrease with decreasing ω. Values of ρ seem not to affect the sample size in a major way: when ω is held constant , ω=1, and ρ is increasing there is no difference in sample size for the chosen values of ρ.

The results for Hypothesis case 2. were similar, see figure 2, but the differences in the average sample sizes were so small that they are perhaps not of practical importance.

Figure 1 The mean, and two times the standard errors, of the sample sizes from the 500.000 simulations of hypothesis case 1, for the different allocation rules. On the x-axis the following allocation rules are represented: TR, RPW(1000.000,1), RPW(10,1), RPW(1,1), RPW(1,10), RPW(1,100.000), MPW. Furthermore, a represents the situation when H_1 is true and b the one when H_0 is true.

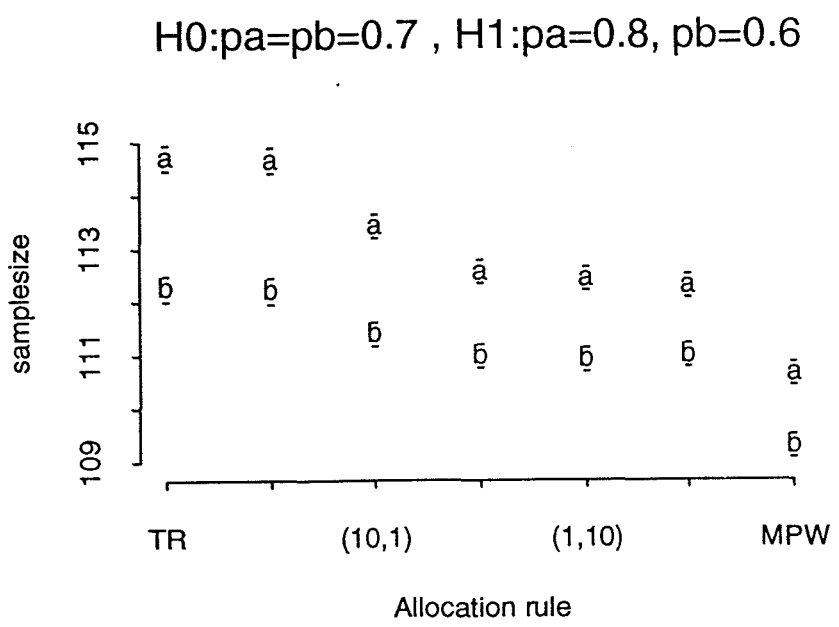
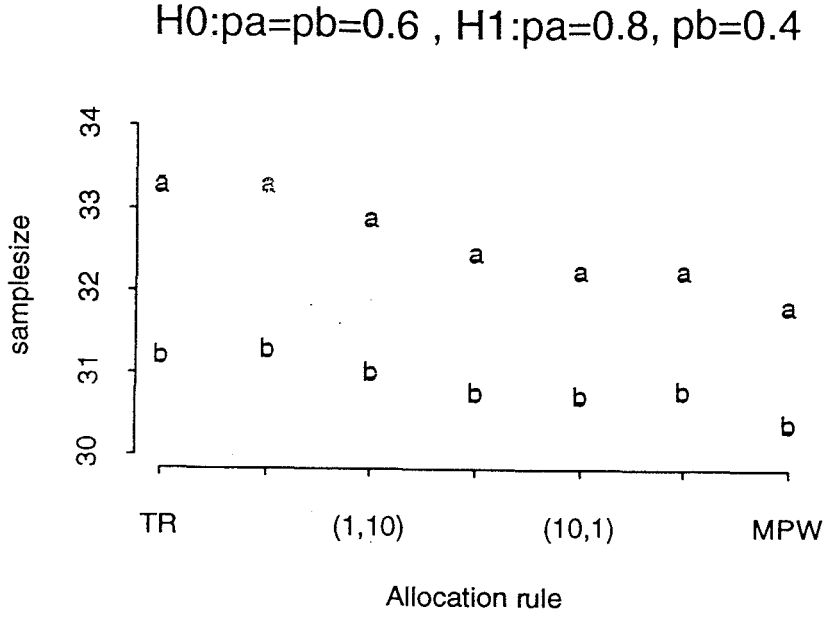


Figure 2 The mean, and two times the standard errors, of the sample sizes from the 500.000 simulations of hypothesis case 2, for the different allocation rules. On the x-axis the following allocation rules are represented: TR, RPW(1000.000,1), RPW(10,1), RPW(1,1), RPW(1,10), RPW(1,100.000), MPW. Furthermore, a represents the situation when H_1 is true and b the one when H_0 is true.



Note that the sample size follows approximately the same pattern both under the null hypothesis and under the alternative hypothesis, but that it is a little smaller under the null hypothesis. That is, the sample size is smaller when the treatments are as good than when there is a true difference between them.

Note that treatment T_2 is the inferior treatment when there is a treatment difference.

The behavior of the number of patients allocated to treatment T_2 follows a different pattern than the sample size, see figures 3 and 4, except for total randomization and RPW(100.000,1). These two allocation rules behave quite similarly, and they are the allocation rules that allocate more patients to treatment T_2 than the others, both when T_2 is inferior and equal to T_1.

When there is a treatment difference MPW seems to allocate the least number of patients to treatment T_2, and the number of patients allocated to the inferior treatment decreases with increasing $\frac{\rho}{\omega}$, which was expected.

When there is no difference between the treatments one could think that the number of allocations to treatments T_1 and T_2 would be the same. This is true for the total randomization and for the RPW(100.000,1) allocation. On the other hand, the other four RPW allocations and the MPW allocation still allocate fewer patient to treatment T_2 than to T_1. This can be understood by looking at the Wald statistic for the RPW and the MPW and by remembering that we have simple hypothesis. Note that because of the simple alternative it is enough that the data shows that one of the statements, $p_A = 0.7$, $p_B = 0.7$, $p_A = 0.8$ or $p_B = 0.6$, is not true, to be able to either accept or reject H_0. This is an interesting and important fact: if we want to test $H_0: p_A = p_B = 0.7$ it is not fair towards H_0 to have a simple alternative unless this simple hypothesis and the simple alternative are the only likely truths.

Figure 3. The mean, and two times the standard errors, of the 500.000 simulations of hypothesis case 1, for the sample sizes from the different allocation rules. On the x-axis the following allocation rules are represented: TR, RPW(1000.000,1), RPW(10,1), RPW(1,1), RPW(1,10), RPW(1,100.000), MPW. Furthermore, a represents the situation when H_1 is true and b the one when H_0 is true.

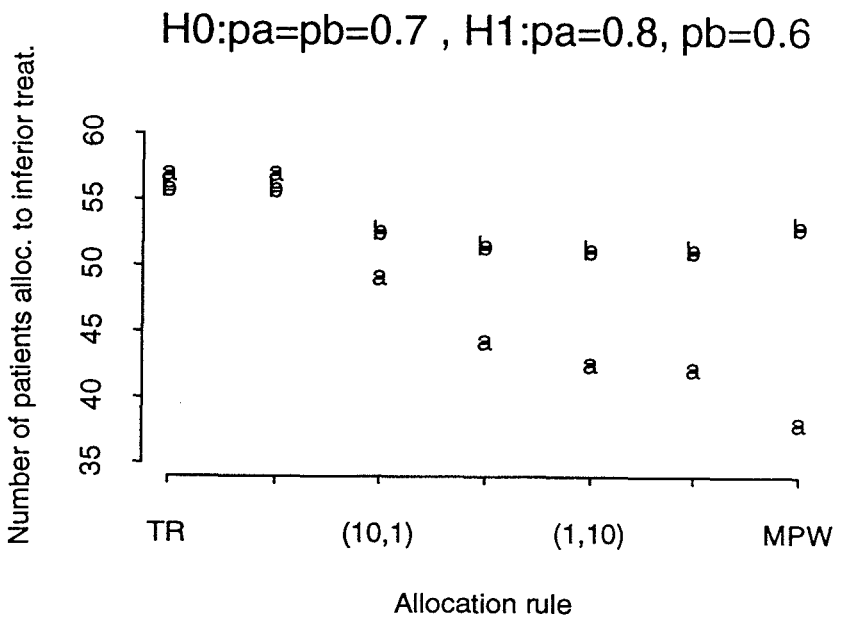
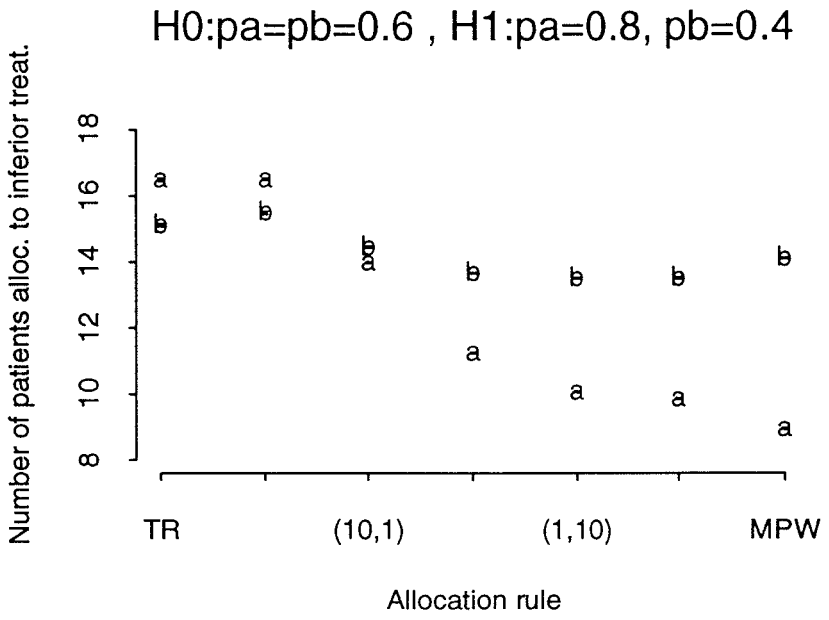


Figure 4 The mean, and two times the standard errors, of the 500.000 simulations of hypothesis case 2, the sample sizes from for the different allocation rules. On the x-axis the following allocation rules are represented: TR, RPW(1000.000,1), RPW(10,1), RPW(1,1), RPW(1,10), RPW(1,100.000), MPW. Furthermore, a represents the situation when H_1 is true and b the one when H_0 is true.



For all allocation rules the true significance level and the true power under the alternative are close to the intended quantities (see the tables in the appendix). Note also that for all allocation rules the standard errors of the expected values seems to be small (see the figures and the tables in the appendix).

Some interesting remarks are that the RPW gets closer to total randomization as ω increases, and for small treatment differences the sample size is larger for total randomization than for the allocations with response dependency, even under H_0. It means that even if there is no treatment difference we obtain a smaller sample size by using a response dependent allocation rule rather than the total randomization.

For large treatment differences the sample sizes are about the same for all allocation rules compared, but there is a large difference in the number of patients allocated to the inferior treatment.

Note also that for the case with less treatment difference, $p_A = 0.8$ and $p_B = 0.6$, the actual number of patients allocated to the inferior treatment differs more between the

allocation rules than in the case with greater treatment difference, $p_A = 0.8$ and $p_B = 0.4$.

6 Discussion

Wald's sequential probability ratio test is originally presented for independent and identically distributed random variables. As shown in Section 4 some important properties of the test, hold for a certain class of response dependent allocation rules, like RPW and the MPW.

We compare the RPW allocation rule to the MPW allocation rule and to total randomization. Two important questions are the expected sample size and the number of patients allocated to the treatment inferior in reality. However, both expectations are hard to derive theoretically, and, thus, they were estimated by simulations.

Regarding the expected sample size and the expected number of patients allocated to the inferior treatment, the MPW is slightly better than the others, for the cases studied, and after the MPW comes the RPW. There are, however, some negative characteristics of the MPW to be considered. The MPW allocation is non-random in the following sense: Given that the response from the previous patient is known, the next allocation is deterministic. In addition, the MPW requires immediate responses.

Non-randomness could, for example, lead to selection bias. By selection bias we mean that when the experimenter knows for certain which treatment will be assigned to the next patient he may, consciously or unconsciously, bias the experiment by deciding beforehand who is or is not a suitable experimental subject.

One could argue that the disadvantages, non-randomness and immediate responses, could be solved by using Zelen's PW allocation. It allocates the treatments with probability ½ if there are a lot of delayed responses, and it tends to be close to the MPW allocation if there are few delayed responses.

The RPW(ω,ρ) allocation rule (RPW(10,1), RPW(1,1), RPW(1,10), RPW(1,100.000)) was quite good, both in terms of the expected sample size and in terms of minimizing the number of patients allocated to the inferior treatment, and it does not have the disadvantages of Zelen's MPW allocation rules mentioned above.

A general remark on the comparisons, in the cases with simple hypotheses, shown here, is that if the responses are allowed to affect the allocation enough the play-the-winner rules not only decrease the number of patients allocated to the inferior

treatment, but also decrease the sample size, compared to the total randomization. For the RPW(1,1) and for the rules with even more response dependence, the simulations indicated the statement above.

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APPENDIX

In the tables to follow the arithmetic mean and the standard error of the mean, of the simulated values, is given for N, N_B and $P_{H_1}(\text{rej.}H_0)$.

Table 1 :

$H_0: p_A = p_B = 0.7$ versus $H_1: p_A = 0.8,\ p_B = 0.6$ when H_0 false and H_1 true.

	P(Y = 1) = ½	RPW (100.000,1)	RPW (10,1)	RPW (1,1)	RPW (1,10)	RPW (1,100.000)	MPW
$\hat{E}[N]$	114.82	114.76	113.53	112.69	112.55	112.42	110.77
$\sqrt{\hat{\sigma}_{\hat{E}[N]}}$	0.12	0.12	0.11	0.11	0.11	0.11	0.11
$\hat{E}[Nb]$	57.40	57.39	49.51	44.64	42.97	42.58	38.46
$\sqrt{\hat{\sigma}_{\hat{E}[Nb]}}$	0.06	0.06	0.05	0.05	0.05	0.05	0.04
$\hat{P}_{H_1}(\text{rej.}H_0)$	0.955872	0.955538	0.955976	0.955760	0.956034	0.955692	0.952918
$\sqrt{\hat{\sigma}_{\hat{P}_{H_1}(rej.H_0)}}$	0.000290	0.000292	0.000290	0.000291	0.000290	0.000291	0.000299

Table 2 :

$H_0: p_A = p_B = 0.7$ versus $H_1: p_A = 0.8,\ p_B = 0.6$ when H_0 true and H_1 false.

	P(Y = 1) = ½	RPW (100.000,1)	RPW (10,1)	RPW (1,1)	RPW (1,10)	RPW (1,100.000)	MPW
$\hat{E}[N]$	112.37	112.32	111.51	111.10	111.03	111.12	109.41
$\hat{\sigma}_{\hat{E}[N]}$	0.12	0.12	0.11	0.11	0.11	0.11	0.11
$\hat{E}[Nb]$	56.19	56.15	52.97	51.82	51.53	51.52	53.34
$\hat{\sigma}_{\hat{E}[Nb]}$	0.06	0.06	0.05	0.05	0.05	0.05	0.04
$\hat{P}_{H_1}(\text{rej.}H_0)$	0.045782	0.045936	0.045710	0.045922	0.046012	0.046292	0.047334
$\hat{\sigma}_{\hat{P}_{H_1}(\text{rej.}H_0)}$	0.000296	0.000296	0.000295	0.000296	0.000296	0.000297	0.000300

Table 3 :

$H_0: p_A = p_B = 0.6$ versus $H_1: p_A = 0.8,\ p_B = 0.4$ when H_0 false and H_1 true.

	P(Y = 1) = ½	RPW (100.000,1)	RPW (10,1)	RPW (1,1)	RPW (1,10)	RPW (1,100.000)	MPW
$\hat{E}[N]$	33.34	33.33	32.94	32.52	32.30	32.30	31.88
$\hat{\sigma}_{\hat{E}[N]}$	0.03	0.03	0.03	0.03	0.03	0.03	0.03
$\hat{E}[Nb]$	16.66	16.67	14.15	11.42	10.24	10.03	9.12
$\hat{\sigma}_{\hat{E}[Nb]}$	0.02	0.01	0.01	0.01	0.01	0.01	0.01
$\hat{P}_{H_1}(\text{rej.}H_0)$	0.959464	0.959676	0.959786	0.959530	0.960056	0.959102	0.957672
$\hat{\sigma}_{\hat{P}_{H_1}(\text{rej.}H_0)}$	0.000279	0.000278	0.000278	0.000279	0.000277	0.000280	0.000284

Table 4 :

$H_0: p_A = p_B = 0.6$ versus $H_1: p_A = 0.8,\ p_B = 0.4$ when H_0 true and H_1 false.

	P(Y = 1) = ½	RPW (100.000,1)	RPW (10,1)	RPW (1,1)	RPW (1,10)	RPW (1,100.000)	MPW
$\hat{E}[N]$	31.26	31.34	31.08	30.82	30.79	30.85	30.46
$\hat{\sigma}_{\hat{E}[N]}$	0.03	0.03	0.03	0.03	0.03	0.03	0.03
$\hat{E}[Nb]$	15.29	15.66	14.62	13.84	13.68	13.69	14.27
$\hat{\sigma}_{\hat{E}[Nb]}$	0.03	0.02	0.01	0.01	0.01	0.01	0.01
$\hat{P}_{H_1}(\text{rej.}H_0)$	0.042368	0.042310	0.042254	0.04288	0.042574	0.04342	0.042822
$\hat{\sigma}_{\hat{P}_{H_1}(\text{rej.}H_0)}$	0.000285	0.000285	0.000285	0.000286	0.000285	0.000288	0.000286

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