ELSEVIER

Controlled Clinical Trials 23 (2002) 662–674

Controlled Clinical Trials

The method of minimization for allocation to clinical trials: a review

Neil W. Scott, M.A. (Hons), M.Sc.[a,*],
Gladys C. McPherson, B.Sc. (Hons), M.Sc.[b],
Craig R. Ramsay, B.Sc. (Hons), Ph.D.[b],
Marion K. Campbell, B.Sc. (Hons), M.Sc.[b]

[a]*Department of Public Health, University of Aberdeen, Aberdeen, UK*
[b]*Health Services Research Unit, University of Aberdeen, Aberdeen, UK*

Manuscript received May 1, 2002; manuscript accepted July 26, 2002

Abstract

Minimization is a largely nonrandom method of treatment allocation for clinical trials. We conducted a systematic literature search to determine its advantages and disadvantages compared with other allocation methods. Minimization was originally proposed by Taves and by Pocock and Simon. The latter paper introduces a family of allocation methods of which Taves' method is the simplest example. Minimization aims to ensure treatment arms are balanced with respect to predefined patient factors as well as for the number of patients in each group. Further extensions of the method have also been proposed by other authors. Simulation studies show that minimization provides better balanced treatment groups when compared with restricted or unrestricted randomization and that it can incorporate more prognostic factors than stratified randomization methods such as permuted blocks within strata. Some more computationally complex methods may give an even better performance. Concerns over the use of minimization have centered on the fact that treatment assignments may be predicted with certainty in some situations and on the implications for the analysis methods used. It has been suggested that adjustment should always be made for minimization factors when analyzing trials where minimization is the allocation method used. The use of minimization may sometimes result in added organizational complexity compared with other methods. Minimization has been recommended by many commentators for use in clinical trials. Despite this it is still rarely used in practice. From the evidence presented in this review, we believe minimization to be a highly effective allocation method and recommend its wider adoption in the conduct of randomized controlled trials.

Keywords: Minimization; Randomization; Clinical trials; Systematic review

* Corresponding author: Neil W. Scott, Department of Public Health, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen AB25 2ZD, United Kingdom. Tel.: +44-1224-559766; fax: +44-1224-662994.
E-mail address: n.w.scott@abdn.ac.uk

PII: S0197-2456(02)00242-8

Introduction

The randomized controlled trial is commonly accepted as the gold standard research method for evaluating health care interventions. Fundamental to its design is that participants are allocated to treatment and control groups at random, thereby controlling selection bias.

In any clinical trial it is desirable not only to achieve similar numbers of patients in each treatment group but also to ensure that patient groups are similar with respect to prognostic factors such as age or stage of disease. Simple (unrestricted) randomization will very often achieve well-balanced groups, especially in larger trials, but there is always a risk that chance imbalances in baseline characteristics will occur. In order to guard against this, stratified randomization has often been employed. This attempts to achieve groups with similar patient characteristics by balancing patient intake into each combination of patient factors, the assignment within strata being made either by simple randomization or by using permuted blocks. However, stratified randomization becomes unworkable as the number of prognostic factors increases, because the number of strata required can quickly exceed the number of patients in the trial [1].

Minimization is a largely nonrandom method of treatment allocation for clinical trials whose use has been recommended by many commentators as a valid alternative to stratified randomization. Our aim was to conduct a systematic literature search on the method of minimization to ascertain the extent of its current use and to determine its advantages and disadvantages compared with other allocation methods.

Methods

An initial search strategy was developed for the MEDLINE database. A selection of papers that had been previously identified opportunistically was used to identify appropriate medical subject headings and text words. The final search strategy was primarily driven by text words, mainly due to the fact that the indexing of methodological papers is less well developed within MEDLINE than that for actual studies. We limited the search to English-language journals published between 1966 and 2000.

Citation searches for the original articles on minimization were also undertaken using the Science Citation Index on Institute for Scientific Information (ISI) Web of Science [2,3]. Personal reference sources were also explored.

Finally, reference lists of identified papers were searched to locate further articles relevant to the topic. This search was not limited to "first-generation" papers as the reference lists of newly identified papers were also searched. Other identified literature relevant to the review was also included where appropriate.

All articles were initially assessed for relevance by one of the four authors and later reviewed in more detail by two authors (G.M. and N.S.). A total of 71 articles were assessed.

To determine the current use of minimization, we additionally reviewed all reports of randomized controlled trials published in the *Lancet* and the *New England Journal of Medicine* during 2001.

The minimization method

Description of minimization

The minimization method was described independently in articles by Taves [2] and Pocock and Simon [3]; Taves' article coined the term "minimization." Important prognostic factors are identified before the trial starts and assignment of a new patient to a treatment group is determined so as to minimize the differences between the groups in terms of these factors. Unlike stratified randomization, minimization works toward minimizing the total imbalance for all factors together instead of considering mutually exclusive subgroups. Table 1 demonstrates how minimization works by considering a hypothetical trial with 16 patients already recruited. If the 17th patient considered is male, aged 38 and with a high risk factor, the decision to allocate to the treatment or control group can be made by comparing the totals for each category and choosing the group that gives most balance overall: in this case the patient would be assigned to the intervention group.

Pocock and Simon define a more general method where treatment assignment depends on three functions [3]: the amount of variation among assignments for any given factor level (D), a measure of the total imbalance in treatment numbers (G), and assignment probabilities to the k arms of the trial $\{p_i\}$ (where p_1 is the probability of assignment to the arm that would lead to the least overall imbalance). D can be determined by the standard deviation, variance,

Table 1. Example of how minimization works using hypothetical trial data

Prognostic factor	Intervention	Control
Sex		
Male	3	5
Female	5	3
Age band		
21–30	4	4
31–40	2	3
41–50	2	1
Risk factor		
High	4	5
Low	4	3

If the 17th patient has factors Male, 31–40, High:

Taves' minimization
Total in intervention group, $3+2+4=9$.
Total in control group, $5+3+5=13$.
Patient allocated to the group with the lower marginal total.
Therefore 17th patient allocated to intervention group because $9<13$.

Pocock and Simon's range method (using unweighted sum and $p_1=1$)
If allocated to intervention group, total imbalance is $|(3+1)-5|+|(2+1)-3|+|(4+1)-5|=1$.
If allocated to control group, total imbalance is $|3-(5+1)|+|2-(3+1)|+|4-(5+1)|=7$.
Patient allocated to the group that would lead to less overall imbalance.
Therefore 17th patient allocated to intervention group because $1<7$.

range, an upper limit of acceptable imbalance or a sign rule, but the most commonly used are the range and variance methods. Total imbalance is usually calculated by taking the sum of the individual imbalances but a weighted sum can be used if some factors are considered more important than others. If $p_1=1$, the assignment is deterministic (as in Taves) and goes automatically to the treatment with least overall imbalance, but the $\{p_i\}$ can also be chosen to decrease the predictability of assignment. It can be shown that the variance method with G an unweighted sum and $p_1=1$ is equivalent to Taves' minimization method [4]. Table 1 provides a demonstration of how the range method works in practice.

Although the term "minimization" can be applied to any of Pocock and Simon's methods, it is most commonly used to refer to the special case described by Taves, which is less complicated to employ in practice. Minimization can be classified as a "dynamic allocation" or "covariate adaptive" method as the allocation depends on the characteristics of patients already recruited. This is distinct from "response adaptive" methods where the allocation can depend on the interim results of the study.

The method of Begg and Iglewicz extends Pocock and Simon's method by minimizing an approximation to the variance of the treatment effect [5]. Their method allows selected interactions to be included. The method of Atkinson also uses optimum design theory, but here the probability of allocation to the underrepresented treatment responds to increasing imbalance rather than just being an arbitrary value [6]. Smith proposes a modification of Atkinson's method [7].

Klotz's method addresses the question of a trade-off between uncertainty and imbalance [8]. His method is similar to that of Pocock and Simon but is more computationally intensive and describes a function for calculating optimal treatment randomization probabilities. Titterington proposes a similar method that involves minimizing a quadratic criterion subject to a balance constraint [9]. The method aims to compromise between unpredictability of assignment and good stratification balance and is said to be simpler than Klotz's method.

A variety of other allocation methods have also been proposed but it is beyond the scope of this paper to describe them in detail [10–12].

Advantages and disadvantages of minimization

The primary reason for using minimization is the desire to achieve balanced groups with respect to both the numbers in each treatment arm and the characteristics of each group. The use of minimization can, however, also lead to indirect benefits including increased persuasiveness and credibility by presenting data indicating that prognostic variables are closely balanced within each treatment group [13]. It has also been suggested that planning to use minimization is a good discipline for making trialists think about prognostic factors before a study starts and for helping ensure adherence to the protocol as the trial progresses [14].

Other benefits of the minimization method have been proposed, such as the ability to include more patient factors than for stratified randomization: this can be particularly valuable in smaller trials in which several factors are known to affect outcome [15]. In addition, minimization can control confounding without the drawback of splitting the patient sample into too many strata [16].

Disadvantages of minimization have also been cited. Peto et al. consider the gains in efficiency and balance relative to complete randomization negligible [17]. They also consider

the use of any stratified method of randomization unnecessary as the added complexity can harm recruitment and adjustments for covariates can be made at the end of the trial. Their arguments have, however, been countered by a number of authors [18–20].

Three further potential drawbacks of using minimization are discussed in separate sections (see Special considerations, below). Firstly, minimization is essentially a deterministic method but statistical tests used in the analysis of the trial make the assumption of random allocation. Secondly, also arising from the nonrandom nature of minimization, are concerns about selection bias due to the fact that the next assignment can be predicted in some situations. Finally, there may be additional organizational complexity when using minimization with the potential to harm recruitment and increase costs.

Comparison of minimization with other methods

A number of authors have used computer simulations to compare minimization with other allocation methods.

Minimization versus simple (unrestricted) randomization

Using their range method Pocock and Simon showed that minimization produced much less chance of imbalance both within factors and overall than using purely random assignment for simulated trials of 50 patients [3]. Begg and Iglewicz also demonstrated that the range and variance methods led to much lower loss of efficiency than simple randomization [5]. Watson and Pearce showed that minimization produced well-balanced groups using entry data from three small trials, two of which had produced imbalances in prognostic groups using simple randomization [21]. Zielhuis et al. again showed that the range and variance methods led to less imbalance within strata and overall using simulated trials of 50 patients [22]. Rover et al. used simulations to compare Pocock and Simon's variance method with simple randomization [23]. In trials with up to 400 patients, minimization always resulted in more balanced groups and was less affected by adding additional prognostic categories. Campbell and McPherson found that for smaller trials simple randomization resulted in greater imbalance in treatment numbers than minimization but for simulated trials of 1000 patients there was little difference [24].

Minimization versus restricted randomization

Taves showed using simulations that minimization resulted in fewer imbalances within prognostic factors than restricted randomization (alternation) and achieved a fourfold reduction in the probability of severe imbalance [2]. In simulations Pocock and Simon's range method similarly outperformed unstratified permuted blocks [3].

Minimization versus stratified allocation methods

Pocock and Simon's range method also performed well against permuted blocks within strata in simulated trials of 50 patients, especially when the number of prognostic factors was greater than three [3]. Therneau used simulations to compare minimization with permuted block randomization within strata with a block size of two for trials of 100 patients [25].

Both methods performed similarly for small number of prognostic factors, but as this number was increased minimization led to much less imbalance. His results indicate that minimization can incorporate 10 to 20 factors without difficulty, but stratified randomization begins to fail when the number of factor level combinations approaches half the sample size.

Minimization versus other allocation methods

More complex methods utilizing optimum design theory have been shown to outperform minimization with respect to efficiency. Simulated trials of 50 patients conducted by Begg and Iglewicz suggest that the range and variance methods of Pocock and Simon result in greater loss of efficiency than their own method [3,5]. However, Zielhuis et al. showed in trials of 50 patients that the variance method led to slightly less imbalance both overall and within strata than for Begg and Iglewicz's method [22]. Atkinson used simulations to compare his "D_A-Optimality" method with minimization [26,27]. Atkinson's method generally performed better than minimization, which was more sensitive to correlations between prognostic factors.

The range versus the variance method

Both Begg and Iglewicz and Zielhuis et al. indirectly compared Pocock and Simon's range and variance methods using simulations [3,5,22]. Although both methods produced similar results the variance method performed slightly better.

Special considerations for the use of minimization

Predictability of next assignment

A strength of simple randomization is that the allocation of future patients to a trial cannot be predicted. The disadvantage of deterministic allocation procedures such as minimization is that in certain cases the next allocation can be predicted with certainty with knowledge of the characteristics of earlier patients. There is therefore a potential for selection bias, which can affect the validity of a trial's results. Even a knowledge of which allocation is more likely to occur next can result in selection bias.

It should be noted that the predictability issue is not just confined to minimization. In permuted block randomization the allocation for the final patient in each block can also be predicted with certainty. Even if blocks of random length are used the most likely allocation can often still be guessed.

Taves realized that the next assignment can usually be predicted if the exact system used in the minimization procedure is known [2]. He showed that minimization was slightly less predictable than restricted randomization but the next allocation could still be guessed with knowledge of just the current group totals in nearly 70% of cases. Pocock and Simon and others have argued that the probability of assignment to the "optimal" treatment according to the minimization algorithm should be set at some value less than one to ensure that the next assignment can

never be predicted with certainty [3]. However, they and others accept that in many trials, particularly multicenter trials, it is acceptable to set this probability to one [3,28].

As previously mentioned, further methods have been proposed that seek a compromise between the conflicting aims of ensuring balanced groups and ensuring unpredictability of assignment [8,9].

Only one report was identified that used simulations to investigate the effect of varying the probability of assignment to the treatment chosen by the minimization algorithm. Pocock and Simon compared allocation systems where the probability of receiving the optimal treatment was reduced from 1 to 0.75 [3].

Implications for the analysis

In his original article Taves recognized that use of his method does have implications for the analysis of the trial [2]. He recommended that adjustment should be made for factors used in the minimization using analysis of covariance, recognizing that minimization is not a random method but that tests of statistical inference are based on the assumption of random assignment to treatment and control groups. Many standard inferential procedures require that every sequence of treatment assignments is equally likely. Only simple randomization has this property, however, thus concerns over the validity of the analysis surround not just minimization but all other allocation methods.

Therefore a disadvantage of adaptive methods like minimization is that the correct statistical analysis is complex and not yet clearly worked out [20,29]. Several authors have discussed how permutation tests can be conducted when analyzing trials where such methods have been used [16,18,30]. Although it is theoretically possible to perform an appropriate permutation test for minimization using simulation, this is in practice not straightforward and makes little difference to the results obtained [31]. Although Green et al. believe that permutation tests are unnecessary provided that minimization factors are used as covariates in the analysis, they refer to a case where a U.S. regulatory body requested that a trial that had used minimization be reanalyzed using permutation tests [30].

Pocock and Simon mention briefly the possibility of accidental bias occurring when patients enter a trial in a nonrandom order [3]. Although the effect of stratifying by a covariate and then ignoring it in the analysis may not be severe, accidental bias can result from using an incorrect hypothetical model for analysis. It is possible that accidental bias decreases when a random element is incorporated into such a systematic design [18]. Halpern and Brown have described how in the case of biased coin randomization the classical analysis will usually yield satisfactory conclusions except for specific circumstances such as trends in outcome of low time frequency in the stratifying variables [20].

Many authors have discussed the effect of minimization on the nominal level of the significance test and on the power of the test (alpha and beta errors). Forsythe and Stitt showed that if the analysis method ignores the fact that minimization has been used, this will result in p-values that are distorted [32]. However, when analysis of covariance was used to compare treatments after adjusting for the effect of the covariate the significance level resulting from minimization was equal to the nominal level of the test. In addition, the analysis of covariance resulting from minimization was more powerful than that resulting from randomization, though the differences were not great.

Birkett used simulations to compare minimization with simple and stratified randomization [33]. Minimization resulted in conservative levels of significance using Student's *t* test, and although minimization produced improvements in power compared to stratification against selected hypotheses, little or no increase in power was seen unless "actual" cutpoints were used. He suggests that the use of analysis of covariance in the analysis may further increase power.

Kalish and Begg found that by simulating data from actual trials *p*-values derived using permuted block randomization and Begg and Iglewicz's method were conservative but were not likely to be severely distorted if the analysis is stratified by the covariates used as analysis prompts [5,34]. Moreover, the inherent conservativeness of exact methods due to discreteness tends to dominate any additional conservativeness due to nonrandom designs.

Tu et al. conducted simulations using data from two actual trials [35]. They found that minimization was inferior to stratified allocation in reducing alpha and beta errors and was nearly equivalent to simple randomization in this regard. They state that the balance in marginal totals achieved by minimization will be sufficient when the effects of prognostic factors do not interact. When such interactions do exist, as is often the case in actual trials, balance between individual strata (cells) is necessary to reduce alpha errors. They believe that minimization enhances credibility by producing marginal balance, but whether it can increase precision depends on whether interactions exist between covariates. They agree that account should be taken of the covariates in the analysis.

Senn argues that factors used in the minimization must also be included in the analysis and that using minimization but not including the covariates in the model is not legitimate [36]. Using quotations from Fisher and Yates and an argument from a Bayesian perspective he argues that balancing for factors that are not included in the model is pointless if not harmful [37].

Although Kalish and Begg state that the consensus is that factors used in the allocation procedure ought to be accounted for in the analysis, they also concede that scientific audiences may find the results of simple, unadjusted treatment comparisons with demonstration of good balance of important factors more convincing than the results of a covariate analysis [16]. Other authors have ignored such theoretical concerns in practice. Vaughan Reed and Wickham state that they do not adjust for covariates because the errors introduced are likely to be less than the errors resulting from imbalance between treatment groups [38]. Watson and Pearce also do not consider that the nonrandom allocation procedure invalidates the statistical assumptions to any great extent as it would still be possible for any individual to be allocated to any treatment [21]. Treasure and MacRae consider that attempts to adjust for imbalances in randomization may lead to uncertainty about the validity of the conclusion [39].

Organizational issues with using minimization

Although the calculations required for assigning treatments using minimization are fairly simple and can be conducted by hand, they may be laborious and impractical in many situations [2,3,38]. White and Freedman have shown how this can be simplified in practice using index cards [28]. While many authors disagree that the implementation of the standard minimization method increases the administrative burden, the use of many prognostic factors and

extensions to the standard method (such as the use of weighting factors with different probabilities) add further complexity. Many investigators have made use of computerized randomization, although the issue of computer downtime has been mentioned [5,25].

In addition, a constantly updated centralized system is required because the allocation of each new patient entering the trial depends on details of previous patients entered being kept up to date. With conventional stratified randomization the entire randomization schedule can be produced and distributed to centers in advance [16,18]. However, for multicenter trials central randomization has other advantages such as the ability to centrally "police" the trial and to guard against selection bias. "Stratified" minimization performed locally by each center is also an option.

A further practical consideration in multicenter trials concerns exactly when patients appear for randomization and how long a gap between recruitment and the need for an allocation is acceptable. Minimization may be logistically more complex to implement in an emergency setting, in which patients can come in at any time and require immediate allocation, than in situations where the allocation is nonurgent and an office hours randomization service is sufficient.

It has been suggested that the use of more complex allocation methods may harm recruitment of clinicians and accrual of patients to the trial [17]. This is not the experience of Kalish and Begg, but they believe that the complexity of the algorithm used may pose practical problems for the administrators of the trial [16]. Programming errors are not uncommon when computerized randomization is used. For example, one recent trial had to rerecruit over 1000 women when a mistake in the minimization algorithm caused serious imbalance [40]. This can be avoided by the routine incorporation of simulation exercises to check the minimization algorithm before recruitment begins [41].

The implementation of more complex allocation schemes such as minimization can be unnecessarily costly, although it has been pointed out that even small gains in efficiency save money, especially for centers conducting many trials simultaneously [16]. Hamilton has demonstrated the benefit of minimization in a situation where the supply of a drug at centers can be limited [42].

The issue of withdrawals after randomization can also be important [22,23,38]. Zielhuis et al. have described a situation when such dropouts caused an actual trial to become imbalanced whereas simulations had shown perfect balance using minimization [22].

Current status of minimization

Evidence from published papers

In 1982 Pocock and Lagakos conducted a survey of 15 centers conducting trials in cancer [15]. Four centers had used minimization (one always, one in 80% of trials and two in one specific trial), but the most common design was permuted blocks within strata. In 1990 Altman and Doré reviewed 80 reports of randomized clinical trials in four leading journals and found that only one of these trials had used minimization [43]. Vaughan Reed and Wickham stated that since its introduction by Taves in 1974 it appeared to have been little used [38]. Ratain and Hochberg and Treasure and MacRae describe minimization as infrequently used and not a

well-known technique, respectively [39,44]. Green et al. state that the use of minimization has been relatively limited due to the administrative burden and concerns about the validity of conventional analysis [30]. Tu et al. believe that minimization and other dynamic allocation procedures are used more often in trials conducted in academic settings than in industry [35].

Empirical evidence

To further determine the current status of minimization we reviewed all 150 reports of randomized controlled trials published in the *Lancet* and the *New England Journal of Medicine* during 2001. Only 6 trials (4%) reported using minimization, whereas 43 (29%) reported using permuted blocks within strata and 19 (13%) employed an unspecified type of stratified randomization. One trial used Efron's biased coin method, one trial the dynamic balancing method of Signorini et al. and one trial urn randomization. The remaining 79 trials (53%) gave no clear information about the allocation method used.

Recommendations on which allocation method to use

Few authors make unqualified recommendations as to whether minimization should be used in practice in preference to other methods. At least two articles come out wholly in favor of the method, the latter referring to minimization as the platinum standard if randomization is the gold standard [38,39].

Other authors cite minimization as the method of choice (or one of a number of methods of choice) in smaller trials when it is desirable to achieve balance in a number of prognostic factors [18,24]. Kernan et al. consider minimization preferable to stratification methods when more than four such variables are used, but Rovers et al. point out that in minimization the expected number of patients in each subcategory should always be greater than five to prevent empty cells [23,45].

Although considering minimization as valid and as efficient as any other allocation method, Senn points out that the method of Atkinson may have a slight gain in efficiency over minimization [6,36,37].

Pocock believes that having a relatively straightforward randomization scheme may be more important than attempting theoretical optimality with more complex designs [1].

Lachin et al. recommend complete, permuted block or urn randomization over covariate adaptive methods like minimization because of the implications for the analysis and because allocation sequences cannot be pregenerated [29].

Recent guidelines for the pharmaceutical industry recommend that a random element should be incorporated into deterministic dynamic allocation procedures like minimization [46].

In choosing the allocation method consideration should also be given to the organizational setup involved, for example the availability of computing facilities and whether trials require enrolment outside office hours [16,21,28].

Discussion

While a number of commentators have reviewed specific aspects of minimization techniques, we believe that this is the first comprehensive review of literature in the field, bring-

ing together both statistical and methodological perspectives. We accept that because of the difficulties with the indexing of methodological papers we may have missed some relevant articles from the review; however, the results from the papers that we did locate provided fairly conclusive evidence of the advantages and disadvantages of the minimization method within randomized controlled trials.

From our review we conclude that minimization is an effective method for allocating participants to treatment groups within a randomized controlled trial. In the majority of cases, minimization has been shown to outperform simple randomization in achieving balanced groups; this greater performance is particularly marked when trial sample sizes are small. Minimization has also been shown to be advantageous compared to stratified randomization methods, as it has the ability to incorporate more prognostic factors.

The main purported disadvantages of minimization are that assignment can be predicted, that analysis assumptions may be compromised due to the "pseudo"-random allocation adopted and that it is organizationally more complex. However, these disadvantages are also true of other allocation methods such as stratification and hence should not be weighted unduly against the use of minimization. There is evidence that misleading results can be obtained if adjustment is not made for the minimization variables in the analysis of a trial.

Despite the advantages of minimization and the recommendations of many commentators to use it, our research has shown that use of the method is still seldom reported in randomized trials. This may have resulted in a number of trials displaying significant treatment imbalance between groups unnecessarily.

We also observed that the use of minimization need not be restricted to patient randomized trials but can also be used to allocate clusters in a cluster randomized trial and patients in a crossover trial [30,47]. Further research into the efficiency of minimization in more complex designs is required.

In summary, therefore, we believe that the results of our review suggest that minimization is a highly effective method for treatment allocation, and we advocate wider adoption of the technique within the clinical trial field.

Acknowledgments

The Health Services Research Unit is core funded by the Scottish Executive Health Department; however, the views expressed are those of the authors.

References

[1] Pocock SJ. Allocation of patients to treatment in clinical trials. Biometrics 1979;35:183–197.
[2] Taves DR. Minimization: a new method of assigning patients to treatment and control groups. Clin Pharmacol Ther 1974; 15:443–453.
[3] Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975;31:103–115.
[4] Freedman LS, White SJ. On the use of Pocock and Simon's method for balancing treatment numbers over prognostic factors in the controlled clinical trial. Biometrics 1976;32:691–694.
[5] Begg CB, Iglewicz B. A treatment allocation procedure for sequential clinical trials. Biometrics 1980;36:81–90.
[6] Atkinson AC. Optimum biased coin designs for sequential clinical trials with prognostic factors. Biometrics 1982;69:61–67.
[7] Smith RL. Sequential treatment allocation using biased coin designs. J R Statist Soc B 1984;46:519–543.

[8] Klotz JH. Maximum entropy constrained balance randomization for clinical trials. Biometrics 1978;34:283–287.
[9] Titterington DM. On constrained balance randomization for clinical trials. Biometrics 1983;39:1083–1086.
[10] Begg CB, Kalish LA. Treatment allocation for nonlinear models in clinical trials: the logistic model. Biometrics 1984;40: 409–420.
[11] Kalish LA, Harrington DP. Efficiency of balanced treatment allocation for survival analysis. Biometrics 1988;44:815–821.
[12] Signorini DF, Leung O, Simes RJ, Beller E, Gebski VJ. Dynamic balanced randomization for clinical trials. Stat Med 1993;12:2343–2350.
[13] Brown BW. Statistical controversies in the design of clinical trials. Technical Report No. 37. 1978. Division of Biostatistics, Stanford University, Stanford, California.
[14] Day S. Commentary: treatment allocation by the method of minimisation. BMJ 1999;319:947–948.
[15] Pocock SJ, Lagakos SW. Practical experience of randomization in cancer trials: an international survey. Br J Cancer 1982;46:368–375.
[16] Kalish LA, Begg CB. Treatment allocation methods in clinical trials: a review. Stat Med 1985;4:129–144.
[17] 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.
[18] Simon R. Restricted randomization designs in clinical trials. Biometrics 1979;35:503–512.
[19] Brown BW. Designing for cancer clinical trials: selection of prognostic factors. Cancer Treatment Reports 1980;64:499–502.
[20] Halpern J, Brown BW. Sequential treatment allocation procedures in clinical trials — with particular attention to the analysis of results for the biased coin design. Stat Med 1986;5:211–229.
[21] Watson HR, Pearce AC. Treatment allocation in clinical trials: randomisation and minimisation compared in three test cases. Pharmaceutical Medicine 1990;4:207–212.
[22] Zielhuis GA, Straatman H, Van 'T Hof-Grootenboer AE, et al. The choice of a balanced allocation method for a clinical trial in otitis media with effusion. Stat Med 1990;9:237–246.
[23] Rovers MM, Straatman H, Zielhuis GA, Ingels K, van der Wilt G-J. Using a balancing procedure in multicenter clinical trials: simulation of patient allocation based on a trial of ventilation tubes for otitis media with effusion in infants. Int J Technol Assess Health Care 2000;16:276–280.
[24] Campbell MK, McPherson G. Simple randomisation or minimisation: the impact of trial size. Control Clin Trials 2001;22:87S.
[25] Therneau TM. How many stratification factors are "too many" to use in a randomization plan? Control Clin Trials 1993;14:98–108.
[26] Atkinson AC. Optimum biased-coin designs for sequential treatment allocation with covariate information. Stat Med 1999;18:1741–1752.
[27] Atkinson AC. The comparison of designs for sequential clinical trials with covariate information. J R Statist Soc A 2002;165:349–373.
[28] White SJ, Freedman LS. Allocation of patients to treatment groups in a controlled clinical study. Br J Cancer 1978;37:849–857.
[29] Lachin JM, Matts JP, Wei LJ. Randomization in clinical trials: conclusions and recommendations. Control Clin Trials 1988;9:365–374.
[30] Green H, McEntegart DJ, Byrom B, Ghani S, Shepherd S. Minimization in crossover trials with non-prognostic strata: theory and practical application. J Clin Pharm Ther 2001;26:121–128.
[31] Buyse M. Centralized treatment allocation in comparative clinical trials. Applied Clinical Trials 2000;9:32–37.
[32] Forsythe AB, Stitt FW. Randomization or minimization in the treatment assignment of patient trials: validity and power of tests. Technical Report No. 28. 1977. Health Sciences Computing Facility, University of California, Los Angeles.
[33] Birkett NJ. Adaptive allocation in randomized controlled trials. Control Clin Trials 1985;6:146–155.
[34] Kalish LA, Begg CB. The impact of treatment allocation procedures on nominal significance levels and bias. Control Clin Trials 1987;8:121–135.
[35] Tu D, Shalay K, Pater J. Adjustments of treatment effect for covariates in clinical trials: statistical and regulatory issues. Drug Inf J 2000;34:511–523.
[36] Senn S. A personal view of some controversies in allocating treatment to patients in clinical trials. Stat Med 1995; 14:2661–2674.
[37] Senn S. Consensus and controversy in pharmaceutical statistics. The Statistician 2000;49:135–176.
[38] Vaughan Reed J, Wickham EA. Practical experience of minimisation in clinical trials. Pharmaceutical Medicine 1988;3:349–359.
[39] Treasure T, MacRae KD. Minimisation: the platinum standard for trials? Randomisation doesn't guarantee similarity of groups; minimisation does. BMJ 1998;317:362–363.

[40] Comparative Obstetric Mobile Epidural Trial (COMET) Study Group UK. Effect on low-dose mobile versus traditional epidural techniques on mode of delivery: a randomised controlled trial. Lancet 2001;358:19–23.
[41] McPherson G, Campbell MK, Grant A. Minimisation: the platinum standard for trials? Control Clin Trials 2002;23:66S.
[42] Hamilton SA. Dynamically allocating treatment when the cost of goods is high and drug supply is limited. Control Clin Trials 2000;21:44–53.
[43] Altman DG, Doré CJ. Randomisation and baseline comparisons in clinical trials. Lancet 1990;335:149–153.
[44] Ratain JS, Hochberg MC. Clinical trials: a guide to understanding methodology and interpreting results. Arthritis Rheum 1990;33:131–139.
[45] Kernan WN, Viscoli CM, Makuch RW, Brass LM, Horwitz RI. Stratified randomization for clinical trials. J Clin Epidemiol 1999;52:19–26.
[46] Lewis JA. Statistical principles for clinical trials (ICH E9): an introductory note on an international guideline. Stat Med 1999;18:1903–1942.
[47] Steptoe A, Doherty S, Rink E, et al. Behavioural counselling in general practice for the promotion of healthy behaviour among adults at increased risk of coronary heart disease: randomised trial. BMJ 1999;319:943–948.