reactions, the study investigators will request that the subjects be unblinded, 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.

VI. 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.

The following example is with blocks of 4 (4-unit blocks) (35). In this example, each block has a constant size of 4 subjects. In blocked randomization, the first 4 subjects are allocated to receive Treatment A or Treatment B, in this order: BBAA. The next 4 subjects receive Treatment A or Treatment B in this respective order: ABBA. And the next 4 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 4 units long. But blocks of other sizes are used in clinical trials, for example 6-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.

VII. BLINDING

Blinding is desired for a number of reasons. Schultz et al. (36) divided these reasons into behaviors of the investigators and behaviors of the study subjects. The term *investigators* encompasses a variety of personnel, including trial designers, physicians and nurses, clerks who enroll study subjects, clerks who randomize the study subjects, and data collectors. Pildal et al. (37) report that there is no uniform standard as to the list of investigator personnel who must be blinded in a double-blind study.

[35] Matts JP, Lachin JM. Properties of permuted-block randomization in clinical trials. *Control Clin Trials.* 1988;9:327–344.

[36] Schulz KF, Chalmers I, Altman DG. The landscape and lexicon of blinding in randomized trials. *Ann Intern Med.* 2002;136:254–259.

[37] Pildal J, Hróbjartsson A, Jørgensen KJ, Hilden J, Altman DG, Gøtzsche PC. Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. *Int J Epidemiol.* 2007;36:847–857.