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The Randomized Clinical Trial

by Carl G. Kardinal, M.D.

Randomized trials tend to reduce and even eliminate investigator and patient bias because patients want to get better and investigators want successful results. With proper stratification, balance between groups can be obtained and bias can be minimized. Randomized trials also negate Muench's Second Law: Results can always be improved by omitting controls.

Perhaps the most serious objections to randomized trials center around ethical issues. A poorly designed or improperly randomized study involving human subjects that will not or cannot answer a scientific question is by definition unethical. However, a well-designed prospectively randomized trial that asks a pertinent, timely, and scientific question is not necessarily ethical.

It has been argued that physicians have an obligation to use their best judgment and recommend the "best" therapy no matter how tentative or inconclusive the data on which that judgment is based. Problems arise when there is uncertainty about the value of a new therapy and doubt regarding the efficacy of standard treatment. Physicians involved in randomized trials make the intellectually honest admission that the best therapy is unknown. However, many physicians have difficulty admitting this to their patients. Still, the random allocation of patients in a well-designed clinical trial is more ethical than experimenting with a new therapy in an unscientific manner or basing treatment on clinical impressions or past experience.

The ultimate protection for human subjects who volunteer to participate in clinical trials is not the institutional review board (IRB), and not an elaborately designed consent form, but rather the responsible investigator who selects candidates based upon scientific merit and appropriateness for a specific clinical situation.

Although the principal aim of treatment trials is research, treatment trials also promote improved patient care, as well as professional education of health care providers. Well-designed treatment trials, in general, offer more than just state-of-the art care; they often are the best available treatment. The general public is currently more aware of the value of treatment trials, and cancer patients, in particular, are seeking out physicians and medical institutions that participate in clinical trials approved by the National Institutes of Health and the National Cancer Institute (NCI).

The factors motivating an individual to participate in treatment trials are complex. Patients with advanced life-threatening diseases such as cancer and AIDS are, as a rule, highly motivated to participate in clinical trials because avant-garde treatment offers them greater hope than standard treatment. As a result, the investigator has an even greater responsibility to meet a patient's needs.

Several years ago Dr. Helen T. Cupper and I evaluated a series of 50 consecutive patients with advanced cancer who were being treated on NCI-approved clinical trials. We discovered three primary factors motivating participation, factors that remain applicable today:

- hope that the new treatment would offer a better chance for control of disease
- altruism (i.e., even if the treatment did not help the individual patient, it might ultimately help others)
- trust that the physician would not have recommended an investigational therapy unless he or she thought it would help. (It is this issue of trust that places enormous responsibility on the physician investigator.)

The factors motivating an individual to participate in a disease prevention trial, such as a chemoprevention trial for breast or prostate cancer, are dependent upon a number of issues, including 1) an individual's perceived risk of developing the disease; 2) the severity of the disease to be prevented; 3) personal or cultural attitudes toward the disease to be prevented (i.e. a fatalistic attitude toward cancer); 4) the perceived efficacy of the proposed intervention; and 5) the perceived risk of the intervention.

The issue of perceived risk is exceedingly important with reference to prevention trials. If an individual believes he or she is at minimal or no risk for the development of a given disease, there is no motivation for participation in a prevention trial. If a woman believes her risk of getting breast cancer is no greater than her risk of being killed in an auto accident or drowning, she is unlikely to participate in the Breast Cancer Prevention Trial and may never even have screening mammograms. This is a major area for public education.

Other important barriers to clinical trials recruitment are cost of the trial, cost of transportation to the treatment/prevention site, cost of child care, lack of knowledge or support by primary care physicians, cultural and religious beliefs, lack of family support, personal safety concerns, and concerns about confidentiality. To be successful, the investigator and the sponsoring institution must be sensitive to all of these issues and work closely to establish a partnership with the subjects and their supportive care system. ■