Nature Precedings : hdl:10101/npre.2008.2102.1 : Posted 21 Jul 2008

Sequential Allocation and Balancing Prognostic Factors in a Psychiatric Clinical Trial

Victor Fossaluza, Juliana B. Diniz, Basilio B. Pereira,

Euripedes C. Miguel and Carlos A. B. Pereira *

Abstract

In controlled clinical trials, each of several prognostic factors should be balanced across the trial arms. Traditional restricted randomization may be proved inadequate especially with small sample sizes. In psychiatric disorders such as obsessive compulsive disorder (OCD), small trials prevail. Therefore, procedures to minimize the chance of imbalance between treatment arms are advisable. This paper describes a minimization procedure specifically designed for a clinical trial that evaluates treatment efficacy for OCD patients. Aitchison's compositional distance was used to calculate vectors for each possibility of allocation in a covariate adaptive method. Two different procedures were designed to allocate patients in small blocks or sequentially one-by-one. Partial results of this allocation procedure as well as simulated ones are shown. In the clinical trial for which this procedure was developed, the balancing between treatment arms was achieved successfully. Simulations of results considering different arrival order of patients showed that most of the patients are allocated in a different treatment arm if arrival order is modified. Results show that a random factor is maintained with the random arrival order of patients. This specific procedure allows the use of a large number of prognostic factors for the allocation decision and was proved adequate for a psychiatric trial design.

KEY WORDS: Clinical research, Randomization, Aitchison's compositional distance

*Victor Fossaluza is Statistician, Institute of Psychiatry and Institute of Mathematics and Statistics, University of São Paulo, São Paulo, Brazil (e-mail address: victor.ime@gmail.com). Juliana Belo Diniz is Psychiatrist, Institute of Psychiatry, University of São Paulo School of Medicine Hospital das Clínicas, São Paulo, Brazil (e-mail address: juliana@protoc.com.br). Basilio de Bragança Pereira is Statistician, School of Medicine, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil (e-mail: basilio@hucff.ufrj.br). Euripedes Constantino Miguel Filho is Psychiatrist, Institute of Psychiatry, University of São Paulo School of Medicine Hospital das Clínicas, São Paulo, Brazil (e-mail address: ecmiguel@usp.br). Carlos Alberto Bragança Pereira is Statistician, Institute of Psychiatry and Institute of Mathematics and Statistics, University of São Paulo, São Paulo, Brazil (e-mail address: cadebp@gmail.com). The results described in this paper were presented at the 2008 Bayesian Biostatistics Conference (Houston, TX, USA, January/2008).

Nature Precedings : hdl:10101/npre.2008.2102.1 : Posted 21 Jul 2008

1. INTRODUCTION

For some specific psychiatric disorders, large trials are fairly rare. Obsessive-compulsive disorder (OCD) treatment, for instance, has only been studied in small trials. First-line treatments such as clomipramine and selective serotonin reuptake inhibitors are typically studied in trials with no more than two hundred patients (Eddy et al. 2004). For second-line treatments, such as pharmacological augmentation strategies, the situation is worse, albeit understandably so (Bloch et al. 2006; Fontenelle et al. 2007). To our knowledge, there have been no trials involving more than one hundred patients. Indeed, most such studies have presented final sample sizes of no more than 15 patients per arm (Bloch et al. 2006).This is in stark contrast to what is seen for studies of common clinical diseases such as hypertension and diabetes. Therefore, specific aspects need to be taken into consideration when implementing clinical trials involving psychiatric patients, especially those with OCD.

In small trials, such as those typically designed to study psychiatric disorders, an imbalance between treatment arms, in terms of prognostic factors, can affect the interpretation of the results. One of the first methods created to address this problem was stratified allocation of individuals (Lachin 1988).The use of this method also reduces the need to adjust statistical data analysis for covariates that work as prognostic factors. The limitation of stratified allocation is that it can only be applied when a small number of covariates are involved. Otherwise, the sample has to be divided into a great number of strata with only a few patients in each (Kernan et al. 1999). To overcome this limitation, it became necessary to devise alternative methods of minimising imbalance among treatment arms.

Pocock and Simon (1975) devised a general procedure for treatment assignment that minimises imbalance among the individual prognostic factors with a logistic similar to that employed to guide the procedure subsequently described. Independently, Taves (1974) also developed a minimisation procedure that will not be discussed in this article, as it is encompassed by the Pocock and Simon method.

Since 1975, various other authors have developed procedures to minimise the chance of imbalance between arms, as previously reviewed (Scott et al. 2002; Pocock et al. 2002). Each method has its specific limitations and complexities. For example, the optimal design technique of allocation allowed the use of continuous variables in their non-categorical format as covariates (Atkinson 1982). However, its complexity and difficulty impeded its practical implementation. This example illustrates that no allocation procedure is ideal. Therefore, novel methods are still required in specific situations.

In response to the need for specifically designed minimisation procedures in clinical trials involving in-

dividuals with OCD, we developed an allocation method that uses the Aitchson distance (Aitchison 1983, 1986; Aitchison and Egozcue 2005) for compositional data. The Aitchson distance was chosen because all prognostic factors used are disposed as categorical data with relative frequencies.

Here, we present the results of allocation of the partial sample collected during the first year of the study for which this procedure was developed, as well as those of simulated samples that varied in terms of the order of patient inclusion.

2. METHODS

2.1 Allocation

For clarity, let us consider the simplest design. Consider a clinical trial in which patients are enrolled sequentially, according to the order in which they enter treatment at the clinic. Each patient is to be assigned to one, and only one, of the two alternative treatments. Imagine that a new patient arrives after the study already has a considerable number of patients under study in each of the two arms: n_1 and n_2. In addition, consider that age, denoted by a, is a factor that we think should be adjusted for. Possible ages are divided into three different categories: A_1 if $a < 30$; A_2 if $30 < a < 45$; and A_3 if $a > 45$. Consider now the following notation:

1. Represent the sample absolute frequencies of n_1 and n_2, respectively, as (n_{11}, n_{12}, n_{13}) and (n_{21}, n_{22}, n_{23}), i.e., for $i = 1$ or 2 and $j = 1$, 2 or 3, n_{ij} is the number of patients of age group A_j in arm i.

2. Represent the compositional vectors (the relative frequency vectors), respectively, as $A_1 = (A_{11}, A_{12}, A_{13})$ and $A_2 = (A_{21}, A_{22}, A_{23})$, i.e., $A_{22} = n_{ij}/n_i$ is the relative frequency of patients in age group A_j in arm i - proportion of age group A_j in arm i.

The allocation of a new incoming patient consists of the following steps:

i. Include the new patient in the first arm, represent the new composition vector as $(A_1)^*$, and calculate a distance between $(A_1)^*$ and A_2, i.e., evaluate the distance $d_1 = \Delta[(A_1)^*; A_2]$.

ii. Include the new patient in the second arm, represents now the new compositional vector by $(A_2)^*$, and compute the distance $d_2 = \Delta[A_1; (A_2)^*]$.

iii. Compare the values of d_1 and d_2. If $d_1 < d_2$, allocate the new patient to n_1; if $d_1 > d_2$, allocate the patient to n_2; and if $d_1 = d_2$, the patient can be allocated to either arm.

Nature Precedings : hdl:10101/npre.2008.2102.1 : Posted 21 Jul 2008

Nature Precedings : hdl:10101/npre.2008.2102.1 : Posted 21 Jul 2008

Note that we make our decision based on the values of the distances between the compositional vectors. By compositional vectors, we understand vectors in which the sum of their components are fixed and known. In our case, as we have relative frequencies, the values of the components are numbers in the interval $[0; 1]$, and the sum of these components is one. Aitchson (1983, 1986) argued that, for compositional data as such, the correct distance measure is not the usual standard Euclidian measure but the one described below.

For some generalities, consider factor a having k (> 1) possible alternatives, in the place of the three considered above, i.e., $A_i = (A_{i1}, A_{i2}, \ldots, A_{ik})$ is the relative frequency vector of arm i ($= 1, 2$). For category j, consider the natural logarithm of the between-arm relative frequency ratio, $r_j = (A_{1j}/A_{2j})$, denoted by $\ln(r_j)$, and the mean of these logarithms, denoted by L:

$$\ln(r_j) = \ln(A_{1j}) - \ln(A_{2j})$$

and

$$L = \frac{\ln(r_1) + \ln(r_2) + \ldots + \ln(r_k)}{k}$$

The Aitchison distance measure between the two compositional vectors A_1 and A_2 is defined as follows:

$$\Delta[a_1, a_2] = \sqrt{\sum_{j=1}^{k} \big(\ln(r_j) - L\big)^2}$$

To exemplify the use of the allocation procedure, let us consider the case of the three aging categories A_1, A_2, and A_3, as before. Suppose that, in one stage of the process, we had the following vectors of absolute frequencies: $n_1 = (3; 7; 5)$ and $n_2 = (5; 6; 6)$. A new patient enrols and is in age category A_2. Table 1 presents the vectors for the calculus of the distances.

Table 1. Vectors of relative frequencies.

Aging	A_1	A_2	A_1^*	A_2^*
A_1	0.2000	0.2941	0.1875	0.2778
A_2	0.4667	0.3529	0.5000	0.3889
A_3	0.3333	0.3529	0.3125	0.3333
Sum	1	1	1	1

The following three expressions represent the intragroup distances, (not) including the new patient:

A. Before the new patient, $\Delta[A_1; A_2] = 0.4702$

B. With the new patient in n_1, $\Delta[(A_1)^*; A_2] = 0.5676$

C. With the new patient in n_2, $\Delta[A_1; (A_2)^*] = 0.3661$

The figures above indicate that the best allocation for a new patient that belongs to age category A_2 is to n_2. This conclusion might appear obvious to the decision maker, as it is desirable to increase the frequency of A_2 in n_2. Note that this choice increases the sample size of n_2. It would be interesting if we could also control the arm sample sizes. Let us also transform the sample size (s) into a compositional factor. Let us consider the vectors $s_1 = (n_1; n_2)/n$ and $s_2 = (n_2; n_1)/n$ as the relative frequencies for n_1 and n_2, respectively. In our example we would have the following:

$$s_1 = \frac{1}{32}(15; 17) = (.47; .53), \quad s_2 = (.53; .47),$$

$$(s_1)^* = (.48; .52) \quad \text{and} \quad (s_2)^* = (.55; .45)$$

Here the * indicates that the new patient entered a specific arm. The new distance values are $\Delta[s_1; s_2] = 0.1770$, $\Delta[(s_1)^*; s_2] = 0.1314$, and $\Delta[s_1; (s_2)^*] = 0.2174$. Clearly, the best allocation would be to the first arm, which has a smaller sample size. Bear in mind that, using age categories, our best choice would have been to allocate the new patient to the second arm. However, the sample size factor indicates that the first arm is the appropriate allocation for the new patient. If the decision maker feels that age is more important than sample size, a larger weight could be given to age than to sample size. For example, consider that we decide to use a weight of 2 for age and a weight of 1 for sample size. We could use the weighting average of the distances to facilitate the decision. The results for our example are as follows:

i. new patient in n_1 produces $D_1 = \dfrac{2\Delta[(A_1)^*; A_2] + \Delta[(s_1)^*; s_2]}{3} = 0.4222$

ii. new patient in n_2 produces $D_2 = \dfrac{2\Delta[A_1; (A_2)^*] + \Delta[s_1; (s_2)^*]}{3} = 0.3165$

The overall distance using the two factors indicates that the new patient should be allocated to n_2 in order to make the arms closer in terms of age and sample size. It is also possible to give equal weights to the two factors. Another point that could be questioned is the constructed factor for sample size. Note that, for comparing factors, we need to have the same range for all factor distance measures. Hence, the definitions of s_1 and s_2 seem to be quite adequate.

The examples discussed below are more specific and have interesting particularities. The first, related to phase one of the trial described below, deals with two arms, four prognostic factors, and simultaneous

Nature Precedings : hdl:10101/npre.2008.2102.1 : Posted 21 Jul 2008

allocation of three patients each time. The second example, related to phase two, deals with seven prognostic factors and one-by-one allocation of patients into three groups.

2.2 Two-phase clinical trial

A study group specialising in OCD delineated a clinical trial that consists of two phases. The objective of phase one is to compare patient responses to pharmacological and psychotherapeutic treatments. There is an expectation of 360 OCD patients to be enrolled in phase one over a 3-year period. However, for logistical reasons, there is no expectation that the numbers of patients allocated to the individual treatment arms will be similar in phase one. There will be times when the pharmacological arm receives more patients than does the psychotherapeutic arm and other times when this relationship is reversed. These changes are necessary because for pragmatic reasons each therapeutic arm accommodates a different number of patients in each moment of the study. As the psychotherapeutic arm involves group psychotherapy, at moments when groups are being initiated a fast inclusion of patients is necessary, but when groups have already been initiated the speed of inclusion need to be diminish as only two groups can be conducted simultaneously.

From previous experience, it is expected that 60% of the patients treated in either of the two arms of phase one will report less than adequate symptom improvement. Patients that participated in the pharmacological arm (n_1) and did not respond to treatment will be invited to participate in phase two. Patients who are non-responders in the psychotherapeutic arm (n_2) of phase one will be invited to participate in the pharmacological arm (n_1), and, if they maintain their treatment resistance in n_1, they also will be invited to participate in phase two. Phase two consists of three arms, the objective being to compare three different pharmacological augmentation strategies. In phase two, unlike in phase one, it is expected that a similar number of patients will be allocated to each of the three arms. Considering expected response rates, drop-out rates, and frequency of refusals to participate in a study using a placebo, it is likely that 30 to 40 patients will be included in each arm. This sample size seems to be adequate according to the investigator hypothesis. The entire clinical trial design is illustrated in Figure 1.

The allocation strategies for the two phases of the trial are different. To accommodate the logistic characteristics of phase one (that require a different pace of patient enrolment for each arm and at different study time points), the designer will receive groups of 3 patients to be allocated into the two groups. On some occasions, it might be necessary to allocate 2 patients to n_1 and 1 to n_2. On other, well-defined occasions, the situation is reversed, n_1 will receive 1 patient, and the other 2 patients will be allocated to n_2.

Nature Precedings : hdl:10101/npre.2008.2102.1 : Posted 21 Jul 2008

Nature Precedings : hdl:10101/npre.2008.2102.1 : Posted 21 Jul 2008

2.2.1 Prognostic factors to be balanced across arms

When the program for allocation was developed for phase one, a smaller number of variables to be adjusted for was chosen, as we did not know how many covariates this new procedure could accommodate without compromising its efficacy in minimising arm imbalance. After the first results of allocation were analysed for phase one, it became clear that the procedure could accommodate a greater number of covariates. Therefore, the program designed for phase two was created with a greater number of hypothesised prognostic factors that could also have been covariates in phase one. The factors used to establish the allocating strategy were chosen based on previous studies. Although the appropriateness of the factors used might be obvious, it is not our intention to discuss this matter in this paper, the sole intention of which is to present the allocation strategy used in the study described. The factors and their categories were as follows:

1. Current age was categorised into three classes: under 30 years of age (A_0); between 31 and 45 (A_1); and over 45 (A_2).

2. OCD symptom severity, as measured using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), was categorised as being in one of eight classes based on ordered scores for each of the two symptom types (obsession and compulsion): ≤ 8 = low (L); 8-15 = moderate (M); and > 15 = high (H). Therefore, the eight possible classes were as follows: $(L;L)$, $(L;M)$, $(L;H)$, $(M;L)$, $(M;M)$, $(M;H)$, $(H;L)$, $(H;M)$, and $(H;H)$. The first and second notations are based on the scores for obsession and compulsion, respectively. Clearly, $(L;L)$ is not considered, as it would indicate no OCD symptoms, and we had no patients in this class.

3. Treatment history was divided into three categories in each phase. In phase one, h_0 indicates no previous appropriate treatment, h_1 indicates one previous course of appropriate treatment without response, and h_2 indicates two or more previous courses of appropriate treatment without response. In phase two, h_0 indicates no Y-BOCS score reduction or Y-BOCS score increase after n_1 in phase one, h_1 indicates a 1-20% reduction in Y-BOCS score after n_1 in phase one, and h_2 indicates a 20-35% reduction in Y-BOCS score after n_1 in phase one.

4. Level of education was divided into four categories: sc_0 indicates no schooling, sc_1 indicates ≤ 8 years of schooling, sc_2 indicates 9-12 years of schooling, and sc_3 indicates higher education (undergraduate or graduate work).

5. Marital status was categorized as si_0 (married, divorced or widowed) or si_1 (single).

6. Genders are indicated by m for male and f for female.

7. Sample sizes are denoted as n_1, n_2, n_3, and $n = n_1 + n_2 + n_3$, respectively, and by the total sample size. Note that there are three arms only in phase two. The compositional view of sample size in arm i ($i = 1, 2, 3$) is the vector $(s_i; 1 - s_i)$ where $s_i = n_i/n$.

For each of these factors, the distance between arms can be computed. The distance values for the seven variables listed above are given by the following symbols: Δ_{age}, Δ_{OCD}, Δ_{his}, Δ_{sch}, Δ_{mar}, Δ_{gen}, and Δ_{sam}. The global distances for phases one and two are, respectively, Δ_1 and Δ_2, defined as follows:

$$\Delta_1 = \frac{1}{9}\Big(2\Delta_{age} + 3\Delta_{OCD} + 3\Delta_{his} + \Delta_{gen}\Big)$$

$$\Delta_2 = \frac{1}{21}\Big(2\Delta_{age} + 4\Delta_{OCD} + 5\Delta_{his} + 2\Delta_{sch} + 3\Delta_{mar} + \Delta_{gen} + 4\Delta_{sam}\Big)$$

As there are three arms in phase two, there are also three vectors. Hence the global distance for phase two should be the average of the three values of Δ_2, i.e., the distance for phase two should be as follows:

$$\Delta_2 = \frac{\Delta_2(n1; n2) + \Delta_2(n1; n3) + \Delta_2(n2; n3)}{3}$$

2.2.2 Phase one allocation strategy

To allocate the patients into the two arms of phase one based on previous studies, it is desirable that some prognostic factors be distributed as homogeneously as possible between the two arms. It is assumed that previous treatment response (assessed through patient interviews) and severity of the disorder (assessed using a specific scale) at the time of inclusion in the study are the most important prognostic factors for clinical response. In addition, although of lesser importance to treatment response, gender and age should also present homogeneous distribution between arms. For logistical reasons, the number of patients enrolled in each treatment arm of phase one could not be the same: the professionals involved in providing treatment are able to assist more patients in the pharmacological arm than in the psychotherapeutic arm; and, over the course of the study, there are moments at which the pace of patient enrolment into the psychotherapeutic arm is, of necessity, more rapid than is that of patient enrolment into the pharmacological arm. It is expected that the pharmacological arm will account for a higher percentage of the final sample. Due the time needed to perform the clinical evaluations, there is a two-week gap between inclusion and allocation. Consequently,

Nature Precedings : hdl:10101/npre.2008.2102.1 : Posted 21 Jul 2008

it is possible to allocate patients simultaneously in groups of three, one to one arm and the remaining two to the other arm (the arm that receives two patients in some steps receiving one in other steps). This simultaneous inclusion of patients guarantees that blinding is not compromised by allocation in small blocks.

The choice of prognostic factors to be balanced between arms is based on reports in the literature indicating that prognostic factors have considerable influence on the results. In addition, having information on these factors at the time of the initial evaluation can inform these choices. As previous treatment response and initial severity are consistently reported to be associated with treatment response in clinical trials evaluating OCD patients (De Haan et al. 1987, Alarcon et al. 1993, Thompsen and Mikkelsen 1995, Mataix-Cols et al. 1999; Steketee et al. 1999), they were included as prognostic factors in order to balance the arms.

Nature Precedings : hdl:10101/npre.2008.2102.1 : Posted 21 Jul 2008

2.2.3 Phase two allocation strategy

Patients entering phase two were those that did not completely respond to the treatment in n1 of phase one (regardless of treatment history). The specialists assumed that treatment response and current severity were highly predictive of phase two treatment response, and that these patients should therefore be distributed homogeneously among the three groups. In addition, it is understood from previous studies that level of education and marital status are significantly associated with poor treatment response and should also be included in the phase two strategy model. Gender and current age should also be distributed homogeneously among the three arms. Another important factor is sample size, which should be as similar as possible among the three arms.

For each patient in phase two, the allocation to one of the three arms needs to be determined during the evaluation conducted at week 12 of treatment. The strategy at this point is sequential, one-by-one allocation of patients who had participated in phase one. Here, in addition to having more than two factors to consider in our attempts to balance the arms, we are dealing with three arms. Bear in mind that the distance measures are defined for two vectors in order to facilitate decisions regarding patient allocation, we consider the average of the three distances between pairs to be the overall distance of the three arms. The proposed solutions for the two phases are described below.

Nature Precedings : hdl:10101/npre.2008.2102.1 : Posted 21 Jul 2008

3. RESULTS

3.1 Partial results for phase one

To perform stratified allocation of patients, an Excel macro was created. The objective of this macro was to divide patients into homogenous subgroups of intervention regarding the factors chosen by investigators. To avoid empty categories in the allocation process, for a factor with k (> 1) categories, we added to each category the fraction $1/k$. Therefore no category had a frequency of 0 at the time of the calculation of the Δ distance. When the optimal allocation process began, 34 patients had already been randomly allocated to one or the other of the two arms.

The partition that provides the best degree of homogeneity between groups is defined as the division that achieved the smaller difference between factor vectors of category relative frequencies. To calculate this measure, the Aitchison distance between two vectors is used, as previously discussed. This distance was chosen based on the assumption that it has the property of preserving the sub-compositional coherence of the simplex space. After the values of Δ_1 are calculated for each possible allocation, the allocation that results in the least intragroup distance is chosen as the optimal allocation.

At this writing, 92 individuals had been allocated to n_1, and 77 had been allocated to n_2. The partial allocation exercise, considering these patients, is shown in Table 2. The results of the reverse order allocation of patients appear within parentheses in the same Table.

Table 2. Partial (reverse order) allocation of 169 patients in phase one.

Prognostic factor	Compositional category	Arm 1 frequencies		Arm 2 frequencies	
		Absolute	Relative	Absolute	Relative
Current age	A_0	45 (45)	0.489	38 (38)	0.494
	A_1	33 (32)	0.359	27 (27)	0.351
	A_2	14 (15)	0.152	12 (12)	0.156
OCD symptom severity	(L;M)	1 (1)	0.011	1 (1)	0.013
	(M;L)	2 (1)	0.022	1 (2)	0.013
	(L;H)	2 (2)	0.022	2 (2)	0.026
	(H;L)	3 (2)	0.033	0 (1)	0.000
	(M;M)	35 (36)	0.380	32 (31)	0.416
	(M;H)	10 (11)	0.109	9 (8)	0.117
	(H;M)	9 (10)	0.098	9 (8)	0.117
	(H;H)	30 (29)	0.326	23 (24)	0.299
Treatment history	h_0	49 (51)	0.533	43 (41)	0.558
	h_1	8 (0)	0.087	2 (0)	0.026
	h_2	35 (41)	0.380	32 (36)	0.416
Gender	m	40 (40)	0.435	34 (34)	0.442
	f	52 (52)	0.565	43 (43)	0.558
Sample size	Arm size	92	0.544	77	0.456
	Complement	77	0.456	92	0.544

3.2 Simulated results for phase two

The phase two allocation system has the same objectives as that of phase one: bring the arms as close together as possible in terms of the relevant prognostic factors. However, in phase two, the logistics for allocation are different from those applied in phase one. We have now three arms and, the patients are allocated sequentially one-by-one. In addition, the factors used for balancing in this phase are not exactly the same. As well as now taking level of education, marital status, and sample size into consideration, the factor history of previous treatment history, unlike in phase one, is based on the relative reduction, during phase one, in the Y-BOCS score. Patients presenting a $> 35\%$ reduction in Y-BOCS score are not included in this phase. To consider sample size as a factor, the proportion of patients in each group will also be included in the distance calculation. Table 3 presents the allocation results for 90 patients selected from among those in n_1 of phase one.

Table 3. Sequential (reverse order) allocation of 90 patients in phase two: patients from phase one.

Prognostic factor	Composition Category	Arm 1 frequencies		Arm 2 frequencies		Arm 3 frequencies	
		Absolute	Relative	Absolute	Relative	Absolute	Relative
Current age	A0	13 (14)	0.433	13 (12)	0.433	14 (14)	0.467
	A1	13 (12)	0.433	12 (12)	0.400	11 (12)	0.367
	A2	4 (4)	0.133	5 (5)	0.167	5 (5)	0.167
OCD symptom severity	(L;M)	0 (1)	0.000	0 (0)	0.000	1 (0)	0.033
	(M;L)	0 (0)	0.000	0 (0)	0.000	0 (0)	0.000
	(L;H)	0 (0)	0.000	0 (0)	0.000	0 (0)	0.000
	(H;L)	1 (1)	0.033	0 (1)	0.000	1 (0)	0.033
	(M;M)	12 (11)	0.400	14 (12)	0.467	10 (13)	0.333
	(M;H)	2 (2)	0.067	2 (2)	0.067	3 (3)	0.100
	(H;M)	4 (3)	0.133	3 (4)	0.100	4 (4)	0.133
	(H;H)	11 (12)	0.367	11 (10)	0.367	11 (11)	0.367
Treatment history	h0	15 (15)	0.500	15 (15)	0.500	15 (15)	0.500
	h1	9 (10)	0.300	10 (9)	0.333	10 (10)	0.333
	h2	6 (5)	0.200	5 (5)	0.167	5 (6)	0.167
Level of education	sc0	14 (15)	0.467	15 (14)	0.500	15 (15)	0.500
	sc1	0 (0)	0.000	0 (0)	0.000	0 (0)	0.000
	sc2	0 (0)	0.000	0 (0)	0.000	0 (0)	0.000
	sc3	16 (15)	0.533	15 (15)	0.500	15 (16)	0.500
Marital status	si0	16 (15)	0.533	15 (15)	0.500	15 (16)	0.500
	si1	14 (15)	0.467	15 (14)	0.500	15 (15)	0.500
Gender	M	13 (13)	0.433	13 (12)	0.433	13 (14)	0.433
	F	17 (17)	0.567	17 (17)	0.567	17 (17)	0.567
Sample size	Arm size	30 (30)	0.333	30 (29)	0.333	30 (31)	0.333
	Complement	60 (60)	0.667	60 (61)	0.667	60 (59)	0.667

4. DISCUSSION

The objective of using this strategy of random allocation of patients in different treatment arms is to avoid intentional bias in group selection. However, treatment group imbalance for prognostic factors can still

Nature Precedings : hdl:10101/npre.2008.2102.1 : Posted 21 Jul 2008

occur (Pocock et al. 2002). These unfortunate results of randomisation can be prevented by using techniques that produce, rather than random allocation, an intentional optimal allocation of patients to each treatment arm.

Another interesting point is the choice of the Aitchison distance to treat compositional data. To illustrate the difference between the Aitchison distance and the standard Euclidian distance, we ask the reader to calculate the two distances for the pairs $(A_1; A_2)$ and $(B_1; B_2)$ of relative frequency vectors defined below:

$$A_1 = (0.1; 0.2; 0.7),\ A_2 = (0.2; 0.1; 0.7),$$

$$B_1 = (0.2; 0.4; 0.4) \text{ and } B_2 = (0.4; 0.2; 0.4)$$

The standard Euclidian measure would produce $D[A_1; A_2] = 0.1414$ and $D[B_1; B_2] = 0.2828$. Note that the Aitchson distance will produce, as expected for an adequate distance, the same value for both pairs: $\Delta[A1; A2] = \Delta[B1; B2] = 0.9803$. Note that, for any category j $(= 1, 2, 3)$, the ratio between frequencies are the same for the two pairs:

$$\frac{A_{1j}}{A_{2j}} = \frac{B_{1j}}{B_{2j}}$$

We also notice that there will be problems if a frequency of 0 occurs for a particular class. It is recommended that prior correction be used, beginning the allocating at a small real number for each category that should be added to the observed absolute frequency. As an analogy to Bayesian categorical data analysis, we would take an equal constant for each category, as in the standard strategy. Our recommendation is to add $1/k$ to the absolute frequencies for each category, thereby avoiding the occurrence of a relative frequency of 0 in any category.

The 'random' aspect of treatment arm selection is preserved, due to the random sequence in which patients arrive for inclusion in clinical trials. The most important property of the allocation strategy defined here is the rationale that allows verification of the fact that the strategy was adhered to. The use of a purely randomised strategy cannot be proved after the trial has been concluded. To ensure that the order in which the patients enter the experiment is random, we consider the reverse order of the first 169 (90) patients in phase one (in phase two). In Table 3, it can be seen how close the results are those obtained for the original order. An interesting fact is illustrated in Tables 4 and 5. We can see that more than half of patients would change arms by reversing the order in which they enter into a phase. In phase one, 90 of the 169 patients would have changed arms if a reverse order was considered. For phase two, considering the reverse order, 48

Nature Precedings : hdl:10101/npre.2008.2102.1 : Posted 21 Jul 2008

of the 90 patients would have changed arms.

Table 4. Phase one patient allocation.

	Reverse order		Sample
Original order	arm 1	arm 2	size
arm 1	47	45	92
arm 2	45	32	77
Sample size	92	77	169

Table 5. Phase two patient allocation.

	Reverse order			Sample
Original order	arm 1	arm 2	arm 2	size
arm 1	15	9	6	30
arm 2	10	11	9	30
arm 3	5	9	16	30
Sample size	30	29	31	90

Nature Precedings : hdl:10101/npre.2008.2102.1 : Posted 21 Jul 2008

This article describes a method of computer-based intentional allocation that has the advantage of being flexible, effective, and feasible for the allocation of each consecutive patient, or group of three patients, in terms of multiple covariates. The development of intentional allocation methods, adaptable to different study designs, can reduce sample sizes without increasing bias. Future studies are warranted in order to determine the possible sample size reduction and to evaluate the effectiveness of this procedure when a great number of covariates are included. The procedure presented here is reliable for the inclusion of up to 6 compositional covariates with 21 possible alternative results. When using this procedure, researchers should include in the allocation strategy any variables suspected of influencing treatment response.

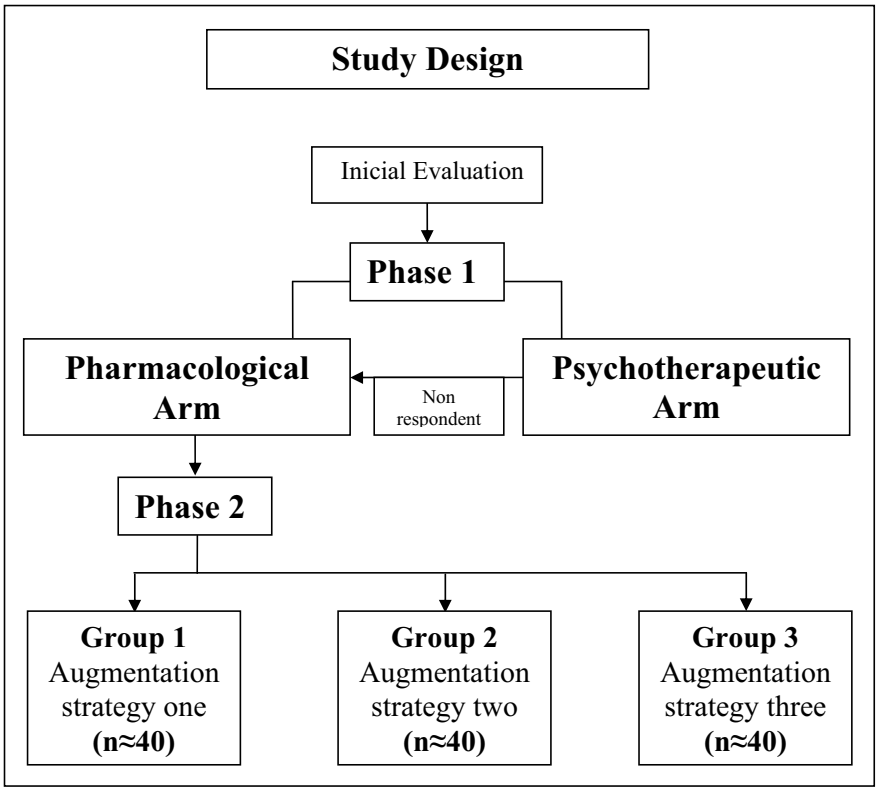
One limitation of the proposed procedure is the need to know the value of each prognostic factor, for each patient entering the study, prior to allocation. Consequently, values of prognostic factors that can only be obtained through long-term evaluations cannot be included in the model. Another issue is the weights given to the allocation factors. For the trial in question, the first author (the psychiatrist responsible for conducting the trial) based the choice of variable weights on the evidence levels of the prognostic factors influencing treatment responses. Although this was an arbitrary decision, it does not favour any allocation tendency that might result in arm imbalance, thereby favouring any particular result in terms of treatment response.

Nature Precedings : hdl:10101/npre.2008.2102.1 : Posted 21 Jul 2008

5. CONCLUSION

In conclusion, the procedure described here can be easily adapted to different study designs. The results of the trial, used as illustration, show that the methodology was reliable for the sample tested. There are, however, some reliability issues that require further investigation, such as the inclusion of cases presenting a great number of factors or factors having a great number of possible alternative categories. Nevertheless, we believe that this paper presents a procedure that will be useful in avoiding imbalance among treatment arms when patient allocation is performed sequentially.

Figure 1: Clinical Trial Study Design.



n = number of patients estimated for each treatment arm.

Trial registration

Clinicaltrials.gov identifier: NCT00466609

Acknowledgements

This study received financial support in the form of grants from the Brazilian governmental agencies the *Conselho Nacional de Desenvolvimento Cientifico e Tecnológico* (CNPq, National Council for Scientific and Technological Development; grant no.: 521369/96-7) and the *Fundação de Amparo a Pesquisa do Estado de São Paulo* (FAPESP, Foundation for the Support of Research in the State of São Paulo; grant nos.: 2005/55628-08 and 06/50273-0). We would like to thank the *Núcleo de Apoio à Pesquisa Clínica* (NAPesq, Clinical Research Support Center) of the University of São Paulo School of Medicine *Hospital das Clínicas* for the technical support provided.

Nature Precedings : hdl:10101/npre.2008.2102.1 : Posted 21 Jul 2008

References

[1] J. Aitchison. Principal component analysis of compositional data. *Biometrika*, 70(1):57–65, 1983.

[2] J. Aitchison. *The Statistical Analysis of Compositional Data*. Chapman & Hall, London, 1986.

[3] J. Aitchison and J. Egozcue. Compositional data analysis: Where are we and where should we be heading? *Mathematical Geology*, 37(7):829–50, 2005.

[4] R.D. Alarcon, J.W. Libb, and D. Spitler. A predictive study of obsessive-compulsive disorder response to clomipramine. *J Clin Psychopharmacol*, 13:210–213, 1993.

[5] A.C. Atkinson. Optimum biased coin designs for sequential clinical-trials with prognostic factors. *Biometrika*, 69(1):61–67, 1982.

[6] M.H. Bloch, A. Landeros-Weisenberger, B. Kelmendi, V. Coric, M.B. Bracken, , and J.F. Leckman. A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. *Mol Psychiatry*, 11(7):622–32, 2006.

[7] E. De Haan, P. Van Oppen, A.J. Van Balkom, P. Spinhoven, L. Hooguin, and R. Van Dyck. Prediction of outcome and early versus late improvement in ocd patients treated with cognitive-behaviour therapy and pharmacotherapy. *Acta Psychiatr Scand*, 96:354–361, 1987.

[8] K.T. Eddy, L. Dutra, R. Bradley, and D Westen. A multidimensional meta-analysis of psychotherapy and pharmacotherapy for obsessive-compulsive disorder. *Clin Psychol Rev*, 24(8):1011–30, 2004.

Nature Precedings : hdl:10101/npre.2008.2102.1 : Posted 21 Jul 2008

[9] L.F. Fontenelle, A.L. Nascimento, M.V. Mendlowicz, R.G. Shavitt, and M. Versiani. An update on the pharmacological treatment of obsessive-compulsive disorder. *Expert Opin Pharmacother*, 8(5):563–83, 2007.

[10] W.N. Kernan, C.M. Viscoli, R.W. Makuch, L.M. Brass, and Horwitz R. Stratified randomization for clinical trials. *J Clin Epidemiol*, 52(1):19–26, 1999.

[11] J.M. Lachin. Statistical properties of randomization in clinical trials. *Controlled Clin Trials*, 9:289–311, 1988.

[12] D. Mataix-Cols, S. Rauch, P.A. Manzo, M.A. Jenike, and L. Bayer. Use of factor-analyzed symptom dimensions to predict outcome with serotonin reuptake inhibitors and placebo in the treatment of obsessive-compulsive disorder. *Am J Psychiatry*, 156:1409–16, 1999.

[13] S.J. Pocock, S.E. Assmann, and L.E. Enos. Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems. *Statist Med*, 21:2917–2930.

[14] S.J. Pocock and R. Simon. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics*, 31(1):103–115, 1975.

[15] N.W. Scott, G.C. McPherson, C.R. Ramsay, and M.K. Campbell. The method of minimization for allocation to clinical trials: a review. *Controlled Clinical Trials*, 23:662–674, 2002.

[16] G. Steketee, J. Eisen, I. Dyck, M. Warshaw, and S. Rasmussen. Predictors of course in obsessive-compulsive disorder. *Psychiatry Res*, 89:229–38, 1999.

[17] D.R. Taves. Minimization: a new method of assigning patients to treatment and control groups. *Clin Pharmacol Ther*, 15(5):443–53, 1974.

[18] P.H. Thomsen and H.U. Mikkelsen. Course of obsessive-compulsive disorder in children and adolescents: a prospective follow-up study of 23 danish cases. *J Am Acad Child Adolesc Psychiatry*, 34(11):1432–40, 1995.