identified a few clinical studies where allocation was poorly controlled, and where there appeared to be consequent bias in the results.

According to Torgerson and Roberts (27), "[a] trial which has had its randomisation compromised may apparently show a treatment effect that is entirely due to biased allocation. The results of such a study are more damaging than an explicitly unrandomised study, as bias in the latter is acknowledged."

Randomization is a consequence of proper allocation. The reverse circumstance is not the case. According to Gluud (28), "[a]dequate randomization requires that the allocation of the next patient be unpredictable."

b. Simple Randomization

Simple randomization refers to the act of flipping a coin for each person enrolling in the trial, and using the coin flip to allocate the person to Treatment A or Treatment B. But according to Schulz and Grimes (29), this method of randomization can lead to errors, especially when the total number of people enrolling in the trial is small. For a clinical trial containing only 16 subjects, where eight are men and eight are women, the ideal clinical trial is one where four men and four women receive Treatment A, and four men and four women receive Treatment B. But it is intuitively obvious that imbalances are expected. The laws of probability inform us that it is quite possible for the coin-flipping technique to assign most, or even all, of the subjects to Treatment B. Other methods of simple randomization, for example, taking note of the subject's birth date (even--numbered birth date vs odd-numbered birth date) may be correlated in some way with some aspect of the subject's medical history, and therefore are not be truly random (30).

c. Stratification

Stratification refers to the act of classifying subjects according to subgroups, and equal allocation of the various subgroups to each of the study arms. In designing a clinical trial, investigators often divide the population into various subgroups. This activity is called stratification. Typically, stratification involves classifying each study subject according to gender, age (over 65 years vs under 65 years), stage of the disease (stage II vs stage III), and so on (31).

Vickers (32) provides a hypothetical example of stratification for a clinical trial on an antipain drug. Prior to enrollment, potential enrollees had two types of pain, for example, *bone pain* and *neuropathic pain*. Allocation according to subgroups might work in the following manner. Imagine that the first subject enrolling in the pain trial had *bone pain*. This subject is allocated to the treatment arm (not the placebo arm). The second subject to enroll has *bone pain*, and is allocated to the placebo arm. The third subject also has *bone pain*, and is allocated to the treatment arm. The fourth

[27]Torgerson DJ, Roberts C. Understanding controlled trials. Randomisation methods: concealment. Br. Med. J. 1999;319:375–6.

[28]Gluud LL. Bias in clinical intervention research. Am. J. Epidemiol. 2006;163:493–501.

[29]Schulz KF, Grimes DA. Generation of allocation sequences in randomised trials: chance, not choice. Lancet 2002;359:515–9.

[30]Berger VW, Weinstein S. Ensuring the comparability of comparison groups: is randomization enough? Control Clin. Trials 2004;25:515–24.

[31]Kundt G, Glass A. Evaluation of imbalance in stratified blocked randomization. Methods Inf. Med. 2012;51:55–62.

[32]Vickers AJ. How to randomize. J. Soc. Integr. Oncol. 2006;4:194–8.