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ON CLINICAL TRIALS

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ABSTRACT

The subject of controlled clinical trials is reviewed. Based on the biomedical literature, the main problems encountered when undertaking a controlled trial are discussed from a logical and practical point of view. Emphasis is placed on the need for careful planning, assignment of responsibilities, sufficient number of observations, and adequate control. Ethical questions are viewed in clinical context. Preliminary steps to a controlled trial are outlined.

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1. INTRODUCTION

Background

In late 1965, a decision was made to transfer the contents of medical records connected with an irradiation technique employed by Donner Pavilion in treatment of certain diabetic patients onto a machine-sensible medium for purposes of analysis by means of computer processing. The basic impetus for this decision was the desire to enhance, if possible, the efficacy of this treatment. The question of a controlled clinical trial was raised, due to the unavailability of comparable data on patients of the same type not so treated. It was felt that an efficient way to broach the issues concerned with controlled trials would begin with a search of the relevant literature. What follows constitutes a report based upon a study of that part of the literature encountered which dealt with, or exemplified, the basic principles of controlled trials in clinical medicine. Statistical subjects are not dealt with as such.

Purpose

The aim of this report is to state clearly the central issues involved in a strictly controlled clinical trail. In a short report, of course, these issues can be discussed only in a general way. Actual wording of many of the most forthright and lucid spokesmen on the subject has been freely utilized;

it is hoped that their succinctness and exactness will repay careful reading. Since quoting out of context runs certain risks, however, this writer acknowledges that any errors of emphasis are his own. One point that recurs in the literature is worth anticipating: that is, the principles involved in a controlled clinical trial are straight-forward, but their successful application depends upon careful and exhaustive planning before the trial begins and a faithful adherence to the plan in executing the trial.

2. CONTROLLED CLINICAL TRIALS

The purpose of this section is to set forth the main ingredients of a controlled clinical trial. In a clinical trial, two or more treatments are to be compared. The individuals comprising a homogeneous set of patients are allocated to the different treatments by means of a random device. Steps are taken to ensure that assessment of treatment effects is unprejudiced. Sufficient observations are made to provide a determinate degree of protection against wrong conclusions. These ideas are amplified below.

A. The class of patients admissible to the trial must be operationally defined. That is, a series of operations is enumerated by which means it is determined whether any given person whatsoever is, or is not, eligible for admission. Ideally, none of these operations involves judgement; in practice, they all do to a greater or lesser degree. Included in the definition should be a description of the method or means of procurement of candidates.

B. The schedules of treatment to be compared are laid down in advance. All such matters as responsibility for administration, dosages, timing, routes of administration, etc. are included in the operational definition. "If clinicians taking part in a trail are free to vary the treatment just as they will then it must be clear that no specific question has been propounded and therefore no

specific answer can be expected" (Ref. 1, p. 280).

This point is worth stressing because it throws light on the difference between uncontrolled treatment and controlled treatment. It is not simply a matter of the presence or absence of a control group; they are logically different catagories of thing. If the treatment regimens are not laid down in advance, then (Ref. 2, p. 117)

> ...At the conclusion of such a trial we can in no circumstances compare the effects of the different regimens of treatment that have been used. These regimens have been determined by the conditions and responses of the individual patients; to observe then, at the end of the trial, the patients' differential conditions and responses in relation to their treatments is merely circular reasoning.

C. The treatments and the patients eligible for admission are related in one important way beyond the medical question of the relative merits of the treatments themselves. That is, given the state of knowledge at the beginning of the trial, it must be ethical to allocate any patient admitted to the trial to any of the treatment groups by means of a totally impartial chance mechanism. Any patient for whom this is not true is, by definition, ineligible for admission. Thus the definition of the class of patients admissible must be consistent with the definition of the treatments being compared.

D. The response criteria and the methods of their assessment must be operationally defined, again in advance of the trial. This, for a treatment the response to which is multidimensional, can be a formidable task. Much will have been wasted if at the end of the trial it is decided that the response criteria chosen were not good measures of the effect of real interest. Since these definitions determine the data collection, they should be pretested.

All methods of assessment are subject to error or bias or both. The so-called double-blind technique removes an important source of bias, namely, conscious knowledge on the part of the observer of the treatment which the subject being observed in fact received. It is used to prevent also any systematic bias in

response on the part of the subjects which might derive from the same thing. The importance of these safeguards is often underestimated.[3,4,5] The function of a placebo enters here.[6]

E. By "design" in the narrow sense is meant the specification of the formal procedures to be used in evaluating the data gathered during the trial. The specification requires that certain information pertaining to the trial be transmitted to the designer, in a quantitative form. Schneiderman lists the following questions in his very readable discussion[7] of the problem of the proper size of a clinical trial:

(a) How big a risk are you willing to take that, when the experiment is over, you will say that the two treatments are importantly different when they really are not?
(b) How big a risk are you willing to take that you will fail to detect an important difference?
(c) What is the smallest difference you think is important enough to find?

The answers to these questions determine the number of patients required in the trial. In general, the smaller the risk under (a) and (b), and the smaller the difference under (c), the more patients are required.

F. An important development in experimental therapeutics has been the adaptation of sequential methods. This is largely the result of the efforts of P. Armitage and I. Bross, building on the original work of Wald.[8]

Sequential designs permit the analysis of data as it is collected. The decision to stop the trial is made as soon as enough information has been accumulated, precluding the necessity of committment to a fixed a priori sample size, and making possible an early verdict.

Sequential methods have been used with effectiveness by clinical investigators in the realm mainly of chemotherapeutic agents whose dominant effects are manifest within a fairly short time after treatment. For discussion of the pros and cons of sequential analysis in clinical trials see Armitage[9-11] and Bross.[12,13]

3. WHAT IS THE BASIC AIM OF A CONTROLLED CLINICAL TRIAL?

At some time or another, a treatment is tried for the first time on one or more patients suffering from a given disease. If the justification of research in therapeutic medicine is improved patient care, the question soon becomes this: In what way, if any, was the subsequent course of illness in treated patients alleviated, compared with the course of illness as it would have been had they not been so treated? It is maintained that a controlled clinical trial is the best way to answer this question (in a significantly altered form) in an efficient and unimpeachable way.

First, inherent in the proposition is the assertion that there exists no special exception to scientific method in medicine. That is, the assertion concerns the notion of what constitutes proof of the efficacy of a given treatment applied to a specific class of patients. "The course of a disease process following a form of therapy must be shown to be improved over the natural course of the disease or over other standard treatment, and in a statistically significant number of cases" (Ref. 14, p. 72).

Secondly, the assertion is frankly contentious: it acknowledges that there are some clinicians who are opposed in principle to controlled clinical trials. This position, it is clear, is an ethical one. "The difference between haphazard therapy and a controlled clinical trial is that in haphazard therapy we carry out the experiments without design on our patients, and therefore our experiments are bad experiments from which it is impossible to learn. The controlled clinical trial means merely introducing the ordinary, accepted criteria of a good scientific experiment" (Ref. 15, p. 165).

That is to say, a controlled clinical trial is an experimental design which is consistent with the ethical limitations involved in therapeutic research. One who was categorically opposed to clinical trials would then be asserting his belief that the ethical limitations are insuperable. This position will not be

discussed here, since there is ample precedent in the literature for controlled trials.

In any case, a typical situation is as follows: there are at least two treatments to be compared, say, the "orthodox treatment" and the "new treatment," both having reference to the same class of patients. Laboratory and clinical data have accumulated, and there is reason to believe that the new treatment is superior, in some sense, to the orthodox treatment. Thus the belief grows that the new treatment is both safe and beneficial. "Neither belief, however, is established without some form of trial in man. Yet a very little experience of medicine shows that very often the beliefs are accepted without adequate trial and that very often they are wrong" (Ref. 16, p. 1044).

The basic aim of the controlled clinical trial is, then, to "...prevent the misinterpretation of coincidence and to restrict the number of variables which may complicate the assessment of the findings..." (Ref. 17, p. 1085). And, again, A. Bradford Hill: "The aim of the controlled trial is very simple: it is to ensure that the comparisons we make are as precise, as informative, and as convincing as possible" (Ref. 18, p. 4).

A controlled trial cannot establish that every patient will do better on, say, the new treatment. "No method of approach can do that. It does tell us that a greater proportion will do better on [it]. And that at least gives a guide to the practising physician faced with the individual patient" (Ref. 18, p. 169).

4. IN WHAT SENSE IS A CONTROLLED CLINICAL TRIAL BEST?

To state that a controlled clinical trial is, without qualification, the best way to compare the effects of two treatments is somewhat sophistical. It is best by definition among a wide class of mathematically formulated alternatives.

It is best in a strictly scientific sense, perhaps. It is an idea whose acceptance depends, as Keynes would say, "...upon a reflective judgement on the true character of the concept." There are undoubtedly situations which, because of exceptional circumstances, call for some sort of research falling short of a strictly controlled clinical trial.

It seems self-evident that, were it not for the ethical limitations inherent in experimental medicine, a procedure such as was outlined in Section 2 would be the best way to proceed, especially in the area of biological experimentation. Nevertheless, a characterization of experimental designs in purely mathematical terms is required to demonstrate the statistical "bestness" implied above. The question cannot be dealt with here (for a very readable and suggestive account see Ref. 19).

On the other hand, there seems to be no simple relationship between the logical components of an experimental design and the weight of the ethical problems encountered when the experimental subjects are patients, and the treatments are therapeutic regimens. Consider the whole controversy over randomization, for example. It is helpful, therefore, to separate the statistical from the ethical in contemplating a strictly controlled clinical trial. "In introducing ideas on experimental design, it is useful to disregard such difficulties for a moment and to consider how the experiment should be planned if it were concerned with plants or animals instead of with human beings" (Ref. 19, p. 23).[21]

There are then some features of the "bestness" of a controlled clinical trial in comparing responses to treatments which can be expressed in practical terms:

. Such methods give, within a year or two years, clear results in a field in which unorganized clinical work might not reach a conclusion in less than ten years (Ref. 22, p. 325).

. By emphasizing accurate and objective methods of assessment, and the use of reliable clinical and laboratory techniques, it can help to raise the standard of medical practice in that community (Ref. 23, p. 150).

. A controlled clinical trial is the quickest way to get knowledge; it improves enormously the good fellowship amongst doctors, and has to my way of thinking an undoubted educational value (Ref. 15, p. 167).

. Thus the alternative to a controlled therapeutic trial on a group of patients is a series of uncontrolled trials on a succession of individuals. There is no evidence that this alternative is safer than the controlled trial, and indeed the evidence from gold therapy in rheumatoid arthritis and atophan in gout would suggest that it is not (Ref. 24, pp. 11-12).

. If the gravity of decisions to be taken is greater than in other research, so much the greater is the need to plan the investigation for the avoidance of bias and for the elimination of subjective judgements about alternative explanations of the results. (Ref. 19, p. 28).

5. WHEN CAN A CONTROLLED TRIAL BE ETHICALLY UNDERTAKEN?

Writers on this subject are unanimous in insisting on one necessary condition for controlled clinical trials: this is the existence of evidence in favor of the proposed treatment. "In short, the controlled clinical trial is ethical when there is some sound presumptive evidence of the value of a new drug, but equally, considerable doubt about its complete superiority, in terms of immediate and long term side-effects, over the currently accepted treatment of choice" (Ref. 25, p. 1294) (see also Ref. 26, pp. 244-5). Medical records analysis can be of considerable help in guiding the investigators' thinking on this point.

Hill goes farther when he says that with every proposed controlled trial there is "...a whole series of ethical problems that have to be closely considered and solved before the trial is set in train and within the particular circumstances of that trial" (Ref. 16, p. 1046). In short, there is no point in dealing with ethical problems that will not arise; that is, the design itself must be specified before each step in the proposed trial which would actually occur need be examined. The discussion proceeds by (1) specifying the medical aims of a trial, (2) specifying the design protocol suitable for the question specified in

the first step, and (3) examining the protocol for ethical problems. The discussion continues until either an acceptable design is obtained (i.e., the questions posed can ethically be answered by controlled trial), or it is concluded that no ethically acceptable design exists (i.e., that no questions of suitable medical significance can be put which can be answered by a controlled trial).

6. WHEN SHOULD A CONTROLLED TRIAL BE UNDERTAKEN?

This is the question on which commentary in the literature is most scanty. Writing particularly on controlled trials of chemotherapeutic agents (on which there exists a relative abundance of commentary, as compared to surgical therapies), Witts has stated: "A therapeutic trial is desirable when a new remedy is introduced or when there is a genuine difference of opinion about the value of a drug in a particular disease" (Ref. 24, p. 10). This reasoning would appear to put the burden of justification for a trial on the shoulders of the skeptics. To advocates of the treatment, Green has suggested that "...where the value of a treatment, new or old, is doubtful, there may be a higher moral obligation to test it critically than to continue to prescribe it year-in-year-out with the support merely of custom or of wishful thinking" (Ref. 17, p. 1090).

Hill stresses that the period between the time a new treatment for a given disease syndrome is introduced and the time the prevailing medical opinion grows to consider unethical the withholding of that treatment (if it does) is the crucial interval during which "...a trial should be begun at the earliest opportunity..." (Ref. 1, p. 279). Against such an eventuality, Finney retorts (Ref. 19, p. 26):

> Nevertheless, medical research is not purely academic. The interests of both the general public and research workers lie in insuring that the superiority of good new treatments is demonstrated, that new treatments which are in reality bad or uselss are detected and discarded before they become part of the tradition of medical practice, and that conclusions are based on trustworthy evidence efficiently obtained.

This question bears considerable discussion and soul-searching.

7. THE QUESTION OF CONTROLS

Before discussing the practical steps involved in considering a controlled clinical trial it is worthwhile to focus on the subject of controls in experimental design, for two reasons. First, this question seems to engender the most controversy and, second, it illustrates for perhaps the same reason the importance of viewing statistical concepts in context.

Leaving ethical questions aside for a moment, it is clear that the questions asked in the first paragraph of Section 3 cannot be answered in the exact form given. Having treated a group of patients we cannot generally go back and "untreat" them. If the treatments being compared are of short duration and do not interact, this effect can be approximated by so-called within-patient comparisons. If one of the treatments permanently alters the patient physiologically, then the patient cannot serve as his own control. "The basic requirement of most clinical trials is concurrent 'controls,' in other words a group of patients corresponding in their characteristics to the specially treated group but not given that special treatment" (Ref. 26, p. 244).

The second exception to the general rule has been described as follows: "If in the past a disease has invariably and rapidly led to death there can be no possible need for controls to prove a change in fatality rate" (Ref. 26, pp. 247-48). "Therapeutic regimens used in diseases whose known courses are quite constant require less rigid controls for evaluation" (Ref. 14, p. 74).

The concept of adequate control is the logically most essential ingredient in an experimental design. Consequently, it is of crucial importance to the success of any controlled trial that its real significance in terms of medical practice be confronted and understood before embarking on the trial itself. It means simply this: all clinicians involved in the trial must agree that, except under prede-

fined or emergency conditions, the treatment allocated to a given patient admitted to the trial by the play of chance inherent in the randomization process shall be the treatment that patient receives, and receives under the schedule laid down by the protocol.

"The question at issue, then, is whether it is proper to withhold from any patient a treatment that might, perhaps, give him benefit" (Ref. 26, p. 244). Hill says elsewhere that the "...essential feature of a controlled trial that determines an answer to this question is that it must be possible ethically to give every patient admitted to a trial any of the treatments involved" (Ref. 16, p. 1046). Thus there is a principle of indifference involved in specifying the treatments to be compared. The probability that it will become necessary during the course of a trial to take a patient off his assigned treatment schedule can be minimized to the extent that there is true indifference built into the design by a careful definition of admission requirements and treatment schedules. Whether or not there is a positive answer to this question is also related to the degree to which the design of the trial allows unambiguous interpretation of the results. "In the interpretation of results, careful attention must then be given to the extent to which the validity of conclusions could be affected by imperfections of design; usually the statistician can do no more than point out the dangers, leaving to the experimenter responsibility for assurances that they are unimportant" (Ref. 19, p. 27).

Hill and others point out that <u>no special treatment</u> does not imply <u>no treatment</u>.[24,26] If a treatment is being subject to strictly controlled clinical trial for the first time, this question involves the planners in another dilemma, illustrated by the following example.

In a clinical trial of long-term anticoagulant therapy in cerebrovascular disease, the investigators faced this situation. They knew the assessment of

any treatment of cerebrovascular disease to be "...greatly handicapped by lack of knowledge of fundamental aspects of the condition" (Ref. 27, p. 597). In spite of foreseeable difficulties, they felt that "...the only satisfactory approach is by a strictly controlled clinical trial, in which the progress of patients receiving the treatment is compared with that of a similar group not so treated, but managed in the same way in all other respects over the same period of time" (Ref. 27. p. 598). In reviewing the history of this treatment the authors concluded that there was "...a considerable weight of evidence to support the use of anticoagulants in chronic cerebrovascular disease, yet none of the studies referred to fulfil[led] the criteria required in a strictly controlled trial" (Ref. 27, p. 598).

This situation must have raised some ethical doubts about withholding treatment from the control group (although the authors do not discuss the point). In any case, the control group received "...apparently identical tablets containing 1 mg. phenindione, an amount insufficient to interfere with the clotting mechanism" (Ref. 27, p. 601). At the end of the trial, the authors stated:

> The incidence of further non-fatal cerebrovascular accidents did not differ significantly between the two groups, but there were four deaths from cerebral haemorrhage and one from haemopericardium in the high-dosage group, compared with none in the low-dosage group. (The difference is not quite formally significant.) It has been concluded that, although anticoagulant therapy may be of benefit in certain restricted types of cerebrovascular disease, its general use in cerebrovascular disease may carry a definite hazard of cerebral haemorrhage.

It is well to remember in this connection that, for a fixed sample size, the probability of missing a real difference between treatment effects increases as the difference between the treatment levels decreases. Hill states the issue raised by such findings rhetorically: "At the start of the trial was it ethical to withhold treatment? At its end was it ethical to give it?" (Ref. 16, pp. 1044-45).

The point here is simply that the problem of defining what is to constitute "orthodox treatment" is a nontrivial one, and is best approached through an impartail weighing of evidence. If, in a situation where there is widespread belief on behalf of the new treatment, the control group receives a partial dosage, additional observations must be made in order to insure a high probability of detecting the difference, if it exists. On the other hand, if the new treatment really is better than a placebo, fewer contrasts will be required to establish this if a true placebo is used.

An example of utilization of the placebo technique in connection with irradiation of pituitary can be found in Ref. 6. "All patients were placed under the x-ray machine and all thought they were actually receiving roentgen radiation; however, actual radiation was not used on the controls" (Ref. 14, p. 73).

8. WHERE TO BEGIN?

Very little has been written concerning the manner of making the originating decision to perform a controlled clinical trial. In the reports of applications consulted for purposes of this paper (sequential medical trials) the various authors invariably began their discussions with a brief outline of the scientific status of the treatments being compared; these "reviews" were taken by this writer to constitute rationales for the trail being reported. None of the reports studied described in administrative terms the events leading up to the trail.

Mainland suggests that the process begins with a study of the literature. "An art cannot be learned merely by reading about it, but reading is helpful. Excellent general guides to controlled trials have been written by pioneers such as Bradford Hill[1,2,16] and Daniels,[22] and a summary of their writings may be useful as an introduction. What we need now is not a repetition of these general introductory statements but more details of controlled trials in various fields..." (Ref. 28, p. 485).

Those writers who have directed their attention in this manner to the practical problems connected with controlled clinical trials (notably Refs. 1, 2, 16, 22, 26, 28, and 29) all emphasize the critical importance of planning--planning that takes place under the aegis of a formal group responsible for the trial. "A specially formed research team under experienced leadership may be placed in control of the whole project, where this is in a single institution or clinic" (Ref. 23, p. 145).

Several of the planning problems such a group must face have already been mentioned:

- the type of case to be treated in the trial must be defined,
- the treatments to be compared must be strictly defined,
- the number of cases must be large enough to provide the desired degree of insurance against wrong conclusions,
- the routine and uniformity of examinations must be established before the trial begins,
- the record keeping must be uniform,
- the side effects of the treatment under trial must be studied as fully as possible.

"Once the details of the plan have been agreed, and the cooperation of all participants has been ensured, the practical conduct of the investigation should raise no difficulties."[22] Mainland cautions (Ref. 28, p. 487) that

> ...Tight plans take time to create, much more time than is dreamed of by those who have not previously taken part in a well-planned trial...[W]hen the planners have the usual other commitments of clinic chiefs and have not previously organized a well-planned trial, time estimates of the following order should be made:
>
> 1. At least a year should be allowed for drawing up the 'protocol' (the document containing the agreed plan) and the corresponding record sheets.

2. During this year, the planners (clinicians and one or more statisticians) should meet for at least 100 hours, e.g., for an eight hour day each month.

3. For every hour spent together, the planners must, individually, spend several hours (sometimes many hours) seeking answers for certain questions. This may entail a search for published or unpublished data or actual exploration.

The surest generalization was therefore expressed by A. B. Hill: "In general it will be seen that the essence of a successful controlled trial lies in its minutiae--in a painstaking, and sometimes very dull attention to every detail" (Ref. 1, p. 282). All writers stress the importance of close and continuous collaboration between clinician and statistician in the matter of design. "One eminent statistician has advised his fellows to eschew any part of a clinical trial in which they have not been active participants from its very inception" (Ref. 29, p. 356).

9. MEDICAL RECORDS ANALYSIS

Some of the key elements in the planning of controlled trial often can be provided by means of an analysis of medical records accumulated as a result of uncontrolled exhibition of the treatment in question during the period preceding a proposed clinical trial. In particular, a systematic analysis of the records connected with the use of the treatment in the past will provide, insofar as is possible, a clear picture of the following:

a. Characteristics of patients admitted for treatment. These data can be examined for homogeneity. Admission procedures in a controlled clinical trial must be formalized. Such a clarification of admission procedures can be aided by means of a clear picture of past policies.

b. Characteristics of treatment employed in the past, especially in terms of relating dosage to patient characterisitics.

c. Characteristics of the course of illness following treatment. This is important in defining methods of assessment and in providing initial estimates

of treatment effect necessary for statistical design.

d. Characteristics of methods of assessment. A good illustration of the relation between medical records analysis and controlled clinical trials involves the construction of a numerical measure of the effect of treatment. Carpenter reports[30] an attempt to establish a simple mathematical relationship (regression equation) between the clinician's assessment of overall response to treatment and certain objectively measurable response variables. It was felt that such an assessment method would serve as a check on clinical assessments, and might be a more systematic means of scoring response to treatment, thereby cutting down on the size of the trial. "Using this methods, a significant result [i.e., in favor of the treatment] has been obtained in a sequential trial of suphasalazine in the treatment of ulcerative colitis. It is estimated that by using this scoring system that result was obtained with about two thirds of the number of patients that would otherwise have been required" (Ref. 30, p. 41).

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