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THE RANDOMIZATION AND STRATIFICATION OF PATIENTS TO CLINICAL TRIALS

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INTRODUCTION

RANDOMIZED controlled clinical trials have gained widespread acceptance among clinical investigators for evaluating the therapeutic benefits of new as well as standard therapies. The term 'randomization', in the context of clinical trials, refers to the assignment of treatments to patients using a chance procedure. This chance procedure is such that neither the investigator nor the patient knows the treatment to be assigned at the time a patient is registered for the study.

Usually a randomization assignment is made using a table of random numbers. A table of random numbers is simply a table having the digits 0–9 such that each digit has the same chance of appearing in every entry. This is a table where there can be 'no errors' because every digit is supposed to be randomly placed. It is such tables which are used to generate randomization schedules. Table 1 is a sample page from a book of random numbers.

Another important reason for using randomization in a clinical trial is that it forms the basis for the validity of many of the statistical procedures used in the analysis of the data. If randomization is present, no further assumptions are required about the patient population in order to make the application of many statistical procedures valid. However, this aspect of randomization will not be considered further in this paper.

The main object of this paper is to discuss various ways of implementing randomization assignments in clinical trials. In all that follows, it shall be assumed for simplicity that there are two therapies under investigation which shall be denoted by the letters *A* and *B*. Furthermore it will be assumed that patients enter a study sequentially in time. The outline of this paper is that Section 1 discusses simple randomization; Section 2 takes up block randomization; adaptive randomization is found in Section 3; section 4 describes 'Play the Winner' randomization; and finally Section 5 discusses complex stratification.

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TABLE 1. PAGE OF RANDOM NUMBERS

2500 FIVE DIGIT RANDOM NUMBERS

53479	81115	98036	12217	59526	40238	40577	39351	43211	69255
97344	70328	58116	91964	26240	44643	83287	97391	92823	77578
66023	38277	74523	71118	84892	13956	98899	92315	65783	59640
99776	75723	03172	43112	83086	81982	14538	26162	24899	20551
30176	48979	92153	38416	42436	26636	83903	44722	69210	69117
81874	83339	14988	99937	13213	30177	47967	93793	86693	98854
19839	90630	71863	95053	55532	60908	84108	55342	48479	63799
09337	33435	53869	52769	18801	25820	96198	66518	78314	97013
31151	58295	40823	41330	21093	93882	49192	44876	47185	81425
67619	52515	03037	81699	17106	64982	60834	85319	47814	08075
61946	48790	11602	83043	22257	11832	04344	95541	20366	55937
04811	64892	96346	79065	26999	43967	63485	93572	80753	96582
05763	39601	56140	25513	86151	78657	02184	29715	04334	15678
73260	56877	40794	13948	96289	90185	47111	66807	61849	44686
54909	09976	76580	02645	35795	44537	64428	35441	28318	99001
42583	36335	60068	04044	29678	16342	48592	25547	63177	75225
27266	27403	97520	23334	36453	33699	23672	45884	41515	04756
49843	11442	66682	36055	32002	78600	36924	59962	68191	62580
29316	40460	27076	69232	51423	58515	49920	03901	26597	33068
30463	27856	67798	16837	74273	05793	02900	63498	00782	35097
28708	84088	65535	44258	33869	82530	98399	26387	02836	36838
13183	50652	94872	28257	78547	55286	33591	61965	51723	14211
60796	76639	30157	40295	99476	28334	15368	42481	60312	42770
13486	46918	64683	07411	77842	01908	47796	65796	44230	77230
34914	94502	39374	34185	57500	22514	04060	94511	44612	10485
28105	04814	85170	86490	35695	03483	57315	63174	71902	71182
59231	45028	01173	08848	81925	71494	95401	34049	04851	65914
87437	82758	71093	36833	53582	25986	46005	42840	81683	21459
29046	01301	55343	65732	78714	43644	46248	53205	94868	48711
62035	71886	94506	15263	61435	10369	42054	68257	14385	79436
38856	80048	59973	73368	52876	47673	41020	82295	26430	87377
40666	43328	87379	86418	95841	25590	54137	94182	42308	07361
40588	90087	37729	08667	37256	20317	53316	50982	32900	32097
78237	86556	50276	20431	00243	02303	71029	49932	23245	00862
98247	67474	71455	69540	01169	03320	67017	92543	97977	52728
69977	78558	65430	32627	28312	61815	14598	79728	55699	91348
39843	23074	40814	03713	21891	96353	96806	24595	26203	26009
62880	87277	99895	99965	34374	42556	11679	99605	98011	48867
56138	64927	29454	52967	86624	62422	30163	76181	95317	39264
90804	56026	48994	64569	67465	60180	12972	03848	62582	93855
09665	44672	74762	33357	67301	80546	97659	11348	78771	45011
34756	50403	76634	12767	32220	34545	18100	53513	14521	72120
12157	73327	74196	26668	78087	53636	52304	00007	05708	63538
69384	07734	94451	76428	16121	09300	67417	68587	87932	38840
93358	64565	43766	45041	44930	69970	16964	08277	67752	60292
38879	35544	99563	85404	04913	62547	78406	01017	86187	22072
58314	60298	72394	69668	12474	93059	02053	29807	63645	12792
83568	10227	99471	74729	22075	10233	21575	20325	21317	57124
28067	91152	40568	33705	64510	07067	64374	26336	79652	31140
05730	75557	93161	80921	55873	54103	34001	83157	04534	81368

Compiled from Rand Corporation, A million random digits with 100,000 normal deviates. The Free Press, Glencoe, Ill., 1955 (with permission).

1. SIMPLE RANDOMIZATION

Simple randomization is the most elementary kind of randomization and is the kind which is carried out in many studies. One prepares a listing of the two treatments according to a table of random numbers. A simple way to do this is to have the even numbers in a table refer to the assignment of treatment A, and odd numbers to the assignment of treatment B. To illustrate, suppose we use the random numbers found in the first five rows in the first column of Table 1 and consider the problem of assigning two treatments to 24 patients. The entire procedure is illustrated in Table 2.

In the 'long run' (as the number of patients increase), the ratio of the number of patients on A relative to the number of patients on B approaches unity. However, if one was to stop at any point in time we would find that the trial would not necessarily have the same number of patients on each treatment. Table 2 illustrates this situation. Small sets of patients randomized in this manner will invariably show such imbalances.

This plays havoc if one wished to conduct interim analysis of the trial. For example, after 8 patient entries, there is only 1 patient on *A* and 7 patients on *B*. Even though the principles of randomization have been followed, it does not look like the way a trial should be planned. All that the statistical theory says is that the ratio of the number of allocations to each treatment will approach unity as the number of patients increase indefinitely. However, with small sets of patients one can have widely discrepant allocations. When several institutions are involved in a trial, simple randomization may result in serious imbalances in treatment assignments within an institution.

TABLE 2. EXAMPLE OF SIMPLE RANDOMIZATION

Problem. Assign two treatments to 24 patients

Random numbers

5 3 4 7 9
9 7 3 4 4
6 6 0 2 3
9 9 7 7 6
3 0 1 7 6

Procedure

If random number is even assign Treatment *A*

If random number is odd assign Treatment *B*

Chronological patient No.	Random number	Assignment	Chronological patient No.	Random number	Assignment
1	5	*B*	13	0	*A*
2	3	*B*	14	2	*A*
3	4	*A*	15	3	*B*
4	7	*B*	16	9	*B*
5	9	*B*	17	9	*B*
6	9	*B*	18	7	*B*
7	7	*B*	19	7	*B*
8	3	*B*	20	6	*A*
9	4	*A*	21	3	*B*
10	4	*A*	22	0	*A*
11	6	*A*	23	1	*B*
12	6	*A*	24	7	*B*

Cumulative patient allocations

Chronological patient No.	Cumulative No. of A's	Cumulative No. of B's	Ratio*
4	1	3	0.33
8	1	7	0.14
12	5	7	0.71
16	7	9	0.78
20	8	12	0.67
24	9	15	0.60

*Ratio theoretically approaches unity in 'long run'.

2. BLOCK RANDOMIZATION

In order to avoid the 'embarrassing' situations which may arise in simple randomization, one could instead use *block randomization*. Block randomization consists of:

(i) Divide the patients into several blocks or groups of equal size. These blocks are usually formed corresponding to the chronological time in which the patients enter the trial.

(ii) Within each block of patients, assign the treatments so that there is an equal allocation for each treatment.

Consider again the problem of assigning two treatments to 24 patients. Using block randomization, we can divide the patients into six groups of four patients each. The grouping is done in the chronological order of patient entry. Then within each group randomly assign two patients to each treatment. This will ensure that after every fourth patient assignment, there will be an equal number of patients on each treatment.

To implement this block randomization, consider all possible ways or patterns of arranging two treatments in groups of four. There are six possible ways as depicted below.

Number of ways of arranging two treatments in groups of four

1	2	3	4	5	6
A	*B*	*A*	*B*	*A*	*B*
A	*B*	*B*	*A*	*B*	*A*
B	*A*	*A*	*B*	*B*	*A*
B	*A*	*B*	*A*	*A*	*B*

Let us number these six possible arrangements with the integers 1–6. Then the random assignment can be made by having the first six integers arranged in random order. Suppose such an order is 2, 6, 4, 3, 1, 5. These numbers correspond to each of the six blocks in the order in which they are to be used. Table 3 summarizes the entire process.

TABLE 3. BLOCK RANDOMIZATION

Procedure

(i) Divide patients into several blocks of equal size. The blocks are formed corresponding to the time patients enter the trial.

(ii) Within each block, assign the treatments so that there are equal numbers for each treatment.

Example

Group 24 patients into 6 blocks of 4 patients each. The first four patients form a block, the next four form another block, etc.

Different patterns of arranging 2 treatments in groups of 4

1	2	3	4	5	6
A	*B*	*A*	*B*	*A*	*B*
A	*B*	*B*	*A*	*B*	*A*
B	*A*	*A*	*B*	*B*	*A*
B	*A*	*B*	*A*	*A*	*B*

Random sequence of integers: 2, 6, 4, 3, 1, 5

Patient No.	1	2	3	4	5	6	7	8	9	10	11	12
Treatment	*B*	*B*	*A*	*A*	*B*	*A*	*A*	*B*	*B*	*A*	*B*	*A*
Pattern			2				6				4	
Patient No.	13	14	15	16	17	18	19	20	21	22	23	24
Treatment	*A*	*B*	*A*	*B*	*A*	*A*	*B*	*B*	*A*	*B*	*B*	*A*
Pattern			3				1				5	

The advantage of the block randomization method is obvious. However if the block randomization is for a single institution the investigator will know exactly which treatment would be assigned to the last patient in the group. In the case of blocks of

four, the investigator would know the treatment assignment for the 4th, 8th, 12th, ..., patient. This is an easier way of guessing what the next treatment would be than holding a sealed envelope up to a light. In addition, knowing the early assignments within a block would enable an investigator to know the remaining assignments which must arise in order to balance out the treatment assignments within the block.

However, if there are several institutions participating in the study and the block randomization is made from a central source, institutions would not know the chronological order of patients entering and hence would not be able to predict every fourth assignment. An important disadvantage to the block randomization is that although the assignment over all institutions would be balanced with regard to treatment allocation, within an institution there may be a serious imbalance in the treatment assignment.

For example, suppose we have 4 institutions. Let us refer to these institutions by α, β, γ, δ. Assume the institutions enter patients sequentially in time as follows: α, γ, α, α, β, δ, δ, γ, α, γ, γ, γ, α, β, δ, γ, δ, α, β, γ, α, β, α, γ. If the block randomization scheme in Table 3 had been followed we would then have:

Institution	No. assigned to *A*	No. assigned to *B*	Total
α	5	3	8
β	0	4	4
γ	3	5	8
δ	4	0	4
	Total 12	Total 12	24

Clearly the block randomization may also lead to undesirable patterns of randomization if one has a multi-institution study. This can be avoided by using block randomization within each institution. However, as pointed out earlier such a scheme will result in the investigator being able to have informed judgment of the treatment allocation for a significant number of patients.

One way to avoid the difficulties associated with using block randomization in a multi-clinical trial is to use *balanced block randomization*. The object is to use block randomization, but to make certain that no imbalances exist within an institution.

The balanced block randomization procedure requires randomization being carried out from a central source. One uses both a, (i) block randomization schedule and, an (ii) auxiliary table of random integers. In practice this auxiliary table may have only the integers 1 and 2 or 1, 2, and 3. The idea is when a patient is registered, one *tentatively* chooses the treatment allocation according to the block randomization schedule. Then calculate the *difference* in the number of treatments allocated to each treatment with this tentative assignment. Choose a random integer from the auxiliary table. If the difference in treatment allocation is less than or equal to the random integer, the tentative assignment is to be used; on the other hand, if the difference is greater than the random integer do not use the tentative allocation, but assign the alternate treatment. The entire block randomization process is conveniently illustrated by Table 4.

Table 5 shows how this randomization procedure works for a four-institution study where the auxiliary random number table contains the integers 1, 2 and 3.

TABLE 4. BALANCED BLOCK RANDOMIZATION

Object To use block randomization in a multi-institution trial, but to make certain that no imbalances exist within an institution.

Define (for each institution)
D=(no. assigned to A)—(no. assigned to B)
n =random integer chosen from auxiliary random number table

Procedure

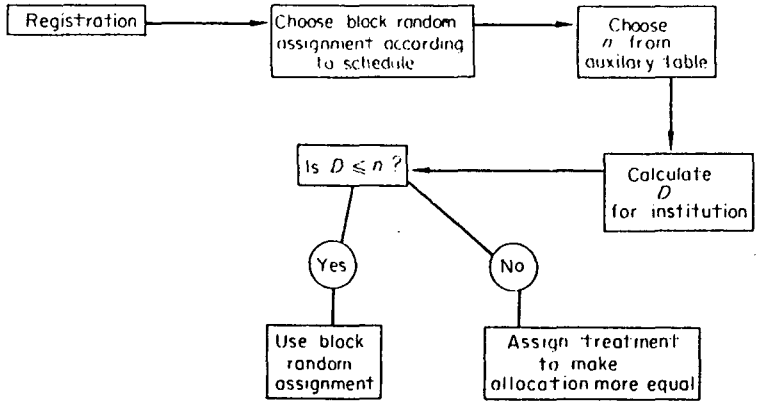

TABLE 5. BLOCK RANDOM ASSIGNMENT (EXAMPLE)

Auxiliary random number table for n=1, 2, 3
1 1 2 3 2 3 1 2 2 3 1 2 3 3 1 2 2 2 3 1 3 1 2 3

Patient No.	n	Institutions α	β	γ	δ
1	1	*B*			
2	1			*B*	
3	2	*A*			
4	3	*A*			
5	2		*B*		
6	3				*A*
7	1				*B*
8	2			*B*	
9	2	*B*			
10	3			*A*	
11	1			*A*	
12	2			*B*	
13	3	*A*			
14	3		*B*		
15	1				*B*
16	2			*A*	
17	2				*A*
18	2	*A*			
19	3		*B*		
20	1			*A*	
21	3	*B*			
22	1		*A*		
23	2	*B*			
24	3			*A*	

Institution	No. allocated to *A*	No. allocated to *B*
α	4	4
β	1	3
γ	5	3
δ	2	2

3. ADAPTIVE RANDOMIZATION

In this section another method of randomization is to be considered which we shall call *adaptive randomization.* It is due to Efron (1971) and is useful when the closed envelope method of randomization is used. Suppose that every time a patient is to be randomized, one calculates:

D=(No. of patients previously assigned to A)—(No. of patients previously assigned to B).

Then the following rule is used:

$D=0$ (no excess) assign patient to either treatment with probability $\frac{1}{2}$,

$D>0$ (excess of A's) assign patient to treatment B with probability p;

$D<0$ (excess of B's) assign patient to treatment A with probability p.

A value of p is used so that $p>\frac{1}{2}$.

Operationally to use this procedure with the closed envelope technique, each institution will have two sets of randomization envelopes. Set I is used if $D=0$; set II corresponds to $D\neq 0$. Set I contains equal numbers of A and B envelopes arranged in a random order. Set II may be constructed by having envelopes marked with the symbols '$=$' or '$\neq$'. The proportion of '$=$' symbols corresponds to the probability p ($p>\frac{1}{2}$). If an envelope having the symbol '$=$' is drawn, then one makes the treatment assignment to make the allocation more equal. If the symbol '$\neq$' is drawn, the assignment is made more unequal. Table 6 illustrates this method when two treatments are allocated to 24 patients using the value $p=2/3$.

TABLE 6. ADAPTIVE RANDOMIZATION (EXAMPLE)

D=(No. of patients previously assigned to A)—(No. of patients previously assigned to B)

Set I Use if $D=0$ (Probability of choosing either treatment is $\frac{1}{2}$)
B B A B A A A B B B A A

Set II Use if $D\neq 0$. (Probability of choosing treatment to make assignment more equal is 2/3)
$=, =, \neq, =, \neq, =, \neq, =, =, \neq, =, =, =, =, =, \neq, =, \neq$
$=$: Signifies choose treatment to make allocation more equal
$\neq$: Signifies choose treatment to make allocation more unequal

Chronological patient number:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Treatment:	*B*	*A*	*B*	*A*	*A*	*A*	*B*	*A*	*B*	*A*	*B*	*B*	*B*	*B*	*A*	*A*	*A*	*B*	*A*	*B*	*A*	*B*	*B*	*B*

Patient No.	Cumulative No. of A's	Cumulative No. of B's
4	2	2
8	5	3
12	6	6
16	8	8
20	10	10
24	11	13

4. PLAY THE WINNER RANDOMIZATION

There are some circumstances where one is comparing two therapies and desires to place more patients on the better treatment. However, at the start of the trial, one does not know which is the better treatment. This might be the case in a dose-finding study where one is really interested in the better dose rather than assigning patients equally

to all doses. Another situation is when one wishes to conduct a trial during the course of normal practice without getting involved in very complicated randomization schemes. One way of reaching the objective to place more patients on the better treatment is to use the following rule Zelen [2].

Play the Winner Rule. A success on a particular treatment generates a future trial on the same treatment with a new patient. A failure on a treatment generates a future trial on the alternate treatment.

Thus with this scheme, as long as one is obtaining a success on a therapy, keep using it. Whenever one observes a failure, switch to the other treatment. To illustrate ideas assume that the outcome of a trial is known before the next patient is entered.

Then a typical sequence of trials may look like the following:

Treatment A: $SSF \quad SSSSF \quad \ldots$

Treatment B: $\quad SF \quad SSF \quad \ldots$

Using this rule results in:

$$R = \frac{\text{mean No. of patients on treatment } A}{\text{mean No. of patients on treatment } B} = \frac{\text{probability of failure on } B}{\text{probability of failure on } A} = \frac{q_B}{q_A}.$$

TABLE 7. CALCULATIONS FOR DIFFERENT FAILURE PROBABILITIES

q_A	q_B	$R=q_B/q_A$
0.10	0.50	5.00
0.50	0.70	1.40
0.90	0.80	1.12
0.95	0.90	1.06

This kind of randomization is likely to be useful where $q_A+q_B \leq 1$ and the failure probabilities are not too close.

5. STRATIFICATION

One of the key dictums in experimentation is to take account of all known factors which may significantly affect the outcome of a trial. Not to do so may introduce biases in the data, which may lead to drawing wrong conclusions and possibly introduce so much variability in the data so as to completely obscure any real differences among the treatments. When the factors influencing response are known, we can take this into account in the initial randomization. Then the randomization is referred to as *stratified randomization*. For example, some factors important for planning cancer studies are: institution, anatomical staging, histological type, prior treatment, general health of patient, demographic factors, etc.

Taking account of these other factors in the initial treatment assignment ensures that each of the therapies has an equal distribution of patients with regard to the important characteristics which may significantly affect response. Of course, using a stratified randomization scheme increases the bookkeeping of the clinical trial. One must weigh the gain in efficiency of the trial against the increased complexity of running the study.

The aim of the stratified randomization in multi-institution clinical trials is to balance these factors over the entire experiment and at the same time balance the

allocation of treatments and disease factors within each institution. The major difficulties are that patients are not equally distributed with regard to combinations of disease factors nor do patients enter a trial such that these factors are uniformly distributed in time.

To illustrate ideas, suppose in a clinical trial on advanced lung cancer involving three institutions, we were to stratify the patients according to whether they were ambulatory or non-ambulatory. Suppose one made up a separate block randomization schedule for each stratum within each institution. Table 8 depicts the schedules for each institution. Also in Table 8 are depicted 12 patient entries and the assignment according to the randomization schedule. Below are summarized results of this randomization. Note that treatment A received twice as many patients as B and the ambulatory assignment is not in balance. It is clear that a fixed block randomization schedule within each institution may result in imbalanced allocations due to the random nature in which the patients enter the trial. When there are more than two stratum this tendency toward imbalance becomes more pronounced.

An alternative randomization strategy is to set up central randomization schemes having the object of balancing the stratification variables over the treatments without necessarily balancing the variables exactly within each institution. To return to the example in Table 8, one can arrange a randomization schedule separately for ambulatory and non-ambulatory patients ignoring institutions. The randomization procedure consists of:

(i) Choose the tentative treatment assignment according to the pre-arranged schedule;

(ii) If D=[(No. assigned to A)—(No. assigned to B)] calculated for that institution is less in absolute value than a key number n, the assignment holds; if not choose the alternate treatment. The key number does not change for the entire trial. The key number is unknown to each participating institution. Recommended key values are n=2, 3, 4.

The entire procedure is illustrated in Table 9 for the sequence of patients shown in Table 8. The fixed key number n is taken to be n=3.

A variation of the above procedure is to choose a different key number n from a table of random integers for each new patient as in the balanced block randomization. Another modification is to have a strict alternating sequence of stratified treatment assignments rather than a block randomization sequence. The example in Table 9 was balanced for every four treatment assignments within each stratum. An alternating sequence $ABAB\ldots$ will have balance for every pair of treatments. *This is only recommended for multi-institution studies.* Although the alternating sequence can in no way be considered random, the entry of patients is random. If the institutions are unaware of the prior entry of patients, the net effect is that the treatment allocation is random within institutions, but alternates (not random) over the entire clinical trial.

The alternating treatment allocation is recommended particularly when a multi-institutional trial has many strata. For example, suppose in a clinical trial on breast cancer we were to stratify according to the factors listed in Table 10. This results in 27 different possibilities. If there are two treatment combinations, we would have 54 different combinations. A possible allocation scheme is to have an alternating randomization scheme for each stratum so arranged that half of the stratum treatment

allocation begin with A, the other half with B. Adjustments are made within institutions as described earlier to prevent imbalances within institutions.

TABLE 8. STRATIFIED BLOCK RANDOMIZATION SCHEDULE FOR THREE INSTITUTIONS (EACH INSTITUTION HAS A SEPARATE RANDOMIZATION SCHEDULE)

Physical state	Ambulatory			Non-ambulatory		
Institution	α	β	γ	α	β	γ
randomization schedules	*A*	*B*	*A*	*B*	*A*	*B*
(fixed in advance)	*A*	*B*	*B*	*A*	*B*	*A*
	B	*A*	*A*	*B*	*B*	*A*
	B	*A*	*B*	*A*	*A*	*B*

Chronological order of entry	Institution	Physical* status	Treatment
1	α	a	*A*
2	γ	na	*B*
3	α	a	*A*
4	γ	na	*A*
5	β	na	*A*
6	β	a	*B*
7	γ	a	*A*
8	α	a	*A*
9	γ	na	*A*
10	α	na	*B*
11	β	a	*B*
12	β	a	*A*

Summary of number of patients assigned by physical status and institution

Factor	Number assigned to *A*	Number assigned to *B*
Physical status		
Ambulatory	5	2
Non-ambulatory	3	2
	8	4
Institution		
α	3	1
β	2	2
γ	3	1
	8	4

*a—ambulatory; na—non-ambulatory.

Other ways of carrying out the stratified randomization are to use the method introduced by Efron or the *Play the Winner Rule*. The Efron method may not be satisfactory if the clinical trial is a multi-institutional trial. However, if the trial involves only a single institution, the Efron method could be effectively used. The *Play the Winner Rule* could also be used separately for each stratum—either in a single or multi-institution trial. It will lead to imbalances among the treatment allocations if there are marked differences between the two treatments. In this case one has to judge whether the potential imbalances are to be tolerated in exchange for more patients on the better treatment within each stratum.

TABLE 9. STRATIFIED SCHEDULE WHICH BALANCES OUT EXACTLY OVER STRATA, BUT ONLY APPROXIMATELY WITHIN INSTITUTIONS

Ambulatory schedule *AABBABABBAABB*
Non-ambulatory schedule *BBAABABABAABBAA*

Chronological Order of entry	Institution	Physical* state	Tentative assignment	$\lvert D \rvert$ †	Final assignment
1	α	a	A	1	A
2	γ	na	B	1	B
3	α	a	A	2	A
4	γ	na	B	2	B
5	β	na	A	1	A
6	β	a	B	0	B
7	γ	a	B	3	A
8	α	a	B	1	B
9	γ	na	A	0	A
10	α	na	B	0	B
11	β	a	B	1	B
12	β	a	A	0	A

Summary of number of patients assigned by physical status and institution

Factor	Number assigned to *A*	Number assigned to *B*
Physical status		
Ambulatory	4	3
Non-ambulatory	2	3
	6	6
Institution		
α	2	2
β	2	2
γ	2	2
	6	6

*a—ambulatory; na—non-ambulatory.

†If $\lvert D \rvert < 3$ use tentative as the final assignment; if $\lvert D \rvert = 3$ use alternate treatment.

TABLE 10. STRATA FOR PLANNING BREAST CANCER TRIAL

Factors	Possible conditions	No. of conditions
Regional lymph nodes	not palpable palpable: fixed to other structures palpable: movable	3
Metastases	negative positive: skin positive: distant organs	3
Menopausal status	pre-menopause post-menopause ≤1 year post-menopause >1 year	3

REFERENCES

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