allocation is made completely at random (44). Let us assume that allocation is accomplished by using a hat containing 50 red balls and 50 green balls. Each person that enters the enrollment office puts a hand into the hat, takes out a ball, and takes it to the pharmacy to receive Treatment A or Treatment B. With use of this method, it is possible for the first 30 or subjects to receive only Treatment A (none receiving Treatment B). It is only after every single ball is taken from the hat, can we be assured that equal numbers of subjects are receiving Treatment A and Treatment B (45). But a reality of clinical trials, is that efficacy and safety are continually monitored. Please contemplate the following hypothetical. Assume that the trial is still in its early phases, and only 30 balls have been taken from the hat, and that nearly all of the subjects are receiving Treatment A. Let us further assume, that Treatment A is an active control, for example, methotrexate (a very toxic anticancer agent), and let us assume that Treatment B is the antibody, trastuzumab (not particularly toxic). Now, returning to the hypothetical, it can be seen that most of the subjects in the early phases of the clinical trial may be experiencing severe toxic reactions, due to the methotrexate. As a consequence of the high prevalence of toxic reactions, the study investigators will request that the subjects be unblinded, and the nature of the treatments revealed, and the available data analyzed. In view of the high prevalence of toxic reactions, the investigators may also bring the trial to a temporary halt, and stop enrolling any more subjects. The above problem can be solved by blocked randomization.

Allocation and randomization by the technique of blocked randomization ensures that roughly equal proportions of subjects are allocated to Treatment A and Treatment B, from the earliest stages of the trial, on through the clinical trial, and as long as new subjects are being enrolled (46).

The following example is with blocks of 4 (four-unit blocks) (47). In this example, each block has a constant size of four subjects. In blocked randomization, the first four subjects are allocated to receive Treatment A or Treatment B, in this order: BBAA. The next four subjects receive Treatment A or Treatment B in this respective order: ABBA. And the next four subjects, respectively, receive Treatments A or B in the order: BBAA. In this way, the allocation is randomized. Also, by using the blocked randomization technique, balance between the number of subjects receiving Treatment A or Treatment B is ensured, from the very start of the trial.

Each block has a defined sequence, that is, AABB, BBAA, ABAB, BABA, ABBA, and BAAB. The particular order in which the blocks are utilized for allocating subjects is totally random. These blocks are four units long. But blocks of other sizes are used in clinical trials, for example, six-unit blocks. The agency conducting allocation does not reveal the block size to the investigator or to the subjects. Moreover, any given trial can use a mixture of 4-unit blocks, 6-unit blocks, or 10-unit blocks, for example. The effectiveness of

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