SPECIAL ARTICLES

A NEW DESIGN FOR RANDOMIZED CLINICAL TRIALS

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Abstract This paper proposes a new method for planning randomized clinical trials. This method is especially suited to comparison of a best standard or control treatment with an experimental treatment. Patients are allocated into two groups by a random or chance mechanism. Patients in the first group receive standard treatment; those in the second group are asked if they will accept the experimental therapy; if they decline, they receive the best standard treatment. In the analyses of results, all those in the second group, regardless of treatment, are compared with those in the first group. Any loss of statistical efficiency can be overcome by increased numbers. This experimental plan is indeed a randomized clinical trial and has the advantage that, before providing consent, a patient will know whether an experimental treatment is to be used. (N Engl J Med 300:1242-1245, 1979)

CONTROLLED experimentation is now regarded as the principal way to collect scientific data on the value of medical treatments. The day is rapidly receding when ex-cathedra judgments dominate therapeutics. The term "clinical trial" is reserved for this type of prospective, controlled experimentation on patients, which represents one of the most important methodologic advances associated with the scientific basis of therapeutics.

CURRENT PRACTICE

Clinical trials can be grouped into two major classifications: randomized and nonrandomized studies. A randomized trial is defined as an experiment on patients in which the therapies under investigation are allocated by a chance mechanism. An important feature of this chance or random assignment of treatment is that neither the patient nor the physician knows the treatment to be used before the patient is formally entered in the experiment. Randomized clinical trials are comparative experiments that investigate two or more therapies. Nonrandomized clinical trials usually involve only one therapy on which information is collected prospectively. An evaluation is generally based on a comparison of the new data with historical control data that were not collected specifically for the comparison. Many difficulties are involved in comparing prospective data with historical control data because of possible biases from many different sources.[1] These potential biases are usually of such magnitude that the results of nonrandomized studies are often ambiguous and not universally accepted unless the therapeutic effect is very large. These same biases are not present to the same degree, if at all, in randomized trials.

Nevertheless, many investigators and patients are reluctant to participate in randomized clinical trials. This reluctance arises in part from the federal regulations *(Title 45, Code of Federal Regulations, Part 46)* for informed consent, which require that patients give informed consent before being entered into a study by a clinical investigator. These regulations are largely an American phenomenon, but similar guidelines are likely to be adopted in other countries.

The informed-consent procedure requires the treating physician to inform the patient about all risks and benefits associated with the trial, the alternative therapies available and the patient's right to withdraw at any time. If the treatments are chosen by randomization, the patient must be so informed. Sometimes the randomization process is described to the patient as "choosing the treatment by computer" or "tossing a coin." Only after a patient consents to participate (and, in a "blinded" study, only after completion of the study) will the actual treatment be known to both the physician and the patient. Ethically, a physician should only participate in such studies if he or she believes that all treatments under study have potentially equal therapeutic benefits.

One of the principal reasons why clinical investigators decline to participate in randomized studies is that they believe that the "patient-physician relation" is compromised in complying with the federal regulations. Even though, in truth, there may be no scientific evidence favoring any one treatment, physicians may find it difficult to tell patients that they do not know which treatment is best. This problem is especially common in discussions of new options for the primary treatment of a disease. For example, it is not an easy matter to discuss randomized clinical trials that use adjuvant therapy for cancer. The physician must tell the patient about a "promising" new adjuvant therapy that is being evaluated because of an "unsatisfactory" failure rate associated with primary therapy alone. Then, the physician must state that the patient may not receive the promising therapy because the new therapy will only be administered to some patients — the choice being made by "a toss of the coin." In diseases whose outcome is poor, patients are anxious to try "anything." The Laetrile experience attests to this behavior. It makes little difference that the bulk of new therapies have been shown to be of slight benefit and that they often generate higher morbidity. The patient prefers the new, "promising" treatment.

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Although not documented, there is reason to believe that many physicians participating in randomized clinical trials do not adequately communicate to the patient that the treatment is chosen by a chance mechanism. Likewise, patients may sign an informed-consent document, but at a later time have no recollection of signing it; they may even deny that consent was ever asked. Sometimes patients are given so much information that they do not comprehend the meaning of the randomization. Also, one must recognize that there is a distinction between legally informed consent and "understanding consent." Many physicians who participate in clinical trials say privately that if they were to comply with the letter and spirit of the federal regulations, very few patients would enter randomized studies.

It may be unrealistic to expect a patient with a serious chronic disease and under unusual stress to go against the physician's recommendation. Often the physician will simply state that he believes it best for the patient to enter the clinical trial and present the patient with documents to sign. In any event, there is serious cause for concern that the federal regulations governing informed patient consent may be unrealistic in practice. Attempts to make the regulations even more restrictive may result in the complete disruption of randomized clinical trials — undermining the scientific basis of therapeutic medicine and harming patients, who would be subject to inadequately tested treatments.

A Proposal

I propose a new way to plan randomized clinical trials. My design has the feature that, before consent is obtained, both patient and physician know whether an experimental treatment will be assigned. Nevertheless, the subsequent clinical trial is a true randomized study.

Consider a clinical trial that compares two therapies. One therapy, designated as A, is a control. The control treatment could be the best standard treatment for that disease. If the standard treatment is to do nothing, then no treatment is given. The other therapy is an experimental therapy designated as B. The object of the clinical study is to evaluate the therapeutic effect of B relative to A.

Figure 1 shows the schema for such a randomized study before the federal regulations for human experimentation were promulgated (details of stratification are omitted from this discussion since they would

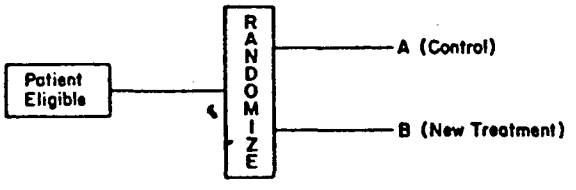

Figure 1. Conventional Randomized Experimental Design before Requirement for Informed Patient Consent.

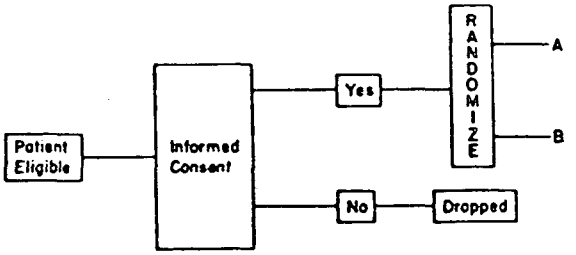

Figure 2. Conventional Randomized Experimental Design with Informed Patient Consent.

unnecessarily complicate the points at issue). Figure 2 shows how the schema is modified by the requirement for informed consent. Patients declining to participate are dropped and generally have no role in evaluation of the therapies.

Figure 3 shows the schema for the new type of experimental design suggested in the paper. After the patient's eligibility is established, the patient is randomized into one of two groups. One group (G_1) is called a "do not seek consent" group. Patients randomized for this group are not approached for consent to enter the clinical trial — they receive the best standard therapy (A). Patients assigned to the second group (G_2) are asked for their informed consent. These patients are asked if they wish to participate in the clinical trial and are willing to receive the experimental therapy B. All potential risks, benefits and treatment options are explained. If the patient agrees, the experimental treatment (B) will be given; if the patient declines to receive the experimental treatment, the patient will (presumably) receive the best standard treatment (A).

The proposed new design has the desirable feature that the physician need only approach the patient to discuss a single therapy. The physician need not leave himself open, in the eyes of the patient, to not knowing what he is doing and "tossing a coin" to decide the treatment. Thus, the patient-physician relation is not compromised. On the patient's side, there is also an important advantage: before providing consent the patient knows which treatment will be given. Many patients agree to participate in a randomized study but have reservations about continuing after the treatment is made known to them. At this point, some decline treatment and are considered "cancelled patients." However, others may continue the treatment, despite their reservations, because of the built-up momentum to do so and their reluctance to renege on their consent. My design requires a decision by the patient only on the experimental treatment. Hence, the patient's decision-making processes should be more straightforward. This new design cannot be used when there are important reasons for conducting a "double-blind" experiment — i.e., a trial in which neither the physician nor the patient knows the identity of the treatment during the course of treatment or its evaluation.

By a minor extension the experimental plan in

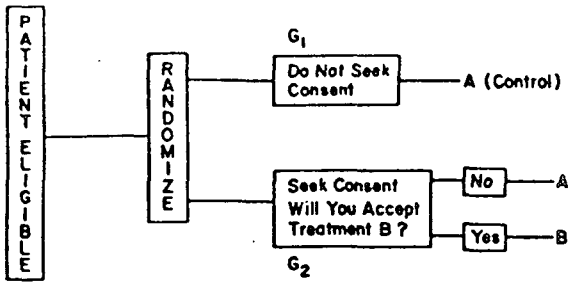

Figure 3. New Design — Patient Is Asked If New Treatment Is Acceptable after Both Options Are Discussed.

Figure 3 can be modified so that a patient assigned to the seek-consent group (G_2) is given a choice between treatments A and B. That is, instead of being presented with the opportunity to receive an experimental therapy, the patient is presented with the two therapies and asked to make a choice (Fig. 4). This approach may be particularly appropriate if one of the therapies is especially disfiguring or disabling. Selection of treatment would be based on the "value system" of the particular patient. At the same time, the clinical study would be a valid, randomized trial.

The analysis of this new design requires that Group G_1 (receiving only treatment A) is compared with Group G_2 (receiving treatment A or B). In other words, the comparison must be made with all patients in Group G_2, regardless of which treatment each received. It is clear that including all patients dilutes the measurable effect of treatment B. Nevertheless, all patients must be included if the analysis is to provide a valid comparison with treatment A. If only a small proportion of patients are willing to take treatment B, this experimental plan may be useless in evaluation of this treatment. However, the refusal of a large proportion of patients to agree to accept B may be interpreted to indicate that it is premature to introduce the experimental therapy into a clinical trial.

There is an apparent loss in statistical efficiency with the proposed new design. If P denotes the proportion of patients in the new plan who accept treatment B, the efficiency of the new design relative to a conventional experimental plan is P^2. This formulation assumes that, in both the conventional and new designs, half the patients are randomized to each group. There is no advantage to randomizing a disproportionate number of patients to either group. The efficiency of P^2 means, for example, that if 90 per cent ($P = 0.9$) accept treatment B, 81 patients ($100\ P^2$) would be needed in a conventional randomized design, as compared to 100 patients for this new design, to permit the same sensitivity in detecting treatment differences.

This loss in efficiency may be illusory, and the new design may be more efficient than a conventional randomized trial. Usually only a proportion of the eligible patients within an institution are approached by the clinical investigator to enter a trial. If adoption of the new design results in the entry of more patients into a study, it can be more efficient than a conventional design. Suppose θ = the ratio between the number of patients entering a study with the new design and the number entering a conventional study. The relative efficiency of the new design to the conventional plan is θP^2. Thus, if the new design results in the entry of twice as many patients, $\theta = 2$ and the efficiency is $2P^2$. If the proportion of patients accepting the new therapy is $P = 0.9$, the relative efficiency of the new design is $P^2 = 2(0.81) = 1.62$. In other words, the new design will be 1.62 times more efficient because twice as many patients are in the study.

Another aspect of the analysis is that one can evaluate the possible biases associated with patient selection of the experimental treatment B. Note that one can compare the patients in Group G_1 (receiving treatment A) with those in Group G_2 who are receiving treatment A because they declined to receive the experimental treatment B. The end points can be compared as well as the patient characteristics between the two groups.

The statistical analyses of the proposed new plan may be limited in that the design may not readily reveal interactions (or interdependencies) between the different effects of treatment and patient characteristics if these characteristics are related to the patient's selection of the therapy. For example, suppose patients in a clinical trial present with an important prognostic characteristic that takes two possible values, such as premenopause or postmenopause, two cell types, prior or no prior treatment and the like. For convenience I shall refer to the condition of this characteristic as α or β. Suppose that experimental treatment B has a better outcome than treatment A only in patients with characteristic β. In addition, consider the extreme situation in which all patients with characteristic β decline to accept treatment B. A comparison of the two groups would show no difference in response. If such a situation did indeed arise, it would be possible to recognize the problem by comparing the characteristics of patients who did and did not consent. Of course, such an extreme situation is unlikely, but the example serves to illustrate the problem.

There can be many variations of this new design. For example, the physician could seek consent from

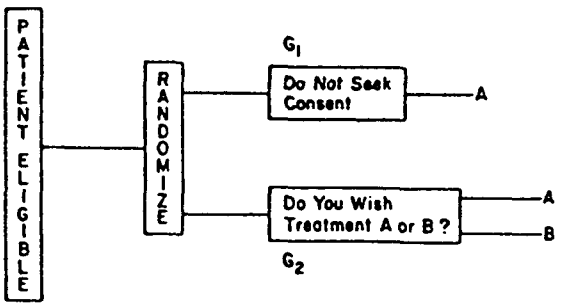

Figure 4. New Design — Patient Is Given Opportunity to Choose Treatment A or B after Both Options Are Discussed.

the G_1 group after randomization, thus assuring consent from all participants in the study. If a patient in this group preferred the experimental treatment to the best standard treatment, the physician would have little choice but to give the experimental treatment. Clearly, there would be a serious loss in efficiency in evaluation of the therapies if more than a small fraction of patients decided on the change.

Ethical Problems

The design proposed in this paper introduces several ethical problems that were not present in conventional, randomized clinical trials. The evaluation of experimental treatment B requires use of the data in the "do not seek consent group" (G_1). These patients are randomly assigned to this group without their knowledge. At least three questions arise. Should these patients be informed about their assignment to best standard treatment? Is it proper to offer only the experimental treatment to a subset of patients? Should permission be obtained to use the patient data?

Should the patient be informed about assignment to Group G_1? One view is that every patient expects to receive best standard therapy. It is only when there are departures from this expectation that the patient should be so informed. The patients in Group G_1 are receiving the therapy that they had every right to expect.

Is it ethical not to offer the experimental treatment to all patients? Receiving an experimental treatment is a privilege that cannot be extended to all patients. Usually, because of limitations in facilities, drugs, personnel and other factors, the experimental treatment can only be given to a subset of available patients. However, as noted above, it is every patient's right to receive best standard therapy. Physicians participating in conventional, randomized or nonrandomized clinical trials do not necessarily invite every eligible patient to participate. In general, the physician approaches those patients who are most likely to consent. A patient may fully understand the therapeutic issues and consent because he considers it in his best interest or wishes to participate in the accumulation of scientific knowledge; consent may be given out of ignorance if the patient is "doing what the doctor thinks best." In some institutions, patients from the higher socioeconomic groups are approached because the physician believes that they will better understand the risks and benefits. In other institutions, patients from the lower socioeconomic groups are approached because they may be more likely to leave the final decision with the physician. The use of the new design avoids this problem. Every eligible patient will have the same opportunity to be assigned to the group with the privilege of receiving an experimental treatment. There is no selection by the physician. This method seems to offer the fairest way to extend a privilege.

Finally, should the patient be informed about the use of the data being generated? The data from Group G_1 will be used, in aggregate, to compare the collective outcome in this group with that in Group G_2. This method is necessary for a statistical analysis of the results. No patient identification is required. The use of these data is no different from the possible uses of data from tumor registries or the retrospective reviews that clinical departments periodically perform to assess their experiences. In general, patients are not consulted about such reviews. In fact, the report of the Privacy Protection Study Commission[2] specifically exempts statistical and epidemiologic research from the requirement for the patient's explicit authorization before use of the data. (This exemption applies only under certain conditions that would be satisfied in research that used the new design.) Alternatively, the patients in this group could be informed that data on their treatment will be ultimately used to evaluate a new therapy. The federal regulations on patient consent only refer to the seeking of consent when a patient is "at risk" because of participation in a clinical trial. The use of the patient data, without identification, would not appear to place the patient at risk.

One further point should be mentioned. Patients in Group G_1, who receive the best standard treatment, will generally be managed better than they would be if a clinical trial were not in progress. Procedures for work-up and patient evaluation will be outlined in great detail. Times of follow-up study will be specified. The quality of the patient record will certainly be superior. Usually, a quality-control committee will determine whether the best standard treatment is given in an optimal manner. Thus, patients in the "do not seek consent group" will also benefit. Their involvement in the study will increase the quality of their care.

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To implement this innovation in planning randomized clinical trials, it is necessary for protocols containing such designs to be reviewed favorably by institution review boards. It is hoped that these boards can hear the issues discussed objectively. In my opinion, the adoption of the new design will lead to better clinical research and, at the same time, help the patient become more fully informed. The implementation of conventional randomized designs raises many questions about how informed patient consent is really obtained, whereas the proposed design provides a realistic method to comply with the spirit of the present federal regulations for informed patient consent.

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