Randomization. Part 2: Minimization

Nikolaos Pandis, Associate Editor of Statistics and Research Design
Bern, Switzerland, and Corfu, Greece

As I explained last month in part 1, during the randomization process, we generate and allocate interventions to trial arms in a way that ensures that neither the investigators nor the participants know or can predict ahead of time what treatment the patients will receive.[1] Simple, restricted block, and stratified randomization methods have been presented so far, and now minimization will be explained. Minimization is a randomization method that ensures balance of important prognostic factors between treatment groups without the disadvantages of stratification.[2,3]

Minimization, a form of restricted randomization, is considered to be a dynamic method, since the randomization list is not produced before the trial starts, but during participant recruitment. Additionally, minimization, in contrast to the previous methods, is considered to be an adaptive randomization technique, since future participant allocation depends on previous assignments.

In the trial example assessing the periodontal condition of orthodontic patients fitted with either conventional or self-ligating appliances, randomization by using the minimization method can assign participants to groups and use 3 prognostic factors: age (<13 or >13 years), sex (male or female), and oral hygiene status before treatment (bad, moderate, or good). The first patient or the first few patients are assigned through simple randomization (like tossing a coin). Let us assume that the first patient was assigned by using simple randomization to the conventional group and has the following characteristics: less than 13 years old, female, and bad oral hygiene (Fig 1). The patient is entered 3 times, which is equal to the number of the prognostic factors that we seek to balance for. The second patient will be assigned to the arm that improves the balance according to the preselected set of prognostic factors between the 2 trial arms. The second patient arrives and has the following characteristics: 11 years old, female, and moderate oral hygiene (Fig 2).

Submitted, revised, and accepted, August 2011.
Am J Orthod Dentofacial Orthop 2011;140:902-4
0889-5406/$36.00

doi:10.1016/j.ajodo.2011.08.016

Predictor	Strata	Conventional	SL brackets
Age in years	<13	1	0
	≥13	0	0
Sex	Female	1	0
	Male	0	0
Oral hygiene	bad	1	0
	moderate	0	0
	good	0	0

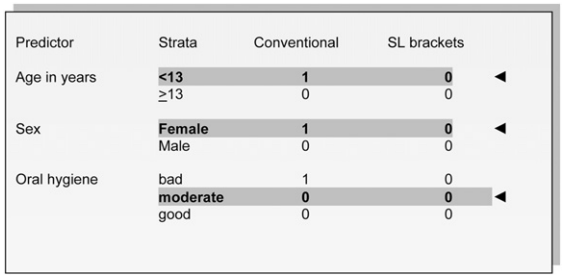
Fig 1. Allocation table after the treatment assignment for the first patient. Each patient is entered 3 times; this is equal to the number of the prognostic factors that we seek to balance for.

The next step is to calculate the marginal totals (marginal totals = sum of counts per treatment arm) at the line indicated by the arrows in each treatment arm for the prognostic factors of the second patient; the objective is to balance the marginal totals of the prognostic factors. On the conventional appliance treatment arm, the sum of the counts for patients enrolled who are younger than 13 years and female, and have moderate oral hygiene is 1 + 1 + 0 = 2; for the self-ligating appliance arm, the marginal total is 0 + 0 + 0 = 0.

Therefore, to improve the balance of age, sex, and oral hygiene status, the second patient must be randomized into the self-ligating appliance arm; the allocation of this patient is shown in Figure 3.

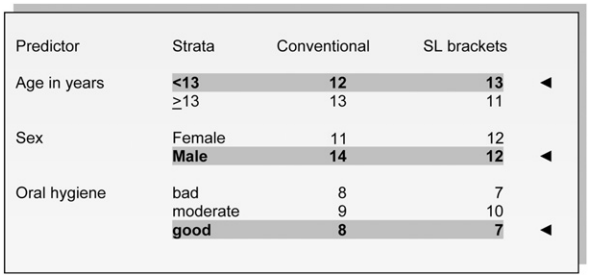
As new patients are recruited, they are randomized with a process that compares the marginal total for each arm (sum of counts per arm indicated by arrows) to the characteristics of the next patient to be recruited. To better understand this, let us assume that we have randomized 49 patients as shown in Figure 4. Then the next patient (number 50) happens to be male, 15 years old, with good oral hygiene. We will calculate the marginal total of his characteristics and allocate him accordingly. We will allocate him to the self-ligating arm, because the conventional appliance marginal total equals 34 (12 + 14 + 8 = 34), whereas, for the self-ligating appliance arm, the marginal total is 32 (13 + 12 + 7 = 32) (Fig 5).

If the marginal totals are equal, simple randomization can be used for the next participant. A potential problem



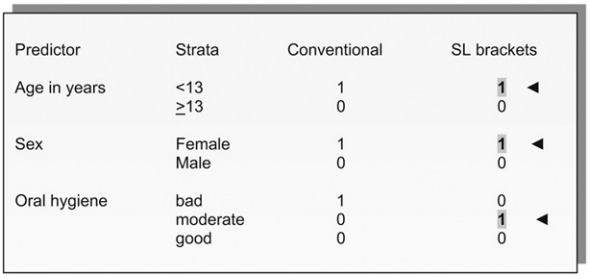
Predictor	Strata	Conventional	SL brackets	
Age in years	**<13**	**1**	**0**	◄
	≥13	0	0	
Sex	**Female**	**1**	**0**	◄
	Male	0	0	
Oral hygiene	bad	1	0	
	moderate	**0**	**0**	◄
	good	0	0	

Fig 2. Allocation table after the treatment assignment for the first patient and when the second patient arrives. *Arrows* indicate the characteristics of patient number 2.



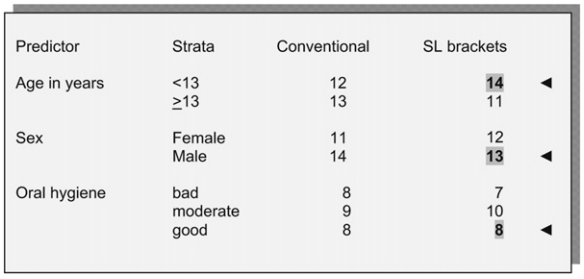
Predictor	Strata	Conventional	SL brackets	
Age in years	**<13**	**12**	**13**	◄
	≥13	13	11	
Sex	Female	11	12	
	Male	**14**	**12**	◄
Oral hygiene	bad	8	7	
	moderate	9	10	
	good	**8**	**7**	◄

Fig 4. Allocation table after the treatment assignment for the 49th patient and when the 50th patient arrives. *Arrows* indicate the characteristics of patient number 50.



Predictor	Strata	Conventional	SL brackets	
Age in years	<13	1	**1**	◄
	≥13	0	0	
Sex	Female	1	**1**	◄
	Male	0	0	
Oral hygiene	bad	1	0	
	moderate	0	**1**	◄
	good	0	0	

Fig 3. Allocation table after the second patient has been randomized. Each patient is entered 3 times. *Arrows* indicate the assignment of patient number 2.



Predictor	Strata	Conventional	SL brackets	
Age in years	<13	12	**14**	◄
	≥13	13	11	
Sex	Female	11	12	
	Male	14	**13**	◄
Oral hygiene	bad	8	7	
	moderate	9	10	
	good	8	**8**	◄

Fig 5. Allocation table after the treatment assignment for the 50th patient. Each patient is entered 3 times. *Arrows* indicate the assignment of patient number 50.

with minimization, especially for single-center trials, is the predictability of the next allocation because knowledge of previous assignments might indicate the next allocation. To reduce the predictability of the next assignment, 1 option is to intentionally bias the allocation toward the arm with lower marginal totals by introducing a random element with a probability greater than 0.5 and lower than 1 ($1 > P > 0.5$). By assigning the treatment of choice with a probability of $1 > P > 0.5$, we favor the group with lower marginal totals (trying to maintain balance), and we reduce the predictability of the allocation. In other words, we are introducing the random element when we want to reduce the predictability of allocation (and of course minimize imbalance) in favor of treatment with self-ligating or conventional appliances depending on which treatment is underrepresented at each particular step, since this is indicated by the marginal totals. So, if the marginal totals indicate that we must assign the next patient to the self-ligating arm, we would give the self-ligating arm, for example, a 0.75 assignment probability ($0.5 < P < 1$) instead of $P = 1$, whereas if we want to assign the patient to the conventional arm, we would give the conventional arm a 0.75 assignment probability (instead of $P = 1$).

Minimization has the advantages of balancing important prognostic factors, but it requires rigorous administrative efforts, especially when there are several prognostic factors, the potential of overmatching, and a higher risk for unmasking. Software is available for applying the method of minimization during randomization.[4,5]

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. This article includes a description of the generation of randomization lists. The next article will discuss allocation concealment and implementation of randomization.

KEY POINTS

- Minimization is a dynamic approach and assigns treatment based on previous allocations (adaptive).
- Randomization with minimization ensures balance in important prognostic factors, without the pitfalls of stratified randomization.

REFERENCES

1. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c869.
2. Pocock SJ. Clinical trials: a practical approach. Chichester, United Kingdom: Wiley; 1993.
3. Scott NW, McPherson GC, Ramsay CR, Campbell MK. The method of minimization for allocation to clinical trials: a review. Control Clin Trials 2002;23:662-74.
4. Evans S, Royston P, Day D. Minim: allocation by minimisation in clinical trials. Available at: http://www-users.york.ac.uk~mb55/guide/minim.htm. Accessed May 15, 2011.
5. Ryan P. Random allocation of treatment blocks. Stata Technical Bulletin. STB-41, p.43-66. Reprinted in Stata Technical Bulletin Reprints 1998;7:297-300.