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Randomization in clinical trials in orthodontics: its significance in research design and methods to achieve it

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SUMMARY Randomization is a key step in reducing selection bias during the treatment allocation phase in randomized clinical trials. The process of randomization follows specific steps, which include generation of the randomization list, allocation concealment, and implementation of randomization. The phenomenon in the dental and orthodontic literature of characterizing treatment allocation as random is frequent; however, often the randomization procedures followed are not appropriate. Randomization methods assign, at random, treatment to the trial arms without foreknowledge of allocation by either the participants or the investigators thus reducing selection bias. Randomization entails generation of random allocation, allocation concealment, and the actual methodology of implementing treatment allocation randomly and unpredictably. Most popular randomization methods include some form of restricted and/or stratified randomization. This article introduces the reasons, which make randomization an integral part of solid clinical trial methodology, and presents the main randomization schemes applicable to clinical trials in orthodontics.

Introduction

Randomization is the process of randomly generating and allocating interventions to trial arms in a way that assures that neither the investigators nor the participants know or may predict ahead of time what treatment the patients will receive. Random assignment of individuals to treatment, with proper allocation concealment is of paramount importance for securing selection bias reduction, controlling unobserved confounders, and improving internal validity of randomized clinical trials (Jadad *et al.*, 1996; Juni *et al.*, 2001; Moher *et al.*, 2010).

As the consolidated standards of reporting trials (CONSORT; http://www.consort-statement.org) group succinctly states (Moher *et al.*, 2010), the advantages of randomization are elimination of selection bias and balancing of both known and unknown prognostic factors during treatment allocation; elimination of prejudice, whether conscious or not, which may result in distributing participants of certain characteristics unequally between treatment arms; and use of probability theory to express the likelihood that any difference in outcome between intervention groups merely reflects chance. Proper allocation concealment shields knowledge of forthcoming assignments, whereas proper random sequences prevent correct anticipation of future assignments based on knowledge of past assignments.

Proper randomization reporting includes 1. generation of the random allocation sequence, including details of any restriction; 2. allocation concealment; and 3. implementation of the random allocation sequence, i.e. information on who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.

In the orthodontic and broader dental literature, the wording of article titles often includes the term 'randomized controlled trial' and the article methods section alludes to random treatment allocation. However, those terms may not always follow the strict criteria assumed for randomized treatment allocation as explained above. Studies in the biomedical literature have indicated that randomization methodology is often not appropriately implemented and/or underreported and that lack of proper randomization has indicated higher probability for bias (Gøtzsche, 1989; Altman and Dore, 1990; Schulz *et al.*, 1994, 1995). In a recent assessment of six major dental journals with the highest impact factor, it was found that items related to randomization were adequately reported in only 9–34 per cent of the articles (Pandis *et al.*, 2010). The authors assigned a score of 1–3 (1 = for no description, 2 = inadequate description, and 3 = for adequate description) for each item relating to randomization. In the *American Journal of Orthodontics and Dentofacial Orthopedics*, for generation of allocation sequence, the frequencies per score were 20 per cent (score 1), 35 per cent (score 2), and 45 per cent (score 3) and for restriction applied in randomization, the frequencies were 40 per cent (score 1), 20 per cent (score 2), and 40 per cent (score 3). The frequency scores for allocation concealment were 50 per cent (score 1), 25 per cent (score 2), and 25 per cent (score 3) and for implementation of allocation 80 per

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cent (score 1), 20 per cent (score 2), and 0 per cent (score 3). Previous studies found also serious underreporting in periodontics (Montenegro *et al.*, 2002), prosthodontics (Dumbrigue *et al.*, 2001; Jokstad *et al.*, 2002), orthodontics (Harrison, 2003), and other fields of dentistry (Sjögren and Halling, 2002). The purpose of this article was to provide an overview of the most common randomization methods and allocation concealment and discuss how these may be implemented in clinical trials in orthodontics.

Methods of randomization

Sequential treatment assignment, as well as allocation schemes that follow, for example, days of the week or days of months, birthdays, or using participant initials are not considered truly random methods and are open to manipulation and subversion of treatment allocation. Those methods have also been characterized as 'quasi-randomization' methods (Pocock, 1993).

The most popular and appropriate methods for orthodontics are presented in the following section.

Simple randomization

Simple randomization allocates participants to treatment arms with no regard to previous assignments unlike adaptive schemes where new treatment allocations may depend on previous ones. This method generates randomization lists via the use of random tables or software capable of producing random numbers and resembles the toss of a coin. Random tables include sequences of numbers that occur randomly, with no discernible pattern and with similar frequency from which we can select numbers horizontally, vertically, diagonally, and from any starting point (Table 1). The random numbers table may be used as follows: for a two-arm trial numbers, 0–4 for treatment A and 5–9 for treatment B may be selected and therefore an allocation sequence using Table 1 and going horizontally for 60 patients would be: BAABBBAAABBABAA (table row1), AAAAABBBAAAABBA (table row 2), BAAAABBB BAABBBB (table row 3); and BBABAAABBBAAAAB (table row 4).

The first two rows on Table 2 display the treatment assignment for the first 30 participants and we can see that treatment allocation is unequal between treatment arms A and B (18 A:12 B). The first 4 rows from Table 2 show the treatment assignment to A and B for 60 participants which is still unbalanced (33A:27B). This is usually the problem with simple randomization that when small numbers of patients are recruited, there is a high chance of unequal number allocation of participants per treatment arm. As the

Table 1 Table of random numbers generated from random.org.

9	0	4	5	7	7	3	1	2	6	7	0	9	2	1
0	0	2	4	4	6	8	5	0	2	2	0	8	9	4
6	0	3	1	1	9	5	7	6	0	1	8	9	9	6
6	8	1	8	0	0	3	8	6	9	3	2	2	3	7
3	5	3	8	3	9	8	5	1	7	1	1	3	5	8
2	3	0	5	8	4	1	6	4	7	1	1	0	1	8
8	9	4	4	5	7	5	0	0	9	9	6	1	8	2
6	6	8	6	1	2	4	4	0	1	7	0	4	0	6
6	2	6	7	1	6	0	8	8	0	4	2	9	8	9
3	5	3	1	2	4	4	4	0	7	1	9	9	9	0
7	7	2	5	1	5	2	4	5	0	2	8	9	5	5
5	1	4	8	4	5	5	4	0	1	8	9	9	3	6
8	7	1	7	0	5	4	2	7	6	5	4	6	6	2
3	9	4	2	5	5	8	5	5	4	4	2	1	7	9
1	7	7	1	1	3	1	3	2	9	4	7	9	1	1
5	8	9	8	2	0	1	8	6	7	1	8	5	7	8
7	5	0	5	4	4	9	0	9	0	9	7	5	0	0
1	3	2	1	0	0	4	3	3	9	6	1	4	1	8
6	2	1	9	2	4	2	6	4	1	6	9	8	9	8
4	6	1	7	3	8	5	5	9	5	1	2	3	2	7
1	7	3	9	7	8	6	3	2	4	5	7	4	0	9
7	6	4	6	0	9	2	5	9	0	0	7	2	9	2
4	7	9	7	1	0	7	5	3	3	7	7	5	2	9
8	7	7	3	8	9	1	3	7	5	9	9	4	8	9
0	5	4	0	0	8	0	0	8	1	9	8	5	6	8
6	8	4	4	9	4	6	0	2	7	5	6	5	7	9
1	4	7	9	0	1	3	9	2	1	8	5	3	3	6
9	2	0	8	4	3	2	8	0	7	4	3	3	2	6
3	6	8	2	6	7	7	8	0	0	1	4	7	3	3
6	3	4	4	3	6	3	7	0	6	5	4	9	1	6
4	0	4	0	6	8	0	4	4	4	9	4	3	4	9
2	9	0	9	1	2	0	9	9	0	1	7	7	5	7
4	5	4	1	7	6	4	6	5	4	0	8	2	7	7

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number to be recruited increases, the imbalances are reduced. However, even in large trial, where data analyses (interim analyses) are performed on smaller sample sizes during the trial, there is still a danger of serious unbalances. Therefore, simple randomization has given way to more precise and unbiased randomization methods (Kang *et al.*, 2008), which will follow.

Restricted randomization/block randomization

Restricted randomization involves some applied constraint in order to assure that trial arms have equal numbers of participants at any time. One method is block randomization, also known as permuted-block randomization, in which treatment assignment is done in blocks of fixed or variable size. Block size must be an integer multiple of the number of treatment groups. Block size may be 2, 4, 6, and 8, for example, and within each block, equal numbers of treatment A and B allocation are included. For example, a block size of 4 may have the following balanced sequences of allocation to treatment A or B: AABB, ABAB, ABBA, BBAA, BABA, and BAAB (Altman and Bland, 1999a,b; Schulz and Grimes, 2002).

One problem, which may arise with small block sizes, is that investigators may predict the next allocation and to alleviate this problem, a variable block size scheme may be adopted in which block size may randomly vary, for example, between 4, 6, and 8. Allocation prediction is usually a problem in trials where blinding is not feasible as it is often the case in orthodontics. Software is available to generate randomization list using random permuted blocks. A user written command for the Stata statistical software package (StataCorp, College Station, Texas, USA) named 'ralloc' (Ryan, 1998) is an excellent tool for this purpose.

Table 2 depicts a treatment allocation sequence generated using the command. The table is for a trial, including 44 patients to be allocated to treatment A or B. There is a variable block size of 4 and 6 with two blocks of size 4 and 6 of size 6, thus equally allocating treatment to A or B to 44 patients (Table 3). A similar list may be also generated using the free software at http://www.randomization.com.

Table 2 Table of treatment allocation generated using the 'ralloc' command in Stata, showing the numbers, the size of the generated blocks, and the treatment allocation to A or B.

Block number	Block size	Treatment
1	6	B
1	6	A
1	6	B
1	6	A
1	6	A
1	6	B
2	6	A
2	6	A
2	6	A
2	6	B
2	6	B
2	6	B
3	4	B
3	4	A
3	4	B
3	4	A
4	4	B
4	4	A
4	4	B
4	4	A
5	6	A
5	6	B
5	6	B
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5	6	A
6	6	A
6	6	A
6	6	B
6	6	A
6	6	B
6	6	B
7	6	B
7	6	A
7	6	B
7	6	A
7	6	B
7	6	A
8	6	B
8	6	B
8	6	B
8	6	A
8	6	A
8	6	A

Table 3 Summary of block size frequency and treatment allocation from Table 2.

Block size	Frequency	Treatment A	Treatment B
4	2	4	4
6	6	18	18

Stratified randomization

As a working example, let us evaluate the formation of caries development on molar teeth of orthodontic patients receiving bonding of molar bondable tubes compared to patients receiving bands in a trial implemented at a number of different locations that serve patient of different socio-economic status. One approach would be to create one randomization list (either simple or blocked) and allocate treatment centrally, using the generated list, for all trial locations. However, if it is assumed that patients at different locations may have different baseline characteristics, which may be important predictors for caries development, randomization through a single list may create imbalances on important predictors between the treatment arms. In other words, it is possible that patients with suboptimal oral hygiene, an important predictor for caries development, are over or underrepresented in one trial arm thus confounding the trial results.

Simple and block randomization do not guarantee balanced treatment groups on important prognostic factors, which may be accomplished by using the method of stratification

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(McEntegart, 2003; Table 4). In this scenario, stratification may utilize separate randomization lists for each location (stratum) and may be combined with blocking to assure equal size trial arms within strata. Stratification may be used on important prognostic factors for the outcome; however, caution should be exercised not to stratify on too many factors because this may result in a large number of strata (Lachin *et al.*, 1988; Weir and Lees, 2003). For example, if in the caries development trial, stratification is performed by gender (two levels), age (more than 15 and less than 15 years), oral hygiene status (bad, good, and excellent), and by centre (three locations); the number of strata introduced would be $2 \times 2 \times 3 \times 3 = 36$. Having multiple strata creates several small subgroups and treatment allocation imbalances by potentially forming several incomplete blocks. If several prognostic factors are considered, perhaps a combination into an index and stratification on the index may be prudent or alternatively the method of minimization may be utilized. Another problem with stratification stems from the fact that ideally all participants should be identified before randomization, which is often difficult for a trial that recruits prospectively. Finally, stratification is more important for trials with small sample sizes where imbalances of important prognostic predictors are more likely.

Minimization

Minimization is a restricted randomization technique that follows a dynamic approach, meaning that the randomization list is not produced before the trial starts but rather as the trial goes on. Minimization, in contrast to the previous schemes, falls in the adaptive randomization category since future participant allocation depends on previous allocations. Patients are randomized to the treatment or control in order to achieve balanced arms in respect to the pre-selected risk/prognostic factors (Pocock and Simon, 1975; Scott *et al.*, 2002).

In the caries development on orthodontic patients' example, randomization may be done using age group, gender, and location as prognostic factors. The first patient is assigned with simple randomization (like tossing a coin), for example, to the orthodontic molar bonds treatment arm; patients are entered three times (once per factor) as shown in Figure 1. The second patient will be assigned to the arm that improves the balance according to the pre-selected set of prognostic factors between the two trial arms. The second patient has the following characteristics: 12-year-old, female, and location 2.

The next step is to calculate the sum of the counts (marginal totals = sum of counts per treatment arm at the line indicated by the arrows) for each treatment arm for the baseline characteristics of the second patient; we seek to balance the marginal totals of the prognostic factors. On the orthodontic molar bonds treatment arm, the sum of the counts for patients enrolled who are younger than 15 years old, female, and from location 2 is orthodontic molar bonds treatment arm marginal total is $1 + 1 + 0 = 2$; for the orthodontic bands arm, the marginal total is $0 + 0 + 0 = 0$.

Predictor	Strata	molar bonds	molar bands	
Age in years	<15	1	0	◄
	≥15	0	0	
Sex	Female	1	0	◄
	Male	0	0	
Location	1	1	0	
	2	0	0	◄
	3	0	0	

Figure 1 Allocation when the second patient arrives.

Table 4 Overview of common randomization methods.

	Simple randomization	Blocked randomization	Stratified randomization	Minimization
Advantages	Simple to use	Equal size trial arms at all times	Equal size trial arms if combined with blocking	Equal size trial arms
	Unpredictable		Assure balance on outcome predictors, especially in small trials	Assure balance on outcome predictors, especially in small trials
Disadvantages	Not equal size trial arms at all times	Assignment may be predicted if small size blocks that do not vary are used, especially if blinding cannot be implemented	Danger for overstratification and imbalances due to incomplete blocks	Complicated especially when several predictors are considered
	Cannot assure balance on outcome predictors, especially in small trials	Cannot assure balance on outcome predictors, especially in small trials	Prediction of allocation when small size blocks in unblind trial is possible	Requires knowledge of details of previous allocations
			Requires identification of participants before group assignment	Not strictly random but a random element may be included

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Therefore, in order to improve balance on age, gender, and location, the second patient must be randomized into the bands arm, and the minimization table is shown on Figure 2. As new patients are recruited, they are randomized with a process, which employs the marginal total for each arm (sum of counts per arm indicated by arrows) and for the patient characteristics. To further explain this, let us assume that we have randomized 41 patients as shown in Figure 3.

Then the patient number 42 who is male, 11 years old and recruited at location number 3, would be allocated to orthodontic molar bonds arm because the orthodontic bonds arm marginal total equals 26 (10 + 10 + 6 = 26), whereas the molar bands arm marginal total is 29 (11 + 11 + 7 = 29). In case the marginal totals are equal, simple randomization may be used for the next participants. By looking at the past assignment, it may be possible to predict the next allocation and to reduce predictability; one option is to intentionally bias allocation towards the arm with the lower marginal totals by introducing a random element with a probability larger than 0.5 and lower than 1 ($1 > P > 0.5$; Pocock, 1993).

Ryan has developed the 'rct_minim' command (http://ideas.repec.org/c/boc/bocode/s457029.html) for implementing the method of randomization with the Stata statistical package, whereas related free software (http://wwwusers.york.ac.uk/~mb55/guide/minim.htm) is also available for this purpose. Minimization has the advantages of balancing on important covariates but requires intensive administrative effort, especially when there are several covariates, has the potential of overmatching and higher risk for unmasking.

Predictor	Strata	molar bonds	molar bands	
Age in years	<15	1	1	◄
	≥15	0	0	
Sex	Female	1	1	◄
	Male	0	0	
Location	1	1	0	
	2	0	1	◄
	3	0	0	

Figure 2 Allocation after second patient has been randomized and when the third patient arrives.

Predictor	Strata	Molar Bonds	Molar Bands	
Age in years	**<15**	**10**	**11**	◄
	≥15	10	10	
Sex	Female	11	9	
	Male	**10**	**11**	◄
Location	1	7	7	
	2	8	6	
	3	**6**	**7**	◄

Figure 3 Allocation when the 42nd patient arrives.

Cluster randomization

In certain situations, the randomization unit is not the individual but rather a cluster, which may be a family, a general practice, a village, or even larger geographical areas. Cluster randomized trials are conducted when individual randomization is not feasible (like water fluoridation), for the sake of convenience, or when the risk of contamination is high. Contamination in clinical trials occurs when participants in the trial arms share information regarding the intervention thus affecting/contaminating the treatment groups and thus not allowing the true effect of the intervention to be recorded due to bias (Hayes and Moulton, 2009b). Cluster randomized trials require more patients because within clusters, responses tend to be more similar thus reducing statistical efficiency (Hayes and Bennett, 1999). In orthodontics as clusters may be considered patients, jaws, jaw quadrants as they include from several to a few teeth. For example, a trial participant may be a cluster contributing 20 teeth for bonding, a jaw a cluster contributing 10, and a quadrant a cluster contributing 5 teeth. Clusters may also be considered repeated measurements on the same participants.

With cluster randomization restricted randomization, stratification and minimization may also be applied. Simple randomization is not appropriate especially with cluster randomized trials because usually the numbers of cluster cannot be very large and large imbalances on important outcome predictors are likely.

Apart from the methods presented above, other randomization schemes are available but are less frequently used and therefore will not be included in this article. For further details, the reader is referred to Martin Bland's directory of randomization software and services at http://www-users.york.ac.uk/~mb55/guide/randsery.htm

Allocation concealment

Allocation concealment is the mechanism used to assure that the produced randomization lists and consequently the treatment to be assigned to the recruited participants cannot be known or predicted by all involved parties. The objective of allocation concealment is to reduce selection bias and it always possible to be implemented. It has been reported that lack of allocation concealment has been associated with larger and biased treatment effects (Pildat *et al.*, 2007; Wood *et al.*, 2008).

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Allocation concealment should not be confused with blinding, which refers to whether patients and investigators know or do not know which intervention has been allocated (Chalmers *et al.*, 1987). The best approach for achieving allocation concealment is to use independent and centralized assignment, which does not involve trial investigators and staff (Haag, 1998). With this method, the randomization lists are held securely, away from the treatment locations, thus reducing the chance of looking at treatment assignments. In this scenario, an eligible patient after consenting and after the recording of his/her baseline characteristics will be assigned to the treatment group by either calling, by himself or with the assistance of the staff, the randomization centre in order to be assigned treatment.

If the external treatment allocation is not feasible, a common and simple method is to enclose assignments into sequentially numbered opaque envelopes. However, this method requires caution because envelopes may be opened and resealed, and therefore, it is suggested that assignment is not visible under the light and the patient's baseline information and name are written outside the envelope before opening it. Envelope storage may be at a different location from the trial site and envelopes that must be torn to open may be utilized. Finally, after treatment, allocation is given envelopes should be securely stored for assessment of allocation concealment procedures (Schulz, 1995). In the dental caries example, for orthodontic patients, a randomization list may be generated per centre and the letters A and B representing the molar bonds and molar bands group, respectively, may be printed, cut out and sealed in opaque envelopes. As the next patient is ready to be allocated treatment, the next envelope in sequence is drawn, opened and the letter A or B dictating allocation is pulled out (Figure 4).

For cluster randomized trials, special precautions are required since the randomization unit is the cluster. The ideal sequence of events would be to identify/recruit clusters and patients, randomize clusters, and then train staff to avoid recruitment bias (Hayes and Moulton, 2009).

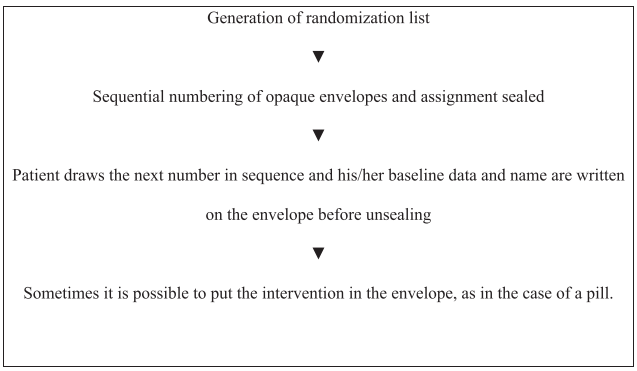

Figure 4 Outline of sequence of events when using sealed opaque envelopes.

Implementation of randomization

Implementation of randomization pertains to identifying by whom, when, and where the procedures of randomization, such as generation of randomization lists, allocation concealment, and treatment assignment, were implemented. Particularly, in small trials, it is possible that the same investigators have performed all above tasks; however, ideally there should be separation between the randomization procedures and the trial implementation. Assuming that the investigator generating the randomization list retains a copy of the list and checks when a new patient is recruited, then if he/she is partial towards an intervention, he/she may randomize the patient to the treatment he/she feels is more likely to prove his/her beliefs. Therefore, even if the first steps of the randomization process are conducted properly but somehow the investigator may subvert randomization, then the whole process will be biased.

Conclusions

Proper randomization is an integral part of proper clinical trial methodology. It aims at randomly assigning treatment to the trial arms without foreknowledge of allocation by the participants and investigators thus reducing selection bias.

Randomization includes generation of random allocation, allocation concealment, and the actual methodology of allocating treatment randomly and unpredictably.

Some of the most popular randomization methods include forms of restricted and/or stratified randomization and minimization.

Appropriate and secure techniques for allocation concealment and implementation of the randomization process are required.

References

Altman D G, Bland J M 1999a How to randomize. British Medical Journal 319: 703–704

Altman D G, Bland J M 1999b Statistics notes: treatment allocation in controlled trials. Why randomise? British Medical Journal 318: 1209

Altman D G, Dore C J 1990 Randomization and baseline comparisons in clinical trials. Lancet 335: 149–153

Chalmers T C, Levin H, Sacks H S, Reitman D, Berrier J, Nagalingam R 1987 Meta-analysis of clinical trials as a scientific discipline. I: control of bias and comparison with large co-operative trials. Statistics in Medicine 6: 315–328

Dumbrigue H B, Jones J S, Esquivel J F 2001 Control of bias in randomized controlled trials published in prosthodontic journals. Journal of Prosthetic Dentistry 86: 592–596

Gøtzsche P C 1989 Methodology and overt and hidden bias in reports of 196 double-blind trials of nonsteroidal anti-inflammatory drugs in rheumatoid arthritis. Controlled Clinical Trials 10: 31–56

Haag U 1998 Technologies for automating randomized treatment assignment in clinical trials. Drug Information Journal 32: 11

Harrison J E 2003 Clinical trials in orthodontics II: clinical trials in orthodontics II: assessment of the quality of reporting of clinical trials published in three orthodontic journals between 1989 and 1998. Journal of Orthodontics 30: 309–315

Downloaded from https://academic.oup.com/ejo/article/33/6/684/697107 by Universitätsbibliothek Bern user on 16 June 2022

Hayes R J, Bennett S 1999 Simple sample size calculation for cluster-randomized trials. International Journal of Epidemiology 28: 319–326

Hayes R J, Moulton L H 2009a Cluster randomized trials. Boca Raton, FL: Chapman & Hall/CRC. Interdisciplinary Statistic Series chapter 7

Hayes R J, Moulton L H 2009b Cluster randomised trials. Boca Raton, FL: Chapman & Hall/CRC. Interdisciplinary Statistic Series Chapter 5 & 6

Jadad A R *et al.* 1996 Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clinical Trials 17: 1–12

Jokstad A, Esposito M, Coulthard P, Worthington H V 2002 The reporting of randomized controlled trials in prosthodontics. International Journal of Prosthodontics 15: 230–242

Juni P, Altman D G, Egger M 2001 Systematic reviews in health care: assessing the quality of controlled clinical trials. British Medical Journal 323: 42–46

Kang M, Ragan B G, Park J H 2008 Issues in outcomes research: an overview of randomization techniques for clinical trials. Journal of Athlete Training 43: 215–221

Lachin J M, Matts J P, Wei L J 1988 Randomization in clinical trials: conclusions and recommendations. Controlled Clinical Trials 9: 365–374

McEntegart D J 2003 The pursuit of balance using stratified and dynamic randomization techniques: an overview. Drug Information Journal 37: 293–308

Moher D *et al.* 2010 CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. British Medical Journal 340: c869

Montenegro R, Needleman I, Moles D, Tonetti M 2002 Quality of RCTs in periodontology. A systematic review. Journal of Dental Research 81: 866–870

Pandis N, Polychronopoulou A, Eliades T 2010 An assessment of quality characteristics of randomised control trials published in dental journals. Journal of Dentistry 38: 713–721

Pildal J, Hróbjartsson A, Jórgensen K J, Hilden J, Altman D G, Gøtzsche P C 2007 Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. International Journal of Epidemiology 36: 847–857

Pocock S J 1993 Clinical trials: a practical approach. Wiley, Chichester, UK, Chapter 5

Pocock S J, Simon R 1975 Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 31: 103–115

Ryan P 1998 Random allocation of treatment blocks. Stata Technical Bulletin. STB-41, pp.43-66. Reprinted in Stata Technical Bulletin Reprints 7: 297–300

Schulz K F 1995 Subverting randomization in controlled trials. Journal of the American Medical Association 274: 1456–1458

Schulz K F, Chalmers I, Grimes D A, Altman D G 1994 Assessing the quality of randomization from reports of controlled trials published in obstetrics and gynecology journals. Journal of the American Medical Association 272: 125–128

Schulz K F, Chalmers I, Hayes R J, Altman D G 1995 Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. Journal of the American Medical Association 273: 408–412

Schulz K F, Grimes D A 2002 Generation of allocation sequences in randomised trials: chance, not choice. Lancet 359: 515–519

Scott N W, McPherson G C, Ramsay C R, Campbell M K 2002 The method of minimization for allocation to clinical trials: a review. Controlled Clinical Trials 23: 662–674

Sjögren P, Halling A 2002 Quality of reporting randomised clinical trials in dental and medical research. British Dental Journal 192: 100–103

Weir C J, Lees K R 2003 Comparison of stratification and adaptive methods for treatment allocation in an acute stroke clinical trial. Statistics in Medicine 22: 705–726

Wood L *et al.* 2008 Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. British Medical Journal 336: 601–605

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