Much work still needs to be done to achieve this. To be useful in health policy at this level, all the targets need to be elaborated further and clear, practical statements must be made on their operation—especially the four targets on health policy and sustainable health systems. The WHO should stimulate the discussion of these important targets, but it should also be careful about being too prescriptive about health systems since this could be counterproductive.

In addition, more attention should be given to the usefulness of the targets in member states. One way of doing this is to rank the countries by target and to divide them into three groups. A specific level could be set for each group. For example, for target 2, three such groups could be distinguished as follows:

- Countries that have already achieved this target
- Countries for which the global target is achievable and challenging
- Countries that find the global target hard to achieve and therefore "demotivating."

The first group needs stricter target levels, and the third group less stringent ones. If a breakdown of this kind is made for each target, some countries may be classified in different groups for different targets. In this way, the targets will provide an insight into the health status of the population and could be useful for policy makers in member states in encouraging action and allocating their resources.

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Statistics notes

How to randomise

Douglas G Altman, J Martin Bland

We have explained why random allocation of treatments is a required feature of controlled trials.[1] Here we consider how to generate a random allocation sequence.

Almost always patients enter a trial in sequence over a prolonged period. In the simplest procedure, simple randomisation, we determine each patient's treatment at random independently with no constraints. With equal allocation to two treatment groups this is equivalent to tossing a coin, although in practice coins are rarely used. Instead we use computer generated random numbers. Suitable tables can be found in most statistics textbooks. The table shows an example[2]: the numbers can be considered as either random digits from 0 to 9 or random integers from 0 to 99.

For equal allocation to two treatments we could take odd and even numbers to indicate treatments A and B respectively. We must then choose an arbitrary place to start and also the direction in which to read the table. The first 10 two digit numbers from a starting place in column 2 are 85 80 62 36 96 56 17 17 23 87, which translate into the sequence A B B B B B A A A A for the first 10 patients. We could instead have taken each digit on its own, or numbers 00 to 49 for A and 50 to 99 for B. There are countless possible strategies; it makes no difference which is used.

We can easily generalise the approach. With three groups we could use 01 to 33 for A, 34 to 66 for B, and 67 to 99 for C (00 is ignored). We could allocate treatments A and B in proportions 2 to 1 by using 01 to 66 for A and 67 to 99 for B.

At any point in the sequence the numbers of patients allocated to each treatment will probably differ, as in the above example. But sometimes we want to keep the numbers in each group very close at all times. Block randomisation (also called restricted

ICRF Medical Statistics Group, Centre for Statistics in Medicine, Institute of Health Sciences, Oxford OX3 7LF

Douglas G Altman, *professor of statistics in medicine*

Department of Public Health Sciences, St George's Hospital Medical School, London SW17 0RE

J Martin Bland, *professor of medical statistics*

Correspondence to: Professor Altman.

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Excerpt from a table of random digits.[2] The numbers used in the example are shown in bold

89	11	77	99	94
35	83	73	68	20
84	**85**	95	45	52
56	**80**	93	52	82
97	**62**	98	71	39
79	**36**	13	72	99
34	**96**	98	54	89
69	**56**	88	97	43
09	**17**	78	78	02
83	**17**	39	84	16
24	**23**	36	44	14
39	**87**	30	20	41
75	18	53	77	83
33	93	39	24	81
22	52	01	86	71

randomisation) is used for this purpose. For example, if we consider subjects in blocks of four at a time there are only six ways in which two get A and two get B:

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

We choose blocks at random to create the allocation sequence. Using the single digits of the previous random sequence and omitting numbers outside the range 1 to 6 we get 5 6 2 3 6 6 5 6 1 1. From these we can construct the block allocation sequence B A B A / B A A B / A B A B / A B B A / B A A B, and so on. The numbers in the two groups at any time can never differ by more than half the block length. Block size is normally a multiple of the number of treatments. Large blocks are best avoided as they control balance less well. It is possible to vary the block length, again at random, perhaps using a mixture of blocks of size 2, 4, or 6.

While simple randomisation removes bias from the allocation procedure, it does not guarantee, for example, that the individuals in each group have a similar age distribution. In small studies especially some chance imbalance will probably occur, which might complicate the interpretation of results. We can use stratified randomisation to achieve approximate balance of important characteristics without sacrificing the advantages of randomisation. The method is to produce a separate block randomisation list for each subgroup (stratum). For example, in a study to compare two alternative treatments for breast cancer it might be important to stratify by menopausal status. Separate lists of random numbers should then be constructed for premenopausal and postmenopausal women. It is essential that stratified treatment allocation is based on block randomisation within each stratum rather than simple randomisation; otherwise there will be no control of balance of treatments within strata, so the object of stratification will be defeated.

Stratified randomisation can be extended to two or more stratifying variables. For example, we might want to extend the stratification in the breast cancer trial to tumour size and number of positive nodes. A separate randomisation list is needed for each combination of categories. If we had two tumour size groups (say ≤ 4 and >4cm) and three groups for node involvement (0, 1-4, >4) as well as menopausal status, then we have $2 \times 3 \times 2 = 12$ strata, which may exceed the limit of what is practical. Also with multiple strata some of the combinations of categories may be rare, so the intended treatment balance is not achieved.

In a multicentre study the patients within each centre will need to be randomised separately unless there is a central coordinated randomising service. Thus "centre" is a stratifying variable, and there may be other stratifying variables as well.

In small studies it is not practical to stratify on more than one or perhaps two variables, as the number of strata can quickly approach the number of subjects. When it is really important to achieve close similarity between treatment groups for several variables minimisation can be used—we discuss this method in a separate Statistics note.[3]

We have described the generation of a random sequence in some detail so that the principles are clear. In practice, for many trials the process will be done by computer. Suitable software is available at http://www.sghms.ac.uk/phs/staff/jmb/jmb.htm.

We shall also consider in a subsequent note the practicalities of using a random sequence to allocate treatments to patients.

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One hundred years ago

Generalisation of salt infusions

The subcutaneous infusion of salt solution has proved of great benefit in the treatment of collapse after severe operations. The practice, it may be said, developed from two sources: the new method of transfusion where water, instead of another person's blood, is injected into the patient's veins; and flushing of the peritoneum, introduced by Lawson Tait. After flushing, much of the fluid left in the peritoneum is absorbed into the circulation, greatly to the patient's advantage. Dr. Clement Penrose has tried the effect of subcutaneous salt infusions as a last extremity in severe cases of pneumonia. He continues this treatment with inhalations of oxygen. He has had experience of three cases, all considered hopeless, and succeeded in saving one. In the other two the prolongation of life and the relief of symptoms were so marked that Dr. Penrose regretted that the treatment had not been employed earlier. Several physicians have adopted Dr. Penrose's method, and with the most gratifying results. The cases are reported fully in the *Bulletin of the Johns Hopkins Hospital* for July last. The infusions of salt solution were administered just as after an operation. The salt solution, at a little above body temperature, is poured into a graduated bottle connected by a rubber tube with a needle. The pressure is regulated by elevating the bottle, or by means of a rubber bulb with valves; the needle is introduced into the connective tissue under the breast or under the integuments of the thighs. There can be no doubt that subcutaneous saline infusions are increasing in popularity, and little doubt that their use will be greatly extended in medicine as well as surgery.

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