Statistics in Question

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ASSESSING CLINICAL TRIALS—SIMPLE RANDOMISATION

Simple randomisation (equivalent to tossing a coin) is the most elementary and probably the most common randomisation procedure in practice (but is not always the best choice: see question 19). Every ploy for guessing the next assignment is equally useless against simple randomisation. Statistical theory determines that the ratio of the number of allocations to each treatment will approach its target as the number of patients increases indefinitely.

Unequal randomisation may be recommended in a wide range of clinical trials in which two treatments are compared: no serious loss of efficiency results from assigning an increased proportion of patients to the experimental treatment (provided the target treatment ratio is not more extreme than 2:1), and there are two advantages—greater clinical experience of the new treatment (compliance, toxicity, etc) is achieved and a more precise estimation of its outcome can be made.

(17) Use the table of random numbers to determine random treatment assignments for the first 30 patients who enter a clinical trial to compare ordinary spectacles and contact lenses for patients with myopia.

COMMENT

The first step in determining random treatment assignments is to set up a correspondence between numbers and treatments. Let odd numbers correspond to ordinary spectacles, and even numbers correspond to contact lenses. The second step is to

determine a convenient systematic way of reading the table of random numbers. The layout reproduced here makes it sensible to use a column of two-digit numbers—for example, 78, 38, 37—and to read down the column.

The third step is to select a starting point. Using a pin I chose *50. For illustration only a fragment from a table of random numbers is reproduced here. Do not use this fragment in practice; consult a more extensive table, select one from the several pages of random numbers therein, and choose a starting point on that page. These selections need not be made in a strictly random fashion—the use of a pin is not unusual, for

Table of random numbers

25 85	52 40	80 50	80 78	58 42	11 31	85 77	77 25	16 08	54 37
58 73	38 58	78 92	12 38	43 41	31 77	97 30	33 45	00 17	60 25
66 04	44 17	00 38	61 37	54 84	38 54	05 96	18 96	20 83	65 29
96 22	27 19	23 83	09 18	22 67	17 31	63 08	80 18	68 08	47 88
29 70	86 38	78 04	51 58	31 92	12 30	98 81	53 09	07 63	23 16
83 86	48 37	00 91	51 91	62 88	04 62	94 63	12 46	51 12	55 22
24 10	43 44	80 33	91 59	46 71	46 72	33 99	13 16	51 34	84 49
26 45	22 19	59 42	70 02	*50 23	78 14	24 16	86 33	37 11	65 36
59 58	24 97	89 51	48 61	85 92	95 83	36 62	06 90	17 23	92 17
14 18	83 76	52 64	91 14	70 66	74 05	47 54	26 81	32 14	91 27
27 70	78 05	51 37	28 77	39 03	63 18	66 74	90 45	23 47	49 80
98 13	78 10	97 38	27 61	27 91	81 70	55 28	35 37	45 76	48 82
94 08	72 66	37 34	44 45	32 26	04 37	80 55	29 88	65 99	63 64
49 76	05 70	91 47	21 85	45 96	57 06	08 49	03 91	19 89	87 10
17 55	25 70	35 57	96 81	80 91	91 05	56 31	55 22	15 63	67 57
57 83	92 42	51 67	49 06	19 44	23 43	39 33	65 52	69 76	98 66
54 36	96 45	91 71	43 43	93 04	71 90	40 81	82 26	56 84	31 32
95 36	83 47	04 07	56 30	59 82	14 82	28 69	27 22	19 47	18 08
61 12	39 28	72 79	97 30	82 43	58 53	40 49	99 71	09 76	60 35
26 27	83 09	88 15	45 34	19 86	67 13	18 50	45 33	02 48	34 58
45 24	50 85	51 89	13 09	85 23	33 26	92 73	47 94	81 86	25 94
44 77	24 50	96 30	18 51	79 05	26 81	87 43	50 71	99 55	32 09
19 79	28 20	23 65	41 96	95 76	81 06	28 11	36 66	67 16	33 42
55 17	44 90	96 22	30 63	61 12	03 95	62 40	29 69	40 05	50 67
73 57	60 29	70 47	76 17	78 45	18 43	68 24	02 39	16 40	86 60
89 02	98 00	17 62	52 94	92 56	80 00	00 26	31 95	24 34	84 41
82 02	00 81	89 86	31 61	31 23	38 70	16 15	93 06	97 44	33 63
52 01	93 94	50 55	19 39	99 45	33 41	40 40	71 54	95 11	19 13
64 80	82 89	45 39	32 76	89 53	80 65	64 77	23 81	89 46	93 31
76 83	74 73	25 33	78 96	68 49	40 11	35 36	17 50	41 41	46 02
16 71	31 07	82 88	89 96	44 21	38 20	**22 77	23 29	83 14	38 06
98 90	44 87	42 03	23 23	87 14	30 08	25 17	46 51	03 58	46 62
34 95	90 75	63 46	67 53	13 59	91 93	58 51	43 69	78 88	37 65
30 27	22 59	07 85	95 97	61 29	31 56	45 21	26 71	99 13	31 37
00 08	48 54	49 72	89 48	59 49	15 41	70 48	69 97	49 77	29 22
33 57	45 38	37 68	28 69	03 29	50 80	59 48	61 60	85 08	65 40
54 34	43 44	14 00	94 50	87 57	68 15	08 20	25 55	19 37	75 38
74 21	68 80	20 75	39 51	58 77	39 47	93 74	54 29	26 18	18 59
65 09	82 46	75 80	58 91	62 39	49 97	01 57	90 83	82 44	47 34
10 43	48 61	60 65	96 45	17 33	03 50	78 26	85 72	61 01	67 75
01 94	95 31	34 40	15 77	57 25	94 76	77 95	34 61	57 90	84 91
57 72	84 03	52 33	45 45	54 58	76 24	11 70	47 64	31 34	00 52
85 89	47 95	04 23	30 42	91 63	50 27	31 88	37 53	93 46	14 34
11 43	25 72	26 18	52 81	68 53	65 65	62 77	29 63	81 17	21 73
73 62	52 21	84 78	63 17	45 28	35 53	60 79	80 43	87 65	80 44
55 91	18 37	95 71	45 13	16 10	65 76	74 52	87 59	10 93	00 48
26 40	72 27	23 11	80 68	17 82	54 90	09 34	15 03	92 54	62 71
28 53	58 92	62 13	56 50	36 18	96 48	96 31	03 67	94 99	60 37
39 70	30 58	87 42	52 62	06 97	20 58	52 63	22 29	13 57	34 10
75 78	85 97	01 92	55 74	85 83	02 12	07 93	32 86	31 21	41 32

example—but steps one, two, and three should be fully documented so that the randomisation can be followed or continued by a colleague. Randomisation by flipping a coin or tossing a die is not recommended because it cannot be checked or reproduced.

The fourth step is to make the treatment assignments accord-

Treatment: ordinary spectacles or CONTACT LENSES

ordinary, ordinary, ordinary, ordinary, ordinary

Even if the last 5 patients were assigned to ordinary spectacles the probability remains $\frac{1}{2}$ that the next patient receives ordinary spectacles (every guessing strategy is equally useless)

ing to the system defined above. Thus I assign patients 1 to 30 as follows:

Patient	Random number	Assignment
1	50	CONTACT LENSES
2	85	ordinary spectacles
3	70	CONTACT LENSES
4	39	ordinary spectacles
5	27	ordinary spectacles
6	32	CONTACT LENSES
7	45	ordinary spectacles
8	90	CONTACT LENSES
9	19	ordinary spectacles
10	93	ordinary spectacles
11	59	ordinary spectacles
12	82	CONTACT LENSES
13	19	ordinary spectacles
14	85	ordinary spectacles
15	79	ordinary spectacles
16	95	ordinary spectacles
17	61	ordinary spectacles
18	78	CONTACT LENSES
19	92	CONTACT LENSES
20	31	ordinary spectacles
21	99	ordinary spectacles
22	89	ordinary spectacles
23	68	CONTACT LENSES
24	44	CONTACT LENSES
25	87	ordinary spectacles
26	13	ordinary spectacles
27	61	ordinary spectacles
28	59	ordinary spectacles
29	03	ordinary spectacles
30	67	ordinary spectacles

The above random assignment results in nine patients only being given contact lenses out of the first 30 who are registered in the trial. Such an unequal allocation is not unusual when simple randomisation is used to assign treatments to a small number of patients.

If there were only 30 patients in the trial then in practice the above assignment would be rejected in its entirety and the simple randomisation procedure repeated until a more balanced assignment was achieved—acceptable limits of imbalance would usually be predetermined—[12:18], say—or a method of restricted randomisation would be used (see next article). To repeat the simple randomisation continue reading down the same column—58, 62, 17—and then from the top of the next column—42, 41, 84—down to 91, 44, 04; this second randomisation assigns contact lenses to 13 patients, ordinary spectacles to 17—a more respectable divide, which would be retained as a practical assignment if the target number of patients for the trial were only 30.

Suppose that the instruction had been to assign patients to one of three treatments: ordinary spectacles, bifocal spectacles, or contact lenses. A correspondence between two-digit numbers and treatments has to be established. One simple scheme is:

00-29 ordinary spectacles
30-59 bifocal spectacles
60-89 contact lenses
90-99 IGNORE

Notice that it is convenient to use only the numbers 00-89, which are divided into three sets of 30 numbers each. Equal weight is thereby given to each treatment. The numbers 90-99 are ignored.

(18) Reassign the 30 patients in question 17 in the ratio 3:2—contact lenses versus ordinary spectacles.

—three out of five patients should be assigned to contact lenses

—set up a correspondence between numbers and treatments

COMMENT

Three out of five patients should be assigned to contact lenses. Let the correspondence between two-digit numbers and treatments be:

00-59 contact lenses
60-99 ordinary spectacles

Read down columns of two-digit random numbers. I begin at **22, 25, 58. Treatment assignments for the first 30 patients are as follows:

Patient	Random number	Assignment
1	22	CONTACT LENSES
2	25	CONTACT LENSES
3	58	CONTACT LENSES
4	45	CONTACT LENSES
5	70	ordinary spectacles
6	59	CONTACT LENSES
7	08	CONTACT LENSES
8	93	ordinary spectacles
9	01	CONTACT LENSES
10	78	ordinary spectacles
11	77	ordinary spectacles

12	11	CONTACT LENSES
13	31	CONTACT LENSES
14	62	ordinary spectacles
15	60	ordinary spectacles
16	74	ordinary spectacles
17	09	CONTACT LENSES
18	96	ordinary spectacles
19	52	CONTACT LENSES
20	07	CONTACT LENSES
21	77	ordinary spectacles
22	30	CONTACT LENSES
23	96	ordinary spectacles
24	08	CONTACT LENSES
25	81	ordinary spectacles
26	63	ordinary spectacles
27	99	ordinary spectacles
28	19	CONTACT LENSES
29	62	ordinary spectacles
30	54	CONTACT LENSES

The actual assignment—contact lenses 16 patients: ordinary spectacles 14 patients—is happily close to the target of 3:2.

(19) *When are there disadvantages in using simple randomisation?*

—if the eventual trial size is less than 100 patients

—in multicentre trials

—if interim analyses are planned

COMMENT

In trials of fewer than 100 patients simple randomisation may too easily result in gravely unequal treatment numbers. One reason why the randomisation list should be prepared in advance of the trial is so that a discrepant allocation can be spotted and an alternative randomisation selected with a more balanced assignment (advice which is pragmatic, not puristic).

Small trials		
The probability of discrepant allocation when 30 patients are assigned by simple randomisation to two treatments is as follows:		
Group sizes		Probability
15	15	0.144
14	16	0.271
13	17	0.223
12	18	0.161
11	19	0.102
10	20	0.056
9	21	0.027
8	22	0.011
7	23 or worse	0.005
		The probability of discrepancy [11,19] or worse is 0.20

The investigator who adopts simple randomisation for a small trial cannot forestall a chance imbalance on some major factor affecting prognosis. For example, in a trial to compare home treatment with sanatorium treatment in tuberculosis patients in Madras¹ 37 (46%) out of 80 patients who were randomised simply to drug treatment at home had extensive cavitation compared with only 22 (28%) of the 79 patients given the same treatment in a sanatorium. Later trials stratified by this important variable—that is, they ensured that patients with extensive cavitation were represented equally in all treatment groups and, likewise, that the proportion of patients with lesser cavitation was also similar across all treatment groups.

A single simple randomisation list cannot be recommended for multicentre trials because even when treatment numbers are balanced over the trial as a whole patients may be unequally allocated between treatments at individual hospitals, which is irksome to those hospitals and seems careless when the trial is reported.

Interim analyses may include far fewer numbers of patients than the eventual report. Although simple randomisation may serve well for the trial as a whole, treatment numbers or the distribution of patient characteristics may be decidedly unequal at the first and perhaps later interim analyses, which become handicapped as a consequence. The problem of imbalance on some patient variable at interim analysis occurs with other randomisation schemes too. A trial of neutron treatment in patients with head and neck cancer is in progress at the Medical Research Council Cyclotron Unit in Edinburgh. Patients are stratified by the site of the primary tumour and by the presence or absence of nodes before restricted randomisation (see next article) to neutron or photon treatment. At the first and second interim review treatment groups were well balanced on these important prognostic variables (as intended) but the ratio of men to women patients was different on the two treatment arms at the first analysis and had not resolved by the second review.

	1st review (Aug 1979)		2nd review (Oct 1980)	
	Photon	Neutron	Photon	Neutron
No of men	15	25	22	35
No of women	15	3	23	9
Total	30	28	45	44

The disadvantages inherent in simple randomisation show the need for methods of restricted and stratified randomisation, which are discussed in the next article.

I am grateful to Professor David F Kerridge for permission to reproduce the table of random numbers from *Tables and Formulae*. I am also grateful to Professor W Duncan and Miss G R Kerr for permission to mention the trial of neutron treatment in patients with head and neck cancer.

Reference

- ¹ Tuberculosis Chemotherapy Centre, Madras. A concurrent comparison of home and sanatorium treatment of pulmonary tuberculosis in South India. *Bull WHO* 1959; **21**: 51-144.

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Letter from . . . Chicago

No bed of roses

GEORGE DUNEA

During the religious strife of the eighth century the Byzantine iconoclast emperors destroyed the icons of the church and persecuted image worship with a zeal that was frequently mollified by nothing less than a plateful of noses. The founder of the dynasty, Leo the Isaurian, had been an obscure itinerant pedlar, who was driving his donkey to the market when a soothsayer promised him the Roman Empire on condition that he should abolish the worship of idols. His son, Constantine V, may well have been a most capable emperor, yet posterity has painted him as a monster; and we read that, while one may excuse the infant for the pollution of his baptismal font (which later earned him the surname Copronymus), one can hardly forgive the adult, whose "lust confounded the eternal distinction of sex and species" and whose "reign was a long butchery of whatever was most noble, or holy, or innocent."¹

Medical iconoclasts

In modern times the iconoclasts have become less fearsome, but their tribe has proliferated, and their zeal has remained undaunted. And now, since "iconoclasm has become a public fashion" and "the position of the doctor is no longer as unassailable or deific as in the past," we find Mrs Cynthia S Smith, publisher of *Medical/Mrs*, joining the ranks of the medical iconoclasts by writing about the "bitter disillusionment, aching loneliness, and degrading loss of respect" of *Doctors' Wives*, and the cruel, shockingly egotistical and irresponsible insensitivity of their husbands—"For we either strike down our idols or reduce them to the approachable category of mere men."²

Mrs Smith excludes from her analysis the dermatologists, anaesthetists, radiologists, pathologists, ophthalmologists, and academic physicians, who "lead orderly programmed, nine-to-five lives" and rarely develop "the arrogant pomposity of the God complex." But the others are in for a rough analysis, for they

lead busy lives full of tension and pressure, spending long hours at playing God and making decisions about life and death, which all too soon goes to their heads, especially as their patients are immensely grateful, the relatives all but kiss their ring, the nurses stand to attention, and the administrators avoid ruffling their feathers. And so they receive little sympathy from Mrs Smith, these splendid but inexperienced young gods, let loose into the world after years of scholastic seclusion, secure in their belief that they can do no wrong, so perfect that they cannot help but abandon the young wives who had put them through medical school, or seduce the occasional nurse, or even make a pass at their patients. And all this time they remain supremely arrogant, pompous, self-centered, insensitive to women's needs, emotionally incompetent and sexually illiterate, forever leering and snickering about sex, and convinced that men should reach orgasm in 20 seconds while the woman may be left to her own devices.

Pity then, not the mother who can still talk with pride about "my son, the doctor," but the poor wife, unhappy and lonely in her ermine jacket, for she has all too soon discovered that marriage to a doctor is no bed of roses. She is sexually frustrated, because her husband is too tired, too bored, or too sexually illiterate. She is emotionally deprived, because her God, who "spends his days and nights among unclad and semiclad doting women," would rather spend his evenings with journals or committees than with wives and children. She is being deceived because she cannot compete with the young nurses in the drama of the "totally primitive" highly sexually charged environment of the operating room, with its danger and blood and power, the surgeon "conquering the man or woman on the table," "the covered faces of the nurses leaving eloquent eyes exposed," "the large group of people skilfully choreographed to perform in perfect harmony," so that "the man who isn't turned on by surgery is either a liar or a eunuch." And so the wife is left lonely and miserable, object of her neighbours' "new hostility to medicine," vulnerable to drugs and alcohol, or finding solace in adultery or women's liberation. Most pitiable of all are the psychiatrists' wives, clearly at fault for being hostile, depressed, obsessed, compulsive, conflicted, euphoric, schizophrenic, passive-aggressive, oedipal, defensive, or psychosomatic—leading our iconoclast editor to suggest that few things are worse than to be the psychologically battered wife of a psychiatrist in Scarsdale.

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