Research Related to Validation of Treatment Modalities by Large-scale Clinical Trials

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SUMMARY The history of randomized, controlled, clinical trials is reviewed. Cooperative clinical trials are reviewed and summarized, and specific needs for future trials are identified. Improved policy on resource allocation decisions for clinical trials vs other forms of research is necessary, particularly as such trials begin to translate improved therapeutic knowledge into community level disease control.

IN 1949 Sir George Pickering, in his presidential address to the Section of Experimental Medicine and Therapeutics of the Royal Society of Medicine, said:

Therapeutics is the branch of medicine that, by its very nature, should be experimental. For if we take a patient afflicted with a malady, and we alter his conditions of life, either by dieting him, or by putting him to bed, or by administering to him a drug, or by performing on him an operation, we are performing an experiment. And if we are scientifically minded we should record the results. Before concluding that the change for better or for worse in the patient is due to the specific treatment employed, we must ascertain whether the result can be repeated a significant number of times in similar patients, whether the result was merely due to the natural history of the disease or in other words to the lapse of time, or whether it was due to some other factor which was necessarily associated with the therapeutic measure in question. And if, as a result of these procedures, we learn that the therapeutic measure employed produces a significant, though not very pronounced, improvement, we would experiment with the method altering dosage or other detail to see if it can be improved. This would seem the procedure to be expected of men with six years of scientific training behind them. But it has not been followed. Had it been done, we should have gained a fairly precise knowledge of the place of individual methods of therapy in disease, and our efficiency as doctors would have been enormously enhanced.¹

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Treatment of atherosclerosis and hypertension has changed dramatically since Sir George made that statement. Therapeutic evaluation has improved since then, but much improvement lies ahead, and the attitudes against systematic assessment of therapeutic safety and efficacy still persist, though they are not as strong as in the 1940s. The history of clinical trials is temporally parallel to the history of the National Heart, Lung, and Blood Institute (NHLBI) and the American Heart Association (AHA). The first paper that fully described methodologic standards for the clinical trial was published by Sir Austin Bradford Hill in 1951.² In 1959, Professor Greenberg published his important methodologic advice on the conduct of cooperative field and clinical trials.³ By the mid-1960s, the Heart Special Projects Committee, a primary review group of the National Heart Institute, had prepared standardized recommendations for use by staff members of the Institute in planning and administering cooperative clinical trials in the cardiovascular field.

Throughout the history of large-scale trials, the ethical basis of the methods has been debated and discussed. In 1951, Bradford Hill said:

The first step in such a trial is to decide precisely what it hopes to prove, and secondly to consider whether these aims can be ethically fulfilled. It need hardly be said that the latter consideration is paramount and must never, on any scientific grounds whatever, be lost sight of. If a treatment cannot ethically be withheld then clearly...
no controlled trial can be instituted. All the more important is it, therefore, that a trial should be begun at the earliest opportunity, before there is inconclusive though suggestive evidence of the value of the treatment. Not infrequently, however, clinical workers publish favorable results on three or four cases and conclude their article by saying that this is the method of choice, or that what is now required is a trial on an adequate scale. They do not seem to realize that by their very publication they have vastly increased the difficulties of that trial or, indeed, made it impossible. For if it be a question of recovery or death, then the ethical situation produced by even inconclusive evidence may at times be such that the treatment cannot be withheld. It can, of course, be argued that more lives will be saved in the long run than are lost in the trial, but such an argument, valid, in my view, be advanced with very great caution. On the other hand, where life and death (or serious after-effects) are not at issue, the problem is clearly eased. It is also eased, more often than not, by the state of our ignorance. For frequently, we have no scientific evidence that a particular treatment will benefit the patient and, as Pickering points out, we are often, willy-nilly, experimenting upon them. It may well be unethical, therefore, not to institute a proper trial.7

This is reminiscent of Chalmers’ more recent advice to “randomize the first case.”8 In 1975 the Ethics Committee of the AHA published a discussion of ethical issues in large-scale clinical trials of cardiovascular disease.9 These issues are still before us.8

From this brief and selective history, it is clear that the methods of large-scale clinical trials of atherosclerosis and hypertension are continuously under discussion and development. The National Institutes of Health (NIH) in general and the NHLBI in particular have devoted substantial attention to improving the design, conduct and analysis of data from such trials. Almost all workers in this field agree: The randomized controlled clinical trial is the gold standard against which all other methods of therapeutic evaluation must be compared. It is the only method locked by law into the regulations for the demonstration of efficacy of new pharmacologic agents. It is the only method that has stood the test of broad application across a wide variety of diseases and treatment modalities.

The dean of applied statisticians, Professor John Tukey of Princeton, recently stated the situation:

Many of us are convinced, by what seems to me to be very strong evidence, that the only source of reliable evidence about the usefulness of almost any sort of therapy or surgical intervention is that obtained from well-planned and carefully conducted randomized, and, where possible, double-blind clinical trials . . . dare we prevent ourselves from obtaining reliable evidence?7

Having spoken in such laudatory terms about the randomized controlled clinical trial, perhaps it should be defined. A randomized controlled trial is a method for comparing two or more treatments for a given disease in which patients are, after admission to the trial, randomly assigned to a treatment group. One of the treatments may be a blank or placebo control group. In practice, randomization is carried out by a formal process using a table of random numbers or an electronic analog of such a table.

One of the earliest large studies in the field of atherosclerosis research was the landmark Cooperative Serum Lipoprotein Study.9 This study improved understanding of the role of serum lipids in the production of atherosclerosis and its sequelae. Its lineal descendants include the National Diet-Heart Feasibility Study, an elegantly designed randomized, fully double-blind trial comparing a therapeutic diet that contained reduced amounts of saturated fat with a “standard” American diet.9 This was one of the most elaborate trials ever attempted and involved producing special foods and supplying them through study commissaries. It also led the Heart Institute and most of the scientific community to the conclusion that a single-factor intervention trial involving dietary manipulation alone was probably not feasible because of the large numbers of participants required, even if only high-risk subjects were selected.

Instead, the Institute embarked upon the Multiple Risk Factor Intervention Trial (MRFIT), which is investigating simultaneous reduction of three risk factors — hypertension, elevated cholesterol and smoking — in a high-risk group of volunteer participants.10 In addition, the Lipid Research Clinics Program of NHLBI has as a major component the Coronary Primary Prevention Trial, a clinical trial that is testing the hypothesis that therapeutic reduction of blood cholesterol will result in a reduction of cardiovascular-related mortality.11

Other atherosclerotic phenomena — particularly, cerebral vascular disease — have been the target of large-scale clinical trials. These include the Cooperative Study on Anticoagulants and Cerebrovascular Disease,12 the Cooperative Study of Extracranial Arterial Occlusion and Insufficiency, which investigated the efficacy of surgical intervention on extracranial atherosclerotic lesions,13 and the Cooperative Study on Stroke and Hypertension, which investigated benefits of reduction of blood pressure in patients with a history of transient ischemic episodes.14

In hypertension, by consensus, the most important investigation has been the work of Freis and his colleagues within the U.S. Veterans Administration.15, 16

In 1971, the NHLBI initiated the Hypertension Detection and Follow-up Program.17 This is an unusual study. It seeks to examine a disease process at the community level, identifying and bringing under treatment all cases of elevated blood pressure within a geographically defined area, and to allocate half of them randomly to an intensive program of sequential pharmacologic intervention, comparing the outcome with that in control subjects referred to usual sources of health care in the community. Such a trial might be called an ecological intervention trial and represents an important new departure for NHLBI. The trial, as is the case for the MRFIT and the Lipid Research Clinics Program, is still in progress, and the final results have not been published.

The Coronary Drug Project investigated several pharmacologic treatments for the management of postcoronary patients using reinfarction and mortality as end points. The trial was instrumental in correcting many false impressions concerning the supposed efficacy of treatments in relatively widespread use at its inception.18 The Coronary Artery Surgery Study may clarify the effect of surgical revascularization procedures on survival and quality of life.19 The
trial is in its early stages, and results of other related investigations are still prompting much discussion.

The NHLBI has been centrally involved in the application of clinical trials to atherosclerosis and hypertension, which are the most important contributors to morbidity and mortality in the United States and most Western countries.

The lack of reference to studies supported by the AHA is conspicuous and must be explained. The mission of the research program of AHA is to use its limited resources to fill gaps in federal and other support programs. As a result, the AHA has traditionally concentrated its research funding efforts on "people programs" rather than on projects. The Established Investigator Program of the AHA was the prototype upon which NIH based its Research Career Development Award. This AHA allocation, plus the overall budgetary limitation mentioned earlier, have made it impossible for the AHA to fund large-scale therapeutic trials. Nonetheless, AHA's role has been monumental in providing publication outlets through its journals, in translating the results of such trials to modified professional practice through education programs and in translating these results into community change.

What is the future of large-scale trials in the validation of treatment and prevention modalities for atherosclerosis and hypertension? Some of the more obvious areas in which this method will be needed are mentioned here.

New noninvasive procedures for assessing the extent and possible regression of atherosclerotic lesions in the carotid, coronary and other arteries promise during the next few years to provide more sensitive end points than are currently available. Present trials suffer because they must use crude outcome criteria such as all-cause mortality, cardiovascular mortality, reinfarction, stroke and the like. These hard end points are necessary either because double blindness is not, in some instances, feasible or because methods of ascertainment suffer from large amounts of observer or other sources of bias and error. More sensitive end points can, in turn, produce more modest sample-size requirements and increase the feasibility of randomized trials. The example of noninvasive measurement of lesions illustrates the importance of a creative partnership between basic and clinical science and an area in which improved health technology can be directly translated into improved health of the general population.

When current large-scale trials are completed, important questions will undoubtedly remain. For example, MRFIT is based on volunteer participants at high risk of developing complications of arteriosclerosis and hypertension. It will be important to learn whether the results of this trial can be replicated in community settings, whether other intervention modalities, possibly including increased physical activity levels, should be added to subsequent trials and whether more sensitive end points can be applied to help reduce the cost of such investigations.

In hypertension, international studies of mild hypertension as well as the Hypertension Detection and Follow-up Program will not answer all questions. New methods for managing the mildly hypertensive patient will be developed and must be evaluated. Most important, however, is the need to pursue nonpharmacologic means for the primary prevention of hypertension. Reduction of body weight, control of dietary salt intake, alteration or reduction of psychosocial stress, and increase of habitual physical activity are all promising possibilities for such intervention, although the state of the art may not yet allow for initiation of a full-scale randomized trial.

Issues of public policy are among the most interesting in large-scale randomized therapeutic trials. How much of the federal medical research budget should be allocated to such trials? There exists at present a dynamic tension between so-called basic scientists (a term which should be reevaluated and replaced — is research at the bench really more basic to the health of the American people than research in the community?) and therapeutic evaluators. Bench scientists often argue that the more dollars allocated to clinical trials, the fewer dollars available for bench research. Others argue that the basic need is to increase the total number of dollars available for all health-related research, including therapeutic evaluation and bench research. There is perhaps no more important area to the health of the American public than that of health technology assessment and transfer. The "full-bucket" model, which asserts that the bucket only contains so many dollars, and if dollars are removed for one purpose, fewer will be available for another, is thought by many advocates of an improved health-research system to be entirely inappropriate as a basis for this debate. We should argue together for a larger and fuller bucket, rather than engaging in meaningless and mutually destructive debates.

Opponents of allocation to clinical trials sometimes argue that such studies often produce negative results. This is a curious position, since as Sir George Pickering suggested, the goal should be to improve effective treatment and to eliminate treatments that are worthless, whatever amount of opinion exists to support these worthless treatments in the absence of rigorous scientific justification based on controlled trials. Furthermore, our reluctance to embark early on randomized trials often means that such trials are only initiated after some substantial doubt arises concerning conventional therapy. Bradford Hill and Thomas Chalmers would have us begin our trials at a much earlier stage, and their reasoning seems compelling.

There is much argument that there should be more emphasis on investigator-initiated research and that large-scale therapeutic trials cannot be investigator-initiated. Review of some of the literature in investigator-initiated research — for example, in the area of the relationship between salt and hypertension — reveals a haphazard and chaotic scientific history in which promising leads are not followed up, in which many studies are too small to be conclusive and in which there is little coherence in overall investigative thrusts. This is not to argue against investigator-
initiated research, but simply to suggest that investigator initiation is not the fundamental issue. Coordination and coherence of research thrusts are the issue, and such coordination can be provided by voluntary action or by funding incentives. NHLBI does not embark on a large-scale therapeutic trial without soliciting opinions from a broad spectrum of non-governmental investigators. The NHLBI Advisory Council offers one level of protection against casual development of major trials, and the various task forces and expert panels convened by NHLBI offer a further safeguard. In this environment, the phrase “targeted research” loses most of its meaning; the targeting is more a product of the natural course of scientific development than an independent federal initiative.

The contribution of large-scale therapeutic trials to the understanding of atherosclerosis and hypertension has been substantial. At the same time, we have also learned to use the method more appropriately. In the next decade, the challenge will be to develop trials that translate improved knowledge from the laboratory and clinical sciences directly into improved health for the American people. The large-scale therapeutic trial is one of the most important devices for improving health through prevention, treatment and rehabilitation.

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