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# Planning Multicenter Clinical Trials: A Biostatistician's Perspective

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**ABSTRACT:** In the planning and management of multicenter clinical trials, the role of the biostatistician has been expanded beyond that of a passive statistical consultant to medical researchers. The biostatistician is a full member of the planning committee from the outset and assumes active participation and direction in protocol development and general study management. This article provides a discussion of this role from the perspective of the coordinating center biostatistician.

**KEY WORDS:** *clinical trials, multicenter, planning, coordinating center*

## INTRODUCTION

One of the most significant developments in medical research in the last 50 years has been the evolution and acceptance of the randomized controlled clinical trial. Although the philosophy of randomized clinical trials continues to be debated in the literature [1-5], most medical investigators would generally agree that the scientific principles embodied in this methodology have provided them a sound logical structure within which to work. Confidence in such a structure led to the application of the clinical trial methodology to medical questions that required resources available only through a multiclinic approach.

Since even the most elementary of clinical trials becomes relatively complex when conducted in a multiclinic setting, and since large sums of money are usually required to fund such trials, inadequate planning can result in considerable waste. The decision to conduct a trial as a multiclinic effort will have design implications for all aspects of the trial. A major goal of the planning effort must be to identify and prepare for potential problems that may involve medical or ethical issues, scientific rationale, or statistical methodology. Conducting a clinical trial simultaneously in several medical centers, all different in local administrative procedures and perhaps in quality of health care, will

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not meet with success unless the magnitude of the management problem is recognized from the start and adequate plans are developed for this function. This management function includes a range of activities for which control procedures must be devised, e.g., the coordination of fiscal activities between funding agencies and participating institutions, the coordination of data collection including development and field testing of common data forms, the statistical analysis and interim report preparation, and the coordination of monitoring committees. It is now a common practice in large-scale multicenter trials for many of the study management responsibilities to be assigned to special study coordinating centers. Such centers typically are staffed with individuals with backgrounds in management, statistics, statistical computing, and data processing.

The authors are biostatisticians at the Perry Point, Maryland Veterans Administration Cooperative Studies Program Coordinating Center (CSPCC) and have participated in the planning of more than 30 studies. The VA is a natural setting for multicenter activities since it has a relatively homogeneous administrative structure [6]. Nonetheless, VA studies are subject to the entire range of problems inherent in multicenter studies. In this article the role of the biostatistician in the study planning process is discussed. A review of the activities associated with planning and development should provide insight that may be useful for investigators and statisticians planning a clinical trial. The function of biostatisticians preparing for planning meetings is discussed and protocol development from the perspective of the biostatistician is reviewed.

## ACTIVITIES PRIOR TO THE FIRST PLANNING MEETING

### The Role of the Biostatistician

A biostatistician consulting on his or her first clinical trial is likely to be unprepared for such an experience, particularly if the trial is a large multicenter trial [7–10]. While statisticians frequently function as consultants, such a role is not adequate for describing the responsibilities of a biostatistician collaborating in a multicenter trial. A review of the literature yields few articles devoted to the role of the biostatistician in the planning of clinical trials. A literature search focusing on clinical trials methodology was reported by Schoolman [11], who reluctantly concluded that “we probably cannot retrieve very much information from the literature which discusses real methodologic problems in the execution of most clinical trials.” Difficulties encountered in obtaining relevant literature were reviewed in the Coordinating Center Models Project [12]. A literature search using the MEDLARS system was conducted for this article on appropriate keywords (clinical trials: collaborative; planning, organization). This search produced fewer than 10 citations that related directly to planning multicenter trials. The lack of relevant literature contributed to the establishment of the Society for Clinical Trials [13].

Among important contributions on the subject of clinical research are those of Hill [14], Mainland [15], and Feinstein [16]. These sources provide an invaluable introduction to clinical research in human subjects. However, the role of the biostatistician is not directly discussed by these authors. Perhaps

the clearest treatment of the subject is given by Ederer [17], who states, ". . . (the) statistician's role in developing a protocol for a clinical trial is much broader than might be supposed by a student completing a course in experimental design. The statistician in a clinical trial needs to be more than a consultant; he or she should be a full fledged partner of the investigative team and must take responsibility for the scientific integrity of the product." To be a "full fledged" member of the scientific team planning a clinical trial, the biostatistician must become involved from the outset. Clinical teams that view the statistician's role as an expert to be consulted only in the event that trials encounter unforeseen statistical problems often find that these problems could have been easily avoided by more thorough planning. The Veterans Administration has adopted as a matter of policy a model for conducting multicenter trials that recognizes the role of the biostatistician as scientific investigator and the importance of his early involvement [6]. Under this model the biostatistician becomes involved in a study when it is funded for planning. Study planning activities are directed and administered through a coordinating center which is organized around a staff of biostatisticians. It is through the biostatistician that the resources of the coordinating center are made available to a study planning committee. He retains a central role in coordinating and managing administrative activities not only during planning but also throughout all other phases of a study.

### **Planning Schedule**

An important decision that should be made early in preparation for planning activities is the selection of an appropriate time frame within which these activities are to be organized. Selection of a time frame requires consideration of the number of planning meetings, the amount of work that must be completed between planning meetings, and the protocol submission deadlines. Submission and meeting dates should be selected so as to infuse the planning activities with some urgency but at the same time should acknowledge the considerable work to be accomplished outside of formal meetings. Clinical technologies and practices can evolve rapidly. If years are spent in designing a trial, the planners may find that many aspects of the trial are outdated before it begins.

The amount of time that can be involved in planning studies is illustrated in Table 1 for 12 VA multicenter studies that have been planned and funded. Most of these studies required two or three planning meetings. The amount of time spent in planning ranged from 9 to 23 months.

### **Committee Selection**

Final decisions on the time frame for planning cannot be made until the planning committee has been selected. Members of this committee should be selected carefully to include not only individuals with demonstrated expertise in the study disease area but also individuals with expertise in other relevant areas. For example, a committee planning a drug study should include individuals familiar with relevant animal research, drug interactions, dose re-

**Table 1** Time (months) Involved in Study Planning for Selected VA Studies

Study	Date planning approved	Number of planning meetings	Number of months in planning
Characteristics of Psychiatric Programs & Their Relationship to Treatment Effectiveness (Ward Milieu)	July, 1972	3	23
Surgical Procedures for Duodenal Ulcer	November, 1974	1	10
Platelet Aggregation in Diabetes	January, 1975	4	17
Antabuse in the Treatment of Alcoholics on Methadone Maintenance	January, 1976	2	9
Patient Compliance and Its Role in Dental Plaque Control	March, 1976	2	11
Pharmacotherapy of Chronic Organic Brain Syndrome	March, 1976	2	20
Community vs. VA Nursing Home Care vs. Hospitalization in Psychiatric Patients	July, 1976	3	19
Evaluation of Anti-Epileptic Drugs in Well Defined Seizure Types	November, 1976	3	11
Drugs and Sleep—Phase III	February, 1977	2	11
A Comparison of Hospital and Home Treatment Programs for Aphasic Patients	March, 1977	3	15
Comparisons of the Peritoneovenous Shunt (LeVeen) and Conventional Medical Treatment Alone for Ascites	March, 1978	2	11
Asymptomatic Carotid Stenosis: Etiological Importance in Development of Stroke	November, 1978	2	11

sponse studies, bioavailability, and so on. The planning committee must represent a wide range of judgment and should include clinicians who will participate in the trial. This must be balanced against a need for eventual agreement on study objectives and study design, particularly if the proposed study treatment is controversial in nature. It is important to consider limiting the size of the committee. Although the optimum committee size will depend on a given study, the Guidelines for VA Cooperative Studies [18] recognizes the potential problems that may occur and sets an upper limit of eight members, two of which are the study chairman and study biostatistician. This is a reasonable approach that has worked well in practice. If necessary, additional individuals are involved as ad hoc consultants.

### Development of an Information Package

An information package should be prepared and disseminated by the study chairman and study biostatistician prior to the first planning meeting. In preparing this package a literature search should be performed and appro-

priate articles included along with a complete bibliography. At this time, the biostatistician must devote sufficient time and energy to what Ederer [17] called "... learning the clinical subject matter." He or she must become "... conversant with the terminology, natural history, available forms of treatment, and epidemiology of the disease under study." In short, the biostatistician "must be prepared to become both a student and teacher during the course of this work. This entails studying and learning in detail the clinical subject matter, and, if necessary, teaching elementary statistical and research design to collaborators." In assuming this role the biostatistician should contribute to the information package those articles on clinical trial methodology and related statistical concepts that will be useful to participants. The information package should also include a detailed agenda and timetable for the completion of all activities, a rough draft of a proposed study protocol complete with suggested study forms, a preliminary budget, a list of potential clinical centers with preliminary screening data, information about study drugs (IND, bioavailability, cost), a draft of informed consent procedures, and so on.

The preparation prior to the first planning meeting requires considerable time and effort, particularly on the part of the study chairman and study biostatistician, but in practice proves to be well worth the investment. The range of tasks that must be accomplished during planning often are the cause of some surprise among study planners. For example, the Coordinating Center Models Project (CCMP) [19] categorized the phases of clinical trials as (1) Initial Design, (2) Protocol Development, (3) Patient Recruitment, (4) Treatment and Follow-up, (5) Patient Closeout, and (6) Termination. The CCMP Research Group provided an exhaustive catalogue of activities associated with and carried out in each phase. More than 90 different activities are listed for the first two phases, Initial Design and Protocol Development.

## DEVELOPMENT OF THE STUDY PROTOCOL

The central thrust of all planning activity is the development of the study protocol. As a full fledged member of the planning committee, the biostatistician should be aware of his or her responsibility regarding several issues that are part of protocol development.

The study protocol should be the complete repository of information on all matters that are relevant to the study and its conduct. Since it must provide the basis for the resolution of any possible challenges during review, it must include a detailed literature review, bibliography, and justification for the trial; a clear and precise statement of study objectives, both primary and secondary; and a specification of the study design, both clinical and statistical. It should state in meticulous detail the rules and methods for executing the trial and for implementation of its organizational structure, including definition of various committee responsibilities, coordinating center responsibilities, reporting hierarchy, meeting schedules, and the like. It should also include plans for monitoring data quality, policies concerning termination of treatment regimens, plans for following dropouts, strategies for optimizing patient recruitment, and policies for publication. The importance of precision and attention to detail in writing a study protocol cannot be overstated. This

**Table 2** Selected Discussion Items for First Study Planning Meeting

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1. Time frame for study planning
  2. Establishment of study leadership
  3. Delegation of responsibilities associated with planning
  4. Development of study protocol
    - a. Study objectives, rationale, and significance
      - (1) Primary objective
      - (2) Secondary objective
    - b. Study design and methodology
      - (1) Patient population, inclusion criteria, exclusion criteria
      - (2) Treatment regimens: procedures for randomization, blinding, standardization
      - (3) Major study outcome variables and other study measures
      - (4) Length of follow-up and frequency of study measurements
      - (5) Sample size calculations and statistical considerations
    - c. Central labs or central data scoring
    - d. Study data forms
    - e. Special equipment needs
    - f. Study budget
    - g. Informed consent procedures
    - h. Plans for pilot screening and hospital recruitment
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is particularly true if a trial is to be carried out in a multicenter setting where standardization of procedures is essential.

A list of discussion items that should necessarily be addressed in a first planning meeting is provided in Table 2. A review of the time frame for planning as well as delegation of various responsibilities associated with planning is important and should be addressed before design issues are discussed. The role of the coordinating center in the planning process should be defined. As a minimum each of the items in Table 2 will need to be addressed in developing the protocol. The primary scientific and design issues for the trial are those regarding study objectives, study population, study treatments, length of trial, and patients' rights. The biostatistician fully shares in the responsibility for initiating planning discussion on any or all of these issues.

### Study Objectives

The substantive scientific issues should be spelled out in the initial protocol draft. The first step in protocol development is achieving a consensus regarding the study objectives. In a collaborative setting, definition of the study objectives is seldom a trivial task. Discussions often reach a stage where several objectives, often competing, emerge as important goals. Since the biostatistician is trained to evaluate each of the objectives from the perspective of implied statistical design and corresponding outcome variables, he should recognize early whether certain objectives are in competition, other objectives are not feasible or, as is frequently true, multiple objectives require several different studies. Even if a number of objectives are compatible, the issue of complexity remains. A clinical trial has the greatest chance for success if it is kept as simple as possible. A trial should be designed to answer a single major question. Secondary questions should be few in number and entertained only insofar as they are feasible within the context of the major study

design. Even the most elementary clinical trials are extremely difficult to manage in a multicenter setting.

Once a consensus has been achieved with regard to the major study objective, consideration and care should be given to its statement. The wording is critical to the study design. A number of authors have pointed out the importance for clinical and statistical design of a careful formulation of study objectives [15,16]. Clearly defined study objectives can more easily be translated into statements of study hypotheses that are consistent with the statistical design.

### **Patient Eligibility and Enrollment**

Implicit in the selection of a patient population to which the results of a study are to be generalized are patient eligibility requirements. These must be specified objectively both as inclusion and exclusion criteria. Procedures should be developed to insure that bias does not enter the patient selection process. Possible sources of bias therefore need to be identified and eliminated during protocol development. This requires that study patient screening procedures be thoroughly examined and that rules for patient selection be clearly specified in the protocol. Plans must be made to collect screening data on both eligible and ineligible patients in order that oversight committees can adequately monitor patient recruitment with regard to bias and standardization. The time immediately following the first planning meeting is ideal for testing the recruitment procedures with small pilot studies in medical centers that will participate in the main trial. Pilot studies serve another valuable purpose by providing estimates of the size of the pool of eligible patients that may be available for enrollment. These estimates are required for determining factors such as duration of patient recruitment and number of participating centers. If these estimates prove unreliable, adaptive strategies may have to be devised during the ongoing phase of the trial [20].

In addition to describing the methods that will be used for patient recruitment, the protocol should also describe procedures for enrollment, especially the rules by which randomization will be performed. There are many methods for carrying out randomization; these depend on such factors as the type of blinding, the number of stratification variables, and the types and degree of balancing which are considered necessary. The biostatistician must provide the necessary guidance to the planning committee in decisions about enrollment and randomization. Complex randomization schemes may be inconsistent with the statistical design in ways that may be obvious only to the biostatistician. An essential adjunct to the enrollment question is a consideration of study policy regarding patient rights. This will require the development of an informed consent package that meets societally and institutionally accepted guidelines for human experimentation.

### **Study and Control Treatments**

The most crucial decisions in planning after the formulation of the study objectives and specification of the patient population involve the selection of appropriate treatment strategies, including the number and type of control

treatments to be employed. A common criticism directed at controversial studies is that inappropriate or questionable treatment strategies were employed to test laudable study objectives. Study planners must anticipate peer criticisms of all proposed treatment regimens and choose the study regimens with the awareness that unless they are perceived as appropriate and generalizable the study results may not be accepted. Careful consideration must be given to all factors associated with a treatment regimen. For example, drug studies may require evidence regarding dose-response, bioavailability, and metabolism under different sets of conditions, including the concomitant use of other drugs; surgery studies may require evidence that the procedure can be performed with a high degree of proficiency and uniformity by study surgeons. In general, in any intervention trial, the study planners must anticipate potential criticism and be prepared to provide evidence that appropriate treatment regimens have been selected.

Another important consideration is the selection of appropriate control groups against which the study interventions can be compared. In some trials, the comparison group may be a standard treatment or therapy; in others, it may be a placebo, such as a sugar pill in a double-blind drug trial, or a sham procedure to mimic an experimental procedure; occasionally, it may be no treatment at all. In selecting control groups, it is important to recognize that estimates of treatment effects will be required for both the study treatment(s) and control treatment(s) in statistical calculations for sample size. Although treatment effects may be well-known in a standard therapy, they may not be known in a placebo or a no treatment group. Study planners should not assume that there will be little or no effect in either placebo or no treatment groups. In certain instances the magnitude of the effect can be surprising. Even in the case of no treatment there may be effects of unknown magnitude present (e.g., better clinical care, more attention, and the like) that are related to participation in a trial. Ethical standards must also be recognized in the selection of control groups. Control groups that appear ideal from the perspective of clinical and statistical design may unfortunately compromise widely accepted ethical principles. The latter are of paramount importance and should be recognized as such in planning. While the selection of study and control treatments must be decided by clinician members of the planning committee, the statistical implications of the selected treatment regimens must be reviewed by the biostatistician.

### **Standardization of Methods**

The study protocol must be specific in developing and elaborating rules for execution of the trial. It must contain standardized clinical operating procedures to which all participating clinical centers adhere in collecting study data. The issue of adherence to protocol is important and must be thoroughly examined during the protocol development phase. Adherence to protocol requirements by clinic staff in participating centers depends strongly on the clarity, detail, and preciseness with which the protocol is written. Study planning will not be complete until systems are developed for monitoring adherence. Quality control systems for study data monitoring can incorporate

sophisticated statistical techniques. The biostatistician must insure that monitoring plans are correctly developed.

Patient compliance with study treatment regimens must also be addressed in the study protocol. In order to provide a fair test for any study intervention, it is essential that measures be taken to ensure that it is followed. Certain interventions, such as surgery, may not be subject to major problems of patient compliance. On the other hand, the effects of any intervention which relies on self-administered activities (e.g., ingestion of study medication by daily pill taking) can be compromised by poor compliance. Patient compliance is often a difficult and illusive factor to measure. Nonetheless, it must be addressed during planning and the study protocol should stipulate the procedures that will be adopted to improve compliance as well as those that are devised to estimate level of compliance.

### **Outcome Variables**

Planners must carefully select outcome variables that are consistent with the objectives of the study. In the development and selection of these variables, the biostatistician must assume a guiding role. Many important issues, both clinical and statistical, are related to the selection of outcome variables. A critical characteristic of the primary outcome variable is how completely it measures those treatment effects on which efficacy should be judged. Some outcome measures are more objectively determined than others. Studies with results based on "hard" data, such as death, are often more credible and more persuasive to many reviewers than those that rely on "soft" data, such as global ratings based on an arbitrary scale.

Each variable must be examined for possible sources of measurement error and bias. Comparability of study measurements across centers can often be enhanced by centralization of such activities as laboratory analyses and ECG readings. There should be no unresolved or undocumented issues regarding validity or standardization. This is of particular concern for soft data. Studies should be performed to provide evidence of validity and both intra- and interrater reliability. Even though "hard" data are more objective they are not always free of subjective elements. For example, death from a specific cause may be a major outcome variable. Study deaths may be attributed to a number of different causes, only some of which are related to the study disease process. Adjudication committees can be established to assure unbiased and uniform judgment among all study centers.

### **Sample Size and Statistical Monitoring**

The selection of the major outcome variable will have a direct impact on the cost and feasibility of the study. Ordinarily it is this variable on which sample sizes are based. It is critical that planning committees be prepared to provide accurate estimates for those characteristics of the outcome variable that are necessary for sample size determinations. If estimates cannot be obtained from previous studies or clinical experience, it may be necessary to conduct pilot studies to provide these estimates. The estimated sample size will affect

such factors as length of patient recruitment period, number of participating centers, acquisition of supplies, and so on, all of which have a bearing on final cost. Inappropriate sample size estimates may result in incorrect cost projections. If the cost is too high, the resources may not be available. If the cost is too low, the successful conclusion of the study may be jeopardized.

Sample size evaluation is essential in planning a successful study. The biostatistician assumes the primary responsibility for this evaluation. He or she must elicit from the other study planners necessary information, such as differences between treatment groups that are considered clinically important, estimates of the standard deviations, as well as the significance level and desired power of the tests. No clinical trial that mobilizes resources of the magnitude of multicenter trials should be started without the selection of an appropriate sample size. Decisions made during this process must be stated in detail in the study protocol.

The development of sample size estimates is only one of many important statistical issues directly in the purview of the biostatistician. Study protocol development requires complete specification of all factors relating to study variables such as metric and statistical characteristics, and time and frequency of measurements. The biostatistician must also develop plans for creation of the computerized study data base system, procedures for monitoring data quality control, and plans for all statistical analyses. These plans must indicate procedures for dealing with multiple interim looks at data and rules for terminating the study. In considering which variables are to be included as study measurements, study planners must be aware that there is a cost associated with each item of information collected. Although measurement of some variables may incur special costs, e.g., the purchase of special equipment, all variables incur data collection and processing costs that are never insignificant. Therefore, substantial justification must be required for the inclusion of each study variable.

The biostatistician also has primary responsibility for developing interim reporting procedures and plans for final analysis. In long-term studies statistical tests are frequently performed at prespecified times during the course of a study. When these tests are performed at a prespecified Type I error level at each such "look," the overall Type I study error rate can be substantially inflated. Interim reporting procedures must be developed as part of the study protocol and the biostatistician must indicate what measures will be employed in the presence of this multiple look problem. Statistical methodologies are presently being developed in this area [21-26]. The biostatistician should incorporate in the study protocol a complete description of the statistical design and plans for final analysis. This should include types of statistical tests to be used, plans for monitoring baseline variables, and models that have been selected for fitting the data. A complete statistical section should review the statistical implications of the study design.

In this article we have discussed various aspects of study planning for multicenter trials, particularly the role of the coordinating center biostatistician in planning and study protocol development. The coordinating center biostatistician assumes responsibilities far beyond those of a passive statistical consultant. As a full fledged scientific member of the planning committee, the biostatistician shares final responsibility for the study design and logic.

The experienced biostatistician can provide invaluable assistance to study planners during the difficult planning phase of multicenter clinical trials.

## REFERENCES

1. Byar DP, Simon RM, Friedewald WT, Schlesselman JJ, DeMets DL, Ellenberg JH, Gail MH, Ware JH: Randomized Clinical Trials: Perspectives on Some Recent Ideas. *N Engl J Med* 295(2):74-80, 1976
2. Gehan EA, Freireich EJ: Non-randomized controls in cancer clinical trials. *N Engl J Med* 290:198-203, 1974
3. Chalmers TC, Block JB, Lee S: Controlled studies in clinical cancer research. *N Engl J Med* 287(2):75-78, 1972
4. Cutler SJ, Greenhouse SW, Cornfield J, Schneiderman MA: The role of hypothesis testing in clinical trials. *J Chron Dis* 19:857-882, 1966
5. Ederer F: Why do we need controls? Why do we need to randomize? *Am J Ophthalmol* 79(5):758-767, 1975
6. James KE: A model for the development, conduct, and monitoring of multicenter clinical trials in the Veterans Administration. *Controlled Clin Trials* 1(3):193-207, 1980
7. Feigl P: Training of statisticians for clinical trials: Introduction. *Biometrics* 36(4):677-678, 1980
8. Hammond D: The training of clinical trials statisticians: A clinician's view. *Biometrics* 36(4):679-685, 1980
9. Peterson AV Jr, Fisher LD: Teaching the principles of clinical trials design and management. *Biometrics* 36(4):687-697, 1980
10. Gehan EA: The training of statisticians for cooperative clinical trials: A working statistician's viewpoint. *Biometrics* 36(4):699-706, 1980
11. Schoolman HM: Retrieving information on clinical trial methodology. *Clin Pharm and Ther* 25(5, p2):758-760, 1979
12. Coordinating Center Models Project. A Study of Coordinating Centers in Multi-Center Clinical Trials. V. Bibliographic Resource for Clinical Trials. National Institutes of Health, Bethesda, MD, 1980
13. Meinert CL: Why another journal? *Controlled Clin Trials* 1(1):1-2, 1980
14. Hill AB: *Controlled Clinical Trials*. Oxford: Blackwell, 1960
15. Mainland D: *Elementary Medical Statistics*. Philadelphia: Saunders, 1963
16. Feinstein AR: *Clinical Biostatistics*. St. Louis: Mosley, 1977
17. Ederer F: The statistician's role in developing a protocol for a clinical trial. *Am Statistician* 33(3):116-119, 1979
18. Collins JF, Carter BD: *Guidelines for VA Cooperative Studies*. Fifth Edition, April 1981
19. Coordinating Center Models Project. A Study of Coordinating Centers in Multi-Center Clinical Trials. VI. Phases of a Multi-Center Clinical Trial. National Institutes of Health, Bethesda, MD, 1979
20. Collins JF, Bingham SF, Weiss DG, Williford WO, Kuhn RM: Some adaptive strategies for inadequate sample acquisition in Veterans Administration Cooperative Clinical Trials. *Controlled Clin Trials* 1(3):227-248, 1980
21. Armitage P, McPherson CK, Rowe BC: Repeated significance tests on accumulating data. *J R Statist Soc A* 132:235-244, 1969
22. McPherson CK, Armitage P: Repeated significance tests on accumulating data when the null hypothesis is not true. *J R Statist Soc A* 134:15-25, 1971

23. Canner P: Repeated analysis of clinical trial data. Proc 9th Int Biometric Conf 1:261–275, 1976
24. Canner P: Monitoring treatment differences in long-term clinical trials. Biometrics 33(4):603–615, 1977
25. O'Brien PC, Fleming TR: A multiple testing procedure for clinical trials. Biometrics 35(3):549–556, 1979
26. Fairbanks K, Madson R: *P* values for tests using a repeated significance test design. Biometrika 69(1):69–74, 1982