A COMPARATIVE STUDY OF VARIOUS ALLOCATION SCHEMES IN A CLINICAL TRIAL

by

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1 Introduction

Assume there are two treatments (0 and 1) in a sequential clinical trial. When a patient arrives, the clinician should assign him a treatment immediately. However, it is not proper for the clinician to decide which treatment is given to the patient. This is because his selection could be affected by prejudices or by some incomplete knowledge. Therefore, we should find some allocation schemes for the clinician to try to get balance between treatment groups.

As an example, suppose that three prognostic factors are to be used:

Prognostic Factor	levels
Sex	0 – male 1 – female
Age	1 – under 20 2 – between 20 and 40 3 – above 40
Race	0 1

Also suppose we already have seven patients in the trial with the prognostic factors as follows:

Patient	Prognostic factors			Treatment
	Sex	Age	Race	
1	1	3	0	1
2	1	1	0	0
3	0	3	1	0
4	1	2	0	1
5	0	2	1	0
6	1	3	1	1
7	0	3	0	1

Now, the eighth patient is coming with prognostic factors:
Sex – 0, Age – 2, Race – 1
Then, which treatment should we assign to him?

In this project, I am going to use different allocation schemes to assign a treatment to the patients.

2 Allocation Schemes

2.1 Completely random allocation

This is the simplest method of allocation. We assign each patient randomly to treatment 0 or 1 with equal probability, independently of the assignment for the other patients, and also ignore his prognostic factors. According to this, we will assign the eighth patient treatment 0 with probability ½, treatment 1 with probability ½, independently of the assignment for the first seven patients.

Compared to the perfectly balanced experiment, completely random allocation has some attractive properties. In the perfectly balanced experiment, we force equal numbers of treatments, for example, the completely non-random design 010101... Then, the experimenter will know for certain what is the next assignment. He may consciously bias the experiment by such decisions as who is or is not a suitable experimental subject. By using the completely random allocation, we can avoid selection bias.

But this method also suffers from some disadvantages. When there are small numbers of subjects in the experiment, the final distribution of treatments can be very unbalanced. For example, if we assign the eighth patient treatment 1, then, we will have distinctly unequal numbers on each assignment. And we know this will happen with probability ½.

To prevent the chance of imbalances, more sophisticated schemes have been devised.

2.2 Permuted block design

This design divides the patients into blocks of even length, say 4. Within each block randomly assign 2 patients to treatment 0 and 2 patients to treatment 1. So, in our case, in the second block, i.e., for patient 5 – patient 8, 2 of them should be assigned treatment 0, 2 of them should be assigned treatment 1. Now, patients 6 and 7 are under treatment 1 and

patient 5 is under treatment 0. So, in order to balance this block, we should assign treatment 0 to our new patient.

In general, if we have n patients, we should divide them into blocks with length 2k ($0<k<n/2$), and within each block randomly assign k units to treatment 0 and k units to treatment 1.

Now, the permuted blocks can be quite effective in eliminating unbalanced designs. But the disadvantage is that at some points, the experimenter knows for certain which treatment the next arrival will be assigned. In our case, the experimenter will know for certain that he will assign treatment 0 to the eighth patient.

In order to achieve balanced experiments without ever giving the experimenter a high probability of guessing the assignment of the next patient, we use the biased coin design.

2.3 Efron's biased coin design

Efron (1971) provided the biased coin design.

Suppose at a certain stage in the experiment a new subject arrives and we already have D more treatment 1 than treatment 0. We will assign the new subject as follows:

If $D > 0$, assign treatment 1 with probability q and treatment 0 with probability p.
If $D = 0$, assign treatment 1 with probability ½ and treatment 0 with probability ½.
If $D < 0$, assign treatment 1 with probability p and treatment 0 with probability q.
Here $p > q$, $p + q = 1$. Efron suggested to use $p = 2/3$; this number is big enough to yield generally good designs.

In our case, for the first 7 patients, 4 of them are in treatment 1 and 3 in treatment 0. So, $D = 4 - 3 = 1 > 0$. We will assign the eighth patient treatment 1 with probability q and treatment 0 with probability p. ($p > q$)

The biased coin design method can achieve greater balance than completely random allocation. But when there are only a few subjects, it is likely to be out of balance.

In the previous designs, we ignore the prognostic factors for the patients. But actually, the prognostic factors can severely affect the response of the patient. So, we should pay attention to it in our design. That is, we should use some methods, which can minimize differences between the treatments, not only in the number of patients but also in patient characteristics.

2.4 The minimization method of Taves

Taves (1974) constructed the minimization method.

According to this method, I draw a table as follows:

Units	Male	Female	< 20	20 – 40	> 40	Race1	Race2	Sum
Treatment 0	2	1	1	1	1	1	2	
Treatment 1	1	3	0	1	3	3	1	
Patient 8	1	0	0	1	0	0	1	
*T0 + P8	3			2			3	
Treatment 1	1			1			1	
Absolute difference	2			1			2	5
Treatment 0	2			1			2	
*T1 + P8	2			2			2	
Absolute difference	0			1			0	1

*T0 + P8 means we assign the eighth patient treatment 0
T1 + P8 means we assign the eighth patient treatment 1

Row 1 and row 2 display the information about the first seven patients. We can see the amount of each treatment with respect to the prognostic factors. Row 3 is the code for patient 8: 'zeros' in all subcategories except male, age 20 – 40, race 2, so only these subcategories are being considered. First, we consider assigning treatment 0 to the patient. Row 4 of the table shows that now we have 3 instead of 2 patients for male, 2 instead of 1 in age 20 – 40, 3 instead of 2 in race 2. Next the absolute difference is determined for these subcategories. The sum of these differences is 5 (right column). The trial procedure is then repeated (row

8) with patient 8 added to treatment 1 rather than treatment 0, and the absolute difference is determined (row 9) which is 1. Since the sum of the differences is less when treatment 1 is added to patient 8, the patient is assigned to treatment 1.

In this method, we consider the numbers of patients in each treatment group who have the same characteristics as the patient about to be assigned. By doing this, we minimize the differences between the treatment groups. The use of randomization occurs only when the placement of the new patient makes no difference in the comparability of the two groups.

2.5 The method of Pocock and Simon

Pocock and Simon (1975) suggested a procedure for treatment assignment that concentrates on minimizing imbalance within the levels of each individual prognostic factor. The improvement of this method compared with the method of Taves is that we have more randomization in this method.

Using their method, we have 3 prognostic factors for which the treatment balance is required, the number of levels of these factors being 2, 3 and 2. For the first seven patients, the combination of treatment and factor level are as follows:

	Factor	1		2			3		
Treatment	Level	1	2	1	2	3	1	2	Total
0		2	1	1	1	1	1	2	3
1		1	3	0	1	3	3	1	4
Total		3	4	1	2	4	4	3	7

Now, the eighth patient is at level 1, 2, and 2, respectively for the three factors. The problem is to determine to which treatment that patient should be assigned.

Denote:

d_{irk}: The range of the treatment difference for level r when treatment k were assigned to the new patient who has level r in factor i. It measures the 'lack of balance'.

G_k: The sum of d_{irk} with respect to i. It represents the 'total amount of imbalance'.

First, consider the results of assigning treatment 0 to the eighth patient:
For factor 1 level 1, treatment numbers would then be 3, 1. Range d_{110} = 2.
For factor 2 level 2, treatment numbers would then be 2, 1. Range d_{220} = 1.
For factor 3 level 2, treatment numbers would then be 3, 1. Range d_{320} = 2.
$G_0 = \sum_{i=1}^{3} d_{irk} = d_{110} + d_{220} + d_{320} = 5$.

Assigning treatment 1 to the patient will get:
For factor 1 level 1, treatment numbers would then be 2, 2. Range d_{111} = 0.
For factor 2 level 2, treatment numbers would then be 1, 2. Range d_{221} = 1.
For factor 3 level 2, treatment numbers would then be 2, 2. Range d_{321} = 0.
$G_1 = \sum_{i=1}^{3} d_{irk} = d_{111} + d_{221} + d_{321} = 1$.

G_1 is smaller than G_0. Therefore, treatment 1 is assigned to the eighth patient with probability p, treatment 0 being assigned with probability q. Here $p > q$ and $p + q = 1$. This means that treatments with small values of G_k have a higher probability of being chosen.

2.6 The method of Begg and Iglewwicz

Begg and Iglewicz (1980) proposed a scheme for balancing the treatments. In their method, the primary endpoint is the comparison of two treatments with respect to an outcome variable that is related to treatment and a number of binary prognostic factors. But sometimes, not all prognostic factors are binary data. In that case, we can combine some similar levels together, and only leave two levels for each prognostic factor. In order to show how to apply this method, I will change the conditions given before. That is, I will change the prognostic factors for the patients as binary data by combining two levels in factor 'age' together. The details are as follows:

Prognostic factor	Levels
Sex	+ Male – Female
Age	+ 40 and under – above 40
Race	+ –

Then, the prognostic factors and treatment for all patients are:

Patient	Prognostic factors			Treatment
	Sex	Age	Race	
1	-	-	+	1
2	-	+	+	0
3	+	-	-	0
4	-	+	+	1
5	+	+	-	0
6	-	-	-	1
7	+	-	+	1
8	+	+	-	?

The table below gives the treatment assignments within each of the eight factor level combinations.

Combination			Treatment	
Factor1	Factor2	Factor3	0 (-)	1 (+)
-	-	-	0	1
-	-	+	0	1
-	+	-	0	0
-	+	+	1	1
+	-	-	1	0
+	-	+	0	1
+	+	-	1	0
+	+	+		
		Totals:	3	4

The marginal totals for each factor and the overall total is:

Factor	Level	Treatment 0 (-)	Treatment 1 (+)
1	-	1	3
	+	2	1
2	-	1	3
	+	2	1
3	-	2	1
	+	1	3
Overall totals:		3	4

Suppose m_{--}, m_{-+}, m_{+-}, m_{++} represent the current treatment-factor totals, the first subscript representing treatment. Now, we will calculate the difference between the treatment imbalances in each of the two levels, that is,

$$(m_{--} - m_{+-}) - (m_{-+} - m_{++}) \qquad (3)$$

Factor	$(m_{--} - m_{+-}) - (m_{-+} - m_{++})$	New patient
1	-3	+1
2	-3	+1
3	3	-1
Overall	1	+1

Since $(-3 \quad -3 \quad 3 \quad 1)\begin{pmatrix} +1 \\ +1 \\ -1 \\ +1 \end{pmatrix} = -8$, the treatment allocation should be positive, i.e. assign treatment 1 to patient 8.

According to this method, when the (n+1)th patient arrives, we should calculate $(m_{--} - m_{+-}) - (m_{-+} - m_{++})$ from the first n patients, then, multiply this with the factor level of the new patient. If the result is negative, we will assign the new patient treatment +. Otherwise, if the result is positive, we will assign treatment – to the new patient.

2.7 Atkinson's D_A-optimum designs

In his article, A.C.Atkinson (1982) mentioned that one disadvantage of Efron's biased coin design is: it does not include balance over prognostic factors, which may affect the response of the patient to the treatment. Then, he uses optimum design theory to provide a procedure of the biased coin type for sequential clinical trials in the presence, or absence of prognostic factors.

First, he introduced some necessary optimum design theory and then applied it to biased coin experiment.

For the linear model $E(Y) = X^T\beta$ with independent observations of variance σ^2, the variance of the least squares estimate of β is: $var(\bar{\beta}) = \sigma^2 (X^TX)^{-1}$, where X^TX is the $p \times p$ dispersion matrix, assumed to be of full rank. The fitted value at x is $\bar{y}(x) = x^T \bar{\beta}$ with $var\{\bar{y}(x)\} = \sigma^2 x^T(x^Tx)^{-1}x$. The optimum design of experiments is concerned with the choice of X to minimize various functions of variance of $\bar{\beta}$. This theory is given by Silvey (1980).

Now, let M be the dispersion matrix of the design: $M = n^{-1} (X^TX)$. It is convenient, instead of $var\{\bar{y}(x)\}$, to consider the standardized variance:

$$d(x) = x^TM^{-1}x \qquad (1)$$

One design criterion, which is known as D-optimality, is to maximize the determinant of M. This minimizes the generalized variance of the parameter estimates.

In a clinical trial interest is often in contrasts between treatment effects. Suppose the contrasts are s linear combinations which are elements of the vector $A^T\beta$, where A is an $s \times p$ matrix of rank $s < p$. The covariance matrix of the least squares estimate $A^T \bar{\beta}$ is proportional to $A^TM^{-1}A$. And the analogue of D-optimality is to maximize the determinant of $\{A^TM^{-1}A\}^{-1}$. Sibson (1974) named this criterion as D_A-optimality. The Equivalence Theorem for D_A-optimality is described by silvey (1980). The analogue of the variance (1) is the quantity:

$$d_A(x) = x^TM^{-1}A\{A^TM^{-1}A\}^{-1}A^TM^{-1}x \qquad (2)$$

Sequential D_A-optimum designs are generated one trial at a time by adding an observation at x where (2) is a maximum.

The design region consists of t points, the ith of which corresponds to allocating treatment i to the next patient. Let the corresponding value of $d_A(x)$ be $d_A(i)$. The sequential construction of the optimum design allocates the (n+1)th patient to the treatment for which $d_A(i)$ is a maximum. If randomization is required, we can choose treatment i with probability:

$p_i = d_A(i)/\{\sum_{i=1}^{2} d_A(i)\}$ (3)

With two treatments and no prognostic factors the model is $E(Y) = \beta_i$, (i=1,2). If interest is in the difference in treatment effects $\beta_1 - \beta_2$, $A^T = (1, -1)$. If, of the n patients, n_1 have received treatment 0 and n_2 treatment 1, then $M = \text{diag}\{n_i/n\}$, a diagonal matrix. Substitution in (2) shows that for the criterion of D_A-optimality:

$d_A(1) = n_2/n_1$, $d_A(2) = n_1/n_2$.

From the biased coin rule (3), the probability of selecting treatment 1 is:

$p_1 = n_2^2/(n_1^2 + n_2^2)$.

In our example, we have $n_1 = 3$, $n_2 = 4$, then, $p_1 = 16/25$, $p_2 = 9/25$. i.e. we will assign the eighth patient treatment 0 with probability 16/25, and treatment 1 with probability 9/16.

Now, we will consider the prognostic factors. If we have n patients in our trial, when the (n+1)th patient comes, which treatment should we assign to him? The linear model is written in partitioned form

$E(Y) = x^T\beta = x_1^T\beta_1 + x_2^T\beta_2$ (4)

Where x_1 is the vector of indicator variables for the treatments and x_2 is the vector of prognostic factors.

To calculate the design, we need to partition the dispersion matrix and let

$$M^{-1} = \begin{pmatrix} M^{11} & M^{12} \\ M^{21} & M^{22} \end{pmatrix}$$

Then, Atkinson suggests writing the general expression (2) as:

$d_A(x) = x_1^T M^{11} B M^{11} x_1 + 2x_1^T M^{11} B M^{12} x_2 + x_2^T M^{21} B M^{12} x_2$

Where $B = A\,(A^T M^{11} A)^{-1} A^T$. The contrast matrix $A^T = (1 \;\; -1)$

Then, we will assign the new patient treatment 0 with probability:

$d_A(0)/[d_A(0) + d_A(1)]$
and assign him treatment 1 with probability:
$d_A(1)/[d_A(0) + d_A(1)]$

In our example, $x_2^T = (0\ 2\ 1)$

$$X = \begin{pmatrix} 0 & 1 & 1 & 3 & 0 \\ 1 & 0 & 1 & 1 & 0 \\ 1 & 0 & 0 & 3 & 1 \\ 0 & 1 & 1 & 2 & 0 \\ 1 & 0 & 0 & 2 & 1 \\ 0 & 1 & 1 & 3 & 1 \\ 0 & 1 & 0 & 3 & 0 \end{pmatrix}$$

$$M = n^{-1}(X^TX) = \begin{pmatrix} 0.42858 & 0 & 0.14286 & 0.85716 & 0.28572 \\ 0 & 0.57144 & 0.42858 & 1.57146 & 0.14286 \\ 0.14286 & 0.42858 & 0.57144 & 1.28574 & 0.14286 \\ 0.85716 & 1.57146 & 1.28574 & 6.4287 & 1.14288 \\ 0.28572 & 0.14286 & 0.14286 & 1.14288 & 0.42858 \end{pmatrix}$$

$A^T = (1\ -1)$

$$B = A(A^TM^{11}A)^{-1}A^T = \begin{pmatrix} 0.0587 & -0.0587 \\ -0.0587 & 0.0587 \end{pmatrix}$$

If $x_1^T = (1\ 0)$, then, $d_A(0) = x_1^TM^{11}BM^{11}x_1 + 2x_1^TM^{11}BM^{12}x_2 + x_2^TM^{21}BM^{12}x_2$
$= 0.44$
If $x_1^T = (0\ 1)$, then, $d_A(1) = x_1^TM^{11}BM^{11}x_1 + 2x_1^TM^{11}BM^{12}x_2 + x_2^TM^{21}BM^{12}x_2$
$=22.9716$
We will assign the new patient treatment 0 with probability
$d_A(0)/[d_A(0) + d_A(1)] = 0.44/(0.44+22.9716)=0.0188$
and assign him treatment 1 with probability $1 - 0.0188 = 0.9812$.

3 A model for a clinical trial

In part 2, we introduced some methods to assign a treatment to the new patient. Next, we want to know their effectiveness and appropriateness in

actual clinical trials. I am going to use computer simulations based on a particular model to do the comparison of these methods.

The model chosen is as follows:

a) There are 10 patients initially in the trial with generated prognostic factors and treatment 1 0 1 0 1 0 1 0 1 0 respectively. Here, I started with a balanced situation, which is easier for the further operation.
b) The number of patients entered into the trial each time, N, is fixed. N = 50 is arbitrarily chosen for the simulation. I ran the simulation 1000 times. This should be large enough to illustrate the general properties of the methods.
c) There are two treatments: 0 and 1. This is the most common situation in controlled clinical trials.
d) There are three prognostic factors: sex, age, race, with 2, 3, 2 levels respectively. Balanced treatment numbers are desired for these prognostic factors. We also assume there is no association among factors.
e) Patients enter the trial sequentially in purely random fashion, the factor levels of any one patient being independent of those for any other.

4 Measure of treatment imbalance

The purpose of all the allocation methods is to avoid 'imbalance' for the treatment. The word 'imbalance' has been used rather loosely so far and is now defined more precisely.

For methods 1, 2, 3 and 7 in which we ignored the prognostic factors:
D1 = total number on the two treatments/2 – number of treatment 1

If D1 = 0, the two treatment are balanced.
If D1 > 0, we have more treatment 0 than treatment 1.
If D1 < 0, we have more treatment 1 than treatment 0.

For methods 4, 5, 6 and 8, which are supposed to balance treatments across prognostic factors, the measure of imbalance should include the imbalance of treatment for each factor combination. A measure of imbalance in these cases is given by Dr. D.P. Wiens (2000):

$$D2 = \sum_{i=0}^{p} S_i^2 = \sum_{i=0}^{p} \frac{1}{n} \sum_{l=1}^{L} n_{.l} \left(\frac{n_{i,l}}{n_{.l}} - \frac{n_{i.}}{n}\right)^2$$

where:

i represent the treatments, in our case, i = 0, 1.

l is the different combination of the prognostic factors, each combination represents one level. In our case, we have 2*3*2 = 12 levels all together. So, overall level L=12.

$n_{i,l}$ is the number of times in the n assignments that a patient at level l receives treatment i.

$$n_{i.} = \sum_{l=1}^{12} n_{i,l}$$

$$n_{.1} = n_{01} + n_{11}$$

I am going to use D1 and D2 as the measures of imbalance later on in the simulation. I will calculate the average for the imbalance after each assignment for all the 1000 simulations; plot it against the number of patients for each method to make the comparison.

5 Result of simulation

Using computer software SAS, I generated 60 patients with prognostic factors sex, age and race in each simulation. The first ten of them already have been assigned a treatment. Assuming patients 11 to 60 are new arrivals who will come sequentially to our trial, I use the above eight different allocation methods to assign the new patient a treatment. After each assignment, I calculated the imbalance for the trial. Then I repeated this procedure 1000 times. Each time, I get 50 data for each allocation method, which represents the imbalance after an assignment. I calculated the average for these 50 data and used the result to compare the effectiveness of different methods.

Table 1 lists the imbalance for those methods without considering the prognostic factors. Among them, the imbalance for the permuted block design is the smallest one, and it follows a pattern: the imbalance is equal to 0 for 4th patient. This is because in our trial we divided the patients into blocks with length 4. This shows both the advantage and disadvantage for the permuted block design: it is effective in reducing imbalance, but we can know for certain which treatment should be given

to the 4^{th} patients. In order to randomize our design, biased coin design and Atkinson's D_A-optimum design without considering prognostic factors are better choices. We can see from table 1, the imbalances for these methods are not very big.

I plotted the absolute value of the imbalance for methods 1, 2, 3 and 7 against the number of patients in figure 1. It is more convenient to examine the distribution of the imbalance from this plot. We can see that besides the permuted block design, Atkinson's D_A-optimum design without considering prognostic factors has relatively small imbalance: all of the number of imbalances for this method are smaller than 0.253. The simplest allocation method, completely random allocation, the number of imbalance has the biggest range, which is from 0.005 to 0.561.

Table 2 lists the imbalance for those methods in which prognostic factors are taken into account. Among them, the method of Begg and Iglewwicz has the biggest imbalance. This is not surprising when we examine the method. In this method, we are only allowed binary prognostic factors. In order to satisfy this condition, we arbitrarily change the prognostic factors into binary data no matter what the prognostic factors really are. This will reduce the precision.

The plot of imbalance for methods 4, 5, 6 and 8 is shown in Figure 2. We find that the imbalance for Atkinson's D_A-optimum design is the smallest one. The range of imbalance is from 0.064 to 0.394. The imbalance for Taves' method is relatively small too. The range is from 0.083 to 0.403. This method is easy to carry out compared to Atkinson's D_A-optimum design.

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Appendix A

Table 1. Average imbalance for method 1, 2, 3 and 7.

No. of patient	1random	2permute	3biased	7akwo
11	-0.279	0.033	-0.307	0.044
12	0.015	0.000	-0.232	0.182
13	0.020	-0.025	-0.126	0.096
14	-0.005	0.101	-0.293	0.040
15	0.040	0.106	-0.227	-0.045
16	-0.035	0.000	-0.263	-0.040
17	-0.162	0.005	-0.308	-0.136
18	-0.136	0.091	-0.333	-0.212
19	-0.131	0.066	-0.379	-0.177
20	-0.106	0.000	-0.293	-0.091
21	-0.141	-0.015	-0.359	-0.045
22	-0.187	0.121	-0.232	-0.010
23	-0.253	0.076	-0.268	-0.056
24	-0.328	0.000	-0.354	-0.111
25	-0.364	0.056	-0.288	-0.237
26	-0.348	0.121	-0.343	-0.131
27	-0.333	0.126	-0.369	-0.197
28	-0.328	0.000	-0.354	-0.081
29	-0.404	-0.035	-0.379	-0.076
30	-0.348	0.020	-0.333	-0.010
31	-0.323	0.106	-0.298	-0.035
32	-0.318	0.000	-0.273	0.010
33	-0.343	-0.025	-0.308	0.086
34	-0.359	0.061	-0.263	0.131
35	-0.303	0.045	-0.338	0.076
36	-0.328	0.000	-0.364	0.162
37	-0.364	0.076	-0.318	0.126
38	-0.379	0.051	-0.313	0.253
39	-0.283	0.056	-0.359	0.106
40	-0.217	0.000	-0.303	0.081
41	-0.172	-0.066	-0.268	-0.025
42	-0.237	0.020	-0.273	-0.051
43	-0.293	0.106	-0.268	-0.096
44	-0.247	0.000	-0.323	0.020
45	-0.222	-0.005	-0.328	-0.056
46	-0.227	0.030	-0.394	0.040
47	-0.263	0.096	-0.389	0.066
48	-0.258	0.000	-0.323	0.172
49	-0.273	-0.035	-0.399	0.157
50	-0.298	-0.081	-0.414	0.121

51	-0.303	0.005	-0.409	0.177
52	-0.338	0.000	-0.374	0.222
53	-0.293	0.015	-0.268	0.197
54	-0.328	0.020	-0.253	0.182
55	-0.414	0.045	-0.318	0.177
56	-0.449	0.000	-0.313	0.192
57	-0.465	0.015	-0.308	0.237
58	-0.460	0.111	-0.253	0.242
59	-0.505	0.136	-0.278	0.247
60	-0.561	0.000	-0.131	0.141

Table 2. Average imbalance for method 4, 5, 6 and 8.

No. of patient	4taves	5ps	6bi	8akw
11	0.146	0.179	0.210	0.137
12	0.403	0.403	0.394	0.395
13	0.370	0.370	0.374	0.370
14	0.326	0.362	0.360	0.362
15	0.295	0.343	0.348	0.343
16	0.285	0.316	0.294	0.323
17	0.263	0.280	0.288	0.293
18	0.250	0.272	0.278	0.278
19	0.244	0.260	0.266	0.271
20	0.258	0.279	0.237	0.279
21	0.205	0.293	0.221	0.229
22	0.220	0.303	0.202	0.193
23	0.188	0.311	0.191	0.159
24	0.188	0.316	0.188	0.163
25	0.159	0.286	0.188	0.133
26	0.158	0.277	0.190	0.127
27	0.164	0.226	0.182	0.121
28	0.150	0.186	0.181	0.132
29	0.158	0.188	0.176	0.136
30	0.137	0.161	0.179	0.118
31	0.116	0.176	0.174	0.100
32	0.107	0.170	0.177	0.094
33	0.109	0.154	0.180	0.078
34	0.111	0.155	0.183	0.080
35	0.093	0.164	0.187	0.090
36	0.103	0.173	0.190	0.099
37	0.106	0.146	0.193	0.106
38	0.093	0.152	0.191	0.090
39	0.093	0.139	0.189	0.081
40	0.088	0.140	0.188	0.082

41	0.083	0.135	0.191	0.074
42	0.086	0.144	0.189	0.080
43	0.087	0.145	0.192	0.079
44	0.091	0.151	0.190	0.071
45	0.090	0.148	0.193	0.075
46	0.082	0.131	0.191	0.072
47	0.085	0.120	0.190	0.072
48	0.090	0.096	0.187	0.064
49	0.096	0.085	0.182	0.068
50	0.090	0.080	0.180	0.071
51	0.090	0.074	0.178	0.066
52	0.086	0.072	0.176	0.067
53	0.087	0.071	0.180	0.069
54	0.088	0.073	0.183	0.072
55	0.088	0.072	0.181	0.069
56	0.089	0.070	0.185	0.072
57	0.087	0.071	0.183	0.069
58	0.086	0.068	0.181	0.069
59	0.093	0.053	0.185	0.076
60	0.100	0.038	0.188	0.078

Appendix B:

Figure 1: Measure of imbalance (absolute value) vs. the number of patients for methods 1, 2, 3 and 7

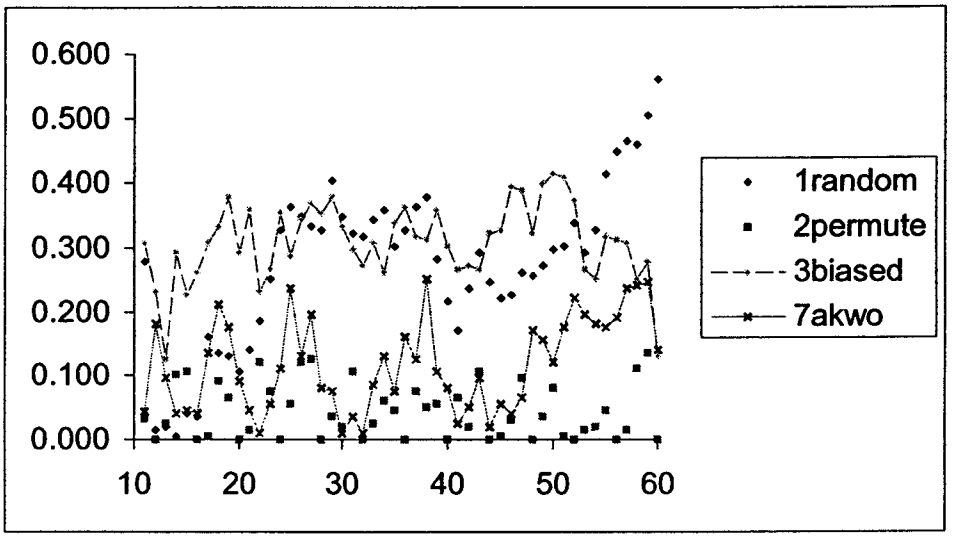

Figure 2: Measure of imbalance vs. the number of patients for methods 4, 5, 6 and 8