simple randomization, for example taking note of the subject's birth date (even numbered birth date versus odd numbered birth date), may be correlated in some way with some aspect of the subject's medical history, and therefore are not truly random (16).

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 versus under 65 years), location of clinic (Wisconsin versus Texas), stage of the disease (Stage II versus Stage III), and so on. While it is useful to classify each study subject according to various criteria, it is even more useful to go one step further, and to ensure that each study arm contains a roughly equal proportion of male subjects, subjects in Wisconsin, subjects with Stage II disease, and so on.

Before continuing, note that stratification of study subjects into various subgroups is not the same thing as allocating study subjects into the various arms of the study.

Vickers (17) provides a hypothetical example of stratification for a clinical trial on an anti-pain 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 subject presents with **neuropathic pain**, so this subject is randomized to the treatment arm. The goal of stratification and allocation is to ensure that roughly equal numbers of subjects with a particular characteristic end up in the treatment arm and in the placebo arm.

Where the design of the clinical trial also contains the subgroups of male and female, prospective subjects are randomized into different blocks, that is, men with bone pain, men with neuropathic pain, women with bone pain and women with neuropathic pain.

In a clinical trial where study design does not have subgroups, subjects entering the trial are allocated by a random order, for example arm A, arm A, arm B, arm A, arm B, arm A, arm A, arm A, arm B, arm B, and so on. But where stratification is included in the study design, the allocation procedure attempts to ensure that arm A and arm B contain the same proportion of subjects with **bone pain**, the same proportion of subjects who have **neuropathic pain**, the same proportion of subjects who are **male**, and the same proportion of subjects who are **female**.

[16] Berger VW, Weinstein S. Ensuring the comparability of comparison groups: is randomization enough? *Control Clin Trials.* 2004;25:515–524.

[17] Vickers AJ. How to randomize. *J Soc Integr Oncol.* 2006;4:194–198.