Statistics in Question

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ASSESSING CLINICAL TRIALS—RESTRICTED RANDOMISATION

Restricted randomisation[1-3] is recommended when investigators want to ensure that the numbers of patients allocated to each treatment are approximately equal in the trial as a whole or in important subgroups of patients, or both. Corresponding methods, in order of increasing complexity, are the method of random permuted blocks, stratified randomisation, and minimisation. These are discussed in this article, but Zelen[1] has given a fuller account. He is also responsible for a new design—randomised consent[4]—which is also discussed.

The method of random permuted blocks is easy to use. In the trial as a whole it guarantees that the numbers allocated to each treatment are equal after every block of so many patients has entered.

Stratification[1] by one factor (perhaps two) that is known to affect prognosis is a safeguard against a chance imbalance between treatment groups with respect to an important variable —for example, the extent of cavitation in tuberculosis or axillary node disease in breast cancer. Stratification, especially in small trials, is recommended so long as the randomisation is still simple to operate. One method is to devise a separate list for each stratum by the method of random permuted blocks—that is, consult different lists according to the extent of cavitation for a patient with tuberculosis.

Stratified randomisation may also be useful in multicentre trials when it is important to avoid treatment imbalance in individual hospitals as well as in the trial as a whole. One way of doing this when there are many centres is to prepare randomisation lists for the trial as a whole, monitor the imbalance in individual hospitals, and intervene to restore the balance within a hospital before the assignments there get too far out of line.

Minimisation,[3] as the word implies, is a method of random assignment that minimises the marginal imbalance in the numbers of patients allocated to different treatments over several (two or more) factors known to affect prognosis, one of which may be a hospital in a multicentre study. The method avoids the limitations of stratified randomisation (see question 21) but has a similar purpose. It works this way: a measure of imbalance is calculated over the set of prognostic factors describing the new patient, who is then most probably, but not invariably, assigned to the treatment that minimises the overall imbalance.

Randomised consent designs[4] have a different rationale: (*a*) to limit the number of patients to whom a full and perhaps distressing explanation is given of the purpose of a randomised trial; and (*b*) to encourage doctors to participate in clinical trials. Some doctors fear that informed consent—as regulated by the Federal Government in the United States, for example—destroys their patients' hope and confidence. These doctors refer no patients or only selected ones for inclusion in clinical trials. Zelen[4] proposed that all eligible patients should be randomised to a "seek consent" or a "do not seek consent" group. The latter receives the standard treatment; the former group is asked to give informed consent to the experimental treatment. Comparison is made between *groups as randomised*, though the "seek consent" group will have a proportion of patients who received the standard treatment—because they so decided after the trial had been fully explained, or because their doctor elected not to confront them with a traumatic explanation. These designs are new and therefore uncommon in published reports.

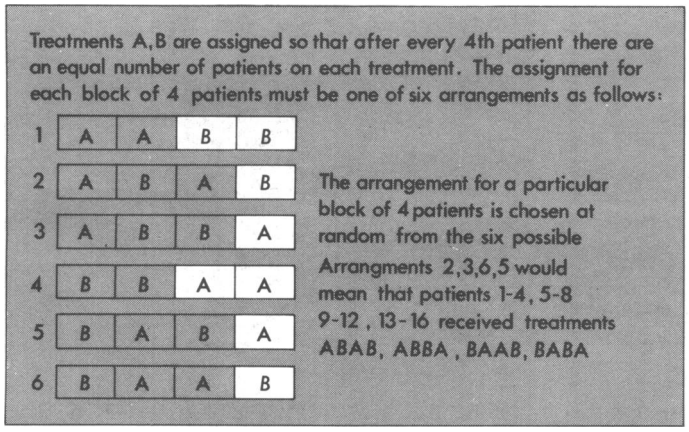
Random permuted blocks

(20) *The doctor has realised that the randomisation plan is to make the numbers allocated to each treatment equal after every block of four patients has entered (see figure). What problem occurs when he can identify the treatments given to the first three patients in any block?*

—selection bias because the treatment for every fourth patient can be deduced

COMMENT

The method of random permuted blocks works well provided that the doctor does not guess the block length (four in my example) and cannot identify the treatments that have been assigned to previous patients in the block. If he can identify the first three assignments and realises that the block length is four then he knows that the last patient in the block must receive the treatment that makes things equal. Selection bias then becomes a problem, especially if the block length is short (equal treatment numbers after every second or every fourth or every sixth patient). In my example selection bias could affect decisions about as many as one-third of the trial patients. Clearly the statistician should not tell the doctor what the block length is and will often take the precaution of varying block length randomly to make the detective work more difficult.



Permuted block randomisation: block length 4. (a) There are 24 arrangements of 3 A's and 3 B's, corresponding to block length 6. (b) Tables of random permutations[5] should be used if there are too many arrangements to list—when block size exceeds six patients, for example.

There are other methods of restricted randomisation that are not liable to selection bias even when treatments are unmasked. They entail simple randomisation when the discrepancy between the numbers of patients in each treatment group is small but give greater weight (probability $\frac{2}{3}$, say) to the treatment group that is deficient in numbers when the deficiency goes beyond a predefined limit. Descriptions have been given by Zelen[1] and Efron.[2]

Stratification

(21) *Why is excessive stratification self-defeating?*

—deters participation in a clinical trial

—results in too many strata with too few patients

—administrative complexity leads to errors

COMMENT

A chance imbalance occurring between treatment groups on factors unrelated to the prognosis is of no practical importance whatsoever. It is only worth considering stratification by variables that are known to affect prognosis. These are usually few. Overzealous stratification is a humbug—factor levels must be multiplied (not added) to yield the total number of subgroups. Even three prognostic factors, such as tumour size, axillary node disease, and menstrual status in breast cancer, each at three levels—tumour size: ≤ 2 cm, 3-4 cm, ≥ 5 cm; axillary node disease: not diseased, mobile, matted nodes; menstrual status: premenopause, menopausal, postmenopause—yield $3 \times 3 \times 3 = 27$ subgroups of patients. For each of these a separate restricted randomisation list must be consulted. Worse still, the distribution of patients is unlikely to be even, so that many strata will include so few patients that the restricted randomisation procedure does not come into play—for example, balancing treatment numbers after every sixth patient is not effective in strata with fewer than six patients. And so treatment numbers need not be equal, even in the trial as a whole. Excessive stratification is therefore self-defeating.

Strata: clinical state at entry to trial	Treatment numbers		
	Disodium cromoglycate	Sulphasalazine	Combination
Clinical attack	5	5	6
Clinical remission			
Inflamed on sigmoidoscopy	7	7	8
Not inflamed on sigmoidoscopy	25	25	19
Total	37	37	33

Stratified randomisation: comparison of disodium cromoglycate and sulphasalazine as maintenance treatment for ulcerative colitis[6] (patients allocated by restricted randomisation in each stratum).

Besides, an adjustment may be made retrospectively at the analysis to cope with moderate differences between treatment groups in relation to a variable—age at menarche, for example—that was not considered important before as a predictor of survival.

Minimisation

(22) *The figure at the top of the next page shows the assignment so far: 60 patients with breast cancer have been randomised to simple mastectomy+radiotherapy or to radical mastectomy. Patient 61 is premenopausal and has a tumour that is 5 cm in size and positive axillary nodes. Which treatment assignment leads to the least imbalance over the relevant (shaded) prognostic factors?*

—simple mastectomy+radiotherapy

—patient 61 is assigned to this treatment with probability greater than $\frac{1}{2}$ but less than 1—that is, the probable assignment is weighted in favour of simple mastectomy+radiotherapy

COMMENT

The second figure shows that of the 15 premenopausal patients who have been treated so far, seven have undergone radical mastectomy. By assigning patient 61 also to radical mastectomy the numbers of such patients would be made the same in both treatment groups. On the other hand, assignment to simple mastectomy+radiotherapy is preferred to minimise the imblance between treatment groups in respect both of patients who have a large tumour and of patients with positive nodes.

A trivial measure of overall imbalance would be the number of votes for and against each treatment. Simple mastectomy+

Balancing treatments over several prognostic factors

Assignment so far...

Treatment	Menstrual status: Pre-menopause	Menstrual status: Post-menopause	Tumour size (cm): ≤2	Tumour size (cm): 3-4	Tumour size (cm): ≥5	Nodes: Negative	Nodes: Positive
Simple mastectomy + radiotherapy (n=30)	8	22	4	14	12	17	13
Radical mastectomy (n=30)	7	23	5	12	13	14	16
Total No of patients	15	45	9	26	25	31	29

Patient 61 is pre menopausal, has tumour size 5cm and positive nodes

radiotherapy wins because it has two votes. But this measure can be criticised because it does not take into account that an imbalance of 13 versus 16 is in more need of correction than one of 8 versus 7. Thus if patient 61 were assigned to radical mastectomy the overall imbalance would then be $(8-8)+(12-14)+(13-17)=-6$, compared with 0 if simple mastectomy +radiotherapy were selected. This more sensitive criterion also favours simple mastectomy+radiotherapy. What happens next is that patient 61 has a high chance—probability $\frac{3}{4}$, say—of being assigned to simple mastectomy+radiotherapy but could nevertheless still be randomised to radical mastectomy—probability $\frac{1}{4}$—which exaggerates the imbalance. It is important to retain the random element—assignment with a probability of less than 1—to avoid selection bias.

Patient description	Assignments so far: Simple mastectomy + radiotherapy	Assignments so far: Radical mastectomy	Favoured assignment for patient 61
Premenopause	8	7	Radical mastectomy
Tumour size ≥5cm	12	13	Simple mastectomy + radiotherapy
Positive nodes	13	16	Simple mastectomy + radiotherapy

Randomised consent design

(23) *Identify at least two disadvantages of randomised consent designs.*

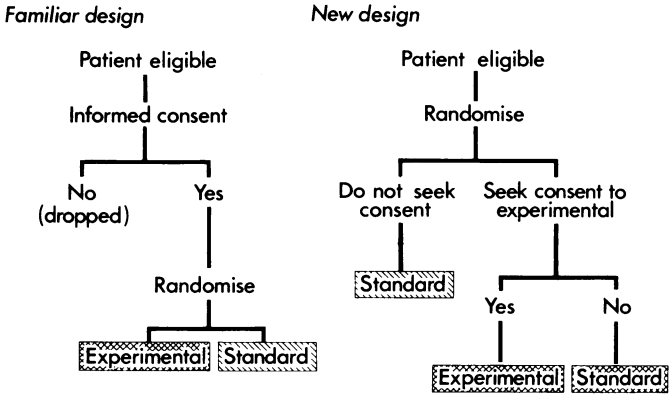
—difficulty in making the trial double-blind

—only patients in the "seek consent" group know that they are taking part in a clinical trial

—doctors may be more persuasive in presenting information about the new treatment to some types of patients than to others

COMMENT

Randomised consent designs[4] have several limitations. The first is that it is difficult to arrange for such a trial to be double-blind, since membership in the group is revealed by whether or not the patient was asked for informed consent to the experimental treatment. The second difference between the randomised groups is that the patients in one group know that the outcome of their treatment is of special interest to doctors. This knowledge may influence compliance with treatment or the patients' reporting of disease status, and so bias the comparison between treatments. A third problem comes when the results are analysed if the proportion of patients who agree to the experimental treatment differs between subgroups. The different proportions of patients need not truly reflect whether the experimental treatment was acceptable to different types of patients but may depend on how persuasively doctors presented the information about the new treatment. The problem is especially tricky if the experimental treatment actually benefits some subgroups but is inferior to the standard treatment in others. This interaction could be hidden in the trial results if doctors, guessing it correctly, advocated the experimental treatment strongly only for those patients in whom they expected the most benefit. When the trial came to be analysed the "seek consent" group would have the better results, but it would be noted that in some subgroups a high proportion of patients refused the experimental treatment. There can be no clear interpretation of the reasons for refusal; refusal is not necessarily an indictment of the experimental treatment, but it may be. Randomised consent designs are useful only when a consistently high proportion of patients in the "seek consent" group accepts the experimental treatment.



Telephone randomisation

(24) *What precautions should be taken if the mechanism for random assignment is (i) sealed envelopes; (ii) coded phials (supplied by the hospital pharmacy or a drug company, for example); (iii) central randomisation office (telephone randomisation)?*

(i) beware of transparent envelopes;

keep a register of trial patients by name, date of registration, and trial number

(ii) ensure that the phials are identical in shape, instruction label, seal, and contents;

the code should give no clue as to the contents of the phial—avoid labels such as "treatment A" or "treatment B";

give expiry date and batch number

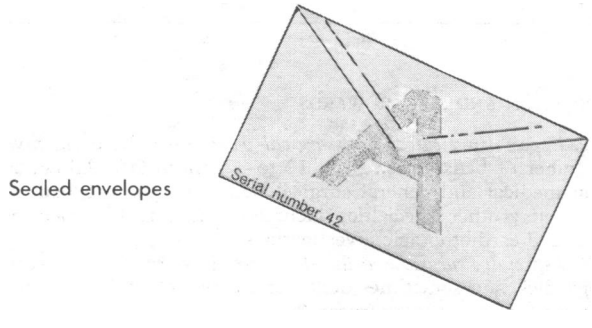
(iii) the best safeguard against the curious and the ingenious;

avoid delay by manning the randomisation office during agreed hours;

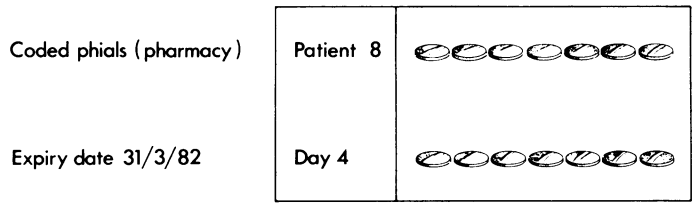
give written confirmation after telephone randomisation

COMMENT

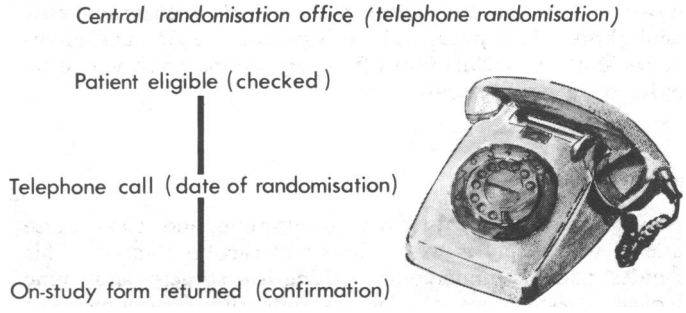
(i) If the random assignments are in sealed numbered envelopes the trial co-ordinator must ensure that the next assignment cannot be read by holding the envelope up to the light. The decision to register a patient in the clinical trial should be made before the treatment is revealed: the decision is appropriate only if the doctor is prepared for that patient to receive any one of the trial treatments, otherwise assignment is contraindicated. One way to defend the integrity of the randomisation scheme is for a trial co-ordinator to hold the sealed envelopes and keep a log of registered patients so that a one-to-one correspondence is set up between patient and sealed numbered assignment. Of course, a master randomisation list is also held.



(ii) When coded phials are prepared in advance by the hospital pharmacy (or elsewhere) it is important that the contents of the phials are indistinguishable and that the phials are identical in shape, instruction label, and seal. The code should identify the phial as for use by patient number 4 in study week 1, say, and should give no clue, however vague, as to the contents of the phial. If two treatments are compared, do not describe these on the phials as treatments A, B since the doctor then has a 50% chance of guessing correctly the assignment for every patient—all he has to do is match code A to the correct treatment. It is also important that if the labelled phials are released by the pharmacy or by a drug company to individual doctors that advice is given about the expiry date of the drugs and about batch numbers if more than one batch has been supplied. It would be most unfortunate if a delay in starting the trial meant that some patients received out-of-date medicines. It is also important to register trial patients formally, either locally or with a central co-ordinator, so that there is no opportunity for substituting one patient for another.



(iii) A central randomisation office removes from individual hospitals or doctors the chore of administering the randomisation and safeguards the scheme from the curious and the ingenious. Telephone randomisation works well provided (*a*) that the randomisation office is manned during well-publicised and agreed hours so that doctors are not kept waiting when they telephone with details about an eligible patient; and (*b*) that the clerk notes the patient's name, the hospital, the name of the doctor who makes the call, and checks the patient's eligibility for the trial. The treatment assignment will then be given out for that patient and registered by the clerk. The date of the telephone call is the date of registration in the trial. Details are then confirmed in writing by the doctor, who submits an on-study form for the patient.



References

1 Zelen M. The randomisation and stratification of patients to clinical trials. *J Chron Dis* 1974;**27**:365-75.
2 Efron B. Forcing a sequential experiment to be balanced. *Biometrika* 1971;**58**:403-17.
3 White SJ, Freedman LS. Allocation of patients to treatment groups in a controlled clinical study. *Br J Cancer* 1978;**37**:434-47.
4 Zelen M. A new design for randomized clinical trials. *N Engl J Med* 1979;**300**:1242-5.
5 Schwartz D, Flamant R, Lellouch J. Randomisation. *Clinical trials*. London: Academic Press, 1980.
6 Willoughby CP, Heyworth MF, Piris J, Truelove SC. Comparison of disodium cromoglycate and sulphasalazine as maintenance therapy for ulcerative colitis. *Lancet* 1979;i:119-22.

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