2. CLINICAL TRIALS IN GENERAL

The evidence considered by the committee was almost wholly derived from randomized clinical trials, and it is appropriate to begin with some general remarks about this type of study.

The effects of drugs, whether beneficial or adverse, can be assessed in various ways. A traditional approach is to present a small number of case reports that are judged against other clinical experience. This kind of comparison between a few observations on a new treatment and a larger experience on standard treatments, may be convincing when the new drug has a clear-cut effect. More often, though, a new treatment produces a small improvement as compared with the standard treatment, or there is a relatively large number of variables that affect the outcome of therapy. In such situations, case studies, however carefully carried out, do not provide clear evidence of the improvement. What is needed is a controlled study using groups of explicitly defined patients who are comparable in all relevant respects, or whose potential lack of comparability can be allowed for in the analysis of the data.

Serious attempts to conduct large-scale controlled trials can be traced back to the 19th century or earlier.(7). The essential ingredients of present-day trials, however, are found notably in those planned during and after World War II, particularly those for the treatment of tuberculosis and cancer, and for prophylaxis against infectious diseases.(*8–12*) We may identify for special comment three aspects of a clinical trial to which much thought has been given; the assignment of treatments to patients, the assessment of the outcome for each patient, and the analysis and interpretation of the results.

It is very desirable that assignment of treatments to patients be done by a random mechanism, the most convenient form of which is a table of random numbers. Randomization ensures that groups are unlikely to differ materially in any prognostic factor, known or unknown. More specifically, it enables the investigator to determine the probability that observed differences in outcome between groups are due to sampling fluctuations rather than to real differences in treatment effects. Only when this probability is small can we feel confident that the treatment effects are really different. Without randomization there is no guarantee that differences in outcome are not due to the investigator's tendency to assign certain treatments predominantly to patients who have a poorer than average prognosis—a tendency of which he might be quite unaware. A further advantage of randomization is that it facilitates the use of methods for maintaining "blind" assessment, although it does not necessarily ensure their success.

If the response to treatment is thought to be influenced by one or more qualitative variables—such as sex, clinic, or stage of disease—a stratified system of allocation may be used to ensure that the treatment groups are balanced for these variables. Alternatively, simple random allocation may be relied on to produce near-equality of the groups for these particular variables, with a post hoc adjustment of the treatment comparisons in the subsequent analysis.

Experience has shown that the assessment of the response of a patient to a specific treatment may sometimes be influenced when either the patient or the investigator knows which treatment is being given. Even if such influence did not apply in a particular instance, it might be very difficult to be confident of this; hence * * *

The analysis of the results of a clinical trial centers on estimating the magnitude of treatment effects and assessing the precision of these estimates. The analysis will need to take account of concomitant variables and to adjust for any large discrepancies in base line characteristics arising despite the randomization. Furthermore, there might be interactions between treatments and various characteristics of patients, i.e., a tendency for the differences between the effects of particular treatments to vary with difference categories of patients.

In evaluating the results of trials, one must bear in mind the important role played by sample size in the ability of a trial to detect a difference of a given size. In trials of chronic diseases, where special importance lies in the rate of mortality or in the incidence of particular episodes of morbidity, the accuracy of the results will increase both with the number of patients entered into the treatment groups and also with the length of the follow-up period. When a trial with a relatively small number of patients or a short follow-up,

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References at end of article.