Handbook of Clinical Trial and Epidemiological Research Designs

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Clinical Research Designs

A clinical trial is an *experiment* conducted with patients as subjects. The principles of good experimental design apply to clinical trials. The strongest experimental design (the "gold standard") is the randomized design in which subjects (patients) are randomly assigned to treatment groups. An important distinction in the purpose of clinical trials is that between therapeutic trials (comparing treatment methods) and prophylactic (or prevention) trials.

For an example of a therapeutic, randomized clinical trial is the study, read **A Controlled Trial of Immunotherapy for Asthma in Allergic Children** published in the *New England Journal of Medicine*, January 30, 1997 -- Volume 336, Number 5.

Key Features of the Randomized Clinical Trial

The randomized clinical trial is characterized by two or more therapeutic treatment groups. These groups are sometimes referred to as *arms*, particularly in cancer trials. One treatment may be a placebo control in which a biologically-inert substance (in a drug trial) is used. Placebo controls cannot always be used because of ethical or practical constraints. Often, the "control" condition is the treatment is the standard of care which is then compared to experimental treatments.

Psychologic and other potentially confounding variables can be controlled by coding the treatment in such a way that the subject cannot tell what it is; this is called a single-blind trial. The best control is where neither the subjects nor the investigators know which treatment a given subject is receiving; this is called a double-blind trial. Again, ethical or practical constraints may make blinding impossible.

Epidemiological (Nonrandomized) Research Designs

Often, for ethical or practical reasons, it is not possible to conduct true randomized studies. For example, we could not ethically design a clinical experiment to test the hypothesis that cigarette smoking causes lung cancer. Study designs have been developed in the field of epidemiology which are used in situations in which randomization is impossible. The designs we will discuss here are the *prospective or cohort study* and the *case-control study* (sometimes referred to as the *case-comparison study*).

In the simplest type of cohort prospective study two groups (cohorts) of subjects are identified, one of which is exposed to a clinical intervention, an environmental condition, or health risk factor, and the other group is

not. Suppose we were interested in the putative effects of aspirin in reducing the likelihood of colon cancer. We could identify the subjects, follow them prospectively through time (ten years, lets say) and determine if those who took one aspirin per day show lower color cancer rates than those who did not (This study is obviously an oversimplification). The major disadvantage of the cohort study, compared to the randomized study, is that the groups may not be equivalent on other factors such as diet or smoking history. For an example of a prospective cohort study read **Menopausal Estrogen and Estrogen-Progestin Replacement Therapy and Breast Cancer Risk** in the *Journal of the American Medical Association*, January 26, 2000, Vol. 283, Number 4.

In the case-control study a group of patients who already have a disease or other outcome (the cases) is compared to another group of controls who do not. Thus, such studies are conducted retrospectively, not prospectively. Suppose we are interested in exposure to environmental tobacco smoke ("second-hand smoke") and its possible exacerbation of asthma in children. We could identify asthmatic children with exacerbated symptoms and determine the proportion of them exposed to environmental tobacco smoke. Then, we identify asthmatic children without the exacerbated symptoms and determine the proportion of them exposed to environmental tobacco smoke. Let us say the incidence (risk) of exacerbation for the exposed group was 2.3% and for the unexposed group was 1.3%. Typically, the relative risk is found in case-control studies. The relative risk is 2.3/1.3 or 1.8. Thus, in this study asthmatic children exposed to environmental tobacco smoke were 1.8 times as likely to show exacerbation of symptoms as were those not exposed. Case-control studies also have the disadvantage, compared to the randomized study, that the groups may not be equivalent on other factors. Nevertheless, case-control studies are highly valuable for studying diseases that take years to manifest themselves, such as many cancers. For an example of a case-control study, read **Plasma Organochlorine Levels and the Risk of Breast Cancer** in *The New England Journal of Medicine* -- October 30, 1997 -- Volume 337, Number 18.

FDA PHASE 1, 2. 3, 4 DRUG TRIALS

The Food and Drug Administration published in the *Federal Register* on December 17, 1997 new guidelines on the design and terminology used in clinical trials. The following information is based on the older model and terminology used in drug trials. However, since existing published clinical trials, and those published in the near future, will use the existing terminology, the following information is still valuable.

Different stages of testing drugs in humans, from first applications in humans (Phase 1) through limited and broad clinical tests (Phase 3), to postmarketing studies (Phase 4).

PHASE 1 DRUG TRIAL: Phase 1 trials include the initial introduction of an investigational new drug into humans. These studies are typically conducted with healthy volunteers; sometimes, where the drug is intended for use in patients with a particular disease, however, such patients may participate as subjects. Phase 1 trials are designed to determine the metabolic and pharmacologic actions of the drug in humans, the side effects associated with increasing doses (to establish a safe dose range), and, if possible, to gain early evidence of effectiveness; they are typically closely monitored. The ultimate goal of Phase 1 trials is to obtain sufficient information about the drug's pharmacokinetics and pharmacological effects to permit the design of well-controlled, sufficiently valid Phase 2 studies. Other examples of Phase 1 studies include studies of drug metabolism, structure-activity relationships, and mechanisms of actions in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes. The total number of subjects involved in Phase 1 investigations is generally in the range of 20-80.

PHASE 2 DRUG TRIAL: Phase 2 trials include controlled clinical studies conducted to evaluate the drugs effectiveness for a particular indication in patients with the disease or condition under study, and to determine the common short-term side effects and risks associated with the drug. These studies are typically well-controlled, closely monitored, and conducted with a relatively small number of patients, usually involving no more than several hundred subjects.

PHASE 3 DRUG TRIAL: Phase 3 trials involve the administration of a new drug to a larger number of patients in different clinical settings to determine its safety, efficacy, and appropriate dosage. They are performed after preliminary evidence of effectiveness has been obtained, and are intended to gather necessary additional information about effectiveness and safety for evaluating the overall benefit-risk relationship of the drug, and to provide an adequate basis for physician labeling. In Phase 3 studies, the drug is used the way it would be administered when marketed. When these studies are completed and the sponsor believes that the drug is safe and effective under specific conditions, the sponsor applies to the FDA for approval to market the drug. Phase 3 trials usually involve several hundred to several thousand patient-subjects.

PHASE 4 DRUG TRIAL: Concurrent with marketing approval, FDA may seek agreement from the sponsor to conduct certain postmarketing (Phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in Phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time. [21 CFR 312.85]

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