

## Epidemiology series

# Generation of allocation sequences in randomised trials: chance, not choice

Kenneth F Schulz, David A Grimes

The randomised controlled trial sets the gold standard of clinical research. However, randomisation persists as perhaps the least-understood aspect of a trial. Moreover, anything short of proper randomisation courts selection and confounding biases. Researchers should spurn all systematic, non-random methods of allocation. Trial participants should be assigned to comparison groups based on a random process. Simple (unrestricted) randomisation, analogous to repeated fair coin-tossing, is the most basic of sequence generation approaches. Furthermore, no other approach, irrespective of its complexity and sophistication, surpasses simple randomisation for prevention of bias. Investigators should, therefore, use this method more often than they do, and readers should expect and accept disparities in group sizes. Several other complicated restricted randomisation procedures limit the likelihood of undesirable sample size imbalances in the intervention groups. The most frequently used restricted sequence generation procedure is blocked randomisation. If this method is used, investigators should randomly vary the block sizes and use larger block sizes, particularly in an unblinded trial. Other restricted procedures, such as urn randomisation, combine beneficial attributes of simple and restricted randomisation by preserving most of the unpredictability while achieving some balance. The effectiveness of stratified randomisation depends on use of a restricted randomisation approach to balance the allocation sequences for each stratum. Generation of a proper randomisation sequence takes little time and effort but affords big rewards in scientific accuracy and credibility. Investigators should devote appropriate resources to the generation of properly randomised trials and reporting their methods clearly.

“... having used a random allocation, the sternest critic is unable to say when we eventually dash into print that quite probably the groups were differentially biased through our predilections or through our stupidity.”<sup>1</sup>

Until recently, investigators shunned formally controlled experimentation when designing trials (panel 1).<sup>2–5</sup> Now, however, the randomised controlled trial sets the methodological standard of excellence in medical research (panel 2).<sup>3,6</sup> The unique capability of randomised controlled trials to reduce bias depends on investigators being able to implement their principal bias-reducing technique—randomisation. Although random allocation of trial participants is the most fundamental aspect of a controlled trial,<sup>7</sup> it unfortunately remains perhaps the least understood.<sup>8,9</sup>

In this article, we describe the rationale behind random allocation and its related implementation procedures. Randomisation depends primarily on two interrelated but separate processes—ie, generation of an unpredictable randomised allocation sequence and concealment of that sequence until assignment occurs (allocation concealment). Here, we focus on how such a sequence can be generated. In a subsequent article, we will address allocation concealment.

## What to look for with sequence generation

*Non-random methods masquerading as random*

Ironically, many researchers have decidedly non-random impressions of randomisation.<sup>8–10</sup> They often mistake haphazard approaches and alternate assignment approaches as random.<sup>11</sup> Some medical researchers even

*Lancet* 2002; **359**: 515–19

Family Health International, PO Box 13950, Research Triangle Park, NC 27709, USA (K F Schulz PhD, D A Grimes MD)

Correspondence to: Dr Kenneth F Schulz (e-mail: KSchulz@fhi.org)

### Panel 1: History of randomised controlled trials

The controlled trial gained increasing recognition during the 20th century as the best approach for assessment of health care and prevention alternatives. R A Fisher<sup>2</sup> developed randomisation as a basic principle of experimental design in the 1920s, and used the technique predominantly in agricultural research. The successful adaptation of randomised controlled trials to health care took place in the late 1940s, largely because of the advocacy and developmental work of Sir Austin Bradford Hill (figure) while at the London School of Hygiene and Tropical Medicine.<sup>3</sup> His efforts culminated in the first experimental<sup>4</sup> and published<sup>5</sup> use of random numbers to allocate trial participants. Soon after, randomisation emerged as crucial in securing unbiased comparison groups.

Rights were not granted to include this image in electronic media. Please refer to the printed journal.

Austin Bradford Hill (1954)

The Wellcome Library, London

## Panel 2: Benefits of randomisation

Proper implementation of a randomisation mechanism affords at least three major advantages:

### *It eliminates bias in treatment assignment*

Comparisons of different forms of health interventions can be misleading unless investigators take precautions to ensure that their trial comprises unbiased comparison groups relative to prognosis. In controlled trials of prevention or treatment, randomisation produces unbiased comparison groups by avoiding selection and confounding biases. Consequently, comparison groups are not prejudiced by selection of particular patients, whether consciously or not, to receive a specific intervention. The notion of avoiding bias includes eliminating it from decisions on entry of participants to the trial, as well as eliminating bias from the assignment of participants to treatment, once entered. Investigators need to properly register each participant immediately on identification of eligibility for the trial, but without knowledge of the assignment. The reduction of selection and confounding biases underpins the most important strength of randomisation. Randomisation prevails as the best study design for study of small or moderate effects.<sup>6</sup>

### *It facilitates blinding (masking) of the identity of treatments from investigators, participants, and assessors, including the possible use of a placebo<sup>3</sup>*

Such manoeuvres reduce bias after random assignment, and would be difficult, perhaps even impossible, to implement if investigators assigned treatments by a non-random scheme.

### *It permits the use of probability theory to express the likelihood that any difference in outcome between treatment groups merely indicates chance*

view approaches antithetical to randomisation, such as assignment to intervention groups based on preintervention tests, as quasirandom.<sup>12</sup> Quasirandom, however, resembles quasipregnant, in that they both elude definition. Indeed, anything short of proper randomisation opens limitless contamination possibilities. Without properly done randomisation, selection and confounding biases seep into trials.<sup>7,13</sup>

Researchers sometimes cloak, perhaps unintentionally, non-random methods in randomised clothing. They think that they have randomised by a method that, when described, is obviously not random. Methods such as assignment based on date of birth, case record number, date of presentation, or alternate assignment are not random, but rather systematic occurrences. Yet in a study that we did,<sup>10</sup> in 5% (11 of 206) of reports investigators claimed that they had randomly assigned participants by such non-random methods. Furthermore, non-random methods are probably used much more frequently than suggested by our findings, since 63% (129 of 206) of the reports did not specify the method used to generate a random sequence.<sup>14</sup>

Systematic methods do not qualify as randomisation methods for theoretical and practical reasons. For example, in some populations, the day of the week on which a child is born is not entirely a matter of chance.<sup>15</sup> Furthermore, systematic methods do not result in allocation concealment. By definition, systematic allocation usually precludes adequate concealment, since it results in previous knowledge of treatment assignment among those who recruit participants to the trial. If researchers report the use of systematic allocation, especially if masqueraded as randomised, readers should be wary of the results, since such a mistake implies

ignorance of the randomisation process. We place more credence in the findings of such a study if the authors accurately report it as non-randomised and explain how they controlled for confounding factors. In such instances, researchers should also discuss the degree of potential selection and information biases, allowing readers to properly judge the results in view of the non-random nature of the study and its biases.

### *Method of generation of an allocation sequence*

To minimise bias, participants in a trial should be assigned to comparison groups based on some chance (random) process. Investigators use many different methods of randomisation,<sup>16–20</sup> the most predominant of which are described.

## Simple (unrestricted) randomisation

Elementary yet elegant describes simple randomisation (panel 3).<sup>21</sup> Although the most basic of allocation approaches, analogous to repeated fair coin-tossing, this method preserves complete unpredictability of each intervention assignment. No other allocation generation approach, irrespective of its complexity and sophistication, surpasses the unpredictability and bias prevention of simple randomisation.<sup>22</sup>

The unpredictability of simple randomisation, however, can also be a disadvantage.<sup>23</sup> With small sample sizes, simple randomisation (one-to-one allocation ratio) can yield highly disparate sample sizes in the groups by chance alone. For example, with a total sample size of 20, about 10% of the sequences generated with simple randomisation would yield a ratio imbalance of three to seven or worse.<sup>24</sup> This difficulty is diminished as the total sample size grows. Probability theory ensures that in the long term, the sizes of the treatment groups will not be greatly imbalanced. For a two-arm trial, the chance of pronounced imbalance becomes negligible with trial sizes greater than 200.<sup>24</sup> However, interim analyses with sample sizes of less than 200 might result in disparate group sizes.

Coin-tossing, dice-throwing, and dealing previously shuffled cards represent reasonable approaches for generation of simple complete randomisation sequences. All these manual methods of drawing lots theoretically lead to random allocation schemes, but frequently become non-random in practice. Distorted notions of randomisation

## Panel 3: Simple randomisation

An almost infinite number of methods can be used to generate a simple randomisation sequence based on a random-number table.<sup>21</sup> For example, for equal allocation to two groups, predetermine the direction to read the table: up, down, left, right, or diagonal. Then select an arbitrary starting point—ie, first line, 7th number:

```
56 99 20 20 52 49 05 78 58 50 62 86 52 11 88
31 60 26 13 69 74 80 71 48 73 72 18 60 58 20
55 59 06 67 02 ...
```

For equal allocation, an investigator could equate odd and even numbers to interventions A and B, respectively. Therefore, a series of random numbers 05, 78, 58, 50, 62, 86, 52, 11, 88, 31, &c, represent allocation to intervention A, B, B, B, B, B, B, A, B, A, &c. Alternatively, 00–49 could equate to A and 50–99 to B, or numbers 00–09 to A and 10–19 to B, ignoring all numbers greater than 19. Any of a myriad of options suffice, provided the assignment probabilities and the investigator adhere to the predetermined scheme.

sabotage the best of intentions. Fair coin-tossing, for example, allocates randomly with equal probability to two intervention groups, but can tempt investigators to alter the results of a toss or series of tosses—eg, when a series of heads and no tails are thrown. Many investigators do not really understand probability theory, and they perceive randomness as non-random. For example, the late Chicago baseball announcer Jack Brickhouse used to claim that when a 0.250 hitter (someone who would have a successful hit a quarter of the time) stroled to the plate for the fourth time, having failed the previous three times, that the batsman was “due”—ie, that the hitter would surely get a hit. However, Jack’s proclamation “he is due” portrayed a non-random interpretation of randomness. Similarly, a couple who have three boys and want a girl often think that their fourth child will certainly be a girl, yet the probability of them actually having a girl is still about 50%.

A colleague regularly demonstrated distorted views of randomisation with his graduate school class. He would have half his class develop allocation schemes with a proper randomisation method, and get the other half to develop randomisation schemes based on their personal views of randomisation. The students who used a truly random method would frequently have long consecutive runs of one treatment or the other. Conversely, students who used their own judgment would not. Class after class revealed their distorted impressions of randomisation.

Moreover, manual methods of drawing lots are more difficult to implement and cannot be checked. Because of threats to randomness, difficulties in implementation, and lack of an audit trail, we recommend that investigators avoid use of coin-tossing, dice-throwing, or card-shuffling, despite them being acceptable methods. Whatever method is used, however, should be clearly indicated in a researcher’s report. If no such description is made, readers’ should treat the study results with caution. Readers should have the most confidence in a sequence generation approach if the authors mention referral to either a table of random numbers or a computer random number generator, since these options represent unpredictable, reliable, easy, reproducible approaches that provide an audit trail.

### Restricted randomisation

Restricted randomisation procedures control the probability of obtaining an allocation sequence with an undesirable sample size imbalance in the intervention groups.<sup>20</sup> In other words, if researchers want treatment groups of equal sizes, they should use restricted randomisation.

#### Blocking

Balanced (restricted) randomisation strives for unbiased comparison groups, but also strives for comparison groups of about the same size throughout the trial.<sup>23</sup> That attribute becomes helpful when investigators plan interim analyses. The use of simple randomisation might, upon occasion, produce quite disparate sample sizes at early interim analyses. Blocking obviates that problem.

The most frequently used method of achieving balanced randomisation is by random permuted blocks (blocking). For example, with a block size of six, of every six consecutively enrolled participants, three will normally be allocated to one treatment group and three to the other. However, the allocation ratio can be uneven. For example, a block size of six with a two-to-one ratio assigns four to one treatment group and two to the other in each block. This method can easily be extended to more than two treatments.

With blocking, the block size can remain fixed throughout the trial or be randomly varied. Indeed, if blocked randomisation is used in a trial that is not double-blinded, the block size should be randomly varied to reduce the chances of the assignment schedule being seen by those responsible for recruitment of participants.<sup>17</sup> If the block size is fixed, especially if small (six participants or less), the block size could be deciphered in a not double-blinded trial. With treatment allocations becoming known after assignment, a sequence can be discerned from the pattern of past assignments. Some future assignments could then be accurately anticipated, and selection bias introduced, irrespective of the effectiveness of allocation concealment. Longer block sizes—eg, ten or 20—rather than smaller block sizes—four or six—and random variation of block sizes help preserve unpredictability.<sup>17</sup>

Investigators who do randomised controlled trials frequently use blocking. Those who report simply that they blocked, however, should make readers sceptical. Researchers should explicitly report having used blocking, the allocation ratio (usually one-to-one), the random method of selection (for example, random number table or computer random number generator), and the block size (or sizes if randomly varied).

#### Random allocation rule

The random allocation rule is the simplest form of restriction. For a particular total sample size, it ensures equal sizes only at the end of the trial. Usually, investigators identify a total sample size and then randomly choose a subset of that sample to assign to group A; the remainder are assigned to group B. For example, for a total study size of 200, placing 100 group A balls and 100 group B balls in a hat and drawing them randomly without replacement symbolises the random allocation rule. The sequence generation would randomly order 100 group A and 100 group B assignments. This method represents one large permuted-block for the entire study, which means that balance would usually only arise at the end of the trial and not throughout.

The random allocation rule maintains many of the positive attributes of simple complete randomisation, especially for statistical analysis, but is more likely to yield a chance covariate imbalance (chance confounding). It is noteworthy that this difference becomes trivial with larger sample sizes.<sup>24</sup> Moreover, unpredictability suffers compared with simple complete randomisation. Particularly in a non-double-blinded trial, scope exists for introduction of selection bias through guessing of assignments (especially toward the end of the trial), but obviously not at the level of permuted-block randomisation with small block sizes.<sup>24,25</sup>

Investigators sometimes apply the random allocation rule by the restricted shuffled approach, which involves identifying the sample size, apportioning a number of specially prepared cards for each treatment according to the allocation ratio, inserting the cards into envelopes, and shuffling them to produce a form of random assignment without replacement.<sup>23</sup> Many investigators probably use this approach, but rarely call it restricted shuffled or the random allocation rule. Instead, they report use of envelopes or shuffling. Indeed, the restricted shuffled approach integrates, and conflates, allocation generation and concealment. Shuffling determines the allocation sequence, which is not optimum. Most importantly, the adequacy of the restricted shuffled approach pivots on proper allocation concealment with envelopes.<sup>7,8</sup>



*Biased coin and urn randomisation*

Biased-coin designs achieve much the same objective as blocking but without forcing strict equality.<sup>16,26</sup> They therefore preserve most of the unpredictability associated with simple randomisation. Biased-coin designs alter the allocation probability during the course of the trial to rectify imbalances that might be happening (panel 4). Adaptive bias-coin designs, with the urn design being the most widely studied, alter the probability of assignment based on the magnitude of the imbalance.

Biased-coin designs, including the urn design, appear infrequently in reports. They probably should, however, be used more often. Use of a computer is easier and more reliable than actually drawing balls from an urn, just as a computer is easier and more reliable than flipping a coin for simple randomisation. In unblinded trials, in which unpredictability becomes most important and the need for balance precludes simple randomisation, an urn design is especially useful. The unpredictability of urn designs surpasses permuted-block designs, irrespective of fixed or randomly varied block size approaches.<sup>26</sup> If readers encounter a biased-coin or urn design, they should consider it a proper sequence generation approach.

*Replacement randomisation*

Replacement randomisation repeats a simple randomisation allocation scheme until a desired balance is achieved. Trial investigators should establish objective criteria for replacement. For example, for a trial with 300 participants, investigators could specify that they would replace a simple randomisation scheme if the disparity between group sizes exceeds 20. If the first generated scheme's disparity exceeds 20, then they would generate an

**Panel 4: Biased-coin and urn randomisation**

Biased-coin approaches alter the allocation probability during the course of the trial to rectify imbalances in group numbers that might be happening. For example, investigators might use simple randomisation with equal probability of assignment—0.50/0.50 in a two-arm trial—as long as the disparity between the numbers assigned to the treatment groups remains below a prespecified limit. If the disparity reaches the limit, then investigators increase the probability of assignment to the group with the least participants—for example 0.60/0.40. Implemented properly, a biased-coin approach can achieve balance while preserving most of the unpredictability associated with simple randomisation.<sup>16</sup>

Adaptive bias-coin designs, with the urn design being the most widely studied, alter the probability of assignment based on the magnitude of the imbalance.<sup>26</sup> The urn design is designated as UD ( $\alpha$ ,  $\beta$ ), with  $\alpha$  being the number of blue and green balls initially and  $\beta$  representing the number of balls added to the urn of the opposite colour to the ball chosen ( $\alpha$  and  $\beta$  being any reasonable non-negative numbers). For example in UD (2,1), an urn contains two blue balls and two green balls—0.50/0.50 probabilities to begin ( $\alpha=2$ ). Balls are drawn at random and replaced for treatment assignments: blue for treatment A and green for treatment B. One additional ball ( $\beta=1$ ) of the opposite colour to the ball chosen is added to the urn. If a blue ball was chosen first, then two blue balls and three green balls would be in the urn after the first assignment—0.40/0.60 for the next assignment. If another blue was chosen second, then two blue balls and four green balls would be in the urn after the second assignment—0.33/0.67 for the next assignment. That drawing procedure repeats with each assignment. The allocation probabilities fluctuate with the previous assignments.

entirely new simple randomisation scheme to replace the first attempt and check it against their objective criteria for disparity. They would iterate until they have a simple randomisation scheme that meets their criteria. Although replacement randomisation seems somewhat arbitrary, it is adequate as long as it is implemented before the trial begins. Moreover, it is easy to implement, ensures reasonable balance, and yields unpredictability. The main limitation of replacement randomisation is that it cannot ensure balance throughout the trial for interim analyses. Though rarely used, this approach emerged as the earliest form of restricted randomisation.<sup>20,27</sup>

**Stratified randomisation**

Randomisation can create chance imbalances on baseline characteristics of treatment groups.<sup>28</sup> Investigators sometimes avert imbalances by use of prerandomisation stratification on important prognostic factors, such as age or disease severity. In such instances, researchers should specify the method of restriction (usually blocking). To reap the benefits of stratification, investigators must use a form of restricted randomisation to generate separate randomisation schedules for stratified subsets of participants defined by the potentially important prognostic factors. Stratification without restriction accomplishes nothing—ie, placebo stratification.

Stratification in trials is methodologically valid and useful, but theoretical and pragmatic issues limit its use to those planning new trials. The added complexity of stratification yields little additional gain in large trials, since randomisation creates balanced groups anyway. Moreover, if imbalance arises, then investigators can statistically adjust on those prognostic variables (preferably preplanned).<sup>28,29</sup> Of greatest concern is that the added complexity of stratifying might discourage collaborators from participating in the trial or from entering participants during busy clinics, either of which affects enrolment. Thus, stratification in large trials offers negligible advantages coupled with important, pragmatic disadvantages. Note one important exception, however: stratification by centre in multicentre trials promises some benefit with no added complexity to the trial implementers within each centre. Also, another potential exception arises in large multicentre trials in which investigators use central randomisation for implementation of the sequence. Central randomisation limits the practical disadvantages of stratification and some gains might be realised in centres with smaller sample sizes.

Stratification might be useful in small trials in which it can avert severe imbalances on prognostic factors. It will confer adequate balance (on the stratified factors) and probably slightly more statistical power and precision.<sup>17</sup> The gain from stratification becomes minimal, however, once the number of participants per group is more than 50.<sup>17</sup> Moreover, stratification can indirectly cause negative effects if investigators seek exact balance within small strata. To achieve that exact balance, investigators often use small, fixed block sizes, which, in turn, hurts unpredictability.

Minimisation incorporates the general notions of stratification and restricted randomisation.<sup>16</sup> It can be used to make small groups closely similar with respect to several characteristics. Minimisation in its strictest sense can be viewed as non-random,<sup>21</sup> but, if used, we prefer a random component. Minimisation has supporters<sup>30</sup> and detractors.<sup>22</sup> In any case, investigators who use minimisation should shield trial implementers from knowledge of upcoming assignments and other information that might facilitate guessing of upcoming assignments.<sup>16</sup>

## Separation of generation and implementation

Investigators often neglect, usually unintentionally, one other important element of randomised controlled trial design and reporting. With all approaches, the people who generated the allocation scheme should not be involved in ascertaining eligibility, administering treatment, or assessing outcome. Such an individual would usually have access to the allocation schedule and thus the opportunity to introduce bias.<sup>8</sup> Faults in this trial component might represent a crevice through which bias seeps into trials. Item ten (Implementation) in the CONSORT statement addresses this topic.<sup>28,31</sup> Researchers should, therefore, state in reports who generated the allocation sequence, who enrolled participants, and who assigned participants. The person generating the allocation mechanism should be different from the person(s) enrolling and assigning. Nevertheless, under some circumstances, an investigator might have to generate the scheme and also enrol or assign. In such instances, the investigator should ensure the unpredictability of the assignment schedule and lock it away from everyone, particularly himself or herself.

## Conclusion

Randomised controlled trials set the methodological standard of excellence in medical research. The key word is randomised, which must be done properly. Generation of a randomisation sequence takes little time and effort but affords big rewards in scientific accuracy and credibility. Investigators should devote appropriate resources to doing the generation properly and reporting their methods clearly.

We thank Willard Cates and David L Sackett for their helpful comments on an earlier version of this report. Much of the material stems from our 15 years of teaching the Berlex Foundation Faculty Development Course.

## References

- Hill AB. The clinical trial. *N Engl J Med* 1952; **247**: 133–19.
- Fisher RA. The Design of Experiments. London: Oliver and Boyo, 1935.
- Armitage P. The role of randomization in clinical trials. *Stat Med* 1982; **1**: 345–52.
- Doll R. Controlled trials: the 1948 watershed. *BMJ* 1998; **317**: 1217–20.
- Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. *BMJ* 1948; **2**: 769–82.
- Peto R. Why do we need systematic overviews of randomized trials? *Stat Med* 1987; **6**: 233–44.
- Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995; **273**: 408–12.
- Schulz KF. Subverting randomization in controlled trials. *JAMA* 1995; **274**: 1456–58.
- Schulz KF. Unbiased research and the human spirit: the challenges of randomized controlled trials. *CMAJ* 1995; **153**: 783–86.
- Schulz KF, Chalmers I, Grimes DA, Altman DG. Assessing the quality of randomization from reports of controlled trials published in obstetrics and gynecology journals. *JAMA* 1994; **272**: 125–28.
- Grimes DA. Randomized controlled trials: “it ain’t necessarily so”. *Obstet Gynecol* 1991; **78**: 703–04.
- Grimes D, Fraser E, Schulz K. Immunization as therapy for recurrent spontaneous abortion: a review and meta-analysis. *Obstet Gynecol* 1994; **83**: 637–38.
- Altman DG. Randomisation. *BMJ* 1991; **302**: 1481–82.
- Schulz KF, Chalmers I, Altman DG, Grimes DA, Dore CJ. The methodologic quality of randomization as assessed from reports of trials in specialist and general medical journals. *Online J Curr Clin Trials* 1995; Doc No 197: [81 paragraphs].
- MacFarlane A. Variations in number of births and perinatal mortality by day of week in England and Wales. *BMJ* 1978; **2**: 1670–73.
- Pocock SJ. Clinical trials: a practical approach. Chichester: Wiley, 1983.
- Meinert CL. Clinical trials: design, conduct, and analysis. New York: Oxford University Press, 1986.
- Friedman L, Furberg C, DeMets D. Fundamentals of clinical trials. St Louis: Mosby, 1996.
- Piantadosi S. Clinical trials: a methodologic perspective. New York: John Wiley and Sons, 1997.
- Lachin JM. Statistical properties of randomization in clinical trials. *Control Clin Trials* 1988; **9**: 289–311.
- Altman DG. Practical statistics for medical research. London: Chapman and Hall, 1991.
- Lachin JM, Matts JP, Wei LJ. Randomization in clinical trials: conclusions and recommendations. *Control Clin Trials* 1988; **9**: 365–74.
- Schulz KF. Randomized controlled trials. *Clin Obstet Gynecol* 1998; **41**: 245–56.
- Lachin JM. Properties of simple randomization in clinical trials. *Control Clin Trials* 1988; **9**: 312–26.
- Matts JP, Lachin JM. Properties of permuted-block randomization in clinical trials. *Control Clin Trials* 1988; **9**: 327–44.
- Wei LJ, Lachin JM. Properties of the urn randomization in clinical trials. *Control Clin Trials* 1988; **9**: 345–64.
- Cox DR. Planning of experiments. New York: Wiley, 1958.
- Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001; **134**: 663–94.
- Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I: introduction and design. *Br J Cancer* 1976; **34**: 585–612.
- Treasure T, MacRae KD. Minimisation: the platinum standard for trials? Randomisation doesn’t guarantee similarity of groups; minimisation does. *BMJ* 1998; **317**: 362–63.
- Moher D, Schulz KF, Altman DG, Lepage L. The CONSORT statement: revised recommendations for improving the quality of reports or parallel-group randomised trials. *Lancet* 2001; **357**: 1191–94.