CLINICAL TRIALS – DESIGN, CONDUCT AND ANALYSIS (PART II)

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20. Interim data analyses for treatment monitoring

Pigs is pigs, data is data.

Jerome Cornfield (1975)

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20.1 INTRODUCTION

An interim analysis is any assessment of data done during the patient enrollment or follow-up stages of a trial for the purpose of assessing center performance, the quality of the data collected, or treatment effects. The kinds of tabulations and interim analyses needed for performance monitoring and data quality control are discussed in Chapter 16. Those discussed in this chapter relate to the treatment monitoring (also referred to as safety monitoring; see Glossary) carried out during the trial.

Major ethical questions arise if investigators elect to continue a medical experiment beyond the point at which more prudent people would have stopped. A case in point is the Tuskegee Syphilis Study, initiated in 1932 and continued into the early 1970s. The study involved enrollment and follow-up of 400 untreated latent syphilitic black males (and 200 uninfected controls) in order to trace the course of the disease. Criticism of the study stemmed from the fact that the syphilitics remained untreated after penicillin, an accepted form of treatment for the disease, became available (see Chapter 14 for references).

The need for treatment monitoring extends to most trials, whether they are done to assess a therapeutic, prophylactic, or diagnostic procedure, and whether they involve a fixed sample or sequential design, crossed or uncrossed treatment structure, short-term or long-term follow-up, or single or multiple clinics. Further, it extends over the life of the trial, beginning with enrollment of the first patient and continuing to the end of follow-up, regardless of how and when treatments are administered and even if patients are no longer being exposed to the study treatments.

Investigators have a responsibility to notify patients as well as the medical community of the preferred course of treatment once the choice is clear. Patients assigned to the inferior treatment should be removed from it (and offered the superior treatment if appropriate) as soon as the choice is clear.

The general need for treatment monitoring has been noted by the National Institutes of Health (National Institutes of Health Clinical Trials Committee, 1979). Published guidelines specify that:

- Every clinical trial should have provisions for treatment monitoring
- The mechanism proposed should be approved by responsible Institutional Review Boards
- Multicenter trials should have an independent treatment monitoring committee that:
  - Includes clinicians with expertise in the disease under study, biostatisticians, and scientists from other relevant disciplines
  - Excludes physicians caring for patients in the trial

A good rule of thumb is to design the trial with treatment monitoring unless there are overriding reasons to the contrary. (See Table 22-1 for classes of trials requiring safety monitoring.) Arguments concerning the logistical difficulties involved in carrying out the monitoring, or that are based on the assumption that the treatments are safe are not acceptable. The same is true for arguments based on the assumption that the treatment differences will be small.

All of the trials sketched in Appendix B include provisions for treatment monitoring. The picture appears to be different when viewed through the published literature. Very few of the papers reviewed in Chapter 2 contained any evidence of such monitoring, even those involving fairly long periods of follow-up. Either none was done or the investigators simply failed to mention it in their reports.

Interim analyses for treatment effects can be useful even if not needed for treatment monitoring. They help to ensure the orderly development of methods and procedures needed for analyses when the study is finished. In addition, they may reveal data deficiencies that can be corrected by modification of the data forms or study procedures.

20.2 PROCEDURAL ISSUES

Several questions must be addressed before any treatment monitoring can be done. One has to do with designation of the individual or group responsible for carrying out the analyses needed for monitoring and for generating the treatment monitoring reports. Normally, the responsibility is vested in the data center for the trial.

A second issue has to do with selection of the individual or group having responsibility for reviewing the monitoring reports and for deciding whether or not the trial should be allowed to continue. This review may be carried out by the same individual or group that was responsible for generation of the reports in the first place, or by someone else. The latter is the case for all the trials sketched in Appendix B and is the preferred mode of operation (see Chapter 23 for a discussion of treatment monitoring committees).

A third issue has to do with the schedule for interim analyses. They may be done on a fixed time schedule (e.g., after every six months) or on one determined by occurrences in the trial (e.g., after a certain number of deaths). All of the trials sketched in Appendix B had schedules (see item 29.g, Table B-4, Appendix B) that called for generation of two or three monitoring reports per year in conjunction with scheduled meetings of the safety monitoring committee. The staffs in the data coordinating centers were responsible for alerting members of the safety monitoring committees to unexpected changes occurring between meetings. In fact, the data coordinating centers in several of the studies (e.g., Coronary Drug Project and Veterans Administration Cooperative Study No. 43) distributed interim reports between meetings to allow members of the committees to call special meetings when appropriate. The frequency of meetings can be expected to increase as a study nears a decision point. For example, the Macular Photocoagulation Study (MPS) required two extra meetings of its safety monitoring committee before it decided in favor of photocoagulation for patients with senile macular degeneration (Macular Photocoagulation Study Group, 1982).

The usefulness of the monitoring process depends on a timely flow of primary outcome data from the generation site to the analysis center. It will be reduced by delays in the flow (e.g., see Chlebowski et al., 1981). It can also be diminished by delays in receiving or processing secondary outcome data based on reading of records, such as ECGs, X rays, or fundus photographs.

The general steps oulined in Section 17.7 concerning preparation of the analysis tape pertain to interim as well as final analyses. Each monitoring report should be based on a defined data set that is used to generate all tables in the report. The analysis tape(s) or disk(s) should be retained for a time following review of the report. Some tapes (disks), especially those used for generation of reports leading to a treatment change, should be kept indefinitely.

20.3 TREATMENT MONITORING REPORTS

The discussion that follows assumes that the reports are generated for review by committees, as described in Chapter 23. Table 20-1 provides a stylized outline of a "typical" report. The outline assumes that other tabulations needed for performance monitoring are contained in a separate report (see Section 16.7 and Table 16-5). Appendix G contains sample tables from the MPS treatment monitoring report and the list of tables appearing in a Persantine Aspirin Reinfarction Study (PARIS) treatment monitoring report.

The report should contain a table of contents

Table 20-1 Content of treatment monitoring reports

A. Table of contents

- List of tables and figures in report and associated page numbers

B. Narrative section

- Summary of main findings
- Discussion of special problems influencing interpretation of results
- Procedures used for preparation of report, including cutoff date for analysis, editing rules, etc.

C. Design summary section

- Purpose of the trial
- List of participating clinics
- Location of data center and other resource centers
- Recruitment goal and sample size specifications
- Study treatments
- Level of treatment masking
- Randomization or treatment unit
- Summary of patient admission criteria
- Prerandomization and follow-up examination schedule
- Projected timetable for the trial, including time for patient recruitment, follow-up, and final analysis

D. Data quality and quantity

- Number of patients randomized by treatment group and clinic
- Summary of missing information as reflected by:
  - Number of missed prerandomization and follow-up visits by treatment group and clinic
  - Number of patients classified as dropouts by treatment group and clinic
  - Number of patients lost to follow-up by treatment group and clinic
  - Number of missing items of information on completed data forms by treatment group and clinic
- Distribution of patients by time of entry (used to indicate the amount of follow-up information being generated and for predicting the amount of data that will be available at some point in the future, e.g., the number of patients who will have at least two years of follow-up by the next time the report is generated)
- Number of delinquent data forms by clinic (and by treatment group if there is concern regarding a differential delinquency rate, e.g., as in unmasked trials)
- Number and percent of deficient data items by clinic (and by treatment group in unmasked trials)
- Inter-aliquot differences in laboratory tests by clinic (and by treatment group in unmasked trials)
- Coding and data entry error rates by clinic with distributed data entry systems (and by treatment group in unmasked trials)
- Enumeration of special data problems that may influence interpretation of the treatment results

E. Population description summary section

- Frequency distribution of selected baseline demographic characteristics, such as age at entry, sex, race, etc., by treatment group
- Descriptive tabulations for selected baseline laboratory and physiological measures (e.g., cholesterol, body weight, diastolic blood pressure, etc.) by treatment group
- Other summary tabulations of entry characteristics needed to provide a baseline for evaluation of subsequent changes by treatment group, with particular emphasis on known or suspected risk factors for the disease or outcome of interest

F. Treatment administration summary section

- Number of patients assigned to each treatment group
- Number of ineligible patients enrolled by treatment group
- Number of patients who refused the assigned treatment by treatment group
- Number of patients who received a treatment other than the one assigned by treatment group
- Summary tables describing the level of adherence over the course of follow-up by treatment group
- Number of instances in which treatment assignments were unmasked (in the case of masked trials) by treatment group

G. Treatment effects summary section

- Number and percent of patients dead by treatment group
- Percent of patients who experienced the primary outcome at, or before, a specified cut-off date by treatment group
- Lifetable analysis of the primary outcome to provide event rates by treatment group over the course of follow-up
- Percent of patients experiencing an indicated secondary outcome by treatment group
- Lifetable analysis of each secondary outcome of interest by treatment group
- Subgroup analyses by treatment group, using selected entry characteristics as a means of adjustment for baseline differences in the composition of the study group and for identification of treatment effects within subgroups
- Multiple linear or logistic regression and Cox regression analysis (see Chapter 18) as a means of adjusting outcome data for differences in the baseline composition of the treatment groups
- Treatment comparisons involving the outcome of primary interest by treatment group and level of treatment compliance
- Summary table of percentages and rates for the primary and secondary outcomes as contained in current report as well as corresponding values from previous reports
- Summary tabulation of patients experiencing indicated side effects by treatment group

H. Special analysis section

- Listing of special problems not covered in other sections of the report, especially any that may temper interpretation of the treatment results
- Special tabulations designed to provide information on the natural course of the disease under study

(Section A, Table 20-1). Pages in the report should be numbered and stapled or bound in some other fashion. The tables and graphs in the report should have titles that are self-explanatory. Axes of graphs should be labelled. All information in the report should be checked for accuracy prior to inclusion.

Section B, the narrative section, should indicate who prepared the summary, the amount of data included in the report (by indicating the cut-off date for data), and should include a summary of the key findings contained in the report. This section should also be used to remind committee members of any deficiencies in the quality of data and of coding or editing procedures that might affect the way in which results are interpreted.

Section C should contain a digest of the key design features of the trial. The section may not be necessary if committee members have an intimate knowledge of the study and meet regularly. It is useful for complicated trials and for committees that meet only a few times a year.

Section D should provide data on the nature of the database. Tabulations indicating the number of missed follow-up visits, the number of dropouts, and number of patients lost to follow-up are important indicators of the completeness and adequacy of the database and should be included in each report.

Section E serves two functions. It should indicate the baseline comparability of the treatment groups and provide a description of the study population. Knowledge of the study population characteristics is important for generalization of treatment findings.

Information on the treatment process is summarized in Section F. It should provide data on patient and physician compliance to the treatment protocol. The treatment results are summarized in Section G. It is the most important and largest part of the report.

A typical report may contain a number of other tabulations distributed throughout the sections already mentioned, or contained in a special section at the end of the report. Some of them may be standard and appear in each report, whereas others may be prepared in response to a specific request and may appear only once.

Reports, after they have been reviewed, should be stored at a central repository (usually the data coordinating center). The written record (minutes of the meeting) generated during review of the report (also stored in the repository) should indicate when the report was reviewed and the specific actions recommended, if any, as a result of review.

20.4 SPECIAL STATISTICAL PROBLEMS

The need to make periodic treatment comparisons of the outcome data over the course of patient enrollment and follow-up gives rise to what is termed herein as the multiple looks problem. Two other problems, termed herein the multiple outcomes problem and the multiple com-

parisons problem, are likely to be encountered as well. The first problem is unique to interim analyses. The other two can arise in conjunction with any data analysis, whether done during, or at the end of the trial.

20.4.1 The multiple looks problem

This problem has been addressed by various authors (e.g., Abt, 1981; Anscombe, 1953, 1954; Armitage et al., 1969; Bailey, 1967; Brown, 1983; Canner, 1977a, 1977b, 1983a, 1983b; Cornfield, 1966a, 1966b, 1969, 1976; Coronary Drug Project Research Group, 1972, 1973b, 1981; Dupont, 1983a, 1983b; National Cooperative Gallstone Study Group, 1981a; Seigel and Milton, 1983; O'Brien and Fleming, 1979; Royall, 1983; University Group Diabetes Program Research Group, 1970e, 1971b, 1975). Some investigators have ignored the problem by behaving as if each look is the only one to be performed and have followed conventional rules for interpreting p-values (i.e., have behaved as if a test result is statistically significant at the 5% level if its p-value is ≤ 0.05). This approach has obvious shortcomings, forcefully illustrated by Anscombe (1954). He has shown that the probability of obtaining a "significant" result approaches unity when a test of significance is performed at various points over the course of a study.

Cornfield (1976) has commented on the same problem in more picturesque terms:

> *Just as the Sphinx winks if you look at it too long, so, if you perform enough significance tests you are sure to find significance, even when none exists.*

He relied on the likelihood principle to address the problem (Cornfield, 1969). Crudely stated, the principle specifies that the information contained in a data set is independent of the way in which the set is ordered (Dupont, 1983a, 1983b). Cornfield's method of analysis yields two probability calculations—one under the null hypothesis of no treatment effect and the other under a specified alternative to the null hypothesis. The ratio of the two probabilities has been referred to as the relative betting odds (RBOs) by Cornfield, since the resulting value provides a measure of the support for the null hypothesis, relative to a specified alternative. (See the University Group Diabetes Program Research Group, 1970e, 1971b, 1975 for illustrations of the method.)

Another approach involves use of simulation techniques to produce monitoring bounds, such as those used in the UGDP and CDP (University Group Diabetes Program Research Group, 1970e, 1975; Coronary Drug Project Research Group, 1973b). Figure 20-1 is a reproduction of the bounds used for the tolbutamide-placebo mortality comparisons in the UGDP. Figure 18-2 is an illustration of the same concept, as used in the CDP. The bounds pictured represent, in effect, the 95% statistical limits of variability that one would expect in the observed test-control treatment differences for the method of comparison used if it were possible to repeat a trial many times under the null hypothesis and assuming a set number of data looks over the course of the trial. Viewed as a decision-making tool, a trial continues so long as the observed test-control difference for the specified outcome remains within the bounds. The test or control treatment is terminated if the observed difference crosses one of the boundaries.

20.4.2 The multiple outcomes problem

This problem arises whenever two or more outcome measures are used to assess the study treatments. The need to look at multiple outcomes exists in most trials, even those designed to focus on a primary outcome measure. Analyses are rarely restricted to that measure alone.

Among the three problems listed, this one is the most difficult to address. It is complicated by the fact that the primary and secondary outcomes of interest are likely to be interdependent (Cupples et al., 1984). The usual approach is to ignore the interdependence and to make comparisons involving the different outcome measures as if they were independent of one another. The practice can lead to erroneous conclusions unless results are interpreted with caution. For example, one might be impressed with a statistically significant difference in nonfatal MI rates favoring the test treatment in a heart study with mortality as the primary outcome. However, the result is only of interest if there was no test-control difference in mortality or if the difference favored the test treatment.

A common practice in trials involving death as the outcome measure is to focus on cause-specific mortality, for example, cardiovascular deaths in MRFIT (Multiple Risk Factor Intervention Trial Research Group, 1982). The tests of significance obtained in such cases must be interpreted in conjunction with those obtained for overall mortality. For example, the lack of a statistically significant tolbutamide-placebo difference for overall mortality in the UGDP (p-value = 0.17) made the study investigators reluctant to draw any conclusion about the excess cardiovascular mortality observed, despite its size (University Group Diabetes Program Research Group, 1970e).

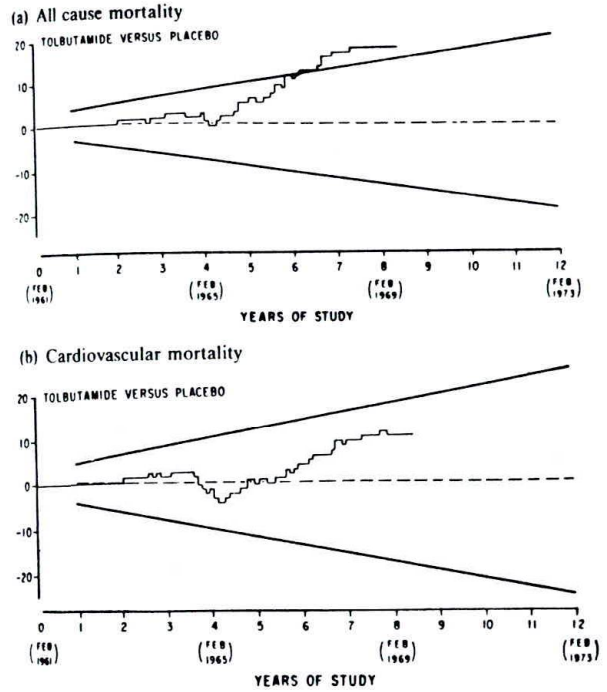

Figure 20-1 Ninety-five percent mortality monitoring bounds for the tolbutamide-placebo treatment comparison in the UGDP.

Source: Reference citation 468. Adapted with permission of the American Diabetes Association, Inc., New York.

Certainly, a practice to be frowned upon is one in which results for only a subgroup of outcomes are reported, as noted in Chapter 18 in connection with discussion of analysis ground rule 3. Readers should be provided with results for the entire set of outcomes (e.g., all deaths) from which the subset (e.g., cardiovascular deaths) was derived or, failing that, for complementary subsets (e.g., cardiovascular versus non-cardiovascular deaths).

20.4.3 The multiple comparisons problem

The multiple comparisons problem arises when an investigator chooses to make several different treatment comparisons all involving the same outcome measure (and all done at the same time point). It has been addressed by various authors, including Bégun and Gabriel, 1981; Dawkins, 1983; Duncan, 1955, 1975; Duncan and Godbold, 1979; Duncan and Brandt, 1983a; Duncan and Dixon, 1983b; Dunnett, 1955, 1964; Miller, 1966, 1977; O'Brien, 1983; Scheffé, 1953; and Tukey, 1951, 1977.

The need arises in two general settings. In the first, the investigator is interested in determining subgroups of patients within the test-treated group that appear to be benefited (or harmed) by the treatment. It can give rise to an indeterminant number of comparisons if the subgroups are identified as a result of data dredging (see Section 20.5). In the second setting, the investigator is interested in comparing each of several different test treatments with the control treatment or with one another. It will give rise to a minimum of t test-control comparisons—one for each test treatment. Other comparisons will be required if the investigator wishes to establish the superiority (or inferiority) of one test treatment relative to other test treatments.

Various frameworks have been developed to deal with the statistical problems involved in making multiple comparisons. A particularly simple one is based on Bonferroni's inequality. The inequality states that the probability of one or more k independent events occurring simultaneously is $< kp$, where p, the probability of a given event, is the same for all k events (Abt, 1981; Feller, 1968). The statement can be used to provide an upper bound on the combined type I error for making k simultaneous comparisons. The probability of rejecting the null hypothesis when it is true with tests of significance for the k comparisons is $k\alpha'$ if each of the k comparisons is made at an α' type I error level. The combined type I error level for all k tests will be less than α if α' is set equal to α/k. The NCGS used the inequality to adjust p-values for individual test-control comparisons presented in that study (National Cooperative Gallstone Study Group, 1981a).

20.5 DATA DREDGING AS AN ANALYSIS TECHNIQUE

Data dredging is a term used to characterize analyses that are done on an ad hoc basis, usually without benefit of a prestated hypothesis, as a means of identifying differences of note within specified subgroups of patients. The subgroups are typically formed by subdividing patients into mutually exclusive subgroups using observed baseline characteristics, as illustrated in Table 18–8.

The practice of data dredging is common and is not unique to clinical trials. In fact, it is the hallmark of most epidemiological research concerned with identifying etiological factors of diseases. Data dredging arises in clinical trials from the desire to identify subgroups of patients who are benefited or harmed by the study treatment. It can occur during the trial or when it is finished. CDP investigators spent a great deal of time doing such analyses in an effort to understand the dextrothyroxine (DT4) treatment results (Coronary Drug Project Research Group, 1970b, 1972). The same was true of MRFIT investigators trying to decide if antihypertensive drug therapy for hypertensive men with an abnormal resting ECG is dangerous (Multiple Risk Factor Intervention Trial Research Group, 1982).

The main concern with data dredging has to do with the statistical interpretation of differences found in this way. Table 20–2 lists general rules that should be followed. They are in addition to those outlined in Section 18.1.

Table 20–2 Ground rules for data dredging via subgroup analyses

- Limit choice of subgrouping variables to baseline characteristics
- Present results for all subgroups defined with a subgrouping variable
- Distinguish between a priori and a posteriori selected subgrouping variables
- Choose cutting points that are independent of observed treatment differences
- Avoid conventional interpretation of significance tests
- When possible, validate findings before reporting on subgroups identified via data dredging
- Report methods and procedures
- Be cautious regarding conclusions

As noted in Table 20–2, the choice of subgrouping variables (see Glossary for definition) should be limited to data collected before randomization (i.e., baseline data). Variables observed after randomization may be influenced by the study treatments and, hence, the subgroups created using them may be subject to selection biases, especially those formed using measures of treatment compliance.

All subgroups formed with a subgrouping variable (two if a single cut-point is used as in Table 18–8, more if multiple cut-points are used) should be looked at and reported. Failure to do so can lead to erroneous impressions if a difference observed in one subgroup is offset by a difference in the other direction in the other subgroup(s).

The fourth point—independence of the choice of the cut-point and observed treatment differences—listed in Table 20–2 is basic. It may be taken for granted when cut-points are set before the start of data collection or when they are dictated by the data collection process. It cannot be if the cut-points are chosen after the start of data collection.

Investigators should be wary of any "significant" differences that are found via data dredging. Conventional rules for interpreting a p-value do not apply to dredged results. Precautions are needed to avoid false proclamations of significance. The precautions may take one of two forms. The first involves use of some method for "adjusting" the p-values for the fact that multiple comparisons were done, as discussed in Section 20.4.3. The second involves a form of internal cross-validation in which only a portion of the data (say half) are used to identify subgroup treatment differences (e.g., see Coronary Drug Project Research Group, 1981). The remaining portion is used to replicate the analysis to determine if both portions of the data identify the same subgroups.

The emphasis here has been on data dredging involving different subgroupings of the patient. A variation involves using different outcome measures. The ultimate form of dredging is to use the two forms in combination.

20.6 THE PROS AND CONS OF STOPPING RULES IN MONITORING TRIALS

A stopping rule is one, usually established before or shortly after the start of patient recruitment, that specifies a limit for the test-control outcome difference which, if exceeded, automatically leads to termination of one or the other treatments depending on the direction of the observed differences (see articles by Dupont, 1983a, 1983b, and related discussion by Brown, 1983; Canner, 1983a, 1983b; Greenhouse, 1983; and Royall, 1983). An example of a stopping rule, using mortality as the outcome and based on a standardized comparison of two proportions, is outlined below. The steps are carried out at each of a series of designated time points over the trial until a stopping point is reached or until the trial is completed.

Sample stopping rule

Step 1. Calculate the proportion of patients dead in the test and control treatment groups, p_t and p_c, respectively, at the first time point at which an interim analysis is required, as specified when the rule was constructed.

Step 2. Evaluate the test statistic:

$$t = \frac{p_t - p_c}{\sqrt{\text{Var}\,(p_t - p_c)}}$$

Step 3. Stop the test treatment and conclude it is inferior to the control treatment if $t > Z$. Stop the control treatment and conclude the test treatment is superior to it if $t < -Z'$. Continue the trial if $-Z' < t < Z$. (The values for Z and Z' will be set by the study investigators. Their size will be a function of the degree of statistical certainty desired before stopping and the amount of "adjustment" to be made for multiple looks. The two values will be equal if symmetry in the decision-making process is desired. Z will be $< Z'$ if more evidence is required to accept the test treatment as beneficial than for stopping it because of possible harmful effects.)

Step 4. Repeat steps 1 through 3 for each subsequent time point until the trial is stopped or until it is finished.

Stopping rules have some appealing features. They are easy to use and they force investigators to think about the analysis process and to specify the outcome measure to be used in evaluating the treatments before the trial starts (see Section 8.3 and Section 9.3.2). However, they also have serious limitations. A major one is that it is virtually impossible to construct rules that deal with all of the contingencies that can arise during the course of the trial. Sometimes it may be necessary to terminate use of a treatment even though the test-control difference is well within the range specified by the rule. For example, just three cases of chronic active hepatitis in the NCGS were enough to raise serious questions as to whether to continue the trial, even though the test treatment showed promise with regard to the primary outcome measure. Further, even if one were clairvoyant enough to anticipate the various conditions that would require stopping the trial, it is not wise to use statistical tests of significance as the sole decision-making tool in the treatment monitoring process. Other factors that will enter in involve judgments concerning:

- The merits of the treatment
- The availability and usefulness of alternative treatments
- The seriousness of the conditions being treated
- The acceptability of the treatment to patients, as evidenced by their willingness to use it, and by the number of side effects it produces
- The clinical importance of the observed difference
- The consistency of the results with other findings in the trial and with other studies

The amount of evidence required for investigators to give up on an elective treatment for which there are alternatives may be less than that required for a treatment considered to be life sustaining for which there are no alternatives. UGDP investigators terminated use of

both tolbutamide and phenformin simply because the treatments were no better than the placebo (University Group Diabetes Program Research Group, 1970e, 1971b, 1975). They did not consider it appropriate to continue an elective treatment that failed to show any promise of benefit.

The judgment as to how long the trial should be continued in the face of a positive result will be influenced by the size of the difference, the length of time it took to emerge, and the degree of certainty investigators have as to the stability of the results. Investigators in both the Diabetic Retinopathy Study (DRS) and MPS continued treatments in those trials for some time after emergence of a positive result (Diabetic Retinopathy Study Research Group, 1976; Macular Photocoagulation Study Research Group, 1982, 1983a). They were concerned that the benefits observed might be offset by subsequent adverse effects. Long-term follow-up data were needed before they felt comfortable offering photocoagulation for untreated control eyes.

20.7 STEPS IN TERMINATING A TREATMENT

Once the decision has been made to stop the test or control treatment a series of steps will be required to implement it (see Section 15.4 for details on patient close-out and Sections 23.6 and 23.7 for comments on procedures for recommending treatment changes). The first step will be to present the results to the clinic staff responsible for implementing the decision. The presentation should be done as soon after the decision to stop as possible and should be designed to acquaint clinic staff with the findings and the reasons for stopping. It may be done from slides or handouts prepared from the treatment monitoring report leading to the decision and should include a discussion of the implications of the results and of the advice to be given patients affected by the change.

Clinic staff should be provided with guidance as to how rapidly they are to proceed in implementing the change. Treatments regarded as dangerous will require deliberate and immediate action. However, even if this is not the case, it is a good idea to proceed with implementation as soon as possible. It is not a good idea to wait until the results are ready for publication, especially if the delay entails continued exposure of patients to a harmful or inferior treatment.

Records should be kept to indicate when each patient was contacted regarding the change and what he was told. Documentation of this sort is important regardless of whether the patient is being taken off an ineffective treatment or is being offered a beneficial one.

Obviously, patients affected by the change should be told of the reasons for the change. However, it is also a good idea to inform other patients in the trial of the change, even though they are not affected by it. They may need reassurance and may be asked to give a new consent for continuation in the trial (see Section 14.6.5).

Patients removed from a treatment but who remain associated with the trial may or may not be given alternative forms of therapy, depending on the treatment options available. Patients in the UGDP and assigned to tolbutamide or phenformin therapy were not offered any other oral hypoglycemic agent when these treatments were terminated. Untreated eyes still eligible for treatment in the DRS were considered for photocoagulation treatment when study investigators were told of results in that trial (Diabetic Retinopathy Study Research Group, 1976).

Patients should be told if they are expected to continue under follow-up after a treatment protocol change. The data may be of some value in characterizing long-term treatment effects. However, their usefulness in this regard will depend on the extent to which patients are exposed to other treatments after the change. Investigators in both the UGDP and CDP elected to have patients continue on the same clinic visit schedule they had before the change. They did so, in part, for the reason mentioned above and also to avoid the morale problems and disruption that might have resulted if some patients had been separated while others were required to continue.

Part V. Management and administration

Chapters in This Part

21. Funding the trial
22. Essential management functions and responsibilities
23. Committee structures of mulitcenter trials

The first chapter in this Part details the nature of funding vehicles for clinical trials, with emphasis on NIH grants and contracts. It also contains specific budgeting suggestions for the various centers in a multicenter trial. Chapter 22 contains an outline of the general principles and practices to be followed in managing a trial. The last chapter contains a review of organizational structures used in mulitcenter trials. The chapter discusses a number of practical issues concerned with the formation and operation of committee structures.

21. Funding the trial

> The hypothesis is unencumbered by any supporting evidence. The budget is the only part of the application which seems to have any substance whatsoever.
>
> Anonymous NIH study section member

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Table 21-6 Factors influencing the choice between direct versus indirect (consortium) funding

21.1 INTRODUCTION

An essential step in the execution of a trial is the acquistion of funding to carry it out. The approach taken is influencd by whether the investigator or sponsor is responsible for initiating the trial. In practice, some trials, at least the larger-scale trials, are initiated through the joint efforts of the sponsor and investigator(s). The Coronary Drug Project (CDP) is a case in point. A special committee was convened by the National Heart Institute (now the National Heart, Lung, and Blood Institute, NHLBI) in early 1961 to explore the desirability, feasibility, and methods needed to initiate a large-scale trial to evaluate the role of lipid-influencing drugs in the treatment of post-myocardial-infarction patients. A group of investigators worked in concert with staff at the Institute to design the study as envisioned by the committee. Funding for the trial started in 1965, about four years after the initial meeting of the special committee (Coronary Drug Project Research Group, 1973a; Zukel, 1983).

The trials sketched in Appendix B represent a mix of investigator (7 out of 14), sponsor (5 out of 14), and sponsor-investigator initiated (2 out of 14) trials. See item 6, Table B-4, Appendix B, for specifics.

No inference can be made as to how a trial was initiated from the type of vehicle used to fund it. The Diabetic Retinopathy Study (DRS) was investigator-initiated but was contract-supported over most of its course. The Diabetic Control

and Complications Trial (DCCT), initiated by the National Institute of Arthritis, Metabolism, and Digestive Diseases—NIAMDD (now the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, NIADDK) has both grant and contract funding. Clinics are funded via grants and the data coordinating center is funded via a cost-reimbursement contract (National Institute of Arthritis, Metabolism, and Digestive Diseases, 1981a, 1981b).

Table 21-1 provides information on the use of grants and contracts for the National Institutes of Health (NIH) extramural trials listed in the 1979 Inventory of Clinical Trials (National Institutes of Health, 1980). See Section 2.1, for details on how the Inventory is compiled.

21.2 NIH GRANT PROPOSALS

21.2.1 Deadlines and review process

Deadlines for unsolicited new applications are February 1, June 1, and October 1 of each year. Deadlines for unsolicited continuation and supplemental applications are March 1, July 1, and November 1. Deadlines for applications solicited by the NIH via requests for application (RFAs) are announced in the solicitations.

All applications are received by the Division of Research Grants (DRG), where they are assigned to specific institutes for administration and payment if they are funded. The assignments may be made in consultation with personnel from the institutes in question, but the final decisions are made by DRG staff. The DRG is also responsible for assigning the applications for initial review. The reviews are carried out by the 80 or so chartered study sections,[1] or by special ad hoc study sections. This review structure is in addition to reviews managed by the various bureaus, institutes, and divisions (BIDs) of the NIH.

The primary responsibility of the study sections is to assess the scientific merit of research proposals received by NIH. Meritorious proposals receive a priority score based on scores assigned by individual members of the study section (1.0 for highest scientific merit through 5.0 for lowest scientific merit). This score, along with a written critique of the application (summary statement), prepared by the executive secretary of the study section (from written comments provided by members of the review group), is forwarded to the institute(s) designated by DRG to administer the grant.

The recommendations of the study section are reviewed by the advisory council (board) of the designated institute. The council is composed of health researchers plus others from outside the health field. Members are appointed by the Secretary of Health and Human Services (HHS) for a specified term, usually four years. The meeting of the council is held about three to four months after the initial review of an application and about six to eight months after the deadline for receipt of the application.

As a rule, only applications recommended for approval by a study section and approved by an advisory council will be funded. Most institutes have the authority to fund a small percentage of approved applications in the absence of council approval. However, such actions are rare. The number of proposals that are actually funded by any given institute will be a function of the priority scores assigned during the initial reviews, the size of the institute's budget, and existing funding commitments.

An applicant will receive a written summary of the results of the initial review, complete with priority score, as soon after the review as is practical. He will receive written notification of the action taken on his proposal after the council has met. This notification will be accompanied by a letter indicating the likelihood of funding in the case of an approved application. An applicant with a proposal recommended for funding that does not have a priority score above the payline (see Glossary) will receive notice to this effect and information concerning prospects for funding in the future. All such applications are kept under active consideration for three consecutive council meetings. They are removed from consideration if they have not been funded within that time.

1. A publication, *NIH Public Advisory Groups*, produced by the Committee Management Staff of the NIH, lists the chartered study sections and their membership.

Table 21-1 Number and percent of NIH extramural sponsored trials, by type of support

	Grant		*Contract*		*Mixed**		*All*	
Type	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*
A. Cancer Institute								
Single center	75	46.9	82	51.2	3	1.9	160	100.0
Multicenter†	340	88.3	38	9.9	7	1.8	385	100.0
All cancer	415	76.1	120	22.0	10	1.8	545	100.0
B. All other institutes								
Single center	153	76.5	47	23.5	0	0.0	200	100.0
Multicenter†	24	33.8	46	64.8	1	1.4	71	100.0
All other	177	65.3	93	34.3	1	0.4	271	100.0
C. Total (A + B)								
Single center	228	63.3	129	35.8	3	0.8	360	100.0
Multicenter†	364	79.8	84	18.4	8	1.8	456	100.0
All	592	72.5	213	26.1	11	1.3	816	100.0

*Includes trials with both grant and contract support and trials with both an intramural and extramural component

†The NIH definition of a multicenter trial is not as specific as the one used in this book and hence includes some studies that would be classified as single center

21.2.2 Application outline

The outline below is based on details provided in the NIH grant application package (PHS 398, revision 5/82).

Section 1: General

- Face page containing project title and other identifying information
- List of key professional personnel to be engaged in proposed project
- Abstract of proposed project (must not exceed designated space)
- Table of contents
- Detailed budget for first 12 months of project
- Budget for total period of support requested
- Budgets pertaining to consortium or contractual arrangements
- Biographical sketch of principal investigator/program director (not to exceed two pages)
- Biographical sketches for other key professional staff (not to exceed two pages per sketch)
- Sources of salary support (including support covered in pending applications) for the principal investigator/program director, as well as for all other key professional staff listed in the proposal
- Description of available resources, facilities, and general research environment

Section 2: Research plan

A. Specific aims (not to exceed one page)
B. Significance of the proposed research (not to exceed three pages)
C. Progress report/preliminary studies (not to exceed eight pages)
D. Experimental design and methods
E. Human subjects
F. Vertebrate animals
G. Consultants
H. Consortium arrangements
I. Literature cited

Section 3: Appendix

This section will contain supplementary materials pertinent to the application. Documents may include published papers, manuscripts still in preparation, proposed forms for data collection, procedure manuals, etc.

21.2.3 Content suggestions

The grant application kit, aside from the general outline provided above, does not specify content requirements. The suggestions contained in Table 21-2 are those of the author. The applicant will have to decide how the material outlined in Table 21-2 will be organized vis-à-vis the general outline given in Section 21.2.2. Most of the items listed in Table 21-2 relate in some way or other to the research plan.

A well-written application will contain an outline of the study design, its rationale, and the procedures that will be used to carry it out. While it may not be practical to provide a detailed protocol and a polished set of data collection forms, sufficient details should be provided to give reviewers an accurate assessment of the data collection approaches to be used.

Table 21-2 Grant application content suggestions for clinical trials

1. Aims and objectives
- Clear statement of the objective of the trial and the outcome measure to be used to judge the success of the treatment
- Secondary aims to be pursued in the trial

2. General design specifications
- Method of randomization
- Level of treatment masking
- Outcome measure of primary interest
- Proposed length of patient follow-up
- General procedures to be used for bias control in the data collection process
- Baseline and follow-up examination schedule and rationale for the schedule
- Outline of data collection quality control procedures

3. Significance of the study
- Importance of the treatment evaluation proposed
- Potential impact of the trial on future patient care procedures

4. Timetable
- Anticipated length of the trial, including start-up period and final analysis
- Time required for protocol development, patient recruitment, patient follow-up, and final data analysis

5. Treatment specifications
- Description of the test and control treatments
- Rationale for choice of treatments, supported with appropriate literature references
- Summary of previous evidence on the safety and efficacy of the proposed treatments
- Method of treatment administration and level of masking

6. Study population
- Patient eligibility and exclusion criteria
- Proposed source of study patients
- Methods of patient recruitment
- Realistic appraisal of ability to meet specified recruitment goal using the stated eligibility and exclusion criteria, preferably done with counts of eligible patients seen in the clinic(s) over a specified time period

7. Sample size specifications
- Patient recruitment goal and anticipated time required to achieve it
- Rationale for stated goal
- Statistical properties of the proposed recruitment goal (e.g., type I and II error protection provided)

8. Data intake
- Specification of types of data to be collected, complete with sample copies of data forms, when possible
- Staff responsible for data collection
- Quality assurance procedures for the data intake process
- Method of data entry and for verification of the accuracy of the data entry process

9. Data processing and analysis
- General methods for receiving, coding, storing, and processing study data
- Quality assurance procedures used to detect deficient data and approach to be used in correcting deficiencies
- Approach to monitoring for treatment effects
- Methods for detecting departures from the study protocol and for monitoring the performance of participating clinical centers
- Outline of general data analysis plans

10. Study organization
- List of centers to be included in the trial and description of responsibilities to be performed by specialty resource centers, such as the data coordinating center, central laboratory, etc.
- Composition of the key leadership group and description of its method of operation
- Method of creating key committees, including an outline of membership qualifications

11. Other procedures
- Outline of patient informed consent process
- Methods of protecting patient confidentiality
- Provisions for secure data storage

12. Facilities description
- Description of clinic facilities, data coordinating center, and other resource centers
- List of special items of equipment required for data collection and analysis
- Description of any other facilities key to execution of the trial

13. Budget and justification
- See Sections 21.4 and 21.5.10

Defects to be avoided include:

- Vague and unsubstantiated claims regarding patient recruitment
- Unrealistic timetable
- Absence of a rationale for the stated sample size
- Clumsily written and fragmented proposal that lacks cohesion and that conveys the impression that it was written in haste by several people who had different perceptions of the work required
- Lack of organizational details concerning methods for carrying out the trial

Investigators should be realistic regarding the time required for patient recruitment. Experienced reviewers are likely to be skeptical of claims regarding patient availability and rate of recruitment unless they are supported with appropriate data.

Care should be taken to make certain that essential data intake and analysis functions are covered in the proposal. A general discussion, unrelated to the specifics of the proposal, is likely to be perceived as a weakness. This is particularly true if study section members perceive a lack of statistical input in the writing effort.

An area often overlooked is the organizational structure of the trial. Organization is important for any activity involving large numbers of people, whether located at a single center or multiple centers. The written proposal should outline the leadership structure proposed and the methods to be used for coordinating trial activities.

21.3 NIH REQUESTS FOR CONTRACT PROPOSALS

21.3.1 Deadlines and review process

As a rule, NIH contract-supported projects will be initiated by the sponsoring institute, via release of a request for proposals (RFP). Unsolicited proposals for contract funding are usually not accepted by the NIH.

Institutes within the NIH are required to advertise their intention to release an RFP in the *Commerce Business Daily* at least ten business days in advance of the projected date of release. It is also announced in the *NIH Guide for Grants and Contracts*. In addition, solicitations may be advertised in selected scientific journals and periodicals.

The RFP will indicate the deadline for response. Responses received after the deadline will not be considered, unless it is in the government's best interest to do so. Requests for extension of the deadline are unlikely to be granted unless the extension applies to all applicants.

The RFP will indicate where responses are to be sent—generally, in the case of NIH-released RFPs, the contracting or review office of the institute that released the RFP. The technical merit review of the responses received by the NIH are either managed by BID review personnel or, for the smaller institutes, by DRG. The review process is similar to that described for grant applications.

21.3.2 Factors to consider when deciding whether or not to respond

A prospective respondent must decide whether or not to prepare a response to an RFP. This decision must be made within a short time period because of the constraints imposed by the deadline for response. Questions to consider when assessing the merits of responding to an RFP are listed in Table 21-3. The questions are written from the perspective of an investigator considering applying for a center in a multicenter trial. The questions in Part A are general and are not related to any particular RFP. Those in Part B are specific to the RFP in question.

A single, or even a few, negative answers to the questions listed need not preclude responding to an RFP, but negative answers to key questions should. The same is true for any RFP that yields a large number of negative or equivocal answers, even if they are not related to key questions.

A major frustration in preparing a response to an RFP can be the amount of time available for response. Most NIH solicitations require a response within 60 to 90 days. The time between the date of release and the deadline for response was as short as 40 days for some of the proposals reviewed by the Coordinating Centers Models Project—CCMP (Coordinating Center Models Project Research Group, 1979b). An investigator should bear in mind that the actual time for response is always less (sometimes a great deal less) than the difference between the date of release and the deadline for response because of time needed to clear adminstrative channels in his institution after the response has been written.

Table 21-3 Questions to be considered when deciding on the merits of a response to a Request for Proposal (RFP)

Part A. General questions

Career goals

- Is the role proposed compatible with your career goals and interests?
- Do you have sufficient time to carry out the study?
- Do you enjoy collaboration with others?
- Are your opportunities for promotion likely to be adversely affected by participation in the project, especially if there are few if any opportunities for recognition as a key author on publications generated from the study?
- Can you function in a committee setting, and are you willing to accept the dictates of such a committee or the sponsor for execution of the trial?

Environment

- Are the stipulations in the business portion of the RFP compatible with the policies of your institution?
- Is the institution in which you work likely to continue in operation for the period of the trial?
- Are the personnel recruitment practices, pay scales, and promotion criteria of your institution compatible with those needed for execution of the trial?
- Is the business office of your institution capable of administering the contract?
- Is the trial compatible with the goals of your institution?
- Would colleagues view your activities in the trial in a favorable light?
- Will you be able to obtain the necessary signatures from administrative personnel in your institution if a proposal is submitted?
- Will you have the active support of your chief if you are selected to carry out the proposed work?
- Will there be adequate space, office equipment, and facilities to do the work if you are funded?
- Does your institution have staff with the required expertise for execution of the study and will you have access to them if you are funded?

Part B. Specific questions concerning the RFP

- Is there sufficient time to prepare an adequate response?
- Is the problem posed worthy of investigation?
- Is the project likely to achieve its stated aim?
- Does the project have a realistic timetable and is it subject to modification if necessary?
- Does the sponsoring institute desire strong investigator input in the operation of the trial (i.e., does it desire more than a service role from applicants)?
- Will there be adequate lead time for development of the study protocol and data forms before the trial is started?
- Are the suggested staffing guidelines realistic?
- Are the suggested funding levels realistic?
- Will it be possible to amend the design and proposed operating tenets of the trial, if necessary?
- Are the duties of the project officer in the sponsoring agency compatible with your perceived role in the trial?
- Are there adequate provisions for data processing and analysis outlined in the RFP?
- Is the reporting schedule for progress summaries during the trial reasonable?

21.3.3 The response

The RFP will contain an outline of required workscope along with a list of general methods and procedures to be used in carrying out the work. It may indicate the level of staffing needed for the study and whether the level stated is to be considered as an absolute or suggested upper limit. The limit may be exceeded if the latter is the case.

The respondent should indicate how the work outlined in the RFP is to be accomplished. Deletions or additions to the workscope as outlined in the RFP and reasons for the changes should be noted in the response. Minor changes may be acceptable if they do not alter the main purpose or aim of the study. Major modifications are likely to cause the sponsor to reject the response.

Instructional material accompanying the RFP should be read before starting work on the response and should be reviewed during its preparation. The material provided will indicate the way in which the response is to be assembled, the number of copies required, the deadline for response, and where it is to be sent.

21.4 THE STUDY BUDGET

21.4.1 Grants

The budget categories for NIH grant applications are listed below. Indirect costs (see Glossary) associated with execution of an NIH grant-supported project are not included in the budget request, except for indirect costs that are to be paid to other institutions (e.g., contractual arrangements with other institutions that are outlined in the application).

NIH grant application cost categories

1. Personnel
2. Consultants
3. Equipment
4. Supplies
5. Travel
6. Patient care costs
7. Alterations and renovations
8. Consortium/contractual costs
9. Other expenses
10. Total direct costs

The budget proposed should be a realistic appraisal of what is needed to carry out the study. It should not conform to a preconceived limit, unless a limit has been set by the sponsor. Requests that extend over multiple years should anticipate normal salary increases. The same is true for anticipated increases in the cost of fringe benefits for personnel. Some institutes of the NIH have escalation ceilings that relate to salary increases in the second and subsequent years of a budget request (e.g., 6% for NHLBI-supported projects).

NIH grant applications require a detailed breakdown of costs for the first year of requested support and a summary of costs for each subsequent year. The detailed breakdown should include the planned time commitment (listed as hours per week or as a percentage based on a full-time effort) and projected salary support for each person or position listed. Detailed information is not required for subsequent years; however, it may be included if the applicant wishes to do so. The added detail can be particularly important if there are large cost increases in the second or subsequent years due to staff additions.

Appendix H contains a sample set of budget tables, as contained in the budget request for the Data Coordinating Center in the Hypertension Prevention Trial (HPT). Only Table H-2 was required. Tables H-3 through H-7 were constructed to facilitate the budgeting process and to provide the reviewers with detailed budgetary data.

Construction of the budget requires specification of an anticipated starting date for the proposed work. This will be stated by the sponsor in the case of a sponsor-initiated study and by the investigator in an investigator-initiated study. The starting date selected should be at least nine months after the submission deadline in the case of investigator-initiated NIH grant applications. This much time will be required for the review and approval process, as outlined in Section 21.2.1.

The proposed expenditures should be justified (see Section 21.5.10). While it is true that the initial review, in the case of NIH funding requests, is designed to focus on scientific merit, budget details and their justification cannot help but influence the review.

21.4.2 Contracts

Most NIH RFPs contain suggested budget categories. The categories below are from Optional Form 60—a form produced by the General Services Administration of the federal government and which is a standard part of most NIH-released RFPs.

NIH contract cost category

1. Direct material
2. Material overhead
3. Direct labor
4. Labor overhead
5. Special testing
6. Special equipment
7. Travel
8. Consultants
9. Other direct costs
10. Total direct costs and overhead
11. General and administrative expense
12. Royalties
13. Total estimated cost
14. Fee or profit
15. Total estimated cost and fee or profit

Most institutes of the NIH require respondents to separate the business and research portions of the response. The separation ensures that the initial review focuses on the technical merit of the proposal without regard to budgetary considerations.

21.5 BUDGET BREAKDOWN

Table 21-4 provides a list of items included under each of the categories listed in Section 21.4.1 for grant applications. The list is intended primarily as a reminder of the type of items to be considered in the budgeting process.

Table 21-4 Direct cost items, by budget category

1. Personnel (Individuals with a direct involvement in the trial and with a stated time commitment. Funds requested should be for salaries plus fringe benefits.)
- Center director and co-director
- Study physicians
- Clinic coordinator
- Laboratory technicians
- Biostatisticians
- Programmers
- Data coordinator
- Data entry personnel
- Research assistants
- Administrative assistant
- Secretaries
- Clerks
- Other personnel

2. Consultants (Individuals paid on a fee-for-service basis and who are not part of any center in the trial.)

Consultants may be needed to:
- Provide expert advice in the diagnosis, classification, or treatment of patients in the trial
- Perform a specialty function, such as reading ECGs, biopsy material, etc.
- Provide expert advice to a resource center in the trial, such as to the data coordinating center for data analysis
- Serve as an expert advisor to the study leadership or sponsor of the trial

3. Equipment (Purchased or leased)
- General office equipment
  - Typewriters
  - Word processors
  - Transcribing and dictating machines
  - Filing cabinets
  - Desks, chairs, and tables
  - Photocopying machines
  - Telephone equipment
  - Miscellaneous office equipment, such as heavy-duty staplers, paper cutter, 3-hole punches, electric staplers, etc.
- Clinic equipment
  - Furniture for examining and waiting rooms
  - Required items of equipment needed for data collection such as a random-zero sphygmomanometer or laboratory equipment for special readings or analyses
  - Items of equipment needed for data collection such as ECG recorder, fundus camera, etc (Requests for standard equipment, regarded as essential to any nonstudy clinic setting, may not be allowed when the budget is reviewed unless the requests are adequately justified. The justification should indicate why existing equipment will not meet the needs of the study).
- Data center equipment
  - Data entry equipment such as key-to-tape or key-to-disk units, intelligent terminals, etc.
  - Computing and related hardware such as tape and disk drives, printers, remote job entry stations, CRTs, portable terminals, etc.
  - Computing software for database management and analyses
  - Mailing equipment, such as postage meter, postage scale, envelope opener, envelope stuffer and sealer, etc.
  - Machines for assembling and binding reports
  - Paper shredder (for disposing of confidential records)

4. Supplies
- General office supplies
  - Paper, pencils, notebooks, typewriter supplies, dictation tapes, etc.
  - Postage
  - Photocopy supplies (e.g., toner, developer, etc.)
  - Supplies for special items of equipment, such as word processors
- Clinic
  - Drugs, syringes, etc.
  - Laboratory reagents and supplies
  - Data forms
  - Patient informational material
  - Mailers for laboratory specimens
  - Supplies for special items of equipment, such as film for fundus camera, etc.
- Data center
  - Computer supplies, such as paper, printer ribbons, magnetic tapes, disks, etc.
  - Data entry supplies, such as punch cards, floppy disks, tape cassettes, etc.
  - Supplies for special items of equipment, such as graphics terminal, plotter, microfilm camera, etc.

5. Travel
- Study staff
  - Local (for mileage charges incurred as part of patient recruitment and home visits)
  - National (for travel and living expenses incurred in conjunction with study-related activities, including clinic site visits and study committee meetings, as well as for travel to selected professional meetings, especially for presenting study-related papers)
  - International (for travel and living expenses for foreign travel required for study and related activities, and for selected professional meetings* related to the needs and goals of the study)
- Consultants (for travel to study center or to study-related meetings)
- Committee members (for travel of members of the advisory-review committee and the treatment effects monitoring committee to study-related meetings)

6. Patient care costs* (Funds in this category are used to pay for procedures carried out on patients that are done primarily for their research value and that are not considered necessary for routine medical care. Hence, they cannot be charged to the patient or his insurance carrier.)

7. Alterations and renovations*
- Renovation of a clinic area
- Air conditioning for computing equipment
- Renovations to accommodate special items of equipment needed in the trial

8. Consortium/contractual costs (Funds in this category are used to cover payments to individuals or groups outside the investigator's institution who have formal agreements to perform specified functions in the study.)

9. Other expenses
- Patient travel to and from clinic
- Equipment maintenance charges
- Telephone installation and monthly usage charges
- Copying and reproduction charges
- Computing time charges
- Data entry charges
- Study insurance
- Books and journals
- Journal page and reprint charges
- Charges for printing and distributing study forms, manuals, etc.
- Fee-for-service charges, such as for laboratory determinations, reading ECGs, etc., if not covered under a consultant or contractual agreement
- Space rental
- Moving charges
- Indirect costs for associated contractual services included in item 8

10. Total direct costs (Sum of cost in above nine categories)

*Categories or items that may not be allowed, or that require special justification.

No single trial will necessarily include all the items listed.

21.5.1 Personnel

A major portion (from 50 to 80%) of the requested support will be for personnel. Actual salaries expected to apply at the start of funding should be used for personnel named in the budget. Salary estimates, using prevailing figures at the applicant's institution, should be used for positions to be filled during the study. The time commitments for personnel should be realistic. That for the center director should be large enough to represent a meaningful role in the operation of the center. Padding the budget by including unnecessary personnel or needlessly large time commitments is unwise and may lead reviewers to question the competence or integrity of the applicant. In addition, it may cause them to make drastic cuts in the budget.

Ideally, applications should carry named investigators in key support positions. This is especially true for the position of deputy director. An alternative, when a deputy is not named, is to indicate the approach to be followed in replacing the center director, should that become necessary. A list of qualifications the individual to be recruited should have and the mechanism for screening and selecting a replacement should be outlined.

Another key support position, vital to data collection, is that of clinic coordinator. The person who fills this position provides a link between patients and physicians in the clinic and between the clinic and the data center.

Large centers may also require a part-time or full-time administrator. Generally, the administrative services available through the investigator's business office will not be adequate to meet the day-to-day administrative needs of the study. The justification should indicate why the position is needed, and why the duties cannot be

performed by personnel in the investigator's business office.

21.5.2 Consultants

Normally, consultants are required to provide services or fulfill functions that cannot be met by salaried personnel in the study. They should not be used to perform essential day-to-day tasks because of their peripheral role in the study. By definition, they should be located outside the applicant's institution. When they are not, they should be listed in the personnel section of the budget.

21.5.3 Equipment

Items of equipment requested may be purchased or leased. The approach proposed will depend on the expected duration of the trial and the anticipated useful life of the items in question. Purchase is usually cheaper than lease if the item is required for three years or longer. Leasing should be considered for equipment needed for less time or when there is a chance it may have to be replaced before the trial is finished. Costs for equipment maintenance and repairs should be included in the "other expenses" category.

The request may include funds for office equipment, such as typewriters, transcribers, and office furniture, except where such costs are proscribed by the sponsor. The request, especially for large-scale trials, may also include equipment needed for data processing as well (see Section 5.2.4 and Table 5-4 for more details).

21.5.4 Supplies

See Part 4 of Table 21-4 for list.

21.5.5 Travel

The need for money for staff-related travel may be nil in a trial carried out in a single institution, but may be sizable in a multicenter trial. Review groups may question the need for the proposed travel by study staff. Hence, the applicant must take pains to explain why it is necessary. Foreign travel, unless directly related to the study, is not likely to be approved. The budget of one center, usually the coordinating center in a multicenter trial, may carry funds for travel costs not covered in the budgets of the other centers, such as for study consultants and for members of the treatment effects monitoring committee.

The budget may include funds to cover transportation for patients who cannot provide their own. Trials requiring long-term patient follow-up may even include funds to cover transportation and related living expenses of patients who must travel long distances to continue in the study. Costs for patient travel are listed in the "other expenses" category in NIH grant applications, since they are not considered a part of the cost for patient care.

21.5.6 Patient care costs

The budget for the study should include funds for experimental procedures that are of no direct benefit to the patient and that are done simply for research purposes. Ordinary patient billing and collection practices should be used to recover costs for procedures that are considered to be an essential part of a patient's care (i.e., those that would be required whether or not the patient was enrolled in the study). It is prudent, when in doubt as to whether costs for a procedure should be billed to a patient or his insurance company, to include costs for the procedure in the study budget.

21.5.7 Alterations and renovations

Budget requests for alterations or renovations can be expected to receive close scrutiny by the sponsor. Normally, funds are not awarded for such purposes, at least via the NIH, unless they are absolutely essential to the study and are well justified. The guidelines stated for grant requests, or as listed in the particular RFP in question, should be consulted before requesting funds for this purpose.

21.5.8 Consortium/contractual costs

The typical application may not require any funds in this category. Funds should be requested only in instances in which the applicant proposes to have certain functions fulfilled outside his own institution (e.g., certain laboratory tests). The group(s) proposed to perform these functions and the reasons for selection should be indicated in the budget request. A contractual or subcontractual[2] arrangement should not be considered if the functions to be performed can be done better or at a lower cost in the applicant's own institution.

2. The term used depends on whether the parent application is a grant or a contract.

All costs in this category should include direct as well as indirect contractor or subcontractor costs. This is true for grant applications as well as contract proposals. A detailed budget, using the categories listed in Section 21.4.1 or 21.4.2, should be provided if the contract or subcontract represents a significant fraction of the total funds requested.

21.5.9 Other expenses

This category, as seen in Table 21-4, includes a variety of items. Several of them, such as computing and laboratory determinations, may be billed either on a fee-for-service basis or under a fixed sum agreement. The cost under fee-for-service agreements is determined by the amount of service rendered, whereas it is fixed in advance under a fixed sum agreement. Agreements of the latter type are easier to administer than fee-for-service agreements. However, the options available in any given case may be limited. For example, most general-use computing facilities will be reluctant to provide computing for a predetermined fixed sum.

Most offices will have photocopying equipment that can be used to meet the copying needs of the project. If so, the budget may simply include an item for copying charges incurred for using that equipment. If not, funds should be included for renting or purchasing needed photocopying equipment.

Some of the budgets for large-scale multicenter trials, such as the CDP and the Hypertension Detection and Follow-up Program (HDFP), included funds for study insurance. The protection provided was over and above that available via an investigator's own institution and extended to all centers in the trial, including the data center, as well as all study committees, including the advisory-review and treatment effects monitoring committees.

21.5.10 Budget justification

All categories and major items within those categories should be justified. The need for some items, such as general office supplies and some of the items in the "other expenses" category, will be self-evident. However, other items, such as proposed renovations or alterations, purchase of costly pieces of equipment, and most travel, will need careful justification. The personnel budget, because of its importance, requires detailed justification. It should be supported with a brief description of the duties and responsibilities of each staff member or position listed and the rationale for the stated time commitment.

It may be useful to provide summary tabulations, such as illustrated in Tables H-6 and H-7, Appendix H, to indicate the way in which funds have been apportioned. The percentage distribution of funds by category of expenditure can help reviewers judge the appropriateness of the allocations proposed. Budgets that are top-heavy with funds for personnel, relative to funds for other categories, should be re-examined before submission. Similar tabulations that break down personnel costs by function to be performed (e.g., data generation versus data analysis) may help to determine whether the proposed distribution of personnel is adequate.

21.6 PREPARATION AND SUBMISSION OF THE FUNDING PROPOSAL

The preparation of the funding proposal involves a great deal more than simply writing the application and assembling it. Some of the preparatory steps include:

- Contacting colleagues to determine if they are willing to participate in the study and to reach agreements with them on time commitments for the work outlined
- Preparation of updated biographical sketches for each professional listed in the proposal
- Collection of salary and fringe benefit information for use in preparing the personnel budget
- Collection of cost information for items of equipment, supplies, travel, computing, and the like
- Collection of letters of agreement from consultants and contractors or subcontractors mentioned in the proposal

Once the application is completed, it should be reviewed to make certain it is properly paginated, that the table of contents is accurate and complete, and that all essential materials, such as biographical sketches and support letters, are included. The budget should receive special attention. Figures should be checked and rechecked for accuracy before the application is submitted.

The application will not be reviewed by the NIH without the proper signatures and assurances. Grant applications must be signed by the

applicant as well as by the senior administrative officer of the applicant's institution. Written assurance (provided by forwarding a properly executed Form HHS 596 to the NIH) from the applicant's Institutional Review Board (IRB) regarding the adequacy of the proposed patient consent procedures and methods for treatment and follow-up must be received within 60 days following the deadline for receipt in order for review to proceed (see Chapter 13).

21.7 NEGOTIATIONS AND AWARD

The size of the award will be determined by the sponsor, using input received during the review process. In rare cases it can exceed the amount requested if the sponsor elects to add funds for expenses overlooked by the applicant. It is more likely that the sponsor will impose cuts, often without consulting the applicant. Agencies, such as the NIH, have formal appeal processes that can be followed if the applicant feels the cuts are unjust or that they jeopardize the success of the project. The appeal may not result in a full restoration of funds, but some redress may be possible if the applicant makes a convincing case.

A greater opportunity for negotiation exists under the contract mode of funding. The peer review process described in Section 21.3.1 is designed to assess scientific merit. Once the reviews are completed, the proposals are ranked on the basis of priority scores. Those with the best scores will be singled out for a second-stage review. These offerors will be given an opportunity to make their best and final offer and may be asked to respond (usually in writing) to a series of questions raised during the initial review. Final contract negotiations will be undertaken with the offeror(s) selected.

Expenditures cannot be made against a pending grant or contract until all necessary documents have been received and signed by the applicant's institution. These include the Notice of Grant Award for NIH grants and a signed agreement bearing all required signatures for contracts. Job commitments should not be made until all the required documents are in hand.

21.8 GRANT AND CONTRACT ADMINISTRATION

The applicant's business office is responsible for receiving money from the sponsor and for making all payments under the award. Administrative questions concerning use of study funds must be cleared through this office. Questions that cannot be answered should be forwarded to the sponsor for resolution. The day-to-day administrative needs of the project, such as preparation of purchase orders, payroll entries, and the like, will be met by general staff in the applicant's department or by staff hired specifically for this purpose using study funds, depending on the size of the project.

21.9 SPECIAL FUNDING ISSUES

21.9.1 Direct versus indirect funding for multicenter trials

A key issue that must be resolved in any multicenter trial deals with the dispersal of funds to the individual centers in the trial. In one case, each participating center submits an application containing design documents common to the entire study, plus operational and budgetary information specific for the center. The award is made to each successful applicant, directly from the sponsor. An alternative approach involves a consortium award (see Glossary) in which one investigator submits a proposal designed to cover the budgetary needs of all the participating centers. If the proposal is funded, that same individual, in conjunction with his business office, assumes responsibility for dispersing funds to individual centers in the trial. Both approaches are used by the NIH for grant- as well as contract-funded trials. The applicants have prime responsibility for choosing the method of fund dispersal in investigator-initiated multicenter trials. The sponsor will have the primary say in sponsor-initiated multicenter trials.

The advantages and disadvantages of the two approaches are summarized in Table 21-5. The factors influencing the choice of one approach over the other are outlined in Table 21-6.

The main advantage of consortium funding is the opportunity it provides for reallocation of funds among centers during the trial. A second advantage has to do with the mechanics of preparing the budget request during the application process. It is usually much easier for one or two key investigators to develop a composite budget for the trial than it is to coordinate development of a series of budgets needed when each center is to be funded directly from the sponsoring agency.

The consortium approach may be necessary in an investigator-initiated proposal if it is not practical to identify all centers to be included in the trial at the time the proposal is submitted. However, review groups can be expected to have trouble recommending funding for any study with unnamed centers, unless they are satisfied with the process proposed by the applicant for center selection.

Table 21-5 Direct versus indirect (consortium) funding for centers in multicenter trials

A. Direct funding (Individual awards to each center direct from sponsor)

Advantages

- Vests all fiscal responsibilities with the sponsor and thereby helps to maintain a clear separation of the fiscal and scientific affairs of the trial
- All centers have identical relationship to the sponsor (i.e., avoids the unbalanced relationship of indirect funding where the lead center has direct funding and all others receive funding via that center)
- Grant or contract administration done through sponsor, usually by experienced personnel
- May be perceived by recipients as a more desirable mode of support than support provided via another center

Disadvantages

- Requires a detailed funding proposal from each participating center
- May preclude the sponsor from redistributing funds among centers once the awards have been made (especially true for NIH grant-supported trials)
- Difficult to coordinate the preparation of individual budget requests, especially if there are only limited opportunities for contacts among applicants when the budgets are being prepared, as in some investigator-initiated trials

B. Indirect funding (Awards to individual centers via a lead center)

Advantages

- Simplifies logistics of preparing the funding request
- Provides flexibility in amount of funds that may be dispersed to any given center

Disadvantages

- Places a heavy administrative burden on the lead center
- Fiscal control exercised by the lead center may have adverse effect on its working relationships with other centers in the study
- Quality of administration provided by lead center highly dependent on experience and competence of the center's business office
- May be viewed by recipients as a less desirable mode of support than support provided direct from the sponsor

A disadvantage with the consortium approach has to do with the difficulties any investigator has in directing both the scientific and fiscal affairs of a trial. The investigator responsible for administration of the consortium award must make fiscal decisions affecting individual centers in the trial, while at the same time playing a key role in the scientific conduct of the trial.

The overall administrative cost of either approach is probably about the same. In the one case the sponsor assumes the major portion of the administrative burden, whereas in the other it is assumed by the director of the lead center.

21.9.2 Work unit payment schedules

Payments for clinics may be a function of the number of patients seen or enrolled. Work unit payment schedules, while not common in NIH-sponsored trials, are used in industry-sponsored trials. PARIS, one of the trials sketched in Appendix B, had clinic payment schedules that were based, in part, on the number of patients seen (Persantine Aspirin Reinfarction Study Research Group, 1980a).

The danger with any payment schedule based on patient load is the temptation it provides for the enrollment of questionable patients, or even for falsifying patient reports to maintain a certain income level. Such payment schedules should not be considered without a monitoring plan designed to guard against such possibilities.

Table 21-6 Factors influencing the choice between direct versus indirect (consortium) funding

Direct funding

Considered when:

- All centers are to be selected before funding is initiated
- The amount of support required for each center is above some minimum
- A leadership structure exists to ensure proper coordination of the individual funding requests

Indirect funding

Considered when:

- Individual centers require only minimal levels of funding
- It is not possible or practical to select all centers before funding is initiated
- It is not practical to coordinate the preparation of a series of individual funding requests

22. Essential management functions and responsibilities

You cannot manage soldiers into battle: you must lead them.

Source unknown

22.1 Management requirements
22.2 Management deficiencies
  22.2.1 Failure to delegate authority with responsibility
  22.2.2 Inadequate provisions for personnel backup
  22.2.3 Ill-defined decision-making structure
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  22.6.1 Separation of treatment administration and data collection personnel in unmasked trials
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Table 22-1 Classes of trials requiring safety monitoring
Table 22-2 Guidelines for committee operations

22.1 MANAGEMENT REQUIREMENTS

Any research activity that involves multiple investigators requires a defined structure for performing necessary activities. The need is most apparent in multicenter trials, but it exists in single-center trials as well, especially if they involve various people performing different functions. A sound structure will provide:

- Delineation and separation of responsibilities
- A communications structure for disseminating essential information needed by personnel to discharge their responsibilities
- Checks and balances in the decision-making process
- Specified goals for measuring progress and performance during the trial
- Ongoing quality assurance and performance monitoring to detect and correct deficiencies in the data generation and processing procedures in the trial
- Appropriate administrative support to implement and carry out functions needed for execution of the trial

22.2 MANAGEMENT DEFICIENCIES

22.2.1 Failure to delegate authority with responsibility

A common deficiency is one in which a member of the research team is expected to perform a specific function but is not given the authority needed to carry it out. This deficiency can result in bottlenecks in decision making. Position-by-position reviews, with the goal of matching authority to responsibility, are necessary at periodic intervals over the course of the trial if the problem is to be avoided.

22.2.2 Inadequate provisions for personnel backup

Key positions in the study must be backed up to assure continuity of operations. Failure to do so can jeopardize the entire study if a key position is vacated at an inopportune time. The backup should be accomplished by designating deputies who are empowered to act in the absence of the persons they represent. The concept applies to committee positions as well as to positions within individual centers. The designations may be via informal understandings for secondary positions, but not for key leadership personnel. Formal appointments are required in such cases to avoid confusion as to the succession of authority. It is interesting to note in this context that only 8 of the 14 trials sketched in Appendix B had a designated vice-study chairman (line 28.b, Table B–4).

22.2.3 Ill-defined decision-making structure

Ambiguity in the decision-making structure of a group is almost always due to the failure of the group leaders to empower specific members of the group with the authority needed to perform designated tasks. Structures with multiple committees or centers that have overlapping domains of responsibility are at greatest risk of having obscure lines of authority. The reluctance of members of the steering committee of a multicenter trial to vest a designated center or defined set of individuals with the authority needed to perform specified tasks in the trial can lead to chaos. The need to obtain approval from the committee before each new step is taken increases the time required to perform a task and is demoralizing to those who must perform it.

22.2.4 Inadequate funding

Attempting to carry out a trial without adequate financial support is a serious mistake, especially if doing so leads to poor quality data or requires patients to assume risks that could be avoided with adequate support. Responsible investigators will not start a trial without adequate financial support. Failing that, they will scale down their efforts to bring them in line with available funding.

22.2.5 Lack of performance standards

There is no way to monitor performance in a trial in the absence of standards for making such assessments. A well-designed and well-managed trial will have a timetable indicating when key activities, such as patient recruitment, are expected to begin and finish. It will have a patient recruitment goal and standards of performance relating to various aspects of the data collection and analysis processes as well.

22.2.6 Failure to separate essential activities

Sound leadership requires separation of essential roles in the trial. Some of these separations are discussed in Section 22.6. Failure to provide needed separations can result in duplication of effort, internal squabbles, and biases in the data collection or analysis of results.

22.2.7 Ill-defined communication structure

The information flow in the trial should proceed through designated channels. Structures involving two or more communication routes, such as in trials with both a data and treatment coordinating center (see Chapter 5 for general discussion and Sketch 13, Appendix B, for specific example), must take special pains to make certain that the structure does not produce conflicting communiques or allow lapses in the communication process.

22.3 PATIENT SAFETY MONITORING: AN ESSENTIAL FUNCTION

Patient safety monitoring, or simply safety monitoring, is any process carried out during a trial that involves the review of accumulated outcome data for groups of patients to determine if any of the treatment procedures practiced should be altered or stopped. This type of monitoring is in addition to that which is done on a per-patient basis by each patient's own study physician.

Safety monitoring may be done by a single person, usually a statistician, in a small trial or by a committee in a large one (see Chapters 20 and 23). It is essential in any trial of treatments that carries risks (see Table 22-1 for classes of trials requiring safety monitoring). Continuation

Table 22-1 Classes of trials requiring safety monitoring

- Trials with a clinical event as the primary outcome measure
- Trials involving treatments that carry potential short-term or long-term risks
- Trials involving treatments with the potential for producing serious side effects
- Any trial that has the potential of generating definitive results before the scheduled conclusion of the trial
- Any trial involving data collection procedures or schedules that either entail risks or inconvenience to the patients or that are costly to carry out

of such trials is justified only so long as there is no reliable way to choose between the test and control treatments. Once data have accumulated to indicate the superiority of one treatment over another, the inferior treatment should be stopped. Ethically, the need for safety monitoring is greatest so long as patients continue to be enrolled and treated in the trial. However, the need exists even after recruitment and treatment is finished (e.g., as in a surgical trial where patients are followed after surgery). Patients who received the inferior treatment by virtue of randomization should have an opportunity to receive the superior treatment (assuming they are still treatable). In any case, the need to inform the medical community of the finding is the same, whether or not new patients are still being enrolled and treated in the trial.

There are also practical reasons for carrying out periodic data analyses during the trial, even if the treatments are innocuous and pose no risks to those receiving them. The costs necessary to continue a trial are not justified once the accumulated results are adequate to make a judgment concerning the treatments. A trial that no longer has a chance of producing any more useful information should also be stopped. By the same token, use of a data collection procedure that entails risk, discomfort, or inconvenience to patients should be stopped once sufficient information has been obtained with it to answer the question it was designed to address, or once it becomes clear that no more useful information can be generated from its use.

22.4 ADVISORY-REVIEW FUNCTIONS

Most trials will require external reviews for various reasons over their course. The reviews will be preparatory to the start of the trial or before implementation of a protocol change during the trial. Examples include:

- Review of patient recruitment experience in order to offer advice to the study leadership or sponsor on the need for additional clinics
- Review of the performance of a clinic in order to offer advice to the study leadership or sponsor on the desirability of continued funding for the clinic
- Review of a recommendation to add a new treatment to the trial or to terminate use of an existing treatment because of adverse effects

The advisory and review functions may be performed on an ad hoc basis by consultants selected by the study investigators or on a regular basis via a committee appointed by the investigators or sponsor of the trial. Such committees, especially when appointed by the sponsor, are usually intended to provide advice to both the sponsor and study investigators. Advice to the sponsor will focus on policy and fiscal issues, whereas advice to the study investigators will center on operational issues.

22.5 COMMITTEE PROCEDURES

The general rules to be followed when forming the committee structure in a trial are provided in Table 22-2. The next chapter provides details on committee structures for multicenter trials. However, such structures are not unique to multicenter trials. They are required in large single-center trials as well.

No committee should be created without a written specification of its charge and duties. It should indicate the composition of the committee, criteria for membership, and voting rights and rules. Some studies, such as MILIS, have actually written bylaws detailing the committee structure and governance of the trial (Multicenter Investigation of the Limitation of Infarct Size Research Group, 1983). Such documentation, whether or not formalized to the degree in MILIS, is essential in avoiding disputes among committees with overlapping or competing functions. Once created, a member of the study staff should be charged with the task of maintaining a running account of committee meetings and of additions or deletions to the charge of the committee and to its membership. A cumulative record of committee membership over the course of the trial is useful when preparing credits for manuscripts.

The committee structure may require major revisions at intervals over the course of the trial. Revisions may be needed as patient recruitment is completed and again in preparation for close-out of patient follow-up and for final analysis of study data. Committees that are no longer needed should be disbanded.

Table 22-2 Guidelines for committee operations

A. General
- Create no more committees than necessary
- Provide a written charge for each committee that outlines the need for it and the function it is to perform
- Indicate the individual or group that has authority to appoint or dissolve committees
- Avoid overlap of responsibilities with other committees
- Outline the relationship of one committee to another and the communications structure for committee-to-committee interactions
- Specify whether or not a committee has decision-making authority; if so, indicate the issues for which it will serve as the final authority and those for which it will serve only in an advisory capacity

B. Chairmanship
- Specify the method of selection (e.g., election or appointment) and the term of office
- Designate a chairman for each committee created; a vice-chairman should also be designated for any committee that is to perform essential ongoing functions in the trial

C. Membership
- Specify the membership criteria for each committee
- Specify the methods to be used for rotation of members (if any), for filling vacancies, and for replacing nonfunctioning members
- Indicate ex officio committee positions (e.g., chairman of the study, director of the data center, etc.)
- Specify conditions that disqualify individuals from filling a committee position, including conflicts of interest

D. Voting
- Specify quorum requirement for conduct of committee business
- Identify voting and nonvoting committee members and ex-officio voting and nonvoting positions
- Specify committee voting rules

E. Documentation and maintenance
- Maintain an up-to-date list of committee members, their respective terms of office, and voting rights
- Designate an individual to serve as committee secretary
- Carry out periodic reviews in which committee charges are updated and committee-to-committee communication structures revised, where appropriate
- Dissolve committees that have completed their work or are no longer functional

22.6 PREFERRED SEPARATION OF RESPONSIBILITIES AND FUNCTIONS

Preferred separations inlcude:

- Separation of personnel responsible for treatment administration and data collection in unmasked trials
- Separation of personnel responsible for patient care from those responsible for safety monitoring
- Separation of the investigative and advisory-review roles
- Separation of sponsor and investigative roles
- Separation of the data collection and data processing functions
- Separation of centers in a multicenter trial

Some of the above separations are desirable simply for reasons of efficiency and proficiency, as suggested in Chapter 5. Others are required for scientific reasons as detailed below.

22.6.1 Separation of treatment administration and data collection personnel in unmasked trials

As noted in Chapter 8, masked administration of the study treatments offers the best safeguard against treatment-related biases in the data collection process. However, masked treatment administration is not always possible and therefore other designs must be used. One approach is to vest responsibilities for administering the study treatments with one group, and those for data collection with a different group (e.g., as was done to some degree in the Macular Photocoagulation Study, Sketch 4, Appendix B, and in the Hypertension Prevention Trial, Sketch 13, Ap-

pendix B). The need for separation is especially important when the outcome measure is subject to observer error. However, it is not always easy to achieve, particularly when the patients themselves may reveal the treatment they have received while outcome measurements are being made. It is much easier to ensure when the outcome measure is based on some reading or determination made by personnel who have no patient contact.

22.6.2 Separation of personnel responsible for patient care and safety monitoring

The ethical underpinnings for a trial rest on the fact that there is no reliable way to choose among the treatments being studied. A physician is willing to allow his patients to be randomized only so long as he remains uncertain regarding the relative merits of the study treatments. He is not, once he believes he knows which treatment is best. Exposure to data and emerging trends as the trial progresses may make him reluctant to enroll new patients or to continue treating those already enrolled once the data suggest one treatment is better than another. Separation of the type suggested avoids this dilemma by shielding the treating physicians from emerging trends and by transferring responsibility for dealing with them to a group not directly responsible for patient care (see Chapter 23). A second and perhaps more convincing argument has to do with the desire to reduce the possibility for feedback bias in the way in which patients are treated and in the data collection process. Biases can creep in if study physicians know the direction of emerging treatment trends.

22.6.3 Separation of investigative and advisory-review roles

The advisory-review process, by its very nature, should be performed by a group that is external to the trial (see Chapter 23). The reasons are obvious. Advice rendered by personnel in the study may be self-serving, especially if rendered by people who are emotionally involved in the trial and who are dependent on it for salary support. In addition, some of the issues requiring review may concern whether funding should be continued in a clinic with a poor patient recruitment or data collection record. Investigators from within the trial may find it hard to take an adverse action against a colleague.

22.6.4 Separation of sponsor and investigative roles

This separation is desirable whether funding is from government or industry. The preferred approach is one in which all of the essential scientific activities for the trial are located outside the sponsoring agency. This separation is particularly important whenever the sponsoring agency has a proprietary interest in the product being tested.

The best example of such separation for an industry-sponsored trial is provided by the Persantine Aspirin Reinfarction Study (PARIS). None of the investigative functions in that trial were associated with the sponsor (Persantine Aspirin Reinfarction Study Research Group, 1980a). The structure of the Anturane Reinfarction Trial (ART), another industry-sponsored trial, represents a step in the right direction, but it failed to provide complete separation. Data center operations were housed in the firm sponsoring the trial (Anturane Reinfarction Trial Research Group, 1980).

22.6.5 Separation of data collection and data processing functions

Every trial will have activities related to data collection as well as those concerned with data processing. These two activities should be carried out by different people under different administrative heads. Effective quality control procedures for the data collection process will be impossible to implement without this separation.

Data processing operations should be on a par with the data collection operations in the trial. The two activities should be provided with separate budgets via different awards direct from the sponsor or via agreements with the chairman of the study as to how funds are to be allocated for the two activities when they are funded out of the same budget.

Separation of these two activities is generally assured in the multicenter trial by creation of a dedicated data center with its own funding. It may be more difficult to achieve in the single-center trial. However, it can be accomplished if the clinic is able to establish a working relationship with another department willing to assume responsibility for the data intake and analyses processes.

22.6.6 Separation of centers in multicenter trials

Centers in a multicenter trial, in addition to being located outside the sponsoring agency, should be administratively distinct from one another. The separation is usually assured by virtue of geographic location. However, there are occasions when two or more centers are located in the same institution. For example, the University of Minnesota housed a clinical center, nutrition coding center, ECG coding center, and coordinating center for MRFIT (Multiple Risk Factor Intervention Trial Research Group, 1982).

The relationship of the data coordinating center to clinics in the trial is of special importance because of the key role it has in monitoring the data collection process (see Chapter 5). The ideal structure is one in which the center is both physically and administratively distinct from all other centers in the trial. It may be difficult for the center to maintain equity in the way in which it interacts with clinics if it is affiliated with one of the clinics in the trial. The actions of the data coordinating center in monitoring the performance of clinics must be viewed by personnel in the clinics as being fair and without prejudice if they are to be effective.

Structures that provide funding via a consortium award (see Glossary) to the lead clinic (see Glossary) should provide a separate budget for the data coordinating center, even if it is located in the same department as the lead clinic. The center should not be headed by the director of the lead clinic, or by any other clinic director in the trial for that matter. The budget and director separation is essential if the center is to have the independence it needs to operate effectively.

Ideally, all centers in a multicenter trial should have the same administrative relationship to the sponsor, and thereby to one another. The administrative equality of centers will help to create a collegial relationship among the investigators and facilitate interaction and communication. The potential for administrative equity is greater when each center is funded directly by the sponsoring agency, or by a board as in PARIS (Persantine Aspirin Reinfarction Study Research Group, 1980a), than when funding is provided via a consortium award.

22.7 SPECIAL MANAGEMENT ISSUES

22.7.1 Disclosure requirements for potential conflicts of interest

Participation in a trial as an investigator is a form of public trust. This trust is violated if the investigator has conflicts of interest that bias the data collection, analysis, or reporting processes of the trial. The mere suspicion of a financial conflict of interest can cause the public to view results and conclusions from the trial as suspect. A case in point, albeit outside the field of clinical trials, is the report of the Food and Nutrition Board (1980) of the National Academy of Sciences on dietary standards. The amount of credence given to the report has been diminished in the eyes of some because of relationships of Board members to segments of the food industry (Wade, 1980).

Some relationships and activities are clear conflicts of interest and should be avoided (e.g., working for a firm producing one of the drugs being tested while serving as a member of the treatment effects monitoring committee). Certainly, investigators involved in drug trials should be free of all consulting and retainer arrangements with any drug firms that stand to gain or lose depending on the results of the trials. The same is true for perquisites (e.g., travel to an exotic place for an investigator and his/her spouse ostensibly for a scientific meeting) offered by manufacturers standing to gain or lose from the trial.

It is prudent to establish mechanisms to monitor for potential conflicts of interest within the investigative group and related committees, including the treatment effects monitoring and advisory-review committees. Systems for disclosure of conflicts are of little value if the persons covered by the systems are insensitive to the issues or activities that can be perceived as constituting a conflict of interest. Any disclosure system, to be useful, should be updated at periodic intervals over the course of the trial. Further, the statements filed by members of the study and related committees must be reviewed by an appropriate body (e.g., the sponsor in government-supported trials or the advisory-review committee) as they are received to identify conflicts that are serious enough to disqualify a person from involvement in the trial. All statements filed should be open for public inspection once results have been pub-

lished (e.g., as was done in the National Cooperative Gallstone Study, 1981b).

22.7.2 Level of compensation for committee members outside the trial

Members of committees, such as the treatment effects monitoring and advisory-review committees, who are not associated with any center in the trial, will usually be paid an honorarium or a consulting fee for meeting activities. Excessively large payments should be avoided since they themselves have the potential of creating a conflict of interest when members are required to decide whether or not a trial should continue. Governmental agencies, such as the National Institutes of Health and the Veterans Administration, typically pay only travel expenses and a standard fee of $100 or $150 per meeting day. Generally, these agencies do not pay members for time spent in travel to or from meetings or for time spent in preparing for them.

22.7.3 Review and approval of proposed ancillary studies

An ancillary study is defined as an investigation, stimulated by the trial and intended to generate information of interest to it. It is designed and carried out by investigators from one or more of the centers in the trial and utilizes resources of the trial, but is not a required part of the design or data collection protocol of the trial. A large-scale multicenter trial may spawn a number of such studies. In fact, the opportunity to engage in such investigations may represent an inducement for investigators to become involved in the trial in the first place and may help them to maintain their interest in the trial as it proceeds (see also Sections 6.3.4 and 6.4.5 and Section 15.2.1).

The leadership of the trial (usually the steering committee) is responsible for establishing the general guidelines and policies concerning the type of studies that may be undertaken, and for review of proposals before they are implemented. The review should focus on:

- Aim and rationale of the proposed investigation
- Type and amount of data to be collected
- Relevance in relation to the main aims of the trial
- Extent to which investigations are likely to interfere with patient enrollment and follow-up, or with established data collection procedures
- Possibilities of biasing the data collection or patient treatment procedures in the trial
- Amount of analytic help needed from the data center
- Amount of study resources needed to carry out the investigations

Investigations that have the potential of reducing a patient's willingness to be enrolled into the trial or to continue after enrollment should not be undertaken for obvious reasons. Patients approached for participation should be informed of the ancillary nature of the investigations being proposed and of their right to refuse without affecting their participation in the trial.

Investigations in masked trials that entail collection of data that have the potential of unmasking treatment assignments in the clinics should be proscribed, or should be done in such a way so as to preserve the mask. The same is true for analyses that have the potential for unmasking treatment assignments. Such analyses may have to wait until the trial is over and the treatment codes have been released.

Ancillary studies involving only modest time commitments from a few study personnel may be supported with funds from the trial. Large undertakings, involving major time commitments from existing study personnel or the recruitment of additional staff, should be done with independent funding.

One of the issues that should be covered during the review is the proposed authorship of papers arising from the investigation and the credit to be given to the trial in such publications. The arrangement proposed should be compatible with the general authorship guidelines established for the trial (see Chapter 24).

22.7.4 Publication and internal editorial review procedures

A key issue in any trial has to do with mechanisms for the review and authorship of study publications. The considerations related to this issue are discussed in Chapter 24.

22.7.5 Publicity and information access policy issues

The leadership of the study is responsible for guidelines concerning investigator-initiated publicity during the trial (see Chapter 24). Most publicity, whether contemplated on a local (e.g., in relation to patient recruitment at individual clinics in a multicenter trial) or national level should be cleared through a central body in the study. Similarly, as noted in Chapter 24, it is prudent to develop general guidelines to indicate how investigators are to deal with requests for information from the news media or from members of the scientific or lay community while the trial is under way.

23. Committee structures of multicenter trials

We shall have long sittings, much fighting is anticipated.

Sir Robert Christensen

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23.1 INTRODUCTION

The three functions discussed in Chapter 22, leadership, safety monitoring, and advisory-review, are usually met through committees in the typical multicenter trial as considered in this book. The main organizational units are listed in Table 23-1. Table 23-2 provides a description of the principal duties of each unit listed.

Table 23-1 Key organizational units

Organizational unit	*Function*	*Other designations**
A. Study chairman	• Head the investigative group and chair the SC	• Study director • Principal investigator
B. Steering committee (SC)	• Leadership body of the investigative group	• Director's committee • Executive committee
C. Executive committee (EC)	• Executor of SC	• Chairman's committee
D. Treatment effects monitoring committee (TEMC)	• Safety monitoring	• Data monitoring committee • Data and safety monitoring committee • Ethics review committee • Ethics committee
E. Advisory-review committee (ARC)	• Advise sponsor and/or investigators on conduct of trial	• Policy advisory board • Policy advisory committee • Advisory committee • Review committee
F. Advisory-review and treatment effects monitoring committee (ARTEMC)	• Advise sponsor and/or investigators on conduct of trial and perform safety monitoring	• Operations committee

*Not used in this book.

Table 23-2 Functions and responsibilities of the main organizational units of multicenter trials

A. Study chairman
- Serve as senior executive officer of the investigative group
- Chair steering committee
- Serve as principal spokesman for the study
- Maintain communications within the study and with the sponsor

B. Steering committee (SC)
- Assume responsibility for general design and conduct of the trial, including preparation of essential study documents, such as manual of operations, data forms, treatment protocol, etc.
- Review data collection practices and procedures, as summarized in performance monitoring reports, from visits to participating clinics, and other means, to identify and correct remediable deficiencies
- Consider and adopt changes in study procedures as necessary and desirable during the course of the trial
- Appoint and disband subcommittees needed for execution of the trial
- Make decisions on resource allocations and on priorities for meeting competing demands in the trial
- Review progress of study in achieving its main goal and take steps required to enhance likelihood o success in achieving them
- Review and implement recommendations from the ARC and TEMC (or ARTEMC) for a treatment protocol change, such as termination of a treatment because of lack of efficacy
- Review and react to other general advice or recommendations from the TEMC and ARC (or ARTEMC)

C. Executive committee (EC)
- Act as the administrative and executive arm of the SC
- Make decisions on behalf of the SC on day-to-day operational issues requiring immediate action
- Assign priorities for activities in the trial, consistent with the dictates of the SC
- Perform executive functions for the trial, including scheduling meetings, preparation of SC and other meeting agendas, etc.
- Coordinate preparation of progress reports requested by the sponsoring agency in conjunction with funding renewal requests and as needed at other times
- Perform other functions assigned by the SC

D. Treatment effects monitoring committee (TEMC)*
- Direct or carry out data analyses needed for assessing treatment effects during the trial
- Review interim reports prepared by the data coordinating center for evidence of adverse or beneficial treatment effects
- Recommend changes in the treatment protocol to the ARC
- Provide advice to the SC on operational procedures affecting the quality of the trial

E. Advisory-review committee (ARC)*
- Advise the sponsor on performance of the trial and whether funding for it should be continued
- Review and approve recommendations from the TEMC for changes in the treatment protocol
- Recommend termination of support of centers when warranted because of poor performance or for other reasons
- Advise the SC and sponsor on important policy issues
- Review performance monitoring reports prepared by the data coordinating center to detect deficiencies in the data collection or intake processes and recommend corrective action when necessary
- Assume responsibility for external review of the data coordinating center and other resource centers in the trial

F. Advisory-review and treatment effects monitoring committee (ARTEMC)
- Committee has the combined functions of the TEMC and ARC

*Functions assumed by the ARTEMC in structures not having a separate TEMC and ARC.

The chairman of the study,[1] in conjunction with the steering committee (SC), or SC and executive committee (EC) when the structure includes both committees, provides the general leadership for the trial. Membership on the committee(s) is generally limited to personnel associated with centers in the trial. Exceptions are cases in which membership is augmented to include consultants with expertise in areas not represented within the study.

1. In this book, the individual chairing the steering committee is considered to be chairman of the study.

The advisory-review functions will be provided through a specially constituted committee, herein referred to as the advisory-review committee (ARC). The same is true for the safety monitoring function; generally, it will be met through a committee herein referred to as the treatment effects monitoring committee (TEMC), or through a committee that fulfills both the advisory-review and safety monitoring functions, herein referred to as the advisory-review and treatment effects monitoring committee (ARTEMC). The ARC and TEMC or

ARTEMC are composed primarily of people not associated with any of the centers in the trial.

All 14 trials sketched in Appendix B included a SC. Several (5 of the 14) also included an EC. Six of the 14 had separate committees for meeting the safety monitoring and advisory-review functions. Four combined the functions into a single ARTEMC and the remaining 4 had only a TEMC or an ARC, but not both (line 27, Table B-4, Appendix B).

The committee structure of a trial is generally more complex than suggested above, as indicated in Table 23-3 for one of the trials sketched in Appendix B—the Coronary Drug Project (CDP; see citation 104 for details). See also citations 346, 375, and 476 for detailed listings of committee structures in the National Cooperative Gallstone Study (NCGS), Persantine Aspirin Reinfarction Trial (PARIS), and University Group Diabetes Program (UGDP). Other references pertinent to the tonic of this chapter include citations 315, 318, and 479.

Table 23-3 Functioning committees of the Coronary Drug Project (Sketch 6, Appendix B)

*CDP committee**	*Function*
• Steering Committee	• As described in Part B of Table 23-2
• Data and Safety Monitoring Committee	• As described in Part D of Table 23-2
• Policy Board	• As described in Part E of Table 23-2
• Criteria Committee	• Establish definitions and criteria used for determining patient eligibility in the trial
• Laboratory Committee	• Review procedures and results produced by the central laboratory for the trial
• Editorial Review Committee	• Review study manuscripts before presentation or submission for publication
• Statistical Committee	• Advise the Coordinating Center on methods of data analysis
• Natural History Committee	• Direct data analyses and paper writing activities concerned with the natural history of coronary heart disease, as based on results obtained from the placebo-treated group of patients
• Mortality Classification Committee	• Classify deaths by cause
• Hepatology Committee	• Plan analyses and review data relating to liver function tests
• Data Repository Committee	• Review ancillary study proposals requiring access to the main study file and establish special data collection procedures and respositories for results of ancillary studies that threaten treatment masking
• Arrangements Committee	• Select site of semiannual investigative group meetings and coordinate arrangements with host city
• Resources Committee	• Advise the SC on future studies and activities involving CDP patients
• Newsletter Committee	• Prepare patient newsletter

*Members of all committees, except those serving on the Data and Safety Monitoring Committee and Policy Board, were appointed by the Steering Committee. Members of the Data and Safety Monitoring Committee were appointed by the Steering Committee or Director of the NHLBI. Members of the Policy Board were appointed by the Director of the NHLBI.

23.2 STUDY CHAIRMAN

The terms *principal investigator* and *chairman of the study* may be synonymous in a single-center trial, but not in a multicenter trial where there are, in effect, multiple "principal" investigators (see Glossary for comment). Someone must be chosen or designated to head the investigative group (IG) and to chair the steering committee in such trials. This individual is referred to as chairman of the study throughout this book. Desired qualities of this individual include:

- A keen intellect
- An understanding of and interest in the area of study
- Research experience, preferably in other clinical trials
- Experience in collaborative research
- A respected research record
- Strong leadership capabilities
- Self-assurance but not arrogance
- The ability to make decisions, but not capriciously
- Integrity
- An ability to listen to others and to modify a stand in the face of convincing arguments
- The ability to compromise
- Evenhandedness and fairness in dealing with others
- Respect for others and their ideas
- Sensitivity to the needs and feelings of others
- Patience and perseverance

Ideally, the individual selected should be chosen with this list in mind. However, in actual fact, there may be little room for choice, especially in an investigator-initiated trial, in which the individual who conceives the trial is the one who heads it. Room for choice is greater in sponsor-initiated trials. The approach used in the Aspirin Myocardial Infarction Study (AMIS) serves as a useful model. A temporary study chairman was appointed by the National Heart, Lung, and Blood Institute (NHLBI) shortly after selection of the clinics and the coordinating centers for the study. A permanent chairman was appointed by the Institute some months later, after input was received from the investigative group regarding possible choices.

The choice, when one exists, should be limited to persons who do not have a strong emotional commitment to any of the treatments being tested and who have open minds concerning their merits. For obvious reasons, the individual selected should be devoid of financial interests in the treatments under test.

The chairman is sometimes selected by a vote of the investigative group. In this case, the choice should be made from a slate of suitable candidates proposed by a nominating committee appointed by the investigative group, or that has been screened in some other way. A popular election, without any screening, can lead to an unwise choice (e.g., selection of a highly popular but poorly qualified individual).

All of the trials listed in Appendix B were headed by persons with M.D. degrees (line 28.a.i, Table B-4, Appendix B). However, only 5 of the 14 chairmen had responsibility for patients in the trials, although several others were located in institutions housing a study clinic. The association with a clinic has advantages and disadvantages. On the one hand, it helps to ensure that the chairman has firsthand knowledge of the data collection procedures in the trial. The knowledge is useful when chairing discussions concerning protocol changes or when writing papers containing results from the trial. On the other hand, the association may make it difficult for the chairman to maintain a balanced and evenhanded approach when dealing with other clinical investigators in the trial, especially if the clinic he is associated with is one of the more inept clinics in the trial. In addition, the need to treat study patients, if the chairman has such responsibilities, may conflict with some of his other responsibilities (e.g., see Section 23.6).

It is perhaps no accident that none of the chairmen for the 13 multicenter trials represented in Appendix B were from coordinating centers or sponsoring agencies. The addition of chairmanship responsibilities on top of those normally assumed by the coordinating center or sponsoring agency is unwise because of the separation requirements discussed in Chapter 22. In addition, the added concentration of power at the coordinating center or sponsoring agency, through the study chairmanship, may make it difficult to establish the checks and balances needed for a robust structure.

As a rule, the chairman will be appointed or elected to serve for the duration of the trial (see item 28.a.iv, Table B-4, Appendix B). The advantage of an appointment without term stems from the continuity of leadership provided when the same person presides over the trial from beginning to end. The main disadvantage is that difficulties can arise if the chairman proves to be an ineffective leader and must be replaced. A term appointment can provide a graceful way out in such cases.

Most of the above considerations pertain to the position of study vice-chairman as well. Ideally, the chairman and vice-chairman should be from different centers in the trial. Location of both individuals in the same center may concen-

trate too much power and influence in a single center and may restrict the range of ideas presented to the SC and investigative group.

23.3 STEERING COMMITTEE

The steering committee is the main leadership committee of the study. It is the body which is responsible for overall direction of the study.

Every multicenter trial must face two key issues in the formation of this committee. The first has to do with center representation on the committee. The issue is easily resolved when the total number of centers in the trial is small (say ten or less) and where, as a result, it is practical to have a position for each center on the committee. However, this form of representation is impractical if the number of centers is large. For example, this method of representation would have led to a steering committee of more than 60 members in the CDP. Clearly, a representative form of government is required in such cases to avoid the expense, to say nothing of the logistical difficulties, involved in convening the committee. The CDP operated with a steering committee of 15 members by providing for a mix of standing and elected members. The chairman and vice-chairman of the study, director of the coordinating center, project officer, and directors of the five clinical centers named in the initial funding application were designated as permanent standing members. In addition, there were four elected members, chosen by the IG from among directors of clinical centers not accorded permanent representation on the committee. Elected members served for a three-year term, with provision for re-election. Terms were staggered to allow for an orderly rotation of elected members.

The SC should not be created under the one-center-one-member rule if there is any likelihood of having to reconstitute the committee later on in the trial under a representative form of government. It is far better to anticipate the need for such a form of government from the outset than it is to attempt to switch to it once the trial is under way.

Several of the trials listed in Appendix B provided SC representation for each center director, even though it led, in some cases, to steering committees with 20 or more members. See item 28.c.iii, Table B-4, Appendix B and Table 23-4 for specifics.

A second issue has to do with the nature of representation on the committee for key professional groups involved in carrying out the study. Formation of the committee along center lines automatically leads to overrepresentation of some types of personnel (e.g., clinical investigators), underrepresentation of others (e.g., personnel concerned with data analysis), and exclusion of still others (e.g., junior personnel performing essential functions in the trial).

Some studies have attempted to rectify this problem by reserving positions on the committee for designated classes of personnel. The approach offers two general advantages. First, it helps to provide the SC with the expertise needed to discharge its leadership functions. Second, it avoids the obvious morale problems that can arise if an important group of personnel in the trial has no voice in the way it is run.

Four of the SCs sketched in Appendix B had clinic coordinators represented (see Glossary for definition). The advantages of such representation have been discussed by Overton (1980) from the perspective of the Aspirin Myocardial Infarction Study. It was the only position represented in the trials sketched in Appendix B, other than the study chairman, vice-chairman, center directors, and project officers. One reason for the lack of representation may have to do with the natural reluctance of any group of senior investigators to dilute their base of power through the addition of members not in key leadership positions in the study. A second reason may have to do with the potential for embarrassment if a second representative from a center speaks or votes against a position held by the center director.

Table 23-5 provides a list of some of the general rules for SC formation (see Table 22-2 for general committee rules). The term of office should be designated when positions are filled. When less than the duration of the trial, terms should be long enough to permit individuals to play meaningful roles on the committee. General rules for filling vacancies should be spelled out before any are encountered. In addition, it is wise to indicate conditions that will lead to cancellation of membership on the committee because of conflicts of interest, lack of interest in the study as expressed by attendance records at committee meetings or in other ways. Termination of inactive members, so that their positions can be filled with new and more active members, is important in maintaining the vitality of the committee.

Table 23-4 Characteristics of steering committees and committees responsible for safety monitoring in the 14 trials sketched in Appendix B

	Steering Committee	*Safety Monitoring Committee**
A. Chairman		
• Primary degree		
M.D.	14	12
Ph.D.	0	4
• Term		
For duration of study	14	16
For specified number of years	0	0
• Patient care responsibilities		
Yes	6	1
No	8	15
B. Vice-chairman		
• Number of trials with vice-chairman	8	2
• Primary degree		
M.D.	7	2
non-M.D.	1	0
• Term		
For duration of study	8	2
For specified number of years	0	0
• Patient care responsibilities		
Yes	6	0
No	2	2
C. Number of members (voting plus nonvoting)		
≤10	2	7
11-15	5	5
16-20	5	1
≥20	2	1
D. Study positions represented		
Study chairman	14	13
Study vice-chairman	8	5
Director of coordinating center	14	13
Project officer	10	13
Clinic coordinator	4	0
Clinic director	13	6
Nonhealth professional or lay representative	0	3
E. Nonstudy members		
Yes	6	12
No	8	2

*Two studies had safety monitoring committees headed by co-chairmen.

23.4 EXECUTIVE COMMITTEE

Most steering committees, even for a trial involving as few as five or six clinics, will be too large to deal with the day-to-day decision making needed for efficient operation of the trial. A smaller, more compact committee will be needed for this purpose (see Part C of Table 23-2). The EC is usually headed by the study chairman and includes the study vice-chairman (if there is one), director of the coordinating center, project officer (in the case of trials funded by the National Institutes of Health), and perhaps a few other members of the IG as well. As a rule, it will meet more frequently than the SC (either face-to-face or via conference telephone).

The usefulness of the committee will be defeated if it has more than a half dozen members

Table 23–5 Do's and don'ts for formation of the steering committee

DO

- Provide for input from the investigative group when organizing the committee
- Consult with the sponsor about the functions and proposed membership of the SC
- Listen to suggestions made by the sponsor regarding organization and function of the SC
- Outline general membership criteria, methods for selecting members, and terms of office
- Provide for representation of all essential skills and disciplines needed for effective operation of the SC
- Set an upper membership limit on the SC and stick to it
- Provide for rotation of at least a portion of the SC members by appointment or election, especially for trials with large numbers of centers
- Designate the study chairman as chairman of the SC
- Designate the study vice-chairman, director of the coordinating center, and directors of other key resource centers as ex-officio voting members of the committee
- Make the project officer an ex officio (voting or nonvoting) member of the committee
- Outline rules for filling vacancies on the committee
- Specify disqualifying conflicts of interest and other conditions (such as poor meeting attendance) that will lead to termination of SC membership

DON'T

- Limit membership on the SC to center directors or senior investigators
- Use appointment to the SC as a method of dispensing rewards or favors
- Include people on the SC known to have conflicts of interest in relation to the study treatments
- Limit voting rights for selection of elected members simply to senior members of the investigative group
- Permit the sponsor to dictate the organizing tenets of the trial

or so. The temptation to make the committee a "mini" steering committee, by including a number of elected representatives from the parent committee, should be resisted. The ability to convene the committee (by phone or in person) on short notice will become progressively more difficult the larger it is.

The concept of delegating executive responsibilities to the EC should be established before the SC is created. Members of the SC may resist creation of the EC once the SC has been established, especially if they view the move as one which lessens their influence in the study.

Only 5 of the 14 trials sketched in Appendix B had formally constituted executive committees (line 27, Table B-4, Appendix B). The number of members ranged from 7 to 10.

23.5 OTHER SUBCOMMITTEES OF THE STEERING COMMITTEE

The SC may commission a number of subcommittees, in addition to the EC, to perform defined tasks (see Table 23-3 for list of CDP standing committees). Care must be taken to avoid needless proliferation of subcommittees and overlap of functions among the committees commissioned. The larger the number of committees, the more cumbersome the organizational structure of the trial, and the greater the likelihood of overlap of functions among the committees.

Only committees that are commissioned to fulfill a continuing need over the course of the trial should be created on a standing basis. Committees that are commissioned to perform time-limited tasks should be designated as ad hoc committees and should be disbanded once the tasks are finished.

Each committee, whether created on a standing or ad hoc basis, should have a defined charge and should have sufficient authority and resources to carry out its charge. It should have a chairman who has responsibility for convening the committee and for reporting to the parent committee as needed. Its members should be derived from the entire IG, not simply from the parent committees, although each subcommittee should have at least one member from the parent committee. The overlap in membership helps to facilitate communications between the two committees.

23.6 TREATMENT EFFECTS MONITORING AND ADVISORY-REVIEW COMMITTEES

The discussion in this section assumes the trial is one that requires both safety monitoring and advisory-review (see Chapter 22). A key design question in this context has to do with whether to vest both functions in the same committee or in two separate committees. Table 23-6 provides an outline of the conditions under which a separate ARC and TEMC may be needed and where a single combined ARTEMC may do.

The main advantage of separate committees has to do with the separation of functions made possible in this way. The separation, among other things, helps to ensure that adequate time will be spent on the safety monitoring process. This assurance is more difficult to achieve when the safety monitoring function is only one of a larger set of responsibilities assumed by an ARTEMC. The use of separate committees also makes it possible for one committee to serve as a check on the other for key decisions involving termination of a treatment because of adverse or beneficial effects. The main disadvantage is the added complexity involved in creating and staffing two committees rather than one.

Whatever structure is chosen should be designed to meet the advisory-review needs of the sponsor and of the investigative group. These needs, while overlapping, are different. Cooperation between the sponsor and investigators will be needed to develop a structure that satisfies both needs.

Appointments to the TEMC and ARC or ARTEMC may be made by the sponsor, or by the study chairman on behalf of the SC. They should be made by the study chairman in cases where the sponsor has a proprietary interest in the treatments being tested. However, it is important, regardless of how the appointments are made, to ensure that the appointments proposed are acceptable to both the IG and the sponsor.

Investigators may have no choice but to proceed with formation of their own treatment monitoring and advisory-review structure if the sponsor has no interest in establishing such a structure or sees no need for it (e.g., as in some investigator-initiated grant-supported trials). The lack of cooperation can lead to problems later on if the sponsor concludes that the structure is inadequate to serve its needs and therefore elects to superimpose its own structure on top of one already in place. This problem occurred in the Program on the Surgical Control of Hyperlipidemia (POSCH). The original structure provided for both a TEMC and ARC, with members of both committees appointed by the study chairman. Later on, as the study progressed and the need in the NHLBI for an advisory and review process independent of POSCH came to be recognized, the Institute requested POSCH investigators to accept an expansion of the two committees via the addition of members appointed by the Institute. This arrangement was sufficient to satisfy the needs of the Institute until well into the trial. However it ultimately moved to create its own ARC. This move required dissolution of the existing ARC and led to a series of discussions (involving the study chairman, chairman of the TEMC, and NHLBI staff) to define the domain and responsibilities of the new ARC in relation to the existing POSCH committee structure.

The typical TEMC and ARC, or ARTEMC, as seen through the sketches in Appendix B, for the most part, is made up of experts from specialty fields of medicine and biostatistics, although, a few included a professional from a nonhealth field (e.g., a lawyer or clergyman) or a lay representative as a means of broadening the perspective of the committee (see item 29.e, Table B-4, Appendix B). The virtues of membership for a nonhealth professional are discussed in a paper by Hamilton (1981).

Table 23-4 provides a summary of the information tabulated in Appendix B (item 29, Table B-4) for the committees that performed safety monitoring (TEMCs in nine trials, ARTEMCs in four trials, and the SC in one trial—the UGDP). All of the committees were chaired by persons with expertise in epidemiology or biostatistics and who had an M.D. or Ph.D. The number of members ranged from 5 to 27, counting voting as well as nonvoting members. Several of the committees restricted voting privileges to mem-

Table 23–6 Considerations leading to a separate ARC and TEMC or a combined ARTEMC

A. Considerations for separate ARC and TEMC

- When treatment monitoring activities require frequent meetings and where each meeting requires a half day or more to carry out the necessary data reviews
- When the TEMC meets other general analysis needs of the study (e.g., is responsible for developing analytic approaches for dealing with special analytic problems)
- When the trial is investigator-initiated and grant-supported
- When the sponsor and/or investigators desire separate committees

B. Considerations for combined ARTEMC

- When the time required for treatment monitoring is small relative to the time required to perform more general advisory and review functions normally assumed by the ARC
- When there is little or no need for advice or guidance concerning the analysis procedures used for assessing treatment effects
- When the trial is sponsor-initiated
- When the sponsor and/or investigator desire a single combined committee

bers not affiliated with any study center. This restriction is a good idea, especially in cases in which study members are dependent on the study for salary support. Most of the committees included the director of the coordinating center, either as a voting or nonvoting member. Representation from this center is essential in the monitoring process because of its key role in data analyses. All of the NIH-sponsored trials sketched included representation of the project office on the committee as well. The majority of the committees also included the study chairman or vice-chairman, again as either voting or nonvoting members.

Inclusion of the study chairman on the TEMC or ARTEMC is open to debate when that person has patient care responsibilities in the trial. The emotional commitment needed to treat can affect any person's scientific objectivity thereby reducing that person's effectiveness on the committee. Further, it can be argued that a study physician who has access to interim results of the trial will be affected by them, thereby increasing the risk of bias in the treatment and data collection processes performed by that person. In addition, having access to the results can create a dilemma for any study physician still involved in recruiting patients for the trial if they suggest one treatment is better than another, even if the trend is not large enough to justify stopping the trial. Shielding study physicians from the interim results protects them from the dilemma mentioned by transferring responsibility to the TEMC or ARTEMC.

The virtues of inclusion have to do with the special qualifications of the study chairman. This person may have the best perspective on the trial and its data collection and treatment processes—a perspective that may be invaluable when the TEMC or ARTEMC is faced with a major decision concerning the study. In addition, the chairman's presence on the committee can be reassuring to other clinical investigators in the trial. In fact, they may be reluctant to delegate responsibility for safety monitoring to any group without such representation.

The approach practiced in some studies has been to include both the chairman and vice-chairman of the study on the treatment effects monitoring committee, whether or not they have treatment responsibilities in the studies. For example, the CDP opted for this approach, even though the vice-chairman of the study had such responsibilities. The TEMC in the Hypertension Detection and Follow-Up Program (HDFP) was reconstituted during the trial to include both the study chairman and vice-chairman.

Ideally, persons selected to serve on the TEMC, ARC, or ARTEMC should have prior experience with multicenter clinical trials. This is especially true for the chairmen of these committees.

All voting members should be screened for conflicts of interest before appointment. In addition, mechanisms should be established to alert the appointing authority to conflicts of interest that may develop during the trial (see Section 22.7 of Chapter 22).

Members of the treatment effects monitoring and advisory-review committees are usually appointed for the duration of the trial. None of the TEMCs, ARCs, or ARTEMCs listed in Appendix B made any provision for term appointments. Undoubtedly, this is due to the desire of the study leaders to maximize continuity of function in these committees via a stable membership. However, this approach, as suggested in Section 23.3, can cause difficulty if members lose interest in the trial. Hence, it is prudent to have some means of dismissing inactive members in the absence of term appointments in order to maintain a properly functioning committee.

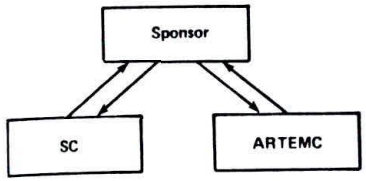
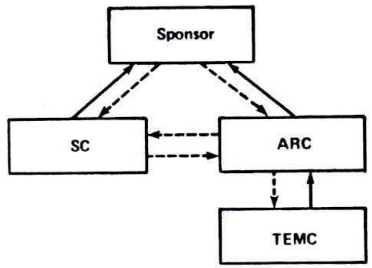
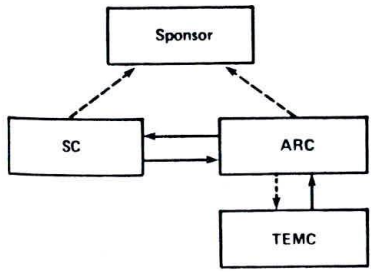
23.7 COMMITTEE-SPONSOR INTERACTION

Smooth interaction of the SC with the TEMC and ARC, or with the ARTEMC in the case of a single committee with combined advisory-review and safety monitoring functions, is essential for operation of the trial. Figure 23-1 provides stylized diagrams of three types of interaction models, as viewed from the perspective of the sponsoring agency. It also outlines the main characteristics of each of the models.

Communications between the SC and the sponsor in the models are concerned with design and operation of the trial. Communications between the ARC or ARTEMC and the sponsor are concerned primarily with assessment of the adequacy of the study design, the nature of the treatment results, and with fiscal affairs. None of the models in Figure 23-1 provides for flow of treatment results to the SC during the trial. Information of this sort passes only in conjunction with a recommended treatment protocol change.

Each of the trials sketched in Appendix B has been classified (by the author) as to type of communication model using the criteria given in

Figure 23-1 Committee-sponsor interaction models

Model	*Characteristics*
Model A. *Sponsor Directive* 	• Trial usually sponsor initiated • Members of ARTEMC appointed by sponsor, sometimes with little or no investigator input • Advisory and review functions provided by ARTEMC, as prescribed by the sponsor • Communication between SC and ARTEMC via the sponsor • Little or no direct communication between SC and ARTEMC • Recommendations for treatment change made by the ARTEMC. Those approved by the sponsor are passed, via the sponsor, to the SC for implementation
Model B. *Sponsor Nondirective* 	• Trial usually investigator initiated and grant supported, or initiated via a joint effort of the investigators and sponsor • Members of the ARC and TEMC may be appointed by the sponsor or chairman of the SC • Appointments made to the ARC and TEMC generally limited to individuals who are acceptable to both the sponsor and investigative group • Advisory and review functions provided by ARC, as prescribed by mutual consent of investigative group and sponsor • ARC provides advice and review for both the sponsor and investigators • Primary communications of the TEMC directed to ARC; limited communications from the ARC to TEMC • Recommendation for treatment change originates with TEMC, reviewed by ARC, and passed to SC, via the sponsor, for implementation • Primary communications from the ARC to sponsor and from SC to sponsor. Only limited communication from the sponsor to the SC, or from the sponsor to the ARC. No direct communication between TEMC and SC or between TEMC and the sponsor • Some direct communication between SC and ARC, but not with regard to treatment results
Model C. *Sponsor Passive* 	• Trial usually small-scale, investigator initiated, and grant supported • Advisory and review function provided by ARC, as prescribed by the SC • ARC has no advisory-review role for the sponsor • Members of ARC and TEMC appointed by chairman of SC. Little or no interest expressed by the sponsor in the selection or appointment process • Virtually no communication from sponsor to SC or from sponsor to ARC • Limited communications from SC to sponsor and from ARC to sponsor • Same communication structure as for Model B regarding ARC and TEMC • Major communications between SC and ARC • Recommendation for treatment change originates with TEMC, reviewed by ARC, and passed by the ARC to the SC for implementation with knowledge of the sponsor, but without its approval

Note: Arrows indicate direction of communications. Solid lines indicate major communication pathways. Dashed lines indicate secondary communication pathways.

Figure 23-1. Four of the 14 trials were classified as sponsor-directive and the remaining 10 were classified as sponsor non-directive (see item 30, Table B-4, Appendix B for specifics).

23.8 CENTER-TO-CENTER COMMUNICATIONS

The coordinating center (or data coordinating center) is the primary communication channel in most multicenter structures. The center will require linkages with each clinic as well as with all other organizational units in the trial to perform its functions effectively. The volume of information flowing in other communications channels, such as those associated with the chairman's office, project office, and other resource centers in the trial, will depend on the way in which coordination responsibilities are divided (see Chapter 5). Generally, it will be small compared with that of the coordinating center or data coordinating center.

Information flowing from the clinics to the coordinating center (or data coordinating center) will consist primarily of data, either as contained on completed data forms or as tapes or disks of data already keyed at the clinics from the data forms. Information flowing from the coordinating center to the clinics will relate to:

- Edit queries concerning completed data forms
- Procedural memos concerning the data collection process
- Manuals of operation or parts or sections of manuals and related revisions
- Approved data forms and related revisions
- Progress reports and clinic performance monitoring reports
- Minutes of study meetings
- Miscellaneous study correspondence

The flow into and out of the clinics should be via a defined pathway. Multiple entry and exit points for the clinic will make it difficult, if not impossible, to control information leaving the clinic and to keep track of information flowing into it. The preferred structure is one in which a single person, usually the clinic coordinator, is designated to serve as the conduit through which correspondence and materials flow into the clinic and through whom data forms and related materials flow out of the clinic. One person who should not serve as a primary channel for routine information flow is the clinic director. The likelihood of a smooth and continuous flow is low because of the multiple commitments and general lack of discipline and interest of such a person in handling routine flows.

The designation of a single individual in the clinic to receive and distribute important procedural information arriving from the coordinating center (or data coordinating center) simplifies the distribution task of the coordinating center. Mailings from the coordinating center to several persons in each clinic is expensive and may not, in any case, work as well as local distribution systems. However, some mailing redundancy is wise to protect against communication breakdowns if the primary channel fails. The HPT data coordinating center used a primary (clinic coordinator) and secondary (clinic director) mail contact for all communications concerning data collection and study procedures. The primary mail contact received originals and all accompanying attachments to mailings from the data coordinating center. The secondary contact received, via a separate mailing, copies of all numbered memos and a list of attachments received by the primary mail contact.

The address directory is an essential communications aid in the multicenter trial. To be useful, it must be up-to-date and should contain the names, mailing addresses, and phone numbers of all study personnel at each participating center. Other useful information in the document includes:

- An indication of the functions of each person listed, including areas of certification for data collection
- The name of the primary and secondary mail contacts at a center
- The deputy director of a center
- List of study committees and the names, addresses, and phone numbers of committee members

The information system of a trial will require a numbering scheme to facilitate the identification of the various documents in the study. The need for a form numbering scheme has already been addressed (Chapter 12). However, the need does not stop there. It extends to other documents as well, such as:

- Committee minutes
- Procedural memos, etc.
- Manuals of operation
- Materials used by clinic staff and patients for treatment administration

The ground rules for document numbering and communications should be established before data collection is begun. Rules should be written and reviewed by the SC before they are promulgated in the study. The rules should be reviewed and, when necessary, revised at intervals over the course of the trial.

Part VI. Reporting procedures

Chapters in This Part

24. Study publication and information policies
25. Preparation of the study publication
26. Locating and reading published reports

Chapter 24 deals with general policy issues involved in the production and publication of study manuscripts. Chapter 25 outlines the content requirements of a finished report and the steps involved in the preparation of such reports. The last chapter contains a review of methods for locating reports of trials in the published literature. It also contains a list of points a reader should consider when reading a report. It closes with a discussion of the responsibilities of persons who critique study publications.

24. Study publication and information policies

Never be so brief as to become obscure.

Tyron Edwards

24.1 Information constraints
24.2 Publication questions
24.2.1 When to publish?
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24.4.6 Outside audits
Table 24-1 Pros and cons of interim publications not related to a treatment protocol change
Table 24-2 Options for initial communication of results
Table 24-3 Long versus short papers
Table 24-4 Pros and cons of individual versus corporate authorship

24.1 INFORMATION CONSTRAINTS

The types of trials described in this book typically require constraints on the flow of information while they are under way. Commonly imposed constraints relate to:

- Randomization (e.g., by withholding details concerning the randomization process from clinic personnel to keep them from predicting future assignments; see Chapter 10)
- Treatment masking (e.g., by constructing methods for assigning and administering treatments so that a patient and his doctor remain masked with regard to treatment assignment; see Chapters 8 and 10)
- Data collection and coding procedures (e.g., through separation of treatment and data collection responsibilities in the clinic so that observations are made and recorded by personnel who are kept ignorant of the treatment received by the study patients; see Chapter 8)
- Treatment monitoring where only selected members of the study organization are privy to interim treatment results (see Chapter 20)

All of the trials listed in Appendix B imposed constraints of these types. All of the coordinating centers withheld details concerning the method of randomization until recruitment was finished or until the end of the study. Most had structures that allowed only certain members of the study group to see interim treatment results. Clinic personnel, as a rule, were not allowed access to outcome data by treatment group until the study was concluded, or until a treatment was terminated.

Information constraints, whether limited to members of the community at large, or to selected study personnel as well, should not be imposed unless there is a good rationale for doing so. Further, they should be lifted as soon as the need for them no longer exists.

24.2 PUBLICATION QUESTIONS[1]

24.2.1 When to publish?

Any investigator who undertakes a trial has a responsibility to make the results obtained from it available for public scrutiny via a published manuscript. The manuscript should be prepared and made available as soon after the results have been obtained as possible. Normally, the manuscript (or manuscripts) describing the results will be produced after the trial has entered the termination stage (see Chapter 3 for stages). Exceptions are cases in which interim publications are needed to report results related to a treatment protocol change, as in the Coronary Drug Project (CDP), Macular Photocoagulation Study (MPS), and University Group Diabetes Program (UGDP). See reference citations 102, 103, 105, 291, 292, 293, 468, 470, 472 for publications of this type.

Investigators in long-term trials should decide whether or not to allow publication of interim results not related to a protocol change. The pros and cons of such publications are outlined in Table 24-1. The preferred policy is one proscribing publication or presentation of treatment results during the trial, except those related to protocol changes. A permissive policy has the potential of compromising the trial, especially in cases where the results can affect subsequent recruitment or treatment patterns in the trial. In addition, it can open the study to criticism if the schedule of publication is perceived as having been designed to maximize the impact of the study.

Pressures to relax the proscription can be expected during the course of most long-term trials. They are most likely to arise from publication of related studies, especially if the results of these studies are contrary to those observed in the trial. Investigators in the Coronary Artery Surgery Study (CASS) were exposed to such pressures because of interim publications coming from a European sister study (European Coronary Surgery Study Group, 1979, 1980, 1982a, 1982b). Ultimately, the proscription was upheld, but not without a considerable amount of debate.

Investigators in some of the larger trials have elected to summarize details of the design, methods, and baseline results in a separate paper. Such papers may be prepared any time after patient recruitment is completed. Ideally, they should be published before any results for the trial have appeared in print, as in CASS (Coronary Artery Surgery Study Research Group, 1981), or in conjunction with the first results publication, as in the UGDP (University Group Diabetes Program Research Group, 1970d). However, in some instances they may not appear until results have been published, as in the CDP (Coronary Drug Project Research Group, 1973a).

Table 24-1 Pros and cons of interim publications not related to a treatment protocol change

Pros
• Provides access to study results as they emerge
• May simplify preparation of the final publication
• Helps to maintain investigator interest in the trial
• Keeps the study in the "public eye"
Cons
• Inconclusive and preliminary nature of the results may lead to confusion
• May reduce investigator enthusiasm for continued patient recruitment or treatment if the interim results are viewed as "discouraging"
• Knowledge of an emerging treatment difference, especially in the case of unmasked trials, may bias subsequent treatment and data collection
• Publicity accorded the interim results may reduce the amount of attention investigators are able to devote to the conduct of the trial, especially if resources needed to carry out the remainder of the trial have to be diverted to respond to criticisms
• Impact of the study and its final conclusions may be diminished because of the way data were presented and analyzed in earlier publications

24.2.2. Presentation or publication?[2]

A key issue to be addressed is the way in which results are announced to the medical community. Options include:

- Making an announcement of the results to the news media with subsequent publication in a medical journal
- Making a presentation of the results at a national meeting (may lead to media coverage), with subsequent publication in a medical journal
- Publication of the results in a medical journal, with no prior public presentations or announcements

Table 24-2 contains summary comments concerning each option.

A presentation should not be made if it precludes publication in the journal of choice. Some journals may regard certain kinds of presentations as tantamount to publication and, hence, may not be willing to publish the results. In addition, various journals, such as the *New England Journal of Medicine*, discourage author-initiated press coverage of results in papers under consideration for publication.

Publicity emanating from presentations may not be in the best interest of patients or members of the medical community responsible for their care, especially if the results presented are controversial and there is a large time gap between presentation and publication. The five-month period between presentation and publication of the tolbutamide results in the UGDP caused difficulties for patients and diabetologists alike (see Chapter 7 for chronology of events). Publicity surrounding the presentation caused many patients on oral hypoglycemic agents to question their physicians regarding the usefulness and safety of the treatment. Physicians had difficulty dealing with their concerns in the absence of a published report detailing the results.

Table 24-2 Options for initial communication of results

A. Announcement of results to news media with subsequent publication in a medical journal
• Approach should be avoided, except where the press release is timed to correspond with publication
• Particularly undesirable when there is a large time gap between initial publicity and publication
• Members of the medical community may resent the advance publicity, especially if they are called upon to respond to questions stimulated by the publicity without benefit of a published manuscript
B. Presentation of results at a national meeting with subsequent publication in a medical journal
• Presentations are often used for initial communication of results to the medical community
• Presentation may provide authors with useful feedback for preparation of the final manuscript
• Approach suffers from the same problems noted in Part A above if presentation leads to news media coverage
• Generally best to forego presentation unless it can be timed to correspond with publication
• Approach should be avoided if presentation precludes publication in the journal of choice
C. Publication of results in a medical journal with no advance presentation or publicity
• Preferred approach, especially for results that are likely to be controversial or that challenge the value of an existing treatment
• Publication may be accompanied or followed by a press release

24.2.3 Where to publish?

The choice should be limited to refereed journals that are covered in *Index Medicus*. Unrefereed journals, proceedings of meetings, and monographs should be avoided both because of the absence of a critical review process as a prerequisite to publication and because of the difficulties involved in identifying and retrieving any paper that is not listed in *Index Medicus*.

The nature of the study will influence the choice of the journal. Results with general implications should be directed to a wide circulation journal. A specialty journal should be considered if the results are of primary interest to a medical subspecialty. Both kinds of journals may be used in some cases, as in the UGDP with the phenformin results. The initial report appeared in the *Journal of the American Medical Association* in 1971. A more extensive report appeared in *Diabetes* in 1975 (University Group Diabetes Program Research Group, 1971b, 1975).

24.2.4 What to publish?

The goal in any publication should be to provide a clear and concise description of the study results. This requires a manuscript that contains carefully constructed graphs and tables that describe the results, as well as a description of the design and methods used in the study. General content requirements are discussed in Chapter 25.

The typical trial may produce only one publication on results. It will come at the end of the study and should contain results on all treatments studied in the trial. The decision as to how much treatment data to include is not so obvious if the paper is generated in conjunction with a protocol change made during the trial. The paper should satisfy the same content require-

1. The term *publication*, as used throughout this chapter and in the next one, relates to a public document. Access may be via a published periodical, book, or the like, or via a public repository for unpublished manuscripts and documents, such as the one maintained by the National Technical Information Service (NTIS).

2. The term *presentation*, as used throughout this chapter and in the next one, relates to a paper concerning a trial that is prepared and read by study investigators before a national meeting of some medical group, but that has not been published (with the exception of an abstract summary appearing in the meeting program).

ments as a paper published at the end of a trial if it serves the same purpose as a final publication. This will be the case in trials involving just one test and control treatment where one of the two treatments is discontinued because of lack of efficacy. The same is true for trials involving multiple test treatments but where one test treatment is considered superior to all others and hence the use of all other treatments is terminated in favor of the superior treatment.

The decision as to what to publish is not so straightforward when the study involves multiple test treatments and when only one of those treatments is to be discontinued. In this case, investigators must decide whether to limit results presented to those for the control treatment and the particular test treatment in question, or to include results from all other test treatments as well. Investigators in the CDP elected to follow the former approach in each of the three papers detailing protocol changes in that study (Coronary Drug Project Research Group, 1970b, 1972, 1973b). They followed this approach even when summarizing results leading to discontinuation of the 5.0 mg dose of estrogen. Results for a sister treatment, involving just half this dosage, were not presented in the report even though they tended to support the decision reached for the high-dose treatment. In fact, the low-dose treatment was discontinued about three years later. UGDP investigators followed the latter approach. They elected to include results for the two insulin treatments in manuscripts concerning terminations of tolbutamide and phenformin, even though the insulin treatments were not affected by the terminations (University Group Diabetes Program Research Group, 1970e, 1971b, 1975).

A complementary decision process is required when preparing the final results for a publication in which some of the treatments were discontinued before the end of the trial. In this case, the investigators must decide whether to include an updated report on the discontinued treatment groups. The UGDP investigators did include summaries for both tolbutamide and phenformin treatments in their final report (University Group Diabetes Program Research Group, 1982). The CDP investigators did not provide such updates in their final report for the three treatments stopped during the trial (Coronary Drug Project Research Group, 1975). However, many of the patients affected by those changes were enrolled and followed in a sister study (Coronary Drug Project Research Group, 1976).

24.2.5 Journal supplements versus regular issues

Investigators in large trials will have to decide whether to concentrate their paper writing efforts at the end of the trial on a single large manuscript or on a series of short manuscripts. The pros and cons of the two approaches are outlined in Table 24-3.

The trouble with any large manuscript has to do with the time and effort to prepare it and get it published. It is easier and often more satisfying to write a series of small papers than one large one. Further, many journals have limits on the length of papers they receive. Editors may be unwilling to consider papers that exceed those limits and those who do may assess page charges to cover the cost of publication. Moreover, they may place them in supplemental issues of their journals. An added disadvantage when publication is via a journal supplement is that there may be problems in locating the issue after it is published. Journal supplements may not be listed in *Index Medicus* and MEDLINE, and even if they are, they may be hard to find in the library if they are not bound and stored with regular issues of the journal.

Table 24-3 Long versus short papers

A. Long papers requiring publication as a supplemental issue of a journal

Comments
- Generally not necessary except for large-scale trials with complicated data sets
- Usually feasible only if study is prepared to cover the page charges associated with journal supplements

Advantages
- Avoids the usual space restrictions imposed on papers contained in regular journal issues
- May provide a more coherent picture of the results

Disadvantages
- Choice of journals limited to those that are willing to publish supplemental issues
- Manuscript is more difficult and time-consuming to prepare
- May be harder to locate and retrieve published papers for reasons mentioned in Section 24.2.5 (see also Chapter 26)

B. Short papers suitable for inclusion in a regular journal issue

Comment
- Task of preparing a series of short manuscripts less onerous than that of preparing one long manuscript

Advantages
- Articles appearing in regular issues of a journal may receive more reader attention and may be easier to locate and retrieve than those appearing in a journal supplement
- Need to generate a number of short papers for submission to the same or various journals over an extended time period may help maintain investigator and public interest in the trial

Disadvantages
- Space limitations by journals may make it difficult to present a coherent picture of the study results in any one paper
- A series of short papers, scattered over time and perhaps journals as well, may make it difficult for readers to obtain a comprehensive view of the study results

The main virtue of a single large manuscript rests in its completeness. It is usually easier for a reader to grasp the significance of a study if all pertinent design details and results are contained in one journal issue than when they are scattered across various issues of the same journal or among issues of different journals. The best strategy may well be a mix of the two approaches, as mentioned in Section 24.2.3 in conjunction with the UGDP phenformin results.

24.3 AUTHORSHIP AND INTERNAL REVIEW PROCEDURES

24.3.1 Introduction

A key issue in any research effort has to do with authorship and writing responsibilities for the papers produced. Basic guidelines should be worked out well in advance of the start of any writing effort. The guidelines that are developed should be reviewed and discussed by the entire investigative body before they are adopted. A good deal of debate may be required before an acceptable policy is developed.

24.3.2 Individual versus corporate authorship

The conventional approach is to list contributing authors in the masthead of the paper. All but 2 of the 113 papers reviewed in Chapter 2 had listings of this type. One paper, citation 113 in Appendix C, did not list any authors. The other paper listed a committee as the author (Management Committee of the Australian Therapeutic Trial in Mild Hypertension, 1980).

A conventional author listing works best for studies that are carried out at a single center and that involve a relatively small number of investigators. It does not work well for large trials, especially those involving multiple centers. It is common in such cases to resort to corporate authorship, for example, as reflected in citations 102 through 109, from the Coronary Drug Project and most of the other citations in this chapter. However, this method of citation is not without problems. It obscures the contribution of individual authors and may work to the disadvantage of young investigators seeking promotion in university settings (Relman, 1979; Remington, 1979). Table 24-4 summarizes the pros and cons of the two authorship approaches.

The list of papers appearing in Table B-3 of Appendix B can be used to assess the authorship policies associated with trials sketched in that appendix. The 130 citations can be classified as

Table 24-4 Pros and cons of individual versus corporate authorship

A. Conventional authorship listing

Advantages
- Commonly accepted form of authorship
- Provides explicit indication of individuals involved in manuscript writing effort

Disadvantages
- Can result in lengthy author listing in a large-scale trial
- Can be an unfair method of dispensing credit, especially if author listing is limited simply to those involved in writing the paper
- Increases the likelihood that the study will be identified with specific individuals rather than with the entire investigative group

B. Corporate authorship

Advantages
- Avoids the interpersonal problems that can arise when it is necessary to name specific authors for key study publications
- Avoids the inequities of the conventional approach to authorship when it is not practical or feasible to list all key study personnel
- Helps underscore the collaborative nature of the study; especially important for multicenter trials
- Makes it possible to retrieve all papers of a study, via MEDLINE, under a standard corporate name, provided that the name appears as part of the title of each paper (see Section 26.2)

Disadvantages
- Corporate authorship may discourage preparation of needed papers, especially by people interested in establishing their research credentials
- Absence of named authors makes it difficult for readers to identify individuals responsible for its preparation

follows: Those listing only a corporate author (55), those listing only individual authors (55), with the remainder containing both the study name and the names of individual authors. The classification is based on author listing as provided by the individual studies. As such, they may differ from the citations appearing in Appendix I (Combined Bibliography). Preference has been given to use of corporate listings in the body of this book to allow all citations for a given study to appear together under the same heading.

The listings in Table B-3 do not necessarily correspond to those appearing in *Index Medicus* or computerized versions of the Index. For example, the author listing for citation 346 (Combined Bibliography), as retrieved via MEDLINE, lists Lachin, Marks, Schoenfield, Tyor, Bennett, Grundy, Hardison, Shaw, Thistle, and Vlahcevic as authors. No mention is made of the NCGS Protocol Committee or the National Cooperative Gallstone Study Group in the author field. Only Schoenfield and Lachin are listed as authors for citation 347 in the MEDLINE file. The official study listing in Appendix B (citation 5.4 in Table B-3) lists 16 other authors and the National Cooperative Gallstone Study Group.

The authorship approach used for specific papers produced in a trial may vary depending on their relevance to the main aims of the trial. Most of the studies sketched in Appendix B that have published papers used a corporate listing (with or without mention of individual authors) for mainline papers, i.e., those containing original treatment results or basic information on the design and methods of the study. Papers of secondary importance to the trial, for example, those related to ancillary studies or to secondary aims of the trials, for the most part, were published using a conventional author format. However, even here exceptions can be noted, such as in the Coronary Drug Project. It used a corporate format for nearly all of its publications.

24.3.3 Writing responsibilities

The head of the investigative group, in conjunction with the leadership committee of the study, is responsible for stimulating the production of manuscripts. The first step in the process is to prepare a list of potential publications early in the course of the trial. The list should be as exhaustive as possible and may include papers that never get written. The entries on the list should be ranked in order of their importance in relation to the aims and needs of the trial. It is also useful to prepare a timetable indicating when work might begin for each paper on the list. The list should be reviewed at periodic intervals over the course of the trial to reflect changes in writing strategies as the trial proceeds.

Most writing efforts will involve a team approach. The team should be designated by the head of the investigative group (in conjunction with the leadership committee). Each team should have a designated chief and should be composed of members with the expertise and resolve needed to write the paper. Papers that involve analyses of study results should include a biostatistician. The number of papers commissioned for development at any one time should be controlled so as not to exceed the manpower and computing resources of the study.

The finished paper may or may not list the writing team. Team members may be included in the masthead of the paper, as in the NCGS papers discussed above, in a footnote to the title of the paper or on the credit page, as in the Coronary Drug Project paper on design, methods, and baseline results (citation 104), or may not be revealed at all, as in CDP results publications (citations 102, 103, 105, 107, and 108).

24.3.4 Credit rosters

Completed papers should contain a general credit roster that lists the centers in the study and their key personnel. The roster should also specify the membership of committees responsible for operation of the trial. The roster serves the dual purpose of documenting individual contributions to the study while at the same time providing readers with information concerning facilities and staff involved in the study. Exemplary credit rosters are contained in citations 104, 346, and 376.

24.3.5 Internal review procedures

The study investigators should subject manuscripts to rigorous review before they are submitted for publication. The review may be carried out by a standing committee of senior investigators from the study or by an ad hoc group appointed for the purpose of reviewing a given manuscript. The CDP used the former approach and had a standing committee of seven senior investigators that was responsible for all reviews. The chairman of the committee selected two or three persons from the committee to review any given manuscript.

It may be useful to supplement the review process by circulating the penultimate draft of a manuscript to the entire investigative group for comments. However, this step should not be used as a substitute for the review processes mentioned above.

The types of papers requiring internal review and the conditions that must be satisfied to clear them for submission to journals should be spelled out before any writing is done. The review and clearance processes will differ depending on the nature of the manuscript. The content and conclusions of papers containing key findings may have to be approved by the entire investigative group before submission. The investigative group may transfer approval authority to the chairman of the editorial review group for more technical papers dealing with results related to a secondary aim of the trial or with the design and methods of the trial. Papers concerning ancillary studies that are published under the names of individual authors may not go through any formal approval process.

24.4 INFORMATION ACCESS POLICY ISSUES

24.4.1 Access to study data during the trial by outside parties

Requests for study results by parties from outside the study can arise before any results have been published. The requests may be politely ignored in privately funded trials but they are not as easily disposed of in those that are federally funded, especially if the requests are made under the Freedom of Information Act (FOIA).[3] This Act has been used in a few instances to force investigators to release data against their will. For example, it was used by the *National Enquirer*, a weekly tabloid, to obtain treatment results from an ongoing trial sponsored by the Veterans Administration (Montgomery, 1979).

There is still a great deal of uncertainty regarding the limits of the Act as it relates to ongoing federally funded trials. Proposals to amend the FOIA to exempt ongoing trials from requests under the Act have been introduced into Congress, but have not been enacted (personal communication with Office of the Director of the National Institutes of Health, July, 1983). There are obvious dangers in allowing any exemptions to the Act. However, unlimited public access to data before a trial is completed has dangers as well. The value of a trial can be compromised with a forced data release. The ensuing publicity may hamper the enrollment of additional patients and may make continued treatment of those already enrolled difficult, if not impossible. Other dangers may be more far-reaching. A pattern of forced releases would almost certainly render future investigators reluctant to undertake long-term trials. The end result would be even less adequate evaluation of treatments than that which exists at present.

Court rulings to date have not been of much help in defining the limits of the Act. Even the United States Supreme Court ruling concerning public access to UGDP data was limited to the specifics of that case (United States Supreme Court, 1980).

Requests for data or analyses not citing the FOIA should be considered on an individual basis. Most of the requests will arise from colleagues and researchers who are interested in some aspects of the disease or treatment being studied. Factors to be addressed in deciding how to respond to requests include assessments of the:

- Efforts involved in meeting the requests
- Medical and scientific importance of the data or analyses requested
- Willingness of the requesters to abide by constraints imposed by study investigators on the uses that can be made of the data or analyses requested

There should be an understanding of the way in which the data or analyses will be used before the request is filled. If the requested data or analyses are to be part of a publication, there should be an agreement as to how the trial will be acknowledged and the level of review authority retained in the trial over analyses or statements produced by the requester. No information should be released that reveals the identity of individual patients, nor should the release permit the requester to carry out analyses by treatment group if the trial is still under way.

3. See documents from the Ethics Advisory Board of the Department of Health and Human Services (1980) for a review of the Act and of testimony concerning the Act in relation to clinical trials.

24.4.2 Access to study data at the conclusion of the trial

Investigators involved in any trial have a responsibility to facilitate access to pertinent study data once the trial is completed. Part of this responsibility can be met with a publication policy that includes extensive data summaries and patient listings (devoid of personal identifiers) for key baseline and follow-up data, such as those provided in appendixes to several of the UGDP publications (University Group Diabetes Program Research Group, 1970e, 1975, 1982). A well-written paper will provide readers with sufficient detail to allow them to verify the accuracy of key analyses. Tables and listings that are too extensive to be published as part of the manuscript can be made available through other means, such as the National Technical Information Service (NTIS, see Glossary).

It is desirable to release the entire data file (except for patient identifying information) during the termination stage of the trial or sooner in trials involving treatment terminations. The usual approach is to prepare a paper listing or magnetic tape of pertinent baseline and follow-up data, which is deposited at a central facility, as was done in the UGDP (University Group Diabetes Program Research Group, 1977). The repository may be the sponsoring agency, the data center, or some other study center (provided it remains in operation after termination of the trial). The NTIS or some commercial repository should be used if there is no center in the study willing or able to assume the repository role.

24.4.3 Access to study forms and manuals

Copies of data forms, manuals, and other design documents used in the trial should be made available to the public once they have been approved for use in the trial, unless there are convincing arguments to the contrary. The arguments should indicate how the study would be harmed if the documents in question were released. Any release proscription should be lifted as soon as possible and always by the time the trial is completed. Multicenter trials should designate the access point for design documents. Publications from the trial should specify the types of documents that are available and where and how they may be obtained.

24.4.4 Inquiries from the press

Queries from the press can arise at any point in the course of the trial. However, they are most likely at the start and when results are presented or published. Press coverage can serve a useful purpose when done in a responsible manner. Publicity at the start of the trial can help with patient recruitment. That arising in conjunction with a presentation or publication of results can help familiarize physicians and patients alike with the key findings of the trial.

Requests for information should be handled as forthrightly and expeditiously as possible. A good reporter will indicate the purpose of his request and will provide respondents with the opportunity to review his copy for errors or misstatements before it is aired or printed. Requests for information having to do with the design and methods of the trial should be honored regardless of when they arise in the course of the trial, unless there are sound operational or scientific reasons for withholding the information. Requests for interim results or other details arising during the trial which, if honored, are likely to compromise patient care or have an adverse effect on the trial must of necessity be denied. Most reporters, once given the rationale for the denial, will appreciate the need for withholding the information.

There should be only one individual authorized to speak for a center in the trial (e.g., the center director or the public relations officer of his institution). All queries received by that center should be referred to that individual for response.

The chairman of the study, director of the coordinating center, project officer, or some other person designated by the investigative group should be chosen to respond to queries concerning the study design or results in multicenter trials. The choice should be made early in the course of the trial and should be made known to all personnel in the various centers in the trial. Investigators should agree on the types of queries that may be answered locally and those that must be referred for response.

Publicity concerning study results in preparation for presentation or publication should be avoided. Publicity arising from "leaks" at those times can serve to divert the energies of study personnel from the task at hand and may anger members of the medical and lay community if they read or hear of results in the news media before they have been presented or published in a scientific forum. Investigators need to avoid actions that may attract unwanted attention. Members of the study group, particularly those privy to interim results, such as members of the safety monitoring committee, need to be reminded of the importance of silence until results have been presented or published. This policy of restraint should be coupled with defensive measures that can be implemented if leaks occur. The measures may include preparation of a statement concerning the study results that can be released to the press if publicity occurs prior to the scheduled publication or presentation. Investigators in the Coronary Drug Project took this precautionary step with each of their mainline results papers (Coronary Drug Project Research Group, 1970b, 1972, 1973b, 1975). Fortunately none of the statements were needed.

Investigators should be mindful of the practices of the organizers of meetings and journals that may lead to unexpected press coverage. Some publishers provide members of the press with copies of selected papers in advance of publication. Others, such as the *New England Journal of Medicine*, while having policies against such practices, offer subscription packages that include provisions for express delivery of journals after they have been printed. Investigators should assume that major newspapers and wire services will have such subscriptions and that they will have their copies several days before they appear on the desks of regular subscribers. Further, it is wise to assume that the program and published abstracts of papers to be presented at national meetings will be available to members of the press before the actual meeting date. The advance publicity concerning the UGDP tolbutamide results arose from distribution of the program of the American Diabetes Association several weeks before the actual meeting date (see Section 7.4 for details).

24.4.5 Special analyses in response to criticisms

Once the results have been published, study investigators may be urged to carry out a number of special analyses by friends and foes of the study. They will have to decide how much time and effort they wish to devote to such activities. The approach taken will depend on the relevance of the requests in relation to the aims and needs of the trial. Certainly, any analysis that has the potential of shedding additional light on the results should be pursued.

As a result, the cost of such analyses will have to be borne by the study, except in cases where they are done simply to satisfy the needs of the requesting party. An intangible benefit from deposit of a data listing or tape with an outside agency, as discussed in Section 24.4.2, has to do with outside requests for analyses. Once the deposit is made, any request can be dealt with by referring the requester to the repository for the data needed to perform his own analyses.

A particularly vexing question has to do with the resources that should be devoted to responding to published critiques of a trial. Some restraint is necessary because of the investment of effort required if the criticisms are extensive. In addition, the energy devoted to response may limit that available for other more essential activities. Investigators in the UGDP were concerned enough about energy dissipation that they limited their responses to criticisms which appeared in refereed journals. They declined to reply to editorials and critiques appearing in unrefereed publications such as the *Medical Tribune*.

There is another reason for restraint. Investigators run the risk of losing objectivity and damaging their credibility if they become too preoccupied with defending their own work. The philosophy needed for a sound investigation is at odds with that needed for advocacy of a position. For this reason, if none other, it is important that responses be thoughtful and devoid of emotion.

24.4.6 Outside audits

It may be necessary to provide for special audits of the study results if there are questions regarding their accuracy. The data records and analyses of the UGDP were subjected to two independent audits (Committee for the Assessment of Biometric Aspects of Controlled Trials of Hypoglycemic Agents, 1975; Food and Drug Administration, 1978). Special clearances will be required if auditors are to be provided access to the medical records of specific patients. To be of any value, the audits should be done by parties who are independent of the study, the sponsoring agency, and firms or groups that stand to gain or lose from the study results. The auditors should prepare a written report of the audit that is then published or placed on file for public access.

25. Preparation of the study publication

Revise and revise and revise—the best thought will come after the printer has snatched away the copy.

Michael Monahan

25.1 Introduction
25.2 Preparatory steps
25.3 Content suggestions
  25.3.1 Title section
  25.3.2 Abstract section
  25.3.3 Introductory section
  25.3.4 Methods section
  25.3.5 Results section
  25.3.6 Discussion section
  25.3.7 Conclusion section
  25.3.8 Reference section
  25.3.9 Appendix section
25.4 Internal review and submission
25.5 Acceptance and publication
Table 25-1 Content suggestions for the study publication

25.1 INTRODUCTION

This chapter focuses on the task of preparing the study findings for publication. The outline in Table 25-1 assumes a single publication that contains a summary of the main findings of the trial, as well as information on its design and operation. In fact, as noted in Chapter 24, a trial may produce a number of publications.

25.2 PREPARATORY STEPS

Most of the preparatory steps needed to write the paper have been alluded to in previous chapters. An essential first step involves preparation of the data for analysis by creation of an analysis tape, as discussed in Section 17.7.

There must be agreement among investigators as to how the paper will be authored and as to who will head the writing team (see Sections 24.3.2 and 24.3.3). The review steps that must be completed before the paper is submitted for publication should be delineated as well. In addition, there should be agreement among the investigators as to who in the study will have review authority over the paper and how conflicts between the authors and the review group will be resolved (see Section 24.3.5).

An essential step involves preparation of an outline of the paper. The outline should be as detailed as possible and should include a mockup of tables needed for the paper. It should be reviewed and approved by the leadership of the study before the writing starts and should be revised as needed during the writing effort.

25.3 CONTENT SUGGESTIONS

Table 25-1 outlines general content suggestions for the publication. The remainder of this section relates to this outline.

25.3.1 Title section

The title is one of the most important parts of any publication. It is the prime item used by readers to screen for publications of interest. A good title is neither cute nor cryptic. It conveys its message in a crisp and succinct manner. It should indicate the main thrust of the paper in as few words as possible. Superfluous words add to its length without making any contribution to content.

Examples of good and bad titles follow, as taken from citations listed in Appendix C. The number in parentheses following each title refers to the citation number in that Appendix.

Cryptic

- Blood pressure in the elderly (16). *What kind of blood pressure? High blood pressure? Low blood pressure? There is no way of knowing from the title if the paper contains data pertinent to the assessment of different forms of antihypertensive treatments in the elderly.*
- Event recording in a clinical trial of a new medicine (89). *What kind of event? What kind of new medicine?*
- Clinical metrology—A future career grade? (122). *Metrology in what area? What is meant by a career grade?*
- Evaluation of toxicity: Clinical issues (175). *What kind of toxicity? What clinical issues?*

Needlessly detailed

- High-dose methotrexate with "RESCUE" plus cyclophosphamide as initial chemotherapy in ovarian adenocarcinoma. A randomized trial with observations on the influence of C parvum immunotherapy (7). *Title could be shortened without much loss of information by deleting the phrase* with observations on the influence of C parvum immunotherapy.
- A clinical trial of alignment of teeth using a 0.019 inch thermal nitinol wire with a transition temperature range between 31 degrees C. and 45 degrees C. (115). *Too much methodological detail.*
- Medical, ethical and legal aspects of clinical trials in pediatrics. Summary of a forum discussion held at the 'International Workshop on Perinatal and Pediatric Aspects of Clinical Pharmacology,' Heidelberg, Federal Republic of Germany, February 27-29, 1980 (143). *Details regarding the meeting are not necessary.*

Good

- Controlled trial of cimetidine in reflux esophagitis (27).
- Amoxycillin versus ampicillin in treatment of exacerbations of chronic bronchitis (53).
- Cimetidine in the prophylaxis of migraine (69).
- Postoperative epilepsy: A double-blind trial of phenytoin after craniotomy (71).

Titles should be written to include the term *trial* to facilitate identification via title scans. One way this can be accomplished is to include the name of the study in the title if it includes the term. Unfortunately, investigators often use other less descriptive terms, such as *study, program,* or *project,* in place of *trial* (see Table B-6 of Appendix B for list of study names). The term *trial* should be added to the title of the paper when it is not part of the official title of the study.

A titling convention in which papers are sequentially numbered, for example, as in the University Group Diabetes Program (UGDP), is worth considering, especially if it is clear from the outset that the study will generate a number of publications. The numbering scheme alerts readers to the existence of other papers in the series.

Some journals require authors to list a few key words that characterize the content of the paper. The words usually appear below the title or abstract of the paper. Key words serve two purposes: They indicate the thrust of the paper to readers, and they help indexers classify it under the proper subject headings in *Index Medicus* and MEDLINE.

25.3.2 Abstract section

The abstract of the paper is second only to the title in importance. It provides a summary of the paper and, as a result, is usually the first and often the only part that is read, other than the title. In addition, inclusion of the abstract in the MEDLINE data file (the computerized version of *Index Medicus*) makes it possible for users of that file to identify the paper by searching the abstract for terms or phrases of interest. The abstract should include the items of information, listed in Part 2 of Table 25-1. A sample abstract, taken from the Persantine Aspirin Reinfarction Study (PARIS), meets most of the content requirements listed (Persantine Aspirin Reinfarction Study Research Group, 1980b).

> *Summary. In the Persantine-Aspirin Reinfarction Study (PARIS) trial, 2026 persons who had recovered from myocardial infarction (MI) were randomized into three groups: Persantine plus aspirin (PR/A) (n = 810); aspirin alone (ASA) (n = 810); placebo (PLBO) (n = 406). The average length of follow-up study was 41 months. Results for the three specified primary end points were: total mortality 16% lower in PR/A and 18% lower in ASA compared with PLBO; coronary mortality 24% and 21% lower; incidence of nonfatal MI plus fatal coronary disease 25% and 24% lower. These differences were not statistically significant by the study criterion (Z ≥ 2.6). By life-table analysis, the rates of coronary mortality and coronary incidence were about 50% lower in the PR/A group than in the PLBO group from 8-24 months, and for*

Table 25-1 Content suggestions for the study publication

1. Title section
- Descriptive title
- List of author-selected key words indicating general content of paper (useful for readers and as an aid to NLM indexers)
- Author(s)
- Source(s) of financial support for the study
- Acknowledgments
- Credit roster (see Section 24.3.4)
- Address for reprint requests

2. Abstract section
- Purpose of study
- Primary outcome measure
- Test treatment(s)
- Control treatment(s)
- Level of treatment masking
- Number of patients enrolled
- Method of treatment allocation
- Conclusion(s)

3. Introduction section
- Historical background of trial
- Rationale for a trial
- Objective(s)
- Rationale for choice of test and control treatment(s)
- Literature review

4. Methods section
- Study population
  - Eligibility and exclusion criteria
  - Method of patient recruitment
- Treatments
  - Study treatments used
  - Method of treatment administration
  - Level of treatment masking
  - Treatment proscriptions
  - Methods of measuring treatment adherence
- Outcome measures
  - Primary and secondary outcome measures
  - Diagnostic criteria for outcome measurements
  - Methods for coding and classifying outcomes
- Design specifications
  - Method of randomization
    - Description of the safeguards used to ensure the integrity of the allocation process
  - List of stratification variables
  - Blocking specifications
    - Description of procedures for packaging and dispensing study medications in the case of masked drug trials
  - Primary outcome measure and rationale for choice
  - Planned length of patient follow-up and rationale for specification
  - Planned recruitment goal
  - Type I and II error protection level for planned recruitment goal
- Patient safeguards
  - Outline of steps for obtaining patient consent
  - Method of updating consent (especially for long-term follow-up trials)
  - Measures taken to protect patient confidentiality
  - Description of procedures used to monitor study results for evidence of treatment effects
- Data collection schedule
  - Sequence of baseline and follow-up visits
  - List of data items collected
  - Definition of missed visits and dropouts
  - Name of person or agency to contact for copies of data forms, study manuals, etc.
- Data processing
  - Cut-off date for data included in manuscript
  - Description of approach and supporting rationale for dealing with missing data and departures from the treatment protocol (statement especially important if analysis method departs from preferred approach described in Chapter 18)
  - Literature references for methods used
  - Description of any special analysis procedures not already described in existing literature
  - Methods for judging statistical importance of differences observed (e.g., simple p-values, adjusted p-values, RBOs, etc.)
- Quality control procedures
  - General data editing
  - Quality control of laboratory tests and for special reading and coding procedures
  - Checks on data entry, programming, and analysis
  - Other quality controls, such as site visits to clinics, training and certification, etc.
- Performance monitoring
  - Measures used for assessing performance of participating clinics and resource centers
  - Frequency of performance assessments
  - Methods used for reviewing performance monitoring reports and for implementing corrective action based on those reviews
- Treatment monitoring
  - Frequency of interim analyses for treatment monitoring
  - Methods used to carry out interim analyses
  - Individual or group responsible for carrying out interim analyses
  - Procedures for implementing protocol changes based on results from interim analyses
- Organizational structure
  - Number and location of participating centers
  - Location of data center
  - Location of other resource centers
  - Standing committees and their membership
  - Mode of funding (e.g., grant or contract, individual or consortium award)
  - Policy on investigator conflicts of interests and method used to monitor for potential conflicts of interest
- Other items
  - Notation and language conventions in manuscript
  - Listing of special actions taken during the trial including:
    - Addition or deletion of a treatment
    - Data purges because of questions concerning data reliability or accuracy
    - Major modifications of data collection forms or coding procedures during the course of the trial

5. Results section
- Number of patients enrolled by treatment group
- Number of deaths by treatment group
- Comparison of treatment groups for the primary and secondary outcome measures using various analytic techniques, including simple comparisons of proportions, as well as lifetable methods, etc.
- Indicators of the completeness of follow-up by treatment group, such as:
  - Number of missed examinations
  - Number of dropouts
  - Number of patients lost to follow-up
- Indicators of treatment adherence, such as:
  - Comparison of treatment groups using an adherence score or some laboratory test
  - Count of number of patients in each treatment group who received none of the assigned treatment
  - Count of number of patients in each treatment group who received an alternative treatment
- Assessment of the comparability of the treatment groups with regard to important baseline characteristics
- Treatment group comparisons for differences in:
  - Occurrence of serious side effects
  - Rate of hospitalization
  - Other general health indicators
- Treatment comparisons by selected baseline characteristics
- Multiple regression analyses using baseline characteristics to provide adjusted treatment comparisons
- Treatment comparisons by level of adherence
- Treatment comparisons by clinic (in multicenter trials)
- Other special analyses relating follow-up data for one variable (e.g., cholesterol level) to a primary or secondary outcome measure (e.g., death)

6. Discussion section
- Discussion of how reported findings relate to previous studies, paying particular attention to those considered to be new and those that are not consistent with findings of previous studies
- Discussion of the implications of the findings
- Enumeration of questions or areas needing further analysis or research

7. Conclusion section
- Statement of conclusion
- Limits on generalization of the conclusions, including discussion of observed statistical power if no treatment difference is detected

8. Reference section
- List of literature references in required journal format
- Suitable reference citations for:
  - References to previous work
  - Data analysis methods
  - Methods not described in the paper
  - Laboratory methods
  - Coding or reading procedures for abstracting information from special records or documents
  - Treatment methods
  - Study rationale
  - Discussion of results
- List of study documents that may be obtained on request, such as study manual of operations, study data forms, data listings, data tapes, etc.

9. Appendix section*
- Descriptions of special procedures needed to understand results, but too detailed to be included in the body of the publication
- List of definitions, codes, diagnostic criteria, etc.
- Special analyses, tabulations, and data listings
- Sample data forms

*Not required if previous publications contain essential details or if authors have provided some other means of supplying them (e.g., by depositing documents containing details in a public repository or by supplying them upon written request).

coronary incidence all Z values were ≥ 2.6; ASA rates were about 30% lower than PLBO rates, and for coronary incidence, Z values were ≥ 2.6 at two points. For these end points, from 8-20 months, PR/A rates were about 30% lower than ASA rates, but all Z values were < 2.0. PR/A and ASA patients entering within 6 months of last MI showed the largest percentage reductions in mortality; only the difference between PR/A and PLBO groups for 3-year coronary mortality yielded a Z value of 2.6.[1]

25.3.3 Introductory section

This section may be short or quite long depending on the nature of the literature review. Its prime purpose is to set the stage for the remainder of the paper. It should indicate why the paper is being written, describe the rationale for the study and its objectives, and should recap research that led to initiation of the study.

25.3.4 Methods section

The details contained in most reports of clinical trials are too sketchy to allow readers to make informed judgments concerning their quality, as noted in Chapter 2 and in Meinert et al. (1984). The absence of essential details is a reflection of the failure of authors and editors alike to recognize their importance in making these judgments.

The contents of the methods section must be checked against some predefined list, such as contained in Part 4 of Table 25-1, if reporting lapses are to be avoided. Information found to be missing when the check is made should be added before the paper is submitted for publication. Details that have to be omitted because of space constraints imposed by the journal should be provided via other means (e.g., in another paper devoted primarily to the design and methods of the trial, or by depositing essential design and operating documents from the trial in some repository for access by interested parties).

25.3.5 Results section

This section is usually the longest one in the paper. Suggestions for its content are outlined in Part 5 of Table 25-1. The essence of a paper should be captured in the tables, charts, and figures it contains. They should be interpretable without reference to supporting text in the body of the paper. The titles and legends accompanying them should be accurately and succinctly written.

1. Reference citation 376. Reproduced with permission of the American Heart Association, Inc., Dallas, Texas.

25.3.6 Discussion section

This section (see Part 6 of Table 25-1) should highlight noteworthy findings appearing in the results section. It should be used to discuss the clinical implications of the findings and to indicate the extent to which they are considered to support or refute previous findings.

25.3.7 Conclusion section

This section (see Part 7 of Table 25-1) may appear at the beginning or end of the paper. It should contain a statement of the conclusions drawn from the trial and of the limitations on the generalizability of the findings. It should also contain a discussion of the statistical power of the study if the conclusion favors the null hypothesis (see Section 9.7).

25.3.8 Reference section

A well-written paper will contain a supporting bibliography. The papers included should be those that are needed to document data collection and analysis methods used in the trial, as well as those needed in the introduction and discussion sections of the paper. The citations should be listed at the end of the paper and should either be arranged alphabetically or in the order in which they are referenced in the text. Most journals will indicate the referencing style to be followed. A paper that is written before a decision is reached on the journal that is to receive it should be referenced using general methods, such as outlined by editors of medical journals (International Committee of Medical Journal Editors, 1982) or in a general desk reference, such as the *Chicago Manual of Style* (University of Chicago Press, 1982).

Only papers cited in the text should be listed in the reference section of the paper. Original articles should be referenced whenever possible. A secondary source, such as a textbook or review article, may be cited if the original article appeared in an obscure or foreign language journal, or if the secondary source helps to explain or expand upon information contained in the original article.

The listing should provide all the authors' names in the case of conventionally authored materials. The preferred approach is to list the last name, followed by the initials of each author. The author field should contain the appropriate corporate designation if the article in question was written on behalf of some research group, institute, agency, or committee. See reference citations 104, 375, 376, 467, 468, 472, and 476 in the Combined Bibliography (Appendix I) for examples.

The citations should include the full titles of the articles being cited. They are useful to readers when scanning the references for articles of interest. They should also include full journal names or accepted abbreviations, such as those used in *Index Medicus* and MEDLINE (National Library of Medicine, 1983). The volume number of the journal, date of publication, and beginning and ending page numbers of each article cited should be listed as well.

The citation listing should be checked for accuracy before the manuscript is submitted for publication. The checking should be done from the actual articles cited and not from MEDLINE printouts or citations listed in other bibliographies.

25.3.9 Appendix section

This section should contain materials that, while important in understanding the paper, are too technical or detailed to warrant inclusion in the main body of the paper. Items that appear in the appendixes of publications (see 104, 375, 467, 468, 472, and 476 cited above) include:

- Details of the sample size calculations
- Baseline frequency distributions
- Sample data forms
- Data collection schedules
- Derivation of analytic procedures
- Special charts or figures
- Data listings
- Special analyses or tabulations
- Descriptions of coding and classification schemes
- Consent statements
- Organizational and administrative documents

The use of appendixes is possible only if the journal in question allows them. Other avenues, such as discussed in Chapter 24 involving supplemental issues of a journal or deposit of key documents at a public repository, will have to be used when appendixes are ruled out by page limitations or other policies imposed by the journal.

25.4 INTERNAL REVIEW AND SUBMISSION

The manuscript should be subjected to a series of reviews and checks before it is submitted for publication. The first review should be done by the authors and should be designed to check for inconsistencies in format or style, for redundant statements, and for reporting deficiencies. The later review should be made using a checklist, such as represented in Table 25-1. The titles and legends of tables, charts, and figures should be checked for clarity of exposition and accuracy. The numerical information presented in tables and graphs should be checked for errors. The text of the paper should be checked to make certain that figures cited agree with the numbers appearing in the tables. Key analyses should be repeated, ideally by a second person, and the results of the two analyses should be compared. All discrepancies should be resolved before the paper is submitted for publication.

Information taken from published literature should be checked against the cited source. This checking process will be simplified if all cited documents are collected as the manuscript is developed. The resulting file will serve as a valuable resource for future papers on the same subject and for checking reference listings and other information contained in the manuscript.

The second round of reviews should be by colleagues selected by the authors or the study leadership (see Section 24.3.5). These reviews will help to identify areas of the paper that are confusing and that need additional work. Major changes proposed during this round of reviews or any of the other reviews outlined above may require a total revision of the paper and another round of checks and reviews.

It is a good idea to allow some time for "maturation" of the paper after it is drafted and before it is submitted for publication. The checking and review processes take time. They will lose much of their value if performed under duress because of the imposition of unrealistic deadlines.

The final draft of the paper should be checked to make certain that the format conforms to that

specified by the journal selected to receive it. The instructions supplied by the journal should be reviewed to make certain that the correct number of copies is submitted and that glossy prints of all figures and charts are provided. The paper should contain the address and phone number of the corresponding (usually senior) author. A copy of the paper and accompanying glossy prints (if any) should be retained by the corresponding author. The cover page of the manuscript should indicate the date the paper was submitted for publication. All previous drafts of the paper should be removed from the author's file and stored elsewhere once it has been mailed to the journal to avoid mixups if the journal, a reviewer, or someone else requests copies of the manuscript before it is published.

25.5 ACCEPTANCE AND PUBLICATION

The journal will carry out its own reviews of the manuscript. They will be used by the editor to reach a decision as to whether to accept the paper. They may also serve as the basis for additional changes to the paper if it is accepted for publication. Publication may take place shortly after acceptance or months later, depending on the backlog of manuscripts awaiting publication and the publication schedule of the journal.

The corresponding author is responsible for ordering reprints. The number ordered should be sufficient to supply co-authors with an appropriate number, as well as all other people listed in the credit roster of the paper.

The corresponding author (or one of the other authors) should establish an archive that contains all documents related to the development and publication of the paper. The initial steps for this process should be taken long before publication. The last steps in the process should take place just after the paper has been published. The completed file should contain:

- Copies of data tapes and computer programs used for analyses included in the paper
- Copies of papers and other documents referenced in the paper
- Intermediate drafts of the paper, particularly those containing major revisions
- A copy of the manuscript submitted for publication
- Copies of written critiques of the paper, as provided by the journal, and correspondence relating to the critiques
- A copy of the manuscript as accepted for publication
- Page proofs
- The published manuscript

The archive should be kept in a safe place and maintained indefinitely. Key documents, such as data tapes and related materials, should be duplicated and stored in separate locations if they are considered irreplaceable.

Errors in the paper detected after publication should be noted by the corresponding author. The journal editor should be informed of those that are serious.

26. Locating and reading published reports

Be sparing of criticism, since the habit of trivial comment weakens the force of real protest.
Alan Gregg

26.1 Introduction
26.2 Bibliography development
26.3 Questions and factors to consider when reading a report from a clinical trial
26.4 Valid and invalid criticisms
26.5 Desirable characteristics of a critic
Table 26-1 Selected printed and computerized databases of published literature and work in progress
Table 26-2 Questions to consider when assessing a published report
Table 26-3 Universal criticisms
Table 26-4 Characteristics of a responsible critic

26.1 INTRODUCTION

This chapter deals with a potpourri of topics related to the identification and evaluation of reports relevant to the design and conduct of clinical trials. Section 26.2 focuses on a review of methods for developing bibliographies of results from clinical trials. Section 26.3 is concerned with issues to be considered when reviewing a published report from a trial. The last two sections are written from the point of view of an individual who is responsible for preparing a written critique of a report from a clinical trial. Section 26.4 provides a discussion of what constitutes valid criticisms. The last section outlines the characteristics of a responsible critic.

26.2 BIBLIOGRAPHY DEVELOPMENT

The development of a bibliography is likely to include any of the following techniques:

- Review of selected journals for papers of interest
- Search of classes of journals, via *Current Contents* or some other means, for titles of interest
- Systematic search of papers or computerized indexes, such as contained in *Index Medicus* or MEDLINE
- Use of the *Science Citation Index* to identify authors who have cited a particular paper (used to identify authors working in a particular field as an aid to building a bibliography of papers related to that field)
- Review of bibliographies of published papers for citations of interest
- Pursuit of leads offered by colleagues or from other sources, such as the news media, regarding specific papers or pieces of work

Table 26-1 contains a list of databases of published reports and work in progress (see also Roper and Boorkman, 1980; Sciotti et al., 1982). The list represents a selection of existing files considered by the authors to be useful in constructing bibliographies related to the design, conduct, and results of clinical trials.

Locating reports of clinical trials is complicated by the way in which they are titled (as discussed in Section 1.3 and in Section 25.3.1) and because of the absence of a subject heading for clinical trials in most existing indexes. A notable exception is *Index Medicus* and MEDLINE, starting with 1980 (see Chapter 2). The usefulness of title searches for identification of trials is limited without such headings. Only 21 of the 130 references (16%) in Table B-3, Appendix B, had the term *trial* in the title. Designers of trials appear to prefer terms such as *study*, *program*, or *project*. Only two of the 14 trials listed in Appendix B had names containing the term *trial* (see Table B-1, Appendix B). Among the 113 trials reviewed in Chapter 2, less than 40% (44 out of 113) of the titles contained the term *trial* or the design words *blind*, *randomized*, or *controlled*.

The difficulty in identifying work in progress extends to methodological work as well. The best that can be done at present is to rely on special annotated bibliographies, such as the one produced by Fletcher and co-workers (Research Development Committee, Society for Research and Education in Primary Care Internal Medicine, 1983) concerning clinical research methods, and by Hawkins (see citations 227 through 230), in her periodic reviews of literature related to clinical trials.

Papers concerned with statistical issues in the design, conduct, or analysis of clinical trials must be

Table 26–1 Selected printed and computerized databases of published literature and work in progress

Database	*Comments*
A. Published literature	
• *Index Medicus*	• Listings of titles, authors, and abstracts of papers appearing in some 2,700 medical journals and periodicals. Publication started in 1879. Published under the title *Index Medicus* beginning in 1960. Entries indexed by author and subject. Has subject heading for clinical trials starting in 1980. Before 1980, articles on clinical trials appeared under the more general heading *clinical research*.
• MEDLINE (Medical Literature Analysis Retrieval System: MEDLARS on Line)	• Computer file of *Index Medicus, International Nursing Index, Index to Dental Literature*, and part of *Hospital Index*. File contains titles, authors, and abstracts of papers appearing in some 3,000 biomedical journals. File may be searched by author or subject. Titles and abstracts can be searched with user-selected words. Introduced in 1966; with abstracts since 1975. Contains subject heading for clinical trials starting in 1980. Before 1980; articles on clinical trials appeared under the heading *clinical research*.
• SCI (*Science Citation Index*)	• Exists both as a paper and computer file (SCISEARCH). The computer file contains all entries published in the *Science Citation Index* plus additional entries from the *Current Contents* series of publications. SCI is unique in that it identifies papers cited in articles appearing in some 2,600 journals and periodicals. The Index allows users to identify articles that reference a particular paper. May be searched by author or title words. Started in 1961. Published on a continuing basis since 1964; computerized version since 1970.
• BIOSIS (*Biological Abstracts*)	• Exists both as a paper and computer file. Includes publications from journals, books, symposiums, reviews, notes, and research communications from the life sciences. Does not have subject headings, only broad headings called *concept headings*. First publication of printed version of the file: 1926; computerized version of file introduced in 1969. Contains citations for some statistical literature.
• CATLINE (Catalog on Line)	• Computer equivalent of *National Library of Medicine Current Catalog*. Includes listing of all serials, monographs, and books (all languages), collected by the National Library of Medicine, and published after 1801. The Catalog was first published in 1966. It has a subject heading for clinical trials beginning in 1980.
• CLINPROT (Clinical Protocols)	• Computer-based data file containing summaries of clinical investigations of new anticancer agents and treatments, with emphasis on clinical trials. File may be searched using an index of 300 clinical terms or via user-selected words.
• CANCERLIT (Cancer Literature)	• Computer-based data file containing over 260,000 citations and abstracts of published literature relating to cancer. Created originally from *Cancer Therapy Abstracts* (started in 1967) and *Carcinogenesis Abstracts* (started in 1963). Both ceased publication in 1980. Titles or abstracts may be searched via user-selected words. Entries since 1980 have been indexed using NLM subject headings, including one for clinical trials.
• EMED (*Excerpta Medica*)	• Computer-based data file containing citations from over 3,500 biomedical journals. File consists of entries from 43 abstract journals and the two literature indexes that make up the printed *Excerpta Medica*, plus selected entries not appearing in the printed publications. Contains citations from June 1974 forward. Has subject headings for clinical trials and controlled clinical trials.
• MATHFILE (*Mathematical Reviews*)	• Computer-based data file of references to mathematical and statistical papers.
B. Unpublished work in progress	
• CRISP (Computer Retrieval of Information on Scientific Projects)	• Computer-based data file of information on research projects currently funded via the NIH and other agencies of the United States Public Health Service. File may be searched by subject, project, agency of support, or investigator. Introduced in 1971. Does not contain heading for clinical trials.
• RAI (*Research Award Index*)	• Paper listing of research grants and contracts awarded by the National Institutes of Health, by fiscal year. Produced from CRISP. Published in two volumes: Volume I is arranged by research subject; Volume II contains sections organized by project, by grant or contract number, and by investigator. Produced since 1962. Does not contain a subject heading for clinical trials.
• NTIS (National Technical Information Service)	• Both a paper-based and computerized data file of over 970,000 documents available through the NTIS. Documents stored at the NTIS are government-sponsored research reports prepared by federal agencies of the United States government or their grantees or contractors. NTIS has been in operation since 1964. The computer data file covers acquisitions at NTIS from 1975 forward.

identified by screening statistical journals or methods journals, such as *Controlled Clinical Trials*. There are a number of indexes that contain citations to statistical and methods papers pertinent to clinical trials (e.g., *Biological Abstracts, Current Contents, Psychological Abstracts, Chemical Abstracts, Public Affairs Information Service* (PAIS), *Mathematical Reviews*, and *Excerpta Medica*), but they are not identified as such in the indexes.

26.3 QUESTIONS AND FACTORS TO CONSIDER WHEN READING A REPORT FROM A CLINICAL TRIAL

Table 26–2 lists questions to be considered when reading a published report. The greater the number of affirmative answers the better the reporting process.

The reader should form his own judgment on the basis of the merits of the study before considering opinions and critiques of others. Reviews supplied gratis by sales people from firms with a proprietary interest in the treatments should be ignored when making the judgment. The same is true for commentaries and editorials on the study appearing in throwaway medical journals.

The reader should be conscious of the motivating forces behind the study and of their possible influence on the conduct of and reports from the study. The conclusions in the paper should be questioned, if not ignored, if they appear to have been written to support the preconceived notions of the sponsor or investigators regarding the merits of the study treatments.

The role of the sponsor in the trial should be considered when reading the paper. Published reports of trials that are carried out by firms produc-

Table 26-2 Questions to consider when assessing a published report

1. General
- Does the manuscript indicate the purpose of the trial and rationale for the treatments studied?
- Does the trial address a relevant question?
- Is the paper in a peer review journal?

2. Investigators
- Have the investigators done any previous work related to the trial being reported? If so, do you consider the work to have been of good quality?
- Does the paper indicate the location and institutional affiliation of the various members of the team responsible for carrying out the trial?
- Does the team include people with appropriate training and expertise for conduct and analysis of the trial?

3. Sponsorship and structural
- Does the paper indicate how the trial was funded?
- Is the role of the sponsor in designing, directing, or analyzing the trial indicated? (Especially important in trials involving proprietary products.)
- Are the key investigators, especially those responsible for analyzing the results and for writing the paper, independent of the sponsor?
- Did responsibility for data collection and analysis in the trial reside with a group of people who were independent of the sponsor?
- Did the authors recognize the possibility of conflicts of interest for study members (especially important if the report concerns a proprietary product) and do they indicate steps taken to avoid such conflicts?
- If the trial involved multiple centers, does the paper list all affiliated centers and the functions performed by each?
- For multicenter trials, does the paper list committees, along with their membership and a brief description of their functions?

4. Study design

a. Outcome measure
- Is the primary outcome measure identified?
- Does it have clinical relevance?
- If multiple outcomes are used, is it clear which one is of primary importance in the trial?

b. Treatments
- Is there a defined test treatment?
- Is the test treatment of any interest and does the administration of it correspond roughly to the way it would be used in general practice?
- Is there an appropriate control treatment?

c. Study population and sample size
- Are the eligibility and exclusion criteria for patient entry into the trial stated?
- Is there a discussion of the type I and II error protection provided with the observed sample size?

d. Allocation
- Is the method of treatment allocation described?
- Does it appear to have been free of selection bias?
- Does it meet the general conditions specified in Section 8.4?

e. Data collection procedures
- Is the data collection schedule described?
- Are patients in the test and control-treated groups enrolled and followed over the same time frame?
- Does the design include adequate provisions to protect against bias in the administration of the treatment and in measurement of the outcome, as evidenced by the use of appropriate masking procedures or other safeguards?

5. Study performance
- Was a recruitment goal for the trial stated? Was it achieved?
- Was the missed examination rate low?
- Was the dropout rate low?
- Was the dropout rate among the treatment groups about the same?
- Was it possible to locate all patients, including dropouts, at the end of the study to update key morbidity and mortality data? If not, was the number who could not be located small and about the same for each treatment group?
- Did all the patients enrolled meet the eligibility criteria of the trial? If not, was the number who did not small?

Table 26-2 Questions to consider when assessing a published report (*continued*)

- Was the proportion of patients who failed to receive their assigned treatment low?
- Was there a reasonably high level of adherence to the treatment regimens over the course of the study?
- Is there a description of the effort made to monitor for departures from the study protocol and for maintaining data quality? Do you consider the procedure to have been adequate, given the needs and goals of the trial?
- Does the paper indicate how laboratory analyses and readings from ECGs and other similar procedures were done?
- Does the paper contain a description of the quality control procedures used to monitor laboratory analyses and readings such as ECGs? Do you consider those procedures adequate, given the needs and goals of the trial?
- Did the laboratory or readers perform the indicated analyses or readings in a masked fashion (i.e., without knowledge of patient treatment)?

6. Data analysis procedures
- Does the methods section of the paper include descriptions of the data analysis procedures used, and are the descriptions supported with appropriate literature references?
- Are the methods of analysis appropriate?
- Is the paper based on data from all study patients? If not, does it contain a statement indicating the rationale for the data selection presented in the report? Is the rationale reasonable?
- Are the key analyses based on original treatment assignment and do they account for all patients enrolled in the trial? If not, is the number of patients not accounted for small and about the same for each treatment group?
- Are data presented to describe the baseline comparability of the study groups?
- Is there an analysis that summarizes primary outcome data by original treatment assignment?
- Are patients who failed to receive the prescribed treatment or who had low adherence to the assigned treatment counted in the treatment group to which they were randomized?
- Do the tables and graphs have intelligible headings and legends?
- Are treatment comparisons adjusted for baseline differences?
- Have the authors used a variety of analytic approaches to support their conclusions, and do they yield consistent results?
- Are there tabulations that describe the treatment trends over time, such as via the use of lifetables or cohort analyses?
- Are data presented in sufficient detail to permit the serious reader to carry out additional analyses?
- Are the results internally consistent?
- Is there a stated cutoff date for the data included in the report, and is there a stated rationale for the date used? (Especially important if the report is based on interim results.)
- Do the authors display statistical sophistication by minimizing the use of *p*-value and significance testing as a means of data interpretation?

7. Discussion
- Have the authors provided a discussion of their results?
- Are the authors familiar with other relevant findings for the treatments being evaluated?
- Do the authors support statements contained in the discussion section with appropriate literature references?

8. Conclusions
- Are the conclusions supported by the analyses presented?
- Have the authors exercised a sufficient degree of caution and conservatism in stating their conclusions?
- Have the authors refrained from overgeneralization of the findings?
- Do the authors limit their conclusions to the types of patients studied and to the treatments investigated?
- If the authors have concluded in favor of the null hypothesis, do they provide a discussion of the type II error possible with the sample size used?

ing the products being tested, or that fail to indicate the source of the funding, should be viewed with a healthy skepticism. The same is true for reports produced by private foundations that derive their funds from unnamed sources or from sources with interests that stand to gain or lose financially, depending on the conclusions stated in the reports. For example, the Kilo, Miller, and Williamson critique (1980) of the University Group Diabetes Program (UGDP) tolbutamide results, simply states that the analyses were supported by the Kilo Research Foundation. Evaluations of the authors' objectivity may very well be influenced by the extent to which support for the Foundation depends on money supplied by manufacturers of the oral hypoglycemic agents.

The reproducibility of the results and the generalizability of the findings reported should be carefully examined. The reader should be skeptical of any results that pertain to a selected subset of the patients or outcomes observed. Unfortunately, it is not always easy to determine if this is the case. The fact that certain patients or outcomes have been excluded will be apparent only if the report contains statements to this effect and data for all patients randomized into the trial. Sometimes the only clue that some patients have been omitted is in the use of a single word or phrase (e.g., as in the use of the term *evaluable patients* or the phrase *analysis by treatment received*).

In general, results from all clinics in a multicenter trial following a common study protocol should be presented in a single publication. However, another way selection can occur is when individual clinics in such trials have the option of analyzing and publishing independently of other clinics. An investiga-

tor at a clinic producing a "statistically significant" treatment difference is more likely to publish than his colleague at a clinic who failed to produce any noteworthy treatment differences. There is no easy way to know if this form of selection occurs unless the authors so indicate.

A judgment should be formed regarding the level of statistical sophistication of the authors. Slavish use of hypothesis testing should be seen as a mark of naivety in the authors. The same is true for simple characterizations of results as significant or nonsignificant, depending on whether or not associated p-values are below or above the magical 0.05 level.

The study design, particularly as it relates to safeguards against biases in the data collection process, should be examined. Some feeling for this may be obtained by observing the extent to which the investigators have attempted to mask data collectors in the trial. Vague statements concerning the method of patient selection and assignment to treatment should raise questions concerning the adequacy of the treatment allocation process. Any suggestion that the authors equate a haphazard (see Glossary) method of assignment to formal randomization (see Glossary for definition of random) should raise doubts regarding the validity of the study.

Part of the assessment should focus on questions concerning the quality and integrity of the data generated. The methods section of the paper should contain sufficient detail to answer questions concerning methods used to edit the data for errors or inadequacies. The absence of any discussion of this kind should raise questions concerning the adequacy of the data collection procedures used.

The reader must decide if the results observed can be explained by differences in the baseline composition of the treatment groups, by a differential dropout rate, or by major differences in treatment compliance. Failure to provide information that allows the reader to address these issues should be viewed as a deficiency in the report.

Finally, a good paper will indicate if the results presented are from interim or final analyses of the data, and if they are of the former type why they are being presented now as opposed to later when the trial is finished.

26.4 VALID AND INVALID CRITICISMS

There is no such thing as a perfect study, only varying degrees of imperfection. The professional critic can always cite one or more of the criticisms listed in Table 26–3 without fear of contradiction. For example, he can always argue that the results of the trial should be ignored because the investigators studied the "wrong" population. Or he can challenge the choice of treatments or the way in which they were administered. And it is always possible to chide investigators because they failed to collect "important" data—at least as viewed from the perspective of the critic. The problem is not coming up with criticisms, but in deciding whether or not they are valid. The trouble with the criticisms listed in Table 26–3 is that they are so broad and sweeping as to be beyond debate.

A criticism, to be valid, should:

- Have some basis in fact
- Be buttressed with supporting evidence
- Make a difference in the interpretation of the results

All three tests should be met. Among the three, the third is the most difficult one to satisfy. For example, it is fairly easy to criticize a trial because of differences in the baseline composition of the treatment groups. However, it is quite another thing to show how those differences might have accounted for the results observed. The variability has to be sizable and must occur in connection with an important predictor of outcome to make any real differences in the results.

Table 26–3 Universal criticisms

- Wrong study population (too old, too young, too sick, too healthy)
- Sample size not large enough
- Treatment groups not comparable with regard to some baseline characteristic
- Important data overlooked in the data collection or analysis processes (key baseline data missing, analysis of some secondary outcome not done)
- Wrong treatments studied (dosage too high, dosage too low, test treatment studied is not used in real life)
- Treatment protocol not followed in all cases
- Treatments not properly administered
- Amount of follow-up inadequate
- Clinical implications of findings questionable
- Design of the study flawed (wrong design, inadequate stratification, wrong method of randomization)
- Execution of the trial faulty
- Errors made in the data collection, coding, or classification processes
- Inappropriate data analysis
- Important subgroups of patients overlooked in the analysis
- Results cannot be generalized to ordinary clinical practice
- Results are inconsistent with previous experience
- Results not definitive

26.5 DESIRABLE CHARACTERISTICS OF A CRITIC

A clinical trial is not designed to produce absolute truth. A good critic will recognize that its main strength is in the framework it provides for comparing one treatment with another and that comparisons among the treatment groups remain valid, given proper methods of treatment assignment, even if the populations studied are select. He will avoid criticism for the mere sake of criticism, and will recognize that criticism, to be useful, must be focused on specific issues concerning the design, execution, or analysis of the trial. He will avoid vague criticisms that are beyond debate. He will formulate his own list of criticisms after reading the original report and related documents and submit each of those criticisms to the tests discussed in the previous section before promulgating them. He will avoid parroting the criticisms offered by others unless he has carried out sufficient analyses of his own to support them.

A critic should recognize that his views may be colored by preconceived notions regarding the treatments studied or by his specific interests, scientific as well as financial, and hence will disclose those interests in his critique. Critiques that are commissioned and supported by a business firm with a proprietary interest in the treatments being evaluated should be so labeled. Feinstein (1971) took pains to disclose his interests in and incentives for doing the UGDP critique. His critique stands in marked contrast to those prepared by others concerning the study, such as those by Schor (1971) and Seltzer (1972). Disclosure of motivations and interests is important in that it permits readers to make their own judgment as to the degree to which they may have influenced the objectivity of the critic. Table 26–4 lists characteristics of a good critic.

Table 26–4 Characteristics of a responsible critic

- Reserves judgment until he has personally reviewed and read all pertinent study reports and documents
- Avoids dogmatic pronouncements
- Appreciates the danger of subgroup analyses and the limitations of a straight significance testing approach to data interpretation
- Refrains from flamboyant statements designed more for effect than for enlightenment
- Persuades through the force of argument rather than via clever debating techniques and rhetoric
- Does not make unsubstantiated claims
- Does not impugn the integrity of others without factual data to support the charge
- Knows the general design strengths and weaknesses of clinical trials
- Understands the concept of randomization and its uses in a research setting
- Concentrates criticisms on weaknesses that could have been corrected by better design procedures, not on weaknesses common to any clinic trial
- Knows his own limitations and seeks the help of others for assessment of areas outside his domain of competence
- Reveals any motivations and incentives (including those of a financial nature) that may have influenced his judgment regarding the trial
- Voluntarily discloses any interests that have the potential of being viewed as a conflict of interest

Part VII. Appendixes

A. Glossary
B. Sketches of selected trials
C. Year 1980 clinical trial publications
D. Activities by stage of trial
E. Sample consent statements
F. Data items and forms illustrations
G. Sample manual of operations, handbook, and monitoring report
H. Budget summary for Hypertension Prevention Trial Data Coordinating Center
I. Combined bibliography

Appendix A contains terms and acronyms used in this book plus terms considered to be common to the class of trials considered herein. Appendix B contains detailed design and operational information on 14 long-term trials. Appendix C provides the list of papers considered for review in Chapter 2. Appendix D relates to Chapter 3. It details the activities of a "typical" trial as it progresses from beginning to end. Appendix E relates to Chapter 14. It contains sample consent forms from the Hypertension Prevention Trial (HPT), Macular Photocoagulation Study (MPS), and the Persantine Aspirin Reinfarction Study (PARIS). Appendix F provides illustrative material related to the construction of data forms, as discussed in Chapter 12. Appendix G contains illustrative materials from a manual, handbook, and treatment monitoring report from the HPT, MPS, and PARIS. It relates to Chapters 16 and 20. Appendix H relates to Chapter 21 and the budgetary process for coordinating centers. Appendix I provides a combined bibliography of all references listed in the various chapters and appendixes of this book, except Appendixes B and C.

A. Glossary

A.1 PREFACE

This appendix sets forth terms and acronymns appearing in this book, plus other terms common to the class of clinical trials considered. Terms from other fields, most notably statistics and epidemiology, are covered, but only to a limited extent. Readers should see Last (1983); Kotz et al. (1982); Kruskal and Tanur (1978); Kendall and Buckland (1960); and James and James (1959) for more comprehensive glossaries of terms for these two fields.

Appendix I contains a list of reference sources used in the Glossary. Citations 69, 125, 128, 263, 272, 309, 330, 332, 343, 431, 438, 491, 495, and 502 represent general reference sources. Sources related to specific terms are cited in conjunction with those terms.

The impetus for this Glossary arose from work of the author in the Coordinating Centers Models Project (Coordinating Center Models Project Research Group, 1979a, 1979c). That work required a vocabulary to facilitate comparative analyses of the design, organizational, and operating features of the trials reviewed in that project.

Communication in clinical trials is confused by use of different terms to designate the same concept, detail, or practice. A case in point involves the term *outcome*, defined herein as a result, condition, or event associated with individual study patients and which is used to assess the efficacy of the study treatments. Other related or equivalent terms include *event, response variable*, and *endpoint*.

Practice in this book varies with regard to use of modifiers of base terms. They are frequently dropped when meanings are considered to be clear without their use. For example, the term *allocation* is often used as shorthand for treatment allocation, and *trial* is frequently used as a shorthand expression for clinical trial. Many of the more commonly used shorthand expressions appear in the Glossary.

Various terms in the Glossary are accompanied by usage notes (e.g., see *endpoint, cooperative clinical trial*, and *blind*). These notes are used to indicate the way in which a specific term is used in this book, or reasons for avoiding its use. Terms with more than one definition, such as *sequential analysis* and *treatment effect*, may be used in different ways depending on the context. Italic print is used to denote terms that are defined elsewhere in the Glossary.

This Glossary, while extensive enough to cover usage conventions in this book, is not comprehensive enough to cover the entire scope of clinical trials. The hope is that it will serve to stimulate others to extend coverage to other classes of trials and that it will lead to greater uniformity of language conventions in the field of clinical trials (Meinert, 1980a).

A.2. GLOSSARY

A

AAW Ask as written.

achieved sample size Observed sample size.

ACTH Adrenocorticotrophic hormone.

active control *Active control treatment.*

active control treatment A *control treatment* that involves use of a pharmacologically or medically active substance. See *inactive control treatment* for opposing term.

ad hoc review group A *review group* that is created for the sole purpose of reviewing a specified application or set of applications. Also referred to as *ad hoc study section*, especially if the applications are for *grant* support.

ad hoc study section A *study section* created to review a specified application or set of applications, especially applications for *NIH grant* support.

ADA American Diabetes Association.

adaptive allocation A *treatment assignment process* in which the *treatment allocation ratio* is allowed to change as a function of the number of patients enrolled, observed *baseline data*, or observed *outcomes* (see Simon, 1977).

adaptive allocation design *Adaptive treatment allocation design.*

adaptive random allocation *Adaptive allocation* in which the *treatment assignments* are made via a *random process.*

adaptive randomization A *treatment assignment process* using *adaptive random allocation.*

adaptive treatment allocation design A *treatment allocation design* in which the *treatment allocation*

ratio is allowed to change over the course of *patient enrollment*.

adaptive treatment allocation schedule A *treatment allocation schedule* constructed using an *adaptive allocation* scheme.

adherence *Treatment adherence.*

adverse drug reaction Any *side effect* associated with use of a drug that has adverse health implications.

adverse side effect Any *side effect* associated with a *treatment procedure* that produces an adverse effect or that has adverse health implications for the patient receiving the treatment.

advisory-review committee (ARC) A committee in the organizational structure of a *trial* that is responsible for advising the *steering committee* and the *sponsor* on operation of the trial. Usually composed of individuals neither directly involved in the execution of the trial nor associated with any of the participating *centers* or *sponsor* of the trial. A *key committee* in the organizational structure of a *multicenter trial*. See *policy board* and *policy-advisory board*.

advisory-review and treatment effects monitoring committee (ARTEMC) A committee that performs the functions of both the *advisory-review committee* and *treatment effects monitoring committee*. A *key committee* in the organizational structure of a *multicenter trial*.

allocation The process of making a *treatment allocation*.

allocation ratio *Treatment allocation ratio.*

allocation schedule *Treatment allocation schedule.*

allocation strata *Treatment allocation strata.*

alternative hypothesis 1. An alternative to the *null hypothesis* that specifies some true underlying difference or set of differences between two or more populations or groups with regard to some function, trait, characteristic, or effect. It may be stated in such a way so as to be concerned with a difference(s) in only one direction (*one-sided alternative hypothesis*) or in either direction (*two-sided alternative hypothesis*) relative to the null value. 2. *Alternative treatment hypothesis.*

alternative treatment hypothesis A hypothesis that states that the true underlying effect of the *test treatment*, as expressed by a specified *outcome measure*, is different from that associated with the *control treatment*.

AMIS Aspirin Myocardial Infarction Study.

analysis by intention to treat A method of data analysis in which the primary tabulations and summaries of *outcome* data are by assigned treatment. See also *analysis by treatment administered*.

analysis by treatment administered A method of data analysis in which the primary tabulations and summaries of outcome data are by treatment administered, not by treatment assigned (see Taylor et al., 1982, for usage example). See also *analysis by intention to treat*.

analysis database The subset of data contained in the *study database* that can be accessed for data analysis. Generally limited to *data* from the study database that have been coded, keyed, and stored electronically for easy retrieval and manipulation.

ancillary study An investigation, stimulated by the *trial* and intended to generate information of interest to the trial, that is designed and carried out by investigators from one or more of the centers in the trial and that utilizes resources of the trial (e.g., money, *study patients*, staff time, etc.), but that is not a required part of the design or data collection procedures of the trial.

applicant Anyone who makes an application to carry out a designated research project, particularly under the *grant* mode of funding. See also *offeror* and *proposer*.

ARC Advisory-review committee.

ART Anturane Reinfarction Trial.

ARTEMC *Advisory-review and treatment effects monitoring committee.*

assigned treatment The *treatment* designated to be administered to a *patient*, as indicated at the time of his *enrollment* into the *trial*.

assignment probability *Treatment assignment probability.*

assignment process *Treatment assignment process.*

assignment unit *Treatment assignment unit.*

award *Funding award.*

B

balancing interval *Treatment block.*

baseline A time point or set of data that serves as a basis for gauging changes in subsequent measurements or observations.

baseline adaptive allocation *A treatment assignment process* in which *assignment probabilities* are allowed to change over the course of the *trial* as a function of observed differences among the treatment groups for one or more *baseline variables*. Changes in the assignment probabilities are made so as to achieve comparable *study groups* with regard to the *variable*(s) used in the adaptive process.

baseline adaptive random allocation *Adaptive random allocation* based on one or more observed *baseline characteristics* of enrolled patients.

baseline adaptive randomization A *treatment assignment process* using *baseline adaptive random allocation*.

baseline characteristic *Baseline variable.*

baseline data 1. The set of *data* collected on a specific *patient* or set of patients during the *prerandomization* and *randomization visits*. 2. The same as definition 1, except excluding data collected at the randomization visit. In this book, data collected at the randomization visit are considered to be part of the baseline data set.

baseline examination An examination that is carried out as part of a *baseline visit* and that is designed to assess a patient's eligibility for *enrollment* into the *trial* and to produce required *baseline data*.

baseline observation An observation or recording of a *baseline variable* made on the *observational unit*.

baseline variable A variable that is measured, observed, or assessed on a *patient* at or shortly before *treatment assignment* and the initiation of *treatment*.

baseline visit 1. A *visit* that takes place either before *randomization* or during the *randomization visit*. 2. Any *prerandomization visit*, excluding the randomization visit. Usage note: The visit at which randomization occurs is considered to be a baseline visit in this book. Reasonable, so long as there are no data collected after randomization, or so long as data collected after randomization are free of treatment effects.

Bayesian analysis A method of *data analysis* that provides a posterior probability distribution for some *parameter* which is a function of observed data and a prior probability distribution for the parameter (see Cornfield, 1966b, 1969).

Bernoulli random variable A *random variable* that is capable of assuming one of two values, e.g., 0 or 1, with fixed probabilities, P and 1-P, respectively (see Feller, 1968).

Bernoulli trial A single replication of an experimental procedure on a defined *observational unit* with a *Bernoulli random variable* as the *outcome*.

BHAT Beta Blocker Heart Attack Trial.

bias 1. A preconceived personal preference or inclination that influences the way in which a measurement, analysis, assessment, or procedure is performed or reported. From Old French *biais*, meaning oblique. From Old Provencal, perhaps from Greek *epikarsios*, meaning oblique. 2. A specified instance of a preconceived preference or inclination.

biased coin randomization A method of *randomization* in which *treatment assignment probabilities* are modified as a function of the observed difference in the number of *patients* already assigned to the *study treatment groups*.

BID Bureau, institute, or division.

binary outcome *Binary variable.*

binary outcome measure An *outcome measure* that can assume only one of two values, such as in a *trial* with death as the outcome measure.

binary variable A *variable* that is capable of assuming one of two possible values, 0 or 1, or more generally E_1 or E_2. The variable is equivalent to a *Bernoulli random variable* if the probabilities of E_1 and E_2 are fixed.

BIOSIS Biological Abstracts (a literature database; see Chapter 26).

blind *Masked.* (Usage note: Term not used because of potential for confusion, especially when used in conjunction with a *trial* where loss of vision is the *outcome measure*, or in a trial involving *patients* who have lost their vision.)

blinded *Masked.* (See *blind* for usage note.)

BLIPS Biometrics Laboratory Information Processing System.

block 1. A group, quantity, section, or segment that is considered as a unit for some purpose, procedure, process, or action. 2. (clinical trials) *Treatment block*.

block size 1. The number of individual elements making up a *block*. 2. *Treatment block size.*

blocking The process of establishing defined groups, as in a *treatment allocation schedule* designed to provide prespecified *treatment block sizes*.

BMDP Bio-Mathematics Data Processing.

business office The office in an investigator's institution with legal responsibility for receiving funds from the *sponsor* and for expenditure of those funds under specified ground rules.

C

CANCERLIT Cancer Literature (a literature database; see Chapter 26).

case-control study (epidemiology) A study that involves the identification of persons with the disease or condition of interest (cases) and a suitable group of persons without the disease or condition of interest (controls). Cases and controls are compared with respect to some existing or past attribute or exposure believed to be causally related to the disease or condition. Also referred to as a retrospective study because the research approach proceeds from effect to cause. The term applies even if cases and controls are accumulated in a prospective manner (Last, 1983, Schlesselman, 1982).

CASS Coronary Artery Surgery Study, including the Coronary Artery Surgery Trial (*CAST*).

CAST Coronary Artery Surgery Trial, see *CASS*.

CATLINE Catalog on Line (a literature database; see Chapter 26).

CC *Coordinating center.*

CCD Committee for the Care of the Diabetic.

CCMP Coordinating Center Models Project.

CCU Coronary care unit.

CDC Centers for Disease Control (a part of the United States Public Health Service), Atlanta, Georgia.

CDP Coronary Drug Project

center An autonomous unit in the structure of a *clinical trial* that is involved in the collection, determination, classification, assessment, or analysis of *data*, or that provides logistical support for the trial. To be counted as a center, the unit must have a defined function to perform, must be administratively distinct from other centers in the trial, and must function during one or more stages of a trial. Centers include *clinical center, data center, coordi-*

nating center, data coordinating center, treatment coordinating center, central laboratory, procurement and distribution center, project office, reading center, and *quality control center*.

center director The administrative head of a *center*.

central distribution of funds A method for distribution of funds in which one *center* in a *multicenter trial* receives funds for execution of the trial and which, in turn, is responsible for distribution of funds to other centers in the trial.

central laboratory A *center* in a *multicenter trial* responsible for performing specified laboratory determinations on specimens collected from *patients* enrolled or considered for *enrollment* into the trial. Not counted as a separate center if administered as part of another center in the trial.

centralized database A *database* held and maintained in a central location, especially in a multicenter trial. See also *distributed database*.

centralized data entry A system in which all *data* generated in a *trial* are received at a central point for keying.

chairman of the study *Study chairman*.

CHD Coronary heart disease.

check digit A single digit that is used to reveal recording errors in some numeric identifier in a record, such as *patient identification number*. It is typically the last digit of the identifier and is assigned when the identifying number is issued. The assigned digit is compared with the one calculated using the identifying number (devoid of the check digit). The entire record is rejected for entry into an existing data file if the assigned digit does not agree with the calculated digit (see Selmer, 1967; Smythe, 1968; Fellegi and Sunter, 1969; and Anderson et al., 1974 for discussion of check digits).

clinic *Study clinic*.

clinic coordinator 1. An individual in a *study clinic* responsible for coordinating the data collection activities for that clinic and who expedites the flow of data and related records from the clinic to the *data center, data coordinating center*, or *coordinating center*. 2. An individual in the data center, data coordinating center, or coordinating center who is responsible for coordinating the receipt of data from study clinics and for communicating with clinics regarding data flow. See *data coordinator*.

clinic director The administrative head of a *study clinic*.

clinic monitor 1. An individual located in the *data center, data coordinating center, coordinating center*, or in the *sponsoring agency* who is responsible for receiving data from participating *clinics* and for initiating communications with those clinics regarding data collection and data flow procedures. 2. *Field monitor*.

clinic visit Any patient visit to the *study clinic* during the *enrollment* or *follow-up* process that is related to the data collection, examination, treatment, or patient care procedures of the *trial*.

clinical center 1. A *center* in the organizational structure of a *clinical trial* that is responsible for recruiting, enrolling, treating, and following *patients* in order to generate required data for the trial. 2. *Study clinic*.

clinical coordinating center *Treatment coordinating center*.

clinical event A change in a patient's state of health characterized by the occurrence of some discrete *event* that is considered to have adverse health implications (e.g., diagnosis of cancer, hospitalization for an MI, initiation of treatment for hypertension, death).

clinical research associate An individual, usually having an advanced degree, typically in medicine, employed by a drug firm to facilitate the initiation and direction of *clinical trials* sponsored by the firm.

clinical trial A research activity that involves administration of a *test treatment* (e.g., a drug, surgical procedure, diagnostic test, or medical device) to some *experimental unit* in order to evaluate the *treatment*. The term is subject to wide variation in usage. In some cases it may refer to the first use of a new treatment in man without any *control treatment*. In other cases it may refer to a rigorously designed and executed experiment involving a test and control treatment and *randomization*. The experimental unit in most cases is man (or a larger unit involving man, such as a hospital ward), but can be some other experimental animal. (Usage note: In this book, the term *clinical trial* or simply *trial* always refers to a *controlled clinical trial* involving human beings.)

CLINPROT Clinical Protocols (a cancer literature database; see Chapter 26).

close of trial The point at which the *trial* is considered to be finished. Marked by completion of the *patient close-out* or *termination stage* of the trial, depending on whether the closing point is associated with completion of *regular follow-up visits* or with data analysis.

close-out The process of separating a *patient* from the *trial* after completion of required *follow-up*.

close-out examination The *final examination* or series of final examinations performed on *patients* just prior to termination of *regular follow-up* in the *trial*.

close-out follow-up visit A *follow-up visit* made by a *study patient* to a *study clinic* that is used for data collection and to carry out specified procedures related to his separation from the *trial*.

close-out stage *Patient close-out stage*.

closed sequential design A *sequential design* that allows the experimenter to terminate the *trial* after a certain number of observations, even if the observed *treatment difference* is not large enough to allow the experimenter to conclude for or against the *test treatment*. Distinct from an *open sequential design*, which requires continuation of the trial until the difference is large enough to warrant a conclusion for or against the test treatment (see Chapter 9).

closed sequential trial A *trial* with a *closed sequential design* (see Chapter 9).

cohort A group of people defined by a common characteristic or set of characteristics. Middle English, from Old French *cohorte*, from Latin *cohors*, meaning enclosed yard, company of soldiers, multitude. One-tenth part of an ancient Roman legion.

common calendar date close-out A method of *patient close-out* in which all patients enrolled in the *trial* are separated from it at or about the same calendar date, regardless of when they were enrolled. See *common period of follow-up close-out* for opposing term. See also Chapter 15.

common period of follow-up close-out A method of *patient close-out* in which *patients* are separated from the *trial* after a specified period of *follow-up* (e.g., after two years). See *common calendar date close-out* for opposing term. See also Chapter 15.

comparative clinical trial Any *clinical trial* involving two or more *treatment groups*. See *controlled clinical trial*.

comparative study A *study* involving two or more defined groups of patients in which groups are compared, one with another, in order to make a judgment regarding the influence of some factor, condition, trait, or procedure that is present or applied to one group but not to the other(s). Synonymous with *controlled clinical trial* if the study entails comparison of different treatments involving patients enrolled and treated over the same period of time.

comparison group The group of *patients* designated or selected for comparison with all other groups in a *study*. The *control-treated group* of patients in a *controlled clinical trial*.

comparison treatment *Control treatment*.

compliance 1. To be in a *compliant* state. 2. A quantitative indication of the compliant state, as in the sentence: Compliance to the protocol was low.

compliant Willing to carry out a set of procedures or practices in accordance with established guidelines or standards.

composite event An *event* that is considered to have occurred if any one of several different *outcomes* are observed (e.g., occurrence of an attack of angina pectoris, a transient ischemic attack, or a myocardial infarction in a trial using a composite vascular event as the *outcome measure*).

computer A programmable electronic device that can be used to store and manipulate data in order to carry out some designated function.

computer terminal Any device (dumb or intelligent) that can be used for data input or output. It may be part of a network of terminals connected to a larger computing facility or may operate independently of all other facilities.

concurrent control A *control* that is based on *data* collected over the same period of time as that used to generate all other data in the study. See also *historical control*.

confounding variable 1. (epidemiology) A *variable* that is related to two factors of interest (e.g., disease state and degree of exposure to some agent in a *case-control study; treatment assignment* and *outcome* in a *clinical trial*) that falsely obscures or accentuates the relationship between the factors (see Breslow and Day, 1980; Last, 1983). 2. A *baseline variable* in a clinical trial that influences the outcome and that has a different distribution in the *treatment groups* being compared.

consortium agreement An agreement between the *sponsor* and one of the *centers* in a *multicenter study* in which the center agrees to receive funds for its own operations and that of other centers in the study and to disperse funds among the centers on an as-needed basis or as specified in the agreement.

consortium award 1. A *grant* or *contract* awarded by the *sponsor* to a *center* for execution of a *study* involving multiple *centers*. The center receiving the *award* assumes responsibility for allocation of funds to all other participating centers in the study. 2. Same as definition 1 except that the award is for support of only certain other centers in the study. Remaining centers are funded in other ways.

continuous variable A *variable* that is capable of assuming any value over a specified range.

contract A legally binding written agreement between the *sponsor* and the *business office* of the investigator's place of employment that outlines the nature and schedule of work to be performed and terms of payment for said work.

contract office The office in the *sponsoring agency* or *lead center* whose members are responsible for negotiating, awarding, and funding contracts.

contract officer The individual in the *sponsoring agency* or *lead center* who is responsible for negotiating, awarding, and funding contracts for specified projects.

control A standard of comparison for testing, verifying, or evaluating some observation or result.

control group *Comparison group, control-treated group*.

control patient A *patient* assigned to the *control treatment*.

control-treated group 1. The group of *patients* in a *trial* assigned to the *control treatment*. 2. The group of patients in a trial who received the control treatment, whether or not originally assigned to that treatment (not used this way in this book).

control treatment The drug, device, test, or procedure administered in a *clinical trial* that serves as the standard against which *test treatments* are evaluated. The control treatment may consist of a placebo medication, sham procedure, a standard treatment regimen, or no treatment of any kind, depending on the study design.

control trial *Controlled clinical trial.* (See *randomized control clinical trial* for comment.)

controlled 1. Constrained, monitored, or watched. 2. A system of observation and data collection that provides a basis for comparison, as with a *comparison group*.

controlled clinical trial A *clinical trial* involving one or more *test treatments*, at least one *control treatment*, and concurrent *enrollment*, *treatment*, and *follow-up* of all *patients* in the trial.

controlled trial *Controlled clinical trial.*

conventional author citation A method of citation in which specific individuals are designated on the title page or elsewhere in a manuscript as its authors. See *corporate author citation* for opposing term.

cooperative agreement 1. An agreement between an institute in the National Institutes of Health and a set of investigators that provides a defined structure for sponsor-investigator cooperation in the design and execution of a research project. 2. Any written agreement between a *sponsor* and *investigator*(s) that provides a defined role for both parties in the design and conduct of a specified research project.

cooperative clinical trial Term frequently used to denote a *multicenter trial.* The term is avoided in this book. Cooperation is required for execution of any trial, whether or not it involves multiple clinics.

coordinating center A *center* in the structure of a study that is responsible for receiving, editing, processing, analyzing, and storing *data* generated in a study and that, in addition, has responsibility for coordination of activities required for execution of the study. See also *data center, data coordinating center*, and *treatment coordinating center.*

coordinating center director The administrative head of the *coordinating center.*

coordinator 1. The individual in the *data center, data coordinating center*, or *coordinating center* who is responsible for coordinating the receipt of *data* from *study clinics* and for communicating with clinics regarding data flow. *clinic coordinator, data coordinator.* 2. The *director* of the *coordinating center.* (Usage note: Term not used in either definition 1 or 2 context in this book.)

corporate author citation A method of citation in which authorship of a given manuscript is ascribed to a corporate entity (e.g., as in a paper listed as having been authored by the Coronary Drug Project Research Group).

cost-reimbursement contract A *contract* in which the amount of money paid to the contractor by the *sponsor* is dictated by reasonable and allowable expenses for the work performed.

Cox proportional hazards regression model A method of analysis developed by D. R. Cox (1972) involving *regression analysis* which is used to adjust observed *event rates*, such as those obtained in a *clinical trial* where *patients* are enrolled over a period of time and followed to a common calendar date, for *variables* (usually observed at *baseline*) which are believed to influence the rates.

CPHA Commission on Professional and Hospital Activities.

CPPT Coronary Primary Prevention Trial, a trial conducted by the Lipid Research Clinics.

CPU Central processing unit (of a computer).

CRISP Computer Retrieval of Information on Scientific Projects (a database of ongoing work; see Chapter 26).

cross contamination *Treatment cross contamination.*

crossed treatment design 1. *Crossover treatment design.* 2. *Factorial treatment structure.*

crossed treatments Two or more *study treatments* that are used in sequence (e.g., as in a *crossover design*) or in combination (e.g., as in a *factorial treatment structure*).

crossover *Treatment crossover.*

crossover design *Crossover treatment design.*

crossover treatment design A *treatment design* that calls for the administration of two or more of the *study treatments* in a specified order to *experimental units* in the *trial.*

crossover trial *Crossover clinical trial.*

crossover clinical trial A *clinial trial* involving a *crossover treatment design.*

CRT Cathode ray tube.

cut-point 1. The point or value in an ordered sequence of values that is used to separate those values into two subparts. 2. *Subgrouping cut-point.*

CV Curriculum vitae.

D

data (pl. of *datum*) Factual information, such as measurements, observations, or statistics, which is used as a basis for reasoning, discussion, or calculation. (Usage note: In this book, the term refers to information collected and recorded on *patients* considered for *enrollment* or actually enrolled in a *trial.*)

data audit The comparison of specific items of information contained in an original *data form* (or some other kind of record) with that produced for some transcribed version of that form or record (e.g., as contained on a listing of the computer data file of the form or record) as a check for discrepancies.

data center 1. A *center* in a study structure that is responsible for receiving, editing, processing, analyzing, and storing data generated in the *study*, but that has few if any of the other general coordination responsibilities assumed by a *data coordinating center* or *coordinating center.* 2. A center in a study structure that is responsible for receiving, editing, processing, analyzing, and storing data generated in the study, regardless of whether or not the center has other more general coordination responsibilities. Used in this sense in this book where there is no need to distinguish between a data center, data coordinating center, or coordinating center, and where the emphasis is on data intake and processing functions.

data collection visit Any *visit* by a *patient* to the *study clinic* that is used for data collection in the *trial.*

data coordinating center A *center* that has the duties of a *data center* as well as general coordination duties for data collection. The modifier *data* is sometimes used in structures having two or more centers with specified coordination responsibilities (e.g., in a structure with both a *treatment coordinating center* and a *data coordinating center*).

data coordinator An individual in the *data center, data coordinating center*, or *coordinating center* who is responsible for coordinating the receipt of data from *study clinics* and for communicating with clinics regarding data flow. Sometimes also *clinic coordinator*, but not in this book.

data dredging A term used to characterize analyses that are done on an ad hoc basis, without benefit of prestated hypotheses, as a means of identifying noteworthy differences.

data editing 1. The process of reviewing *data* for the purpose of detecting deficiencies or errors in the way they are collected or recorded. 2. The process of detecting deficient or erroneous values on completed *data forms.*

data entry 1. The process of keying *data*, as contained on completed *data forms*, in order to render information into an arrangement more suitable for storage and subsequent use, usually for tabulations and analyses, especially on a *computer.* 2. The process of filling out a *data form.*

data field 1. A space on a *data form* or in an electronic *record* designated to contain, or that actually contains, alphabetic or numeric characters of information recorded in response to a specific *data item* on the form. 2. The actual collection of alphabetic or numeric characters used to denote information recorded in response to a specified question or statement on a data form.

data file A collection of *data records.* The collection may be of paper records or of electronic records that are arrayed in some way.

data form A collection of *data items* all arrayed on the same paper *record.*

data item 1. A question or statement and related area to be used by the respondent in answering the question or completing the statement appearing on a *data form.* 2. *Data field.*

data monitoring committee 1. *Treatment effects monitoring committee.* 2. A committee with *treatment effects monitoring* responsibilities plus other monitoring responsibilities, such as those needed for assessing data quality or for assessing the performance of clinics participating in a *trial.* 3. A committee that is responsible simply for monitoring data quality and the performance of *centers* in a trial (i.e., has no treatment effects monitoring responsibilities).

data record A collection of *data items* that is treated as a unit for some purpose or function.

data reduction 1. The process of taking *raw data*, as recorded on *study forms*, and of codifying and classifying them in such a way so as to condense them into a form suitable for data entry and electronic storage. 2. The process of taking data already contained in an electronic record and summarizing them, through the use of various classification schemes and arithmetic manipulations, so as to condense them into a form suitable for tabulations, analyses, listings, etc.

data and safety monitoring committee *Treatment effects monitoring committee.*

data system A package of interrelated procedures or routines that are performed by hand or computer to carry out some function or set of functions (e.g., data management or data analysis).

database A collection of data files that are organized in a specified manner and that are accessed by designated personnel for designated purposes.

datum Singular of *data.*

DCC *Data coordinating center.*

DCCT Diabetes Control and Complications Trial.

dedicated computer A *computer* that is under the exclusive control of a single user (or group of users) and that is used for a specified project, function, or activity.

DESI Drug Efficacy Study Implementation.

design unit The *observational unit* used for sample size calculations in a *trial.* Usually a *patient*, but may be some larger unit in special cases, such as in trials using hospital wards, families, or the like as the *treatment unit.* Always a patient in this book.

DHEW Department of Health, Education and Welfare (a department in the executive arm of the United States government until May 1980; its functions are now met by the Department of Health and Human Services and the Department of Education).

DHHS Department of Health and Human Services (a department in the executive arm of the United States government).

diagnostic clinical trial A *clinical trial* designed to evaluate the usefulness of some diagnostic procedure, tool, or device.

diagnostic trial *Diagnostic clinical trial.*

dichotomous variable A *discrete variable* that has only two possible values. *Binary variable.*

direct award An award of funds (*grant* or *contract*) made directly from the *sponsor* to a study *center.* See also *indirect award.*

direct distribution of funds Distribution of funds to *centers* in a *study* directly from the *sponsor*, as in *direct awards.*

direct patient contact Patient contacts that are initiated by the *study clinic* for the purpose of patient recruitment and that are directed at specified patients without any reliance on interviewing persons, agencies, institutions, or generalized advertising campaigns to make the contacts. See also *indirect patient contact* and Chapter 14.

direct patient recruitment Any method of patient recruitment that involves *direct patient contact*.

direct research cost The cost for salaries, equipment, supplies, and the like associated with the actual design, conduct, and analysis of a research project. See also *indirect research cost*.

director *Center director*.

discrete variable A *variable* that is capable of assuming only certain values over a defined range, as for *dichotomous* (binary) or *polychotomous variables*. See also *continuous variable*.

distributed data analysis Any arrangement in a *multicenter trial* whereby investigators in the various *centers* have access to the *analysis database*, or portions of it, for the purpose of carrying out data analyses.

distributed data entry A method of *data entry* in *multicenter trials* where data generated at the *clinics* are keyed on site.

distributed data system A *data system* that is established and maintained at the various *clinics* in a *multicenter trial* in order to perform functions normally carried out at the *data coordinating center*.

distributed database A *database* that is made up of component parts which reside at geographically diverse locations (e.g., in clinics in a *multicenter trial*).

distribution center *Procurement and distribution center*.

DMSO Dimethyl sulfoxide.

double-blind *Double-masked* in this book. See *blind* for usage comment.

double-blinded *Double-masked* in this book. See *blind* for usage comment.

double-blinded clinical trial *Double-masked clinical trial*.

double-mask *Double-masked*.

double-masked 1. A procedure in a *clinical trial* for issuing and administering *treatment assignments* by code number in order to keep *study patients* and all members of the clinic staff, especially those responsible for patient treatment and data collection, from knowing the assigned treatments. 2. Any condition in which two different groups of people are purposely denied access to a piece of information in order to keep that information from influencing some measurement, observation, or process.

double-masked clinical trial A *clinical trial* with *double-masked* administration of the *study treatments*.

DRG Division of Research Grants of the *National Institutes of Health*.

drop-in A term sometimes used (not in this book) to denote a *patient* in a *clinical trial* who, although assigned to one *study treatment*, receives one of the other study treatments in place of, or in addition to, the *assigned treatment*. See *treatment crossover* for related term.

dropout A patient enrolled in a *clinical trial* who is either unwilling or unable to return to the *study clinic* for *regular follow-up visits*.

DRS Diabetic Retinopathy Study.

drug trial A *clinical trial* in which the *test treatments* are drugs.

dumb terminal A *computer terminal* that can act as an input or output device, but that does not have independent processing capabilities (as opposed to an *intelligent terminal*).

dynamic allocation *Adaptive allocation*.

dynamic randomization *Adaptive randomization*.

dynamic treatment allocation schedule *Adaptive treatment allocation schedule*.

E

early stopping 1. A condition or provision incorporated into the design of a *clinical trial* that enables investigators to terminate *patient recruitment* or *treatment* if data accumulated during the trial suggest an adverse or beneficial *treatment effect*. 2. A term used to characterize an action involving termination of a *study treatment* in a trial because of adverse or beneficial treatment effects.

early stopping rule *Stopping rule*.

EC *Executive committee*.

ECG *Electrocardiogram*.

ECOG Eastern Cooperative Oncology Group.

edit check The process of reviewing a *data item* on a completed *data form* for deficiencies in the way it is completed or in the value reported.

edit query A statement generated from a review of a completed *data form* that draws attention to a suspected deficiency in an item of information on the form and that requires some action by personnel responsible for generation of the data to clear the query.

editorial review committee A committee created in the organizational structure of an *investigative body* that has responsibility for reviewing manuscripts produced by that body.

effective sample size *Sample size* after reductions due to *dropouts* and *treatment noncompliance*. See *expected effective sample size* and *observed effective sample size*.

EFM Electronic fetal monitoring.

EMED Excerpta Medica (a literature database; see Chapter 26).

endpoint 1. A *primary* or *secondary event* that, when observed in a *patient*, leads to termination or alteration of *treatment* or *follow-up*. 2. A primary or secondary event observed in a patient during the course of treatment or follow-up. 3. *Outcome*. 4. *Early stopping*. 5. *Stopping rule*. (Usage note: The term, *endpoint* is not used in this book because of the potential for confusion. Use of the term in the sense of definitions 1, 2, or 3 can mean that patients are no longer eligible for treatment or follow-up once they experience a specified event. This is obviously true where the event is death, but need not be so for nonfatal events. In fact, the design of the *trial* may require continued treatment and follow-up of patients over the entire course of the trial, regardless of the number of nonfatal "endpoints" observed. See *event*, *clinical event*, *primary outcome*, and *primary event* for preferred terms.)

enrollment *Patient enrollment*.

enrollment process *Patient enrollment process*.

equal allocation *Equal treatment allocation*.

equal treatment allocation A scheme in which the *assignment probability* in the *randomization process* for any one *treatment* is the same as for every other treatment in the *trial*. See *uniform treatment allocation*.

estimated sample size The number of *patients* required for a *study*, as derived from a *sample size calculation* or in some other way.

ETDRS Early Treatment of Diabetic Retinopathy Study.

ethics committee 1. *Treatment effects monitoring committee*. 2. *Institutional review board*.

ethics review committee 1. *Treatment effects monitoring committee*. 2. *Institutional review board*.

evaluable patient *Evaluable study patient*.

evaluable patients *Evaluable study patients*.

evaluable study patient A *study patient* who is regarded by investigators in the *trial* as having satisfied certain conditions (e.g., developed a tumor of a certain size during the trial, followed the assigned treatment) and, as a result, is retained for analysis purposes (a patient not satisfying the conditions is not so retained).

evaluable study patients The subgroup of *study patients* considered by investigators in the *trial* to satisfy certain conditions and, as a result, are retained for analysis purposes. Patients not satisfying the conditions are not so retained.

event 1. An occurrence, incident, or experience, especially one of some significance. 2. *Binary outcome measure*. 3. *Clinical event*. 4. The actual occurrence of a condition, trait, or characteristic that is defined by a binary outcome measure.

event rate The number of events experienced by a specified number of *patients* in a specified unit of time.

examination *Patient examination*.

executive committee (EC) One of the *key committees* in the organizational structure of a *trial*. Responsible for direction of the day-to-day affairs of the trial. Usually consists of the *officers of the study* and perhaps others selected from the *steering committee*. Headed by the chairman or vice-chairman of the steering committee and reports to that committee.

expected allocation ratio The *allocation ratio* expected using a given set of *treatment assignment probabilities*. See *specific allocation ratio*.

expected effective sample size The number of *randomization units* (usually *patients*) specified when the *trial* was planned, less reductions due to anticipated losses from *dropout* and treatment *noncompliance*.

expected power The *power* computed for a given *treatment comparison* when the *trial* was planned (see Chapter 9).

experimental unit *Treatment assignment unit*.

explanatory trial Term used to characterize *trials* that are designed to explain how a treatment works (see Schwartz and Lellouch, 1967; Sackett and Gent, 1979; Sackett, 1980). Term not used in this book. See also *management trial*.

F

factorial structure *Factorial treatment structure*.

factorial treatment structure A *treatment structure* in which one *study treatment* is used in combination with at least one other study treatment in a *trial*, or where multiples of a defined dose of a specified treatment are used in the same trial. See *partial* and *full factorial treatment structure*.

FDA Food and Drug Administration (a regulatory agency of the United States government, located in Rockville, Maryland).

feasibility study A preliminary study designed to determine the practicality of a larger study. See *pilot study*.

field monitor An individual employed by the *sponsor* or a *center* of a *trial* (e.g., *coordinating center*) to visit participating *clinics* to monitor data collection procedures. See *clinic monitor*.

final data analysis The term given to data analyses carried out at the end of the *trial*, normally in the *termination stage*, for characterizing results obtained from the trial.

final examination *Final patient examination*.

final patient examination 1. The last *examination* of a *patient* prior to *close-out*. 2. The last examination of a patient prior to *enrollment*.

fixed allocation Any method of *treatment assignment* involving a *fixed treatment allocation ratio*.

fixed allocation design *Fixed treatment allocation design*.

fixed allocation ratio *Fixed treatment allocation ratio*.

fixed allocation schedule *Fixed treatment allocation schedule*.

fixed-cost contract A *contract* in which there is a prior agreement between the *sponsor* and the investigator's institution on the amount to be paid for work to be performed, regardless of the actual costs incurred.

fixed sample size design A design in which the number of *patients* to be enrolled is considered to be fixed in advance of the start of *patient enrollment* for the *study*. The number may be determined from a *sample size calculation*, or via other considerations (e.g., cost, patient availability). It is conventional to consider any study that does not involve a *sequential design* as involving a fixed sample size design, even if the number is not determined before the start of the trial. See *sequential design* for opposing term.

fixed treatment allocation design A *treatment allocation design* in which the *treatment allocation ratio* is fixed.

fixed treatment allocation ratio An *allocation ratio* that remains fixed.

fixed treatment allocation schedule A *treatment allocation schedule* based on fixed *treatment assignment probabilities*.

fixed treatment randomization A *treatment assignment process* in which the *treatment assignment probabilities* remain fixed.

FOIA Freedom of Information Act (see Chapter 24).

follow-up *Patient follow-up*.

follow-up cohort 1. A group of *patients* enrolled into a *trial* during the same time period. 2. A group of patients enrolled at different time points, but who are followed for the same length of time (e.g., each patient for two years).

follow-up data *Data* collected on a *patient*, or a set of patients, after *enrollment* into a *trial*.

follow-up data collection visit Any *data collection visit* that takes place after a patient is enrolled into the *trial*.

follow-up examination A *patient examination* made at a *follow-up visit*.

follow-up observation An item of data collected on a *patient* (or larger *treatment unit*) after *enrollment* in a *trial*.

follow-up study *Prospective follow-up study*.

follow-up variable A *variable* observed on individual patients (*treatment units*) after *enrollment* into a *trial*.

follow-up visit Any *patient clinic visit* that takes place after the *randomization visit* for study-related purposes. See *required* and *nonrequired follow-up visit* for classes of follow-up visits. See also *treatment adjustment, regular, interim, close-out, post-close-out*, and *post-trial follow-up visit* for specific types.

free treatment arm 1. A *treatment* that is selected by the *study physician* or *study patient*. 2. A *study group* that receives the *treatment* selected by study physicians or study patients.

FTE Full-time equivalent.

full factorial structure *Full factorial treatment structure*.

full factorial treatment structure A *treatment structure* in which each *study treatment* is used in combination with every other study treatment. The treatments may involve different drugs or procedures, or different levels or doses of the same treatment.

funding agency The institution, organization, or foundation that provides fiscal support for a given study. *Sponsoring agency*.

funding award A *grant* or *contract* awarded to an institution for a designated project.

funding office The office responsible for fiscal negotiations with the *centers* of a *study* and for the disbursement and administration of funds for use in the study. *Grants management office, contract office*.

funding officer The head of the *funding office*. *Grants management officer, contract officer*.

FY Fiscal year.

G

general-use computer A computer that is used by a variety of users working on unrelated tasks or studies.

grant A *funding award* from the *sponsor* to an investigator, via his institution, to support designated work. A grant, as opposed to a *cooperative agreement* or *contract*, is generally made in anticipation of relatively little involvement in the work by the sponsor.

grants management office The office in the *sponsoring agency* whose members are responsible for negotiating and awarding *grants* and for disbursement of funds for execution of grant-funded projects. See *contract office* for corresponding term in contract-funded work.

grants management officer The individual in the *sponsoring agency* with legal authority to negotiate grant *awards* and to disburse funds in connection with those awards. See *contract officer* for corresponding terms for contract-funded projects.

group sequential analysis A method of *interim data analysis* that is carried out after *enrollment* of a specified number of patients, as discussed by Pocock (1977) and DeMets and Ware (1980).

H

handbook *Study handbook*.

haphazard A process occurring without any apparent order or pattern. Distinct from random, as used in this book, in that there is no mathematical basis for characterizing a haphazard process.

hard endpoint *Hard outcome*.

hard outcome Any *outcome measure* that is not subject to serious errors of interpretation or measurement. Usually death or some other explicit *clinical event*.

HDFP Hypertension Detection and Follow-Up Program.

health scientist administrator An individual at the *National Institutes of Health* who is responsible for providing technical and scientific assistance to investigators in a grant-funded study.

HEW (Department of) Health, Education and Welfare, *DHEW*.

HEX Committee Human experimentation committee. See *institutional review board*.

HHS (Department of) Health and Human Services, *DHHS*.

historical control A *control* that is based on *data* collected in a period of time previous to that used for generation of data on the *test-treated* group of patients. See *concurrent control* for opposing term.

historical control group A group of patients (may be loosely or explicitly defined) considered to have the same disease or condition as the *study group*, but who were diagnosed and treated in a period of time prior to that of the study group and who received the conventional form of therapy for that time. Historical control groups are generally only useful for evaluations of treatments involving rare diseases with highly predictable *outcomes* and where it is considered impractical or unethical to carry out a *controlled clinical trial*.

historical controls A collection of *patients* used as a *comparison group* who were diagnosed and treated for the disease or condition of interest in the past and in a period of time that predates the period of time covered for other *study groups*.

HPT Hypertension Prevention Trial.

human experimentation committee *Institutional review board*.

human volunteers committee *Institutional review board*.

I

ID Identification.

ID check digit A digit that is part of the *identification number* of a record and that is used as a check for transcription errors in that number. See *check digit*.

IDE *Investigational Device Exemption* (see IND for corresponding term for drugs).

IDEA *Investigational Device Exemption Application* (see INDA for corresponding term for drugs).

identification number *Patient identification number*.

IG *Investigative group*.

IMPACT International Mexiletine Placebo Antiarrhythmic Coronary Trial.

inactive control treatment A *control treatment* that is not considered to have any pharmacological or physiological effect. A *placebo treatment* or *sham procedure*. See also *active control treatment*.

IND Investigational New Drug (see IDE for corresponding term for medical devices).

INDA *Investigational New Drug Application*.

indirect award A *funding award* made to one *center* via another using funds received from the *sponsor*, as in a *consortium award*.

indirect patient contact Methods of patient contact that are initiated by the *patient*, his own physician, or some other intervening person, agency, or institution, for the purpose of patient recruitment. See *direct patient contact* for opposing term and Chapter 14.

indirect patient recruitment Any method of *patient recruitment* that involves *indirect patient contact*.

indirect research cost The cost incurred by the institution housing a research project for general administrative support and for providing space, heat, light, and the like in connection with the project. See *direct research cost* for opposing term.

informed consent The voluntary consent given by a patient to participate in a *study* after being informed of its purpose, method of treatment, procedure for assignment to treatment, benefits and risks associated with participation, and required data collection procedures and schedule.

initial design stage The first stage of a *trial*. Concerned with design and planning (see Chapter 3 and Appendix D).

institutional review board A committee or board, as set forth in United States Public Health Service guidelines for research involving humans and appointed by authorities in a research institution, constituted to review and approve studies to be carried out on humans in that institution. The review focuses on the ethics of the proposed research and on the adequacy of the proposed patient *informed consent* process.

intelligent terminal A *computer terminal* that can be used to perform data processing independent of the computer to which it is connected (as opposed to a *dumb terminal*).

interaction 1. (statistics, James and James, 1959) A case in which one *variable*, y, is a function of another, x, and in which variation in x associated with a given change in y is affected by the value assumed by a third variable, z. Interaction is said to exist between y and z. 2. (clinical trials) A situation in which the magnitude of the *test-control treatment difference* for the *outcome* of interest depends upon the value assumed by a third factor, such as age or prior disease state of the *study patients*.

interaction effect *Treatment interaction effect*.

interim analysis *Interim data analysis*.

interim data analysis 1. Any data analysis carried out during the *trial* for the purpose of *treatment effects monitoring*. 2. Any data analysis done before the trial is finished, for whatever reason, but usually concerned with assessments of *treatment effects*. (Usage note: Strictly speaking, the term applies to any fixed sample size or sequential trial where such analyses are done. However, it is conventional to reserve the term for use with *fixed*

sample size designs. That convention is followed herein.)

interim follow-up visit In this book, any *visit* by a study patient to the *clinic* after *randomization* that is not part of the required sequence of *follow-up visits* and that is initiated by the *study patient* or *study physician* because of some medical or treatment problem. Not counted as a *required follow-up visit* unless it takes place within the specified time period for a required visit and all the required procedures for that visit are carried out as part of the interim visit. See *nonrequired follow-up visit*.

interim result 1. Any *test-control treatment difference* observed during the *trial*. 2. A test-control treatment difference observed during the trial that results in a treatment protocol change.

interim visit *Interim follow-up visit*.

intervention study A study in which there is an effort to change the natural course of a disease or condition by attempting to alter the risk factors or precursors associated with that disease or condition.

intervention trial Technically, any *clinical trial*, since administration of any *treatment* in a trial setting is a form of intervention. However, the term is usually reserved for trials in which the test treatment entails life-style changes.

Investigational Device Exemption Application (IDEA) An application directed to the Food and Drug Administration by the manufacturer of a *medical device* or independent investigator for permission to evaluate the device in humans (Food and Drug Administration, 1983). See *Investigational New Drug Application* for corresponding term for drugs.

Investigational New Drug Application (*INDA*, also *IND*) An application directed to the Food and Drug Administration (made by submitting a *Notice of Claimed Investigational Exemption for a New Drug*) for permission to evaluate a drug (new or old) for a new indication in humans. See *Investigational Device Exemption* for corresponding term for *medical devices*.

investigative body *Investigative group*.

investigative group The entire staff involved in a *study*. Includes *center directors*, representatives from the *sponsoring agency*, members of all study committees and key support staff.

investigative team *investigative group*.

investigator *Study investigator*.

I/O Input/output.

IRB *Institutional review board*.

IRSC International Reflux Study in Children.

IUD Intra-uterine device.

K

Kaplan-Meier product limit A nonparametric method developed by Kaplan and Meier (1958) for estimating *follow-up event rates* using conditional probabilities. The method is especially well suited to situations, such as encountered in clinical trials, where *patients* are enrolled over a period of time and followed to a common calendar time point.

key committee In this book any of the following: *steering committee, executive committee, advisory-review committee, treatment effects monitoring committee*, or alternatively, the steering committee, executive committee, and *advisory-review and treatment effects monitoring committee*. Also *major committee*.

L

label insert *Package insert*.

landscape-style page orientation A form of orientation in which printed and visual information is arrayed on the long axis of a page. See also *portrait-style page orientation*.

lay representative A member of a committee, usually the *advisory review* or *advisory-review and treatment effects monitoring committee*, who is chosen to represent *patients* in the *trial* and who has no recognized research credentials.

lead center 1. A *center* designated in a *multicenter* study to take the lead in testing or performing certain procedures in a study or that is designated to assume a leadership role in the direction of the study. 2. The center responsible for disbursing funds to other centers in a study funded under a *consortium agreement*.

lead clinic 1. The *clinic* in a *multicenter trial* that is responsible for testing patient examination and data collection procedures to be used in a trial. 2. The first clinic funded, especially when that clinic is responsible for developing and testing data collection procedures to be used in a *study*.

lifetable An assembly of *data* in table or graph form that summarizes the survival (or mortality) experience of the *observational units* (*patients* in this book) from some specified starting point. The starting point may be based on age, as in most lifetables compiled by demographers, or on some event, such as diagnosis of disease, or *enrollment* into a *study*, in the case of a *clinical trial*.

lifetable analysis A method of analysis that relies on a count of the number of *events* observed and the time points at which those events occurred, relative to some zero point. The event may be death or some other event. In *clinical trials*, the time to an event for a *patient* is usually measured from the *time of enrollment*. *Treatment effects* are assessed by comparing *event rates* in the different *treatment groups*.

likelihood principle (statistics) A principle that implies that the magnitude of the probability associated with a given outcome of an experiment under hypothesis A relative to the magnitude of the probability associated with that outcome under hypothesis B contains all the information provided by the data from the experiment in choosing between the two hypotheses (Cornfield, 1966b; Dupont, 1983a).

log rank test statistic A *test statistic* used to compare the distribution of event times among different groups (usually with some censoring) in a clinical trial. See *Mantel-Haenszel test statistic* and Chapter 18.

loss to follow-up Any loss of *follow-up data* on a *study patient* after *enrollment* into a *trial*. The loss may occur because of the patient's refusal or inability to return to the *study clinic* for follow-up *data collection visits*, or because of the inability of clinic staff to locate the patient for collection of information not requiring a *clinic visit*.

losses to follow-up The sum total of information lost because of *loss to follow-up*.

lost to follow-up A patient who can no longer be followed for the *outcome* of interest, e.g., a patient who is unwilling or unable to return to the *clinic* for *follow-up examinations* in the case of a *clinical trial* using an outcome measured at the clinic, or a patient who cannot be located for subsequent *follow-up* in the case of a trial involving mortality or some other outcome that can be measured outside the clinic setting.

lost to mortality follow-up A person whose vital status cannot be determined, either because the person cannot be traced or because of insufficient identifiers to query data files such as the *National Death Index*. Losses to mortality follow-up in a *clinical trial* arise from *patients* who drop out and who cannot be located for subsequent contacts.

LRC Lipid Research Clinics.

LRC-CPPT Lipid Research Clinics-Coronary Primary Prevention Trial.

M

mainline paper Paper detailing the design, methods, or baseline results of the *trial* or containing original results related to the primary objective of the trial and written by study personnel commissioned by the *investigative group* or their representative.

major committee *Key committee*.

management trial Term used by some to characterize a trial that is designed primarily to provide information on the value of a treatment in normal usage (see Schwartz and Lellouch, 1967; Sackett and Gent, 1979; Sackett, 1980). Term not used in this book. See also *explanatory trial*.

Mantel-Haenszel test statistic A *test statistic* developed by Mantel and Haenszel (1959) to test for the equality of proportions in two groups over a series of independent 2×2 tables. In the case of comparing the probability of failure at different points in time, the statistic is equivalent to the *log rank test statistic* (see Chapter 18).

manual of operations *Study manual of operations*.

mask A condition imposed on an individual (or group of individuals) for the purpose of keeping that individual or group of individuals from knowing or learning of some fact or observation, such as *treatment* assignment. (Usage note: Term used in place of *blind* in this book. See entry for *blind* for reasons.)

masked The condition of having a *mask* in place, e.g., as in a *single-*, *double-*, or *triple-masked* trial.

matching placebo A pill (capsule or tablet) that is designed to resemble in shape, texture, size, taste, etc., a therapeutically active drug and that is used as the *control treatment*.

MATHFILE Mathematical Reviews (a literature database; see Chapter 26).

mean priority score The mean of the *priority scores* assigned by individual members of a *review group*.

medical device A diagnostic or therapeutic contrivance that does not interact chemically with a person's body. Includes diagnostic tests, kits, pacemakers, arterial grafts, intraocular lens and orthopedic pins (Food and Drug Administration, 1983).

medical liaison office *Project office*.

medical liaison officer *Project officer*.

medical research associate *Clinical research associate*.

MEDLARS Medical Literature Analysis Retrieval System.

MEDLINE Medical Literature Analysis Retrieval System on Line.

MeSH Medical subject heading.

MI Myocardial infarction.

MILIS Multicenter Investigation for Limiting Infarct Size.

monitoring Ongoing evaluation of a continuing process to determine when and if changes in that process are necessary for reasons of efficiency, data quality, safety, etc.

Monte Carlo simulation A method of simulating some stocastic process or procedure using random or pseudo-random numbers.

MPS Macular Photocoagulation Study.

MRFIT Multiple Risk Factor Intervention Trial.

multicenter Having more than one *center*.

multicenter clinical trial 1. A *clinical trial* involving two or more *clinical centers*, a common *study protocol*, and a *data center, data coordinating center*, or *coordinating center* to receive, process, and analyze *study data*. 2. A clinical trial involving two or more *clinics*. 3. A clinical trial involving at least one clinical center and one or more *resource centers*. (Usage note: A trial, to qualify as multicenter in this book, must satisfy definition 1. Trials simply involving two or more clinical centers, as specified in definition 2, do not qualify as multicenter unless

they have a common study protocol and a center to receive and process *data* from the study. A trial involving a single clinic, whether or not supported by other resource centers, is classified as a single-center trial in this book.)

multicenter trial *Multicenter clinical trial.*

multiple comparisons In this book, a term used to refer to the fact that two or more *treatment comparisons*, each involving the same *outcome measure*, are made or are to be made at a designated time point in the course of the trial. The comparison may involve all members of the treatment groups or subsets (e.g., as in analyses involving subgroups of patients defined by the presence or absence of some *baseline characteristic*.)

multiple linear regression analysis (statistics) A method of data analysis using a *multiple linear regression model*. Often used in *clinical trials* to adjust treatment results for differences in the baseline composition of the *treatment groups*.

multiple linear regression model (statistics) A mathematical model in which the *outcome variable*, y_i for the ith *patient* is written as a function of a series of independent observations, $X_{1i}, \ldots, X_{ki}$, *parameters*, $\beta_0, \ldots, \beta_k$, and an error term, ϵ_i. The usual form of the model, when no *interaction* terms are required, is:

$$y_i = \beta_0 + \beta_1 X_{1i} + \beta_2 X_{2i} + \cdots + \beta_k X_{ki} + \epsilon_i$$

The model derives its name from the fact that all parameters enter as linear terms (i.e., all raised to unit power). The independent variables, X_{ji}, for $j = 1, \cdots, k$, in the *clinical trial* setting are usually *baseline characteristics*. The outcome variable may be a continuous measure or a *binary outcome*, such as life-death.

multiple logistic regression analysis (statistics) A method of data analysis using a *multiple logistic regression model*. Often used in *clinical trials* to adjust observed treatment results for differences in the baseline composition of the *treatment groups*.

multiple logistic regression model (statistics) A mathematical model in which an *outcome variable*, y_i for the ith patient, is written as:

$$y_i = 1/(1 + e^{\tau_i})$$

where e is the natural constant, the quality τ_i, is a function of a series of observations, $X_{1i}, \cdots, X_{ki}$, made on the ith patient and that are independent of y_i, the model *parameters*, and the error term ϵ_i. The usual form for τ_i, when no interaction terms are required, is:

$$\tau_i = \beta_0 + \beta_1 X_{1i} + \beta_2 X_{2i} + \cdots + \beta_k X_{ki} + \epsilon_i$$

The model is especially well suited for analyses of event data since probability estimates derived from it lie between 0 and 1.

multiple looks In this book, a term used to refer to the fact that *treatment comparisons* are made or are to be made at various time points over the course of a *trial*.

multiple outcomes In this book, a term used to refer to the fact that a *trial* involves several different *outcome measures*, each of which is used or is to be used to make *treatment comparisons*.

N

National Death Index (NDI) A central registry of deaths, started in 1979 and operated by the National Center for Health Statistics of the United States Public Health Services (see reference citation 345).

National Institutes of Health (NIH) A group of institutes and related support structures located in Bethesda, Maryland, that is part of the United States Public Health Service. Responsible for funding basic and applied research in the health field. Also initiates and carries out medical research on an intramural and extramural basis.

natural history of disease 1. The course of a disease when left untreated. 2. The course of a disease when treated with standard modes of therapy.

natural history study A *prospective follow-up study* designed to yield information on the natural course of a disease or condition. Such studies generally focus on the *control-treated group* in a *clinical trial* (especially one in which the *control treatment* is a *placebo* or standard medical care).

NCDS National Cooperative Dialysis Study.

NCGS National Cooperative Gallstone Study.

NCI National Cancer Institute (part of the NIH).

NCR No carbon required (a type of paper).

NDA *New Drug Application.*

NDI *National Death Index.*

negative control *Inactive control treatment.*

negative control treatment *Inactive control treatment.*

NEI National Eye Institute (part of the NIH).

New Drug Application (NDA) An application submitted by the manufacturer of a drug to the Food and Drug Administration for a license to market the drug for a specified indication (see *Pre Market Approval Application* for corresponding term for *medical devices*).

NHLBI National Heart, Lung, and Blood Institute (part of the NIH and previously the National Heart Institute).

NIADDK National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (part of the NIH and previously the National Institute of Arthritis, Metabolism, and Digestive Diseases).

NIAID National Institute of Allergy and Infectious Diseases (part of the NIH).

NIAMDD National Institute of Arthritis, Metabolism, and Digestive Diseases (now the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases).

NICHD National Institute of Child Health and Human Development (part of the NIH).

NIDR National Institute of Dental Research (part of the NIH).

NIGMS National Institute of General Medical Sciences (part of the NIH).

NIH *National Institutes of Health.*

NINCDS National Institute of Neurological and Communicative Disorders and Stroke (part of the NIH).

NLM National Library of Medicine (part of the NIH).

noncompliance Not in *compliance* with a designated procedure. Usually in reference to some treatment or data collection procedure in this book.

noncompliant 1. The absence of a *compliant* state in relation to a designated procedure. 2. Term used to describe a patient who is unable or unwilling to follow the *assigned treatment* regimen.

noncrossover design A design for a *clinical trial* in which a *patient* is assigned to receive only one of the *study treatments*. See also *crossover design*.

nonfactorial treatment structure A *treatment structure* that has no factorial structuring.

nonhealth professional A member of a committee, usually the *advisory-review* or *advisory-review and treatment effects monitoring committee*, chosen for expertise in an area outside the health field (e.g., philosophy, theology, law).

nonmasked clinical trial A *clinical trial* that does not involve any *treatment masking*.

nonmasked trial *Nonmasked clinical trial.*

nonrandom Any method that does not conform to the statistical definition of *random*. Used primarily in this book in contexts where there is a need to emphasize the nonrandom nature of a haphazard or systematic process.

nonrandom clinical trial A *clinical trial* that uses a *nonrandom* method of *treatment assignment*.

nonrandom trial *Nonrandom clinical trial.*

nonrequired follow-up visit Any *visit* by the *patient* to the *clinic* after the *randomization visit* that is not part of the required sequence of *follow-up visits*. The visit may be initiated by the patient or by study personnel, and includes *interim follow-up visits*, nonrequired *post-close-out follow-up visit*, as well as *post-trial follow-up visits*. Data generated at such visits are not generally used to satisfy data collection needs for *required follow-up visits*, unless they take place within the *time windows* for those visits and all necessary procedures are carried out during the visits.

nonsequential design A design that does not involve a *sequential design. Fixed sample size design.*

nonuniform treatment allocation A *treatment allocation* scheme in which the *assignment probabilities* for the various *study treatments* differ.

Notice of Claimed Investigational Exemption for New Drug A notice filed with the Food and Drug Administration by a drug sponsor or independent investigator requesting permission to test a new drug, or an existing one for a new indication, in humans. See *Investigational New Drug Application* and *phase I, II, III,* and *IV trials*.

NTIS National Technical Information Service, located in Springfield, Virginia, and affiliated with the United States Department of Commerce.

null hypothesis 1. (statistics) A hypothesis that postulates no underlying difference in the populations or groups being compared with regard to the factor, trait, characteristic, or condition of interest. 2. *Null treatment hypothesis.*

null treatment hypothesis A hypothesis that states that the true underlying effect of the *test treatment*, as expressed by a specified *outcome measure*, is no more or less than for the *control treatment*.

number adaptive allocation *Adaptive allocation* using the difference in the number of *patients* assigned to the various *treatment groups* as the basis for adapting the *treatment allocation ratio*.

number adaptive random allocation *Adaptive random allocation* using the difference in the number of *patients* assigned to the various *treatment groups* as the basis for change of the *treatment allocation ratio*.

number adaptive randomization A *treatment assignment process* using *number adaptive random allocation*.

O

observation variable A condition or characteristic associated with individual *patients* (e.g., age, history of myocardial infarction, blood glucose level) that may assume different values and that is observed and recorded at one or more time points over the course of data collection.

observational unit An identifiable unit, always a *patient* in this book but may be a collection of individuals in other contexts (e.g., as characterized by household members, a hospital ward, or an entire community), that forms the basis for data collection and analyses. Usually synonymous with *treatment assignment unit* in a *clinical trial*.

observed allocation ratio The actual *allocation ratio* in a completed *trial*.

observed effective sample size The *observed sample size* after reduction due to *dropouts* and treatment *noncompliance*.

observed power The actual *power* for detecting a specified *treatment difference*, given an *observed sample size*, observed outcome *event rate*, and observed *losses to follow-up* due to *dropout* and *noncompliance*.

observed sample size The number of *patients* enrolled in a *study*.

observed treatment difference The actual *treatment difference* observed either at the end of the *trial* or at some designated time point during the trial.

offeror The party or individual who offers or proposes to carry out a designated research project, normally indicated via submission of a formal proposal to the *sponsoring agency*. Term normally reserved in the *National Institutes of Health* lan-

guage for proposals received in response to a *request for proposal* (RFP) and funded via the contract mechanism. See *applicant* and *proposer*.

officers of the study In this book, generally taken as the chairman and vice-chairman of the *steering committee*, the *director* of the *data center, data coordinating center*, or *coordinating center*, and *project officer*.

OMB Office of Management and Budget (office in the executive arm of the United States government).

one-sided alternative hypothesis *One-tailed alternative hypothesis.*

one-sided test (statistics) *One-tailed test.*

one-tailed alternative hypothesis An alternative to the *null hypothesis* that specifies a range of permissible values of all which lie to one side of the null value (e.g., H_o:$\mu_1 = \mu_2$ versus H_A:$\mu_1 > \mu_2$). See also *two-tailed alternative hypothesis.*

one-tailed test (statistics) A statistical *test of significance* based on the null value of no difference versus the set of all alternative values that are either to the right or to the left of the null value (e.g., the set indicating a positive treatment effect in a *clinical trial*. See also *two-tailed test.*

open clinical trial 1. A *clinical trial* in which a *study physician* or *study patient* decides on the treatment to be administered. *Nonrandom clinical trial.* 2. A *nonmasked clinical trial.* 3. A clinical trial with an open sequential design. (Usage note: Term not used in this book. Trials satisfying definition 1 are referred to as nonrandom trials. Trials satisfying defintion 2 are referred to as nonmasked trials.)

open label trial 1. *Nonmasked drug trial.* 2. Any *nonmasked trial.* (Usage note: The term *open label* not used in this book because of potential for confusion, e.g., with *open clinical trial*, and because nonmasked is considered to be more descriptive.)

open sequential design A *sequential design* in which *enrollment* of *patients* continues until the *test treatment* is shown, in a statistical sense, to be either better or worse than the *control treatment*. Distinct from a *closed sequential design*, which allows for termination of enrollment after observation of a specified number of *outcomes*, even if it is not possible to draw a conclusion for or against the test treatment.

open sequential trial A *trial* with an *open sequential design.*

operations committee The term used in Veterans Administration sponsored *multicenter trials* to designate the standing committee that performs the functions of the *treatment effects monitoring committee* and some of the functions of the *advisory-review committee.*

outcome 1. A result, condition, or *event* associated with individual *study patients* that is used to assess the efficacy of the *study treatments.* 2. *Primary* or *secondary outcome, event.* 3. An observed event in a particular patient.

outcome adaptive allocation *Adaptive allocation* based on *outcomes* observed for enrolled *patients.*

outcome adaptive random allocation *Adaptive random allocation* based on *outcomes* observed for enrolled *patients.*

outcome adaptive randomization A *treatment assignment process* using *outcome adaptive random allocation.*

outcome event The *event* of primary interest in a *trial*, e.g., the one used for *sample size calculations* and for key data analyses in the trial.

outcome measure An *observation variable* recorded for *patients* in the *trial* at one or more time points after *enrollment* for the purpose of assessing the effects of the *study treatments*. See *outcome variable.*

outcome variable An *observation variable* recorded for *patients* in the *trial* at one or more time points after *enrollment* for the purpose of assessing the effects of the *study treatments*. See *outcome measure.*

outlier Any value, reading, or measurement that is outside established limits and, for this reason, is questioned or considered to be in error.

P

***p*-value** (statistics) A value associated with an observed *test statistic* that indicates the probability that a value as extreme or more extreme than the one observed will arise by chance alone in repeated replications of a study.

package insert A document approved by the Food and Drug Administration and furnished by the manufacturer of a drug for use when dispensing the drug, which indicates approved uses, contraindications, and potential *side effects*. See *label insert.*

PAHO Pan American Health Organization.

PAIS Public Affairs Information Service (a literature database; see Chapter 26).

parallel design *Parallel treatment design.*

parallel treatment design A term sometimes used (but not in this book) to refer to *treatment designs* involving *uncrossed treatments*. See *noncrossover design.*

parameter 1. (statistics) A constant appearing in a mathematical expression that characterizes some population, process, or the like, whose true value is generally unknown but that can be estimated. 2. (clinical medicine) *Observation variable.* (Usage note: Not used in the latter context in this book.)

parent center 1. The *center* to which *satellite centers* report. 2. *Lead center.*

parent clinic 1. The *clinic* to which *satellite clinics* report. 2. *Lead clinic.*

parent institution 1. The institution that has administrative responsibilities for a specified *study center* and associated investigators. 2. The center responsible for disbursing funds to other centers in a study funded under a *consortium agreement.*

PARIS Persantine Aspirin Reinfarction Study.

partial factorial structure *Partial factorial treatment structure.*

partial factorial treatment structure A *treatment structure* involving some but not all possible combinations of the treatments used in the *trial.*

partially masked clinical trial 1. A *clinical trial* in which some, but not all, of the *study treatments* are administered in a *single-* or *double-masked* fashion. 2. A clinical trial in which some, but not all, of the staff in a *clinic* are masked to *treatment assignment.*

participant *Study participant.*

patient Shorthand for study patient in this book. From Middle English *pacient*, from Old French *patient*, from Latin *patiēns*, from the present participle of *patī*, to suffer.

patient close-out The process of separating patients from a *clinical trial* at the end of the *treatment and follow-up stage* (see Chapter 3 and Appendix D).

patient close-out stage The stage of a *trial* in which patients are separated from the trial at the end of the *treatment and follow-up stage* (see Chapter 3 and Appendix D). The fifth stage of a *trial* in this book.

patient compliance The degree to which a *patient* follows a prescribed set of procedures or routines. Synonymous with *treatment adherence* when the procedures or routines in question are those concerned with administration of a patient's *assigned treatment.*

patient enrollment The act of enrolling a *patient* (*treatment unit*) into a *trial.* In this book, considered to occur when the *treatment assignment* for the patient is revealed to clinic staff, or when *treatment* is initiated when assignments are known in advance of *enrollment.*

patient enrollment process The process of enrolling *patients* into a *clinical trial.* The process includes all the examinations and data collection procedures associated with the *prerandomization* and *randomization visits.*

patient examination Any *examination* done to evaluate a *patient* to determine eligibility for *enrollment* into a *trial* or to provide *follow-up data.*

patient follow-up A process involving periodic contact with *patients* enrolled in a *clinical trial* for the purpose of administering the *assigned treatment*(s), observing the effects of treatment(s), modifying the course of treatment(s), or for collecting required *data.*

patient identification number A unique sequence of numbers, or numbers and letters, that are used to identify a *patient.*

patient monitoring *Patient safety monitoring.*

patient population *Study population.*

patient recruitment The process of identifying suitable patients for *enrollment* into a *clinical trial.*

patient recruitment goal The number of *patients* scheduled to be enrolled into the trial. Usually set before the trial starts, or shortly thereafter, via a *sample size calculation* or via practical considerations.

patient recruitment quota A specification, usually set before *patient recruitment* is started or shortly thereafter, that indicates the mix of patients to be enrolled with regard to some characteristic, trait, or condition (e.g., the number of males versus females).

patient recruitment stage The stage of a *clinical trial* concerned primarily with *patient recruitment* (see Chapter 3 and Appendix D). The third stage of a trial in this book.

patient safety monitoring 1. Any ongoing process of reviewing accumulated outcome data for groups of *patients* in a *trial* to determine if a designated treatment procedure should be altered or stopped. *Treatment effects monitoring.* 2. The process of watching for treatment effects in an individual patient (term not ordinarily used in this context in this book).

payline A term used in connection with National Institutes of Health *grants* to indicate the *priority score* required on an approved application to permit payment. The payline is a function of the number of approved applications received by an institute, the distribution of priority scores across applications, and the amount of money available for new research initiatives by the institute.

performance monitoring An ongoing process carried out over the course of a *trial* to assess the performance of some *center*, group of centers, or some other task-oriented group in the structure of a trial.

phase I trial The first stage in testing a new drug in man. Performed as part of an approved *Investigational New Drug Application* under Food and Drug Administration guidelines. The studies are usually done to generate preliminary information on the chemical action and safety of the drug using normal healthy volunteers. Usually done without a *comparison group* (see Food and Drug Administration, 1977c; Pines, 1980).

phase II trial The second stage in testing a new drug in man. Performed as part of an approved *Investigational New Drug Application* under Food and Drug Administration guidelines. Generally carried out on patients with the disease or condition of interest. The main purpose is to provide preliminary information on treatment efficacy and to supplement information on safety obtained from *phase I trials.* Usually, but not always, designed to include a *control treatment* and *random allocation* of patients to treatment (see Food and Drug Administration, 1977c; Pines, 1980).

phase III trial The third and usually final stage in testing a new drug in man. Performed as part of an approved *Investigational New Drug Application* under Food and Drug Administration guidelines. Concerned primarily with assessment of dosage effects and efficacy and safety. Usually designed to include a *control treatment* and *random allocation* to treatment. Once this phase is completed the drug manufacturers may request permission to market the drug by submission of a *New Drug Application* to the Food and Drug Administration, assuming the results of the *phase I, II* and *III trials* are consistent with such a request (see Food and Drug Administration, 1977c; Pines, 1980).

phase IV trial Generally, a *randomized controlled trial* that is designed to evaluate the long-term safety and efficacy of a drug for a given indication and that is done with Food and Drug Administration approval. Usually carried out after licensure of the drug for that indication (see Food and Drug Administration, 1977c).

PHS Physicians' Health Study.

PI Principal investigator.

pilot study A preliminary study designed to indicate whether a larger study is practical. See *feasibility study*.

placebo A pharmacologically inactive agent given to a patient as a substitute for an active agent and where the patient is not informed whether he is receiving the active or inactive agent.

placebo-controlled clinical trial A *clinical trial* in which *patients* assigned to the *control treatment* receive a *placebo*.

placebo effect The effect produced by a *placebo*. The effect in *placebo-controlled clinical trials* is generally measured by comparison of the effect observed in *patients* receiving the placebo treatment with the effect observed in patients receiving the *active treatment*.

placebo reactor A *patient* who reports *side effects* normally associated with the *test treatment* while receiving a *placebo*.

placebo treatment 1. A treatment involving the use of a *placebo*. 2. A treatment that is harmless.

play the winner treatment allocation scheme An *outcome adaptive allocation* scheme based on work of Robbins (1952, 1956) in which the next *treatment assignment* is a function of the success or failure of the *test treatment*, as assessed in the last *patient* enrolled. A success would cause the next assignment to be made to the test treatment. A failure would cause the next assignment to be made to the *control treatment*. Modified by Zelen (1969) so as not to require complete dependence on the outcome observed in the last patient enrolled. The goal is to minimize the number of patients assigned to the inferior treatment.

PMA Pre-Market Approval (PMA) application (for a new *medical device*; see *New Drug Application* for corresponding term for drugs).

PO 1. *Project office*. 2. *Project officer*.

policy-advisory board *Advisory-review committee*.

policy board *Advisory-review committee*.

polychotomous variable A *discrete variable* that may assume two or more different values.

portrait-style page orientation A form of orientation in which printed and visual information is arrayed on the short axis of a page (e.g., as the pages in this book). See *landscape-style page orientation* for opposing term.

POSCH Program on the Surgical Control of Hyperlipidemia.

positive control *Active control treatment*.

positive control treatment *Active control treatment*.

post-close-out follow-up visit 1. Any *follow-up visit* of a *patient* that takes place after his separation from the *trial*, as indicated by completion of the *close-out follow-up visit*. 2. Any follow-up visit which takes place after completion of the *close-out stage* of a trial. 3. *Post-trial follow-up visit*.

post-close-out visit *Post-close-out follow-up visit*.

post-marketing surveillance Term used by the Food and Drug Administration to characterize any procedure, implemented after licensure of a drug for a given indication, that is designed to provide information on the actual use of the drug for that indication and on the occurrence of related *side effects*. The surveillance usually involves survey techniques rather than *controlled trials*.

post-randomization examination Any *patient examination* made by *clinic* personnel during a *post-randomization follow-up visit* for *data collection*.

post-randomization follow-up visit Any *visit* by a patient to the *clinic* after the *randomization visit, required* as well as *nonrequired* follow-up visits. The former class includes *treatment application and adjustment, regular, close-out*, and *post-close-out follow-up visits*.

post-randomization visit *Post-randomization follow-up visit*.

post-stratification The process of classifying *patients* into *strata* after they have been enrolled in the *study*—usually for data analysis purposes.

post-treatment follow-up 1. Any *patient follow-up* after the first application of the *assigned treatment*, especially in *clinical trials* involving a single application of the treatment, e.g., as in most surgery trials. 2. *Post-trial follow-up*.

post-trial follow-up A term used to refer to any form of *patient follow-up* after completion of the *close-out stage* of a *trial*.

post-trial follow-up stage One of the seven stages of a trial in this book (see Chapter 3 and Appendix D). Defined as an optional stage that occurs during or after completion of the *termination stage* of the trial and that is designed to provide *follow-up data* on mortality or some other *outcome measure*.

post-trial follow-up visit 1. Any *follow-up visit* that takes place after the *close of the trial*, the main purpose of which is to enable clinic personnel to collect *data* on a *primary* or *secondary outcome measure* to assess *treatment effects*. 2. The same as 1 except that the visit may take place any time after the *close-out follow-up visit*. See *post-close-out follow-up visit*.

power The probability of rejecting the *null hypothesis* when it is false.

Pre-Market Approval (PMA) application An application to the Food and Drug Administration for permission to market a specified *medical device* (Food and Drug Administration, 1983). See *New Drug Application* for corresponding term for drugs.

prerandomization examination Any *examination* that is part of the evaluation process of a *patient* for *enrollment* into a *trial* and that is carried out before the *randomization examination*.

prerandomization visit Any *visit* made to the *clinic* by a potential *study patient* for the purpose of evaluation for *enrollment* into the *trial* and that takes place prior to the *randomization visit*.

pretreatment examination Any *examination* done on a *patient* before the initiation of *treatment* and that is a required part of the procedures for the *trial*. Synonymous with *prerandomization examination* if *randomization* and initiation of treatment take place during the same visit.

prevention trial *Prophylactic trial*.

primary event 1. A *primary outcome variable* that is binary. 2. The actual occurrence of a *primary outcome*.

primary outcome 1. The *event* or condition the *trial* is designed to ameliorate, delay, or prevent. 2. The actual occurrence of a *primary event* in a *study patient*.

primary outcome variable The *outcome variable* that is designated or regarded as key in the design or analysis of the results of a *trial*. Generally, the variable used for *sample size calculations* in the design of the trial or, when no sample size calculation is made, for the main avenue of data analyses.

primary prevention trial A *prophylactic trial* that involves *patients* selected for the absence of a specified disease or condition and a *test treatment* that is being used ostensibly to prevent or delay the onset of that disease or condition.

principal investigator 1. The designation used by the *National Institutes of Health* to denote the individual named on a *grant* application who is responsible for directing the proposed research. 2. The lead scientist in a research project. (Usage note: It is best to avoid use of the term to designate the head of a *center* in a *multicenter trial*. It should be used in such settings only when there is a single individual, such as the *chairman of the study*, who is regarded by everyone in the trial as the principal investigator. Otherwise some other term, such as *center director*, should be used.)

priority score 1. The score assigned to a research application by an individual member of a *review group* that reflects that individual's judgment regarding the scientific merit of the proposal. In *National Institutes of Health* grant reviews the score may range from 1 (high scientific merit) to 5 (low scientific merit). 2. The score assigned to a research application as computed from the scores assigned by individual reviewers of the application.

procurement center *Procurement and distribution center*.

procurement and distribution center A facility in the structure of a *clinical trial* that is responsible for procuring, packaging, and distributing a needed supply or product (e.g., drugs, laboratory supplies, forms) to selected *centers* in the trial.

program director 1. The individual who heads a research project. 2. *Principal investigator*. (Usage note: Term not used in the context of a *multicenter trial* in this book. See usage note appearing under *principal investigator* for reason.)

program office 1. *Project office*. 2. An office containing a *project office* for several different but related studies.

program officer *Project officer*.

project director 1. The individual who heads a research project. 2. *Principal investigator*. (Usage note: Term not used in the context of a *multicenter trial* in this book. See usage note appearing under principal investigator for reason.)

project office 1. The office, located in the *sponsoring agency* and usually staffed with one or more individuals trained in a medical or research field, that is responsible for dealing with technical, scientific, and programmatic aspects of a *grant*- or *contract*-funded project. 2. *Program office*.

project officer 1. The individual in the *sponsoring agency* who is responsible for dealing with technical, scientific, and programmatic aspects of a *grant* or *contract*-funded project. 2. *Health scientist administrator* in *National Institutes of Health* grant-funded projects. See also *program officer*.

prophylactic trial A *trial* that is designed to assess the efficacy of a treatment procedure aimed at preventing the development or progression of a specific disease or condition.

proposer The party or individual who proposes, normally via submission of a written proposal, to carry out a designated research project. See also *offeror* and *applicant*.

prospective follow-up study A study in which people with a specific attribute or characteristic are identified and then observed for some period of time thereafter for the occurrence of the outcome or condition of interest, usually disease or death. The study may or may not involve a *comparison group*. *Clinical trials* represent a special subset of prospective follow-up studies.

prospective study *Prospective follow-up study*.

protocol *Study protocol*.

protocol development stage The second stage of a

clinical trial in this book. Usually undertaken after the initiation of funding and characterized by work involving development of the *protocol* and procedures needed to carry out the trial (see Chapter 3 and Appendix D).

pseudo random number A number that has been generated via a deterministic process, that has, or appears to have, the properties of a *random number*, e.g., as with some computer-generated "random" numbers (see Knuth, 1969).

PSRO Professional Standards Review Organization.

Q

quality assurance Any procedure, method, or philosophy for collecting, processing, or analyzing data that is aimed at maintaining or improving the reliability or validity of the data and the associated procedures used to generate them.

quality control center One of the possible *resource centers* in a *trial*. Defined as the *center* with responsibility for quality assurance for one or more aspects of the data collection or analysis processes. (Usage note: Term not used in this book except where there is a specified center with designated quality control functions that are over and above those normally assumed by the *data center, data coordinating center*, or *coordinating center*.)

quasi random number *Pseudo random number.*

R

R and D Research and development.

RAI Research Award Index (a database of research funded by the United States Public Health Service; see Chapter 26).

random (general) 1. Having no specific pattern or objective. Of or designating a chance process in which the occurrence of previous events is of no value in predicting future events. From Old French, *random*, meaning force, violence, impetuosity. 2. Sometimes used as a synonym for haphazard, but never in this book. Usage in this book always refers to a formal process meeting, or believed to meet, the conditions specified under the statistical definition of random.

random 1. (statistics) A term used to refer to a sequence of observations, activities, assignments, etc., that is the result of a chance process in which the probability of any given sequence is known or can be determined. 2. The term used to refer to a process that meets the probability conditions outlined above.

random allocation A method for assigning *patients* to *treatment* using a *random process*.

random number A number generated or drawn via some defined *random process*.

random process Any method or procedure that yields output that has the defined mathematical properties of a *random variable*.

random variable A *variable* that may assume any one of a number of different values, where the set of possible values is determined by a probability distribution, such as Bernoulli or normal.

randomization 1. The process of assigning patients (*treatment units*) to treatment using a *random process*, such as via use of a table of random numbers. 2. The process of deriving an order or sequence of items, determinations, specimens, readings, or the like using a *random process*.

randomization examination A *patient examination* that is done during the *randomization visit*.

randomization unit *Treatment assignment unit.* Usually *patient*, but may be a larger unit, as in studies involving families, hospital wards, or the like.

randomization visit The *clinic visit* at which the *patient* is *randomized*.

randomized The condition of having been assigned to a *treatment* via a *random process*. Normally considered to have occurred when the *treatment assignment* is revealed to any member of the clinic staff, e.g., when the envelope containing the treatment is opened at the *clinic*.

randomized control clinical trial Term sometimes used (e.g., Chalmers et al., 1981) to emphasize the nature of the *randomization process* in relation to the *control treatment* (i.e., that patients are randomly assigned to the control treatment). (Usage note: Phrase not used in this book. The preferred term is *randomized controlled clinical trial*).

randomized control trial *Randomized controlled clinical trial.* (See *randomized control clinical trial* for usage note.)

randomized controlled clinical trial A *clinical trial* (always in man in this book) that involves at least one *test treatment* and one *control treatment*, concurrent *enrollment* and *follow-up* of the *test-* and *control-treated groups*, and in which the treatments to be administered are selected by a *random process*, such that neither the patients nor the persons responsible for their selection or treatment can influence the assignments, and where the assignments remain unknown to the patients and clinic staff until the patients have been determined to be eligible for *enrollment* into the trial (and then may be revealed to patients and clinic personnel only by letter or number codes in *masked trials*).

randomized controlled trial *Randomized controlled clinical trial.*

raw data 1. Measurements and observations recorded on study *data forms*. 2. Unedited computer-generated listings of data from study data forms, prior to use of reduction and summary procedures needed for data analysis.

RBO *Relative betting odds.*

RCT 1. *Randomized clinical trial.* 2. *Randomized controlled trial.*

reading center A *center* that is responsible for interpreting and codifying information from a specified set of materials, records, or documents (e.g., ECGs, fundus photographs, chest X rays, biopsy or autopsy specimens, death certificates) provided by the *clinical center*(s) in the *study*.

record (n). A paper or electronic document that contains or is designed to contain a set of facts related to some occurrence, transaction, or the like.

recruitment goal *Patient recruitment goal.*

recruitment log A log maintained by a *clinic* that lists each *patient* considered for *enrollment* into a *study*. Usually maintained to provide a description of the characteristics of the population screened for enrollment. See *screening log*.

recruitment quota *Patient recruitment quota.*

regression to the mean A phenomenon that occurs when a second determination or measurement is made only on those individuals with an extreme initial determination or measurement. On average, the second determination or measurement tends to be less extreme than the initial one. Term originally coined by Sir Francis Galton (1886) to characterize the tendency for tall parents to produce shorter offspring and vice versa.

regular follow-up visit A *required follow-up visit*, the main purpose of which is to enable clinic personnel to carry out treatment assessment and data collection procedures, as specified in the study protocol. Called regular because such visits are normally required at fixed periods over the course of *follow-up*. Does not include visits done simply for treatment application or treatment adjustment.

relative betting odds A method of analysis developed by Cornfield (1966b) involving the ratio of two likelihood functions computed under the *null hypothesis* and a specified alternative.

request for application (RFA) A document prepared and distributed by a *sponsoring agency* to solicit applications for *grant* support to perform work described in the request.

request for proposal (RFP) A document prepared and distributed by a *sponsoring agency* to solicit proposals for execution of specific work. Normally used in conjunction with *contract* funding.

required follow-up visit Any *follow-up visit* that is a required part of the *study protocol* and that is to be done at a specified time after the *randomization visit*. Visits include *treatment application and adjustment, regular, close-out*, and *post-close-out*, and *post-trial follow-up visits*.

research group *Investigative group.*

resource center Any *center*, other than a *clinical center*, identified in the structure of a *trial*, that is involved in performing a specified set of support functions. The term includes *data center, data coordinating center, treatment coordinating center, coordinating center, central laboratory, reading center, quality control center, project office*, and *procurement and distribution center*.

response variable *Outcome variable.*

restricted allocation scheme Any allocation scheme in which the *treatment allocation schedule* is designed to satisfy certain preset constraints, as in *blocking* in a *fixed allocation schedule*.

restricted random allocation *Restricted allocation scheme* involving use of a *random process* to make *treatment assignments*.

restricted randomization The process of generating or issuing *treatment assignments* via a *restricted random allocation* treatment schedule.

restricted treatment allocation schedule A *treatment allocation schedule* that is constrained to yield the *expected allocation* ratio, as with *blocking* in a *fixed allocation schedule*.

review group A group of individuals, normally recruited by the *sponsoring agency* or its representative, charged with the review of a specific research proposal or set of research proposals for scientific merit. *study section.*

RFA *Request for application.*

RFP *Request for proposal.*

risk factor Any environmental exposure, personal characteristic, or event that affects the probability of developing a given disease or experiencing a change in health status (Morgenstern and Bursic, 1982).

risk factor analysis (epidemiology) Any analysis, usually involving regression or *subgroup analyses*, that is aimed at identifying *risk factors* for a given disease or condition.

RJE Remote job entry (via a *computer terminal*).

routine follow-up visit *Regular follow-up visit.*

S

safety committee *Treatment effects monitoring committee.*

safety monitoring *Treatment effects monitoring.*

safety monitoring committee *Treatment effects monitoring committee.*

sample size 1. The actual number of *patients* enrolled in a *study*. 2. The anticipated number of patients to be enrolled in a study, or the *patient recruitment goal*.

sample size calculation A mathematical calculation, usually carried out when a *trial* is planned, that indicates the number of patients to be enrolled in order to provide a specified degree of statistical precision for a specified *type I* and *type II* error protection (see Chapter 9).

sample size requirement The sample size yielded by a *sample size calculation*. See *recruitment goal*.

SAS Statistical Analysis System (a package of data analysis programs).

satellite center A *center* that is subservient to the *parent center* and that is organized to perform a designated set of functions considered to be part of the workscope of the parent center.

satellite clinic A *clinic* that is subservient to the *parent clinic* and that is organized and operated to

screen, identify, enroll, treat, or follow a segment of the *study population* that cannot, for matters of convenience or other reasons, be seen at the parent clinic.

SAW Show as written.

SC Steering committee.

scheduled follow-up visit *Required follow-up visit.*

SCI Science Citation Index.

screening log *Recruitment log.*

secondary event 1. A *secondary outcome variable* that is binary. 2. The actual occurrence of a *secondary outcome.*

secondary outcome 1. An *event* or condition related to the *primary outcome* but of less clinical or medical importance than the primary outcome. 2. The actual occurrence of a *secondary event* in a *study patient.*

secondary outcome variable An *outcome variable* that is known or believed to be related to the *primary outcome variable* and that is used, in addition to the primary outcome variable, for evaluation of treatments in the trial (e.g., observation of patients for the occurrence of nonfatal myocardial infarctions in a *clinical trial* using death as the *primary outcome* measure). 2. Any other outcome variable, regardless of its relationship to the primary outcome variable, that is used for treatment evaluation.

secondary paper Paper dealing with a secondary objective of the *trial* and written by study personnel commissioned by the *investigative group* or their representative.

secondary prevention trial A *prevention trial* involving *patients* with a history of some disease or condition in which the *test treatment* is administered to prevent or delay further development or progression of that disease or condition. For example, a *drug trial* involving use of a daily dose of aspirin over a period of years for prevention of myocardial infarction in patients with a prior history of myocardial infarction.

secular trend A trend or pattern that is time related; temporal trend.

self-checking digit *Check digit.*

sequential analysis 1. The analysis done after *enrollment* of a *patient*, pair of patients, or larger *block* of *patients*, in a *sequential trial* to determine whether additional patients should be enrolled. The decision is made by observing the *test-control difference* in observed *outcomes*. Enrollment of the next patient, pair of patients, or block of patients is carried out if the difference does not exceed prespecified boundary limits. 2. Periodic analyses carried out for *treatment monitoring* in trials with *fixed sample size designs*. (Usage note: Use in the context of definition 2 is avoided in this book. See *interim analysis* for preferred term.)

sequential design Any design in which the decision as to whether to enroll the next patient, pair of patients, or *block* of *patients* is determined by whether the cumulative *treatment difference* for all previous patients is within specified limits. *Enrollment* is continued if the difference does not exceed the limits. It is terminated if it does.

sequential trial 1. A trial involving a *sequential design*. 2. Term sometimes used (but not in this book) in conjunction with a *fixed sample size design* in which decisions concerning the *enrollment* of additional *patients*, or the continued *treatment* and observation of patients already enrolled, is dependent on accumulated *data* in the *trial.*

sham Something false presented to be genuine; a spurious imitation. Derived from the word *shame*, meaning trick or fraud.

sham procedure A procedure designed to resemble the real one and that is performed on a *patient* for the purpose of masking the patient or the patient's *study physician* as to whether the patient has received the real procedure.

side effect A secondary by-product of an action or procedure. Usually *treatment side effect* in this book.

significance level (statistics) 1. The permissible *type I error* level for a test of the *null hypothesis* with a specified *test statistic*. The null hypothesis is accepted if the test statistic yields a *p-value* which is larger than the specified level and is rejected if it is equal to or less than this value. 2. *p-value.*

significance test *Test of significance.*

significance testing (statistics) The act of carrying out a *test of significance.*

simple randomization *Unrestricted randomization.*

simple treatment structure *Nonfactorial treatment structure.*

single-blind *Single-masked* in this book. See *blind* for usage comment.

single-blinded *Single-masked* in this book. See *blind* for usage comment.

single-blinded clinical trial *Single-masked clinical trial.*

single-center trial 1. A *clinical trial* involving only one *clinic* (with or without *satellite clinics*) and no other *resource center*. 2. A trial involving only one clinic and a *center* to receive and process data. 3. A trial involving only one clinic and one or more resource centers. 4. A trial with no clinical centers, but one or more resource centers, as in the Physicians' Health Study sketched in Appendix B. 5. A *clinical trial* involving two or more clinical centers, but no center to receive and process *study data*. 6. A trial with multiple clinics not having a common *study protocol* (see usage note under *multicenter clinical trial*).

single-mask *Single-masked.*

single-masked A condition where certain persons (e.g., *study physicians*) are informed of some fact or condition whereas other persons (e.g., *patients*) are purposefully denied information regarding that fact or condition.

single-masked clinical trial 1. A *clinical trial* in which treatments are administered in such a manner that patients in the trial are not informed of whether they have been assigned to the *test* or *control treatment*, but clinic staff are. 2. A clinical trial in which the patient knows the treatment assigned, but the treating physician, examiner, or observer does not. (Usage note: Term not used in the context of definition 2 in this book.)

site visit A visit to a *center* or prospective center in a *trial* by personnel from outside that center for the purpose of assessing its performance or performance potential in the trial.

soft endpoint *Soft outcome.* (See usage note for *endpoint.*)

soft outcome Any *outcome measure* that is subject to major errors of interpretation or measurement. Usually, a measurement or assessment that depends on clinical judgment.

software Computer programs and related manuals and documents needed to operate them.

specified allocation ratio The particular *allocation ratio* used in constructing the *allocation schedule.*

sponsor *Sponsoring agency.*

sponsoring agency The institution, organization, or foundation that provides fiscal support, and often administrative and scientific support as well, for a given project. See *funding agency.*

SPSS Statistical Package for the Social Sciences.

SSIE Smithsonian Scientific Information Exchange.

stages of a clinical trial An arbitrary classification to characterize the stages of a trial. The stages used in this book are: Initial design, protocol development, patient recruitment, treatment and follow-up, patient close-out, termination, and (optional) post-trial follow-up (see Chapter 3 and Appendix D).

standard treatment The accepted mode of treatment for a given disease or condition. Equivalent to the *control treatment* in *clinical trials* when chosen to mimic standard medical practice.

statistical significance (statistics) *p-value.*

steering committee (*SC*) 1. A committee responsible for directing the activities of a designated project. 2. One of the *key committees* in the organizational structure of a *multicenter clinical trial.* Committee responsible for conduct of the *trial* and to which all other committees report, except the *treatment effects monitoring committee* and *advisory-review committee* or *advisory-review and treatment effects monitoring committee.*

stop condition 1. A condition encountered when carrying out a procedure (e.g., completing a *data form*, performing a *patient examination*) that requires the person performing the procedure to terminate the procedure until or unless the condition can be removed. 2. A defined condition that, when encountered for a *patient* enrolled in a *trial*, requires or permits clinic personnel to take some action related to that patient, such as instituting a change in treatment or terminating *follow-up* of that patient.

stop item An item or response category on a *data form* that when used or checked indicates the presence of a *stop condition* (see Chapter 12).

stopping boundary The set of values formed by a line or set of lines (or curves), usually specified before or shortly after the start of patient recruitment, which, if exceeded, indicates the existence of a *test-control treatment difference* that satisfies certain statistical properties (e.g., has a *p-value* of less than a certain size). The boundaries will be used as a basis for stopping the *trial* when developed in conjunction with a *sequential design*, but not necessarily when used in conjunction with a *fixed sample size design.*

stopping rule A rule, usually set before or shortly after the start of patient recruitment, that specifies a limit for the observed *test-control treatment difference* for the *primary outcome*, which, if exceeded, automatically leads to termination of the *test* or *control treatment*, depending on the direction of the observed difference.

strata (pl. of stratum) A series of distinct levels or layers. In this book, generally *subgroups* of patients formed by classification on some *variable* or set of variables, usually *baseline variables.*

stratification 1. The process of classifying *observation units* into *strata*. 2. The process of classifying *patients* into strata as part of the *randomization* process or for purposes of data analysis.

stratification variable A *variable* used to classify the *observational units* into *strata.*

stratified allocation A method of *treatment assignment* in which *patients* are first classified into defined *subgroups* based on one or more *baseline variables* and then assigned to *treatment* within the defined subgroups.

stratified random allocation *Random allocation* within defined *allocation strata.*

stratified randomization A *treatment assignment process* using *stratified random allocation.*

stratum (sing. of *strata*) A layer, level, or defined *subgroup.*

study 1. A general term used to refer to any one of a variety of research activities involving the collection, analysis, or interpretation of data. 2. Often used in this book as a synonym for *clinical trial.* 3. A project involving multiple types of investigations, only one of which is a clinical trial (e.g., as in the Coronary Artery Surgery Study since it includes both a clinical trial and an uncontrolled *prospective follow-up study.*

study chairman Chairman of the *steering committee.*

study clinic A facility with defined responsibilities for recruiting, enrolling, treating, and following *patients* in a *trial.*

study database The entire set of *data*, whether or not codified and keyed for storage in a *computer*,

collected on study *patients*, as contained on official *data forms* of the *trial*. Note: Data contained in patients' charts, unless transcribed onto official study data forms, are not considered part of the study database.

study group 1. Any defined group of patients on whom specified data are collected. 2. The entire group of patients included in a *study*. 3. Often synonymous with *treatment group*, as used in this book. 4. The group of investigators carrying out a study, especially a *multicenter* study. (Usage note: Term not used in the sense of definition 4 in this book.)

study handbook A book that contains a series of tables, charts, figures, and specification pages that detail the main design and operating features of a *study*, largely without use of written narrative.

study investigator General term used in this book to designate any individual who has a key role in the design, conduct, or analysis of a *study*.

study manual of operations A document or collection of documents that describes the procedures used in a *center* or set of centers in a *clinical trial* (e.g., manual of operations for *study clinics, coordinating center* manual of operations, ECG *reading center* manual of operations).

study participant 1. A term sometimes used in place of *study patient* when there is a desire to avoid the connotation of illness, as in *trials* involving well people. 2. *Study investigator* (but not in this book).

study patient Term used in this book to characterize an individual considered for *enrollment* or actually enrolled into a *trial* regardless of whether or not there is a perceived need for medical care. See *study subject* and *study participant*.

study physician Any physician associated with a *study clinic* who is responsible for administering the *study treatments* to *patients* in the *trial* or who is responsible for patient care, as dictated by the *study protocol*.

study population 1. The set of patients enrolled in a *trial*. 2. The entire set of patients considered for *enrollment* into the trial (not used in this context in this book).

study protocol A narrative document that describes the general design and operating features of a *trial*. Distinguished from the *study manual of operations* by its generality and absence of specific details needed for day-to-day execution of the trial.

study section 1. Any *review group* of the *National Institutes of Health*, especially one that is chartered to carry out reviews of research applications in a general area of research and that meets at regular intervals during the calendar year to perform those reviews. 2. A group of individuals, normally recruited by the *sponsoring agency* as its representatives, charged with the review of a specific research proposal or set of research proposals to assess scientific merit. See *review group*.

study subject General term used to denote an individual enrolled in a study. Not used in this book. The advantage of the term, as opposed to *study patient*, is that it avoids the connotation of illness—useful in cases where well people are being studied. The disadvantage is that it carries a connotation of subjugation—a notion that is at variance with the concept of informed consent and a patient-investigator partnership.

study treatment General term used throughout this book to refer to either a *test* or *control treatment*.

study vice-chairman The individual elected or designed to perform the functions of *study chairman* in his absence.

subgroup A subpart of the *study population* distinguished by a particular characteristic or set of characteristics (e.g., males under age 45 at entry).

subgroup analysis Any data analysis that focuses on a selected *subgroup* or *patients*. Generally in this book, any analysis that is aimed at elucidating *treatment differences* within a defined subgroup of patients.

subgrouping cut-point The value of a *subgrouping variable* used to separate patients (*treatment units*) into *subgroups*. For example, formation of subgroups of patients less than 35 years of age, 35 through 54 years of age, and 55 years of age or older requires use of cut-points at 35 and 55 years of age.

subgrouping variable A *variable*, such as age, used to classify *patients* (*treatment units*) into *subgroups*. Usually a *baseline characteristic* for most *subgroup analyses* in *clinical trials*.

subject *Study subject*.

support center *Resource center*.

surgical trial A *trial* in which the *test treatment* is a surgical procedure.

surrogate outcome An *outcome*, based on some test or measurement, that is used instead of a *clinical event* in the design or analysis of *clinical trial*.

surrogate outcome variable A test, measurement, score, or some other similar *variable* that is used in place of a *clinical event* (e.g., use of blood pressure change in place of clinical hypertension) in the design of a *trial*, or in summarizing results from it. Used because the variable is believed to be correlated with the clinical event of interest and because of its perceived utility in yielding detectable *treatment differences*.

survival analysis 1. Any method of data analysis that focuses on the length of survival of the *observational units*. 2. *Lifetable analysis*.

T

technical group *Investigative group*.

TEMC *Treatment effects monitoring committee*.

terminal *Computer terminal*.

termination stage The sixth and usually last stage of a *clinical trial* as used in this book. Concerned primarily with analysis of the study results (see Chapter 3 and Appendix D).

test-control difference *Test-control treatment difference*.

test-control treatment difference The postulated or observed difference between the *test-* and *control-treated groups* of *patients* with regard to a specified *outcome measure*.

test group A group of *patients* defined by the study design—patients assigned to the *test treatment* in a *clinical trial*—who are contrasted with the *control group* of patients to reach a conclusion regarding some factor, condition, or treatment.

test of significance (statistics) 1. The evaluation of observed data by calculating a specified test statistic and then deriving the associated *p-value*. 2. *Test statistic*.

test statistic 1. The formula or computing algorithm used to carry out a *test of significance*. 2. The numerical value provided by the formula or computing algorithm for a specified test of significance using a defined data set.

test-treated group 1. The group of *patients* assigned to the *test treatment*. 2. The group of patients who receive the test treatment. (Usage note: Use of the term in this book is always from the point of view of the *assignment process*, regardless of the treatment actually administered.)

test treatment The drug, device, or procedure to be evaluated in a particular *trial*.

therapeutic trial A *trial* designed to test the safety and efficacy of a particular drug, device, or procedure that is considered to have therapeutic value.

throwaway medical journal A pejorative term used to characterize a medical periodical that is distributed by a profit-making firm to a segment of the medical community free of charge.

time of enrollment The time point at which a patient (*treatment unit*) is regarded as having officially entered the *trial* and after which is regarded as a part of the *study population*. Operationally, the time point at which the *treatment assignment* is revealed to clinic staff, or when *treatment* is initiated when assignments are known in advance of *enrollment*.

time window The permissible time interval for performing a specified *baseline* or *follow-up examination*.

toxic drug reaction An *adverse drug reaction* that results in morbidity or mortality.

toxic side effect An *adverse side effect* that results in morbidity or mortality.

treatment 1. The act of treating, as in caring for a *patient*. 2. The specific regimen, method, or procedure being tested in a *clinical trial*.

treatment adjustment follow-up visit *Treatment application and adjustment follow-up visit*.

treatment adjustment visit *Treatment application and adjustment follow-up visit*.

treatment adherence The degree to which a *patient* follows his assigned treatment regimen. See *treatment compliance*.

treatment allocation 1. The process of assigning *patients* to *treatment*. 2. The *treatment assignment* of a particular patient.

treatment allocation design The plan for assigning *patients* to *treatment*.

treatment allocation ratio The ratio of the number of *patients* assigned or to be assigned to the *test-treated group* to those assigned or to be assigned to the *control-treated group* (e.g., an allocation ratio of 1:2 in a completed trial is one in which twice as many patients were assigned to the *control treatment* as were assigned to the *test treatment*).

treatment allocation schedule The schedule used for issuing *treatment assignments*.

treatment allocation strata *Strata*, designated before the start of *patient enrollment* and defined by *baseline characteristics*(s) or clinic, that are used to define subsets of *patients* who are assigned to *treatment* using *allocation schedules* constructed for the individual strata.

treatment application and adjustment follow-up visit A *follow-up visit*, the main purpose of which is to enable clinic staff to apply or adjust treatment, depending on patient needs and study specifications.

treatment application and adjustment visit *Treatment application and adjustment follow-up visit*.

treatment application follow-up visit *Treatment application and adjustment follow-up visit*.

treatment application visit *Treatment application and adjustment follow-up visit*.

treatment arm Term sometimes used in place of *study treatment*, or *study group*, especially in cancer *trials* (but not in this book).

treatment assignment The *treatment* to be administered to the *assignment unit* (usually a *patient*, but may be some other larger unit such as all members of a family or members of a hospital ward) as indicated in the *treatment allocation schedule*.

treatment assignment probability The probability associated with a specified *treatment assignment*. The value is fixed over the course of *patient enrollment* in *trials* with *fixed allocation designs*. It changes in trials using *adaptive allocation designs*.

treatment assignment process The process of assigning *patients* to treatment in a *clinical trial*.

treatment assignment unit The unit used in the *treatment assignment process*, usually *patient*, but the unit may be made up of multiple individuals in special cases such as in a *trial* involving treatment of a family unit or an entire hospital ward. Equivalent to *randomization unit* in trials involving *random allocation*.

treatment block A *block* consisting of a prespecified number of *patients*, all enrolled in reasonably close proximity to one another and assigned to the various *study treatments* in such a way so as to satisfy a preset *allocation ratio*. See also *treatment block size*.

treatment block size The number of allocations required for a specified *treatment block*. For example, a random allocation schedule for a *trial* involv-

ing two treatments, constructed using blocks of size 8 and an allocation ratio of 1:1, would require constraints on the *assignment process* such that the *specified allocation ratio* is satisfied after every eighth assignment.

treatment comparison Any comparison involving two or more of the study *treatment groups* for a designated *outcome* or *follow-up variable*.

treatment compliance The degree to which a *patient* follows his *assigned treatment* regimen. See *treatment adherence*.

treatment coordinating center A *center* in a *clinical trial* that is responsible for coordinating the development and administration of the *treatment protocol*, but that has few or no other responsibilities for coordinating other aspects of the trial. Usually present only in *multicenter trials* involving a complicated treatment protocol. See also *coordinating center* and *data coordinating center*.

treatment cross contamination Any instance in which a *patient*, who was assigned to receive one *treatment* in a *trial*, is exposed to one of the other *study treatments* during the course of *treatment* or *follow-up*.

treatment crossover Any change of *treatment* for a *patient* in a *clinical trial* involving a switch of *study treatments*. The switch may be planned, as in a *crossover trial*, or may be unplanned, as in the case of a *noncrossover trial* in which a patient assigned to one treatment is exposed to one of the other study treatments sometime during the *trial*. Unplanned crossovers are said to result in *treatment cross contamination*.

treatment design The portion of the study design that specifies the *treatments* to be evaluated, the nature of the *treatment structure*, and the way in which the treatments are to be administered.

treatment difference 1. A difference observed between the *test-* and *control-treated* groups of *patients* for some specified *outcome measure*. 2. Any specified or observed difference for a designated *outcome* or *follow-up variable* involving two or more *treatment groups* in the *trial*.

treatment effect 1. An effect attributed to the *test treatment*. Usually in *clinical trials* inferred from a comparison of the *test-* and *control-treated groups* of *patients* using observed results for a specified *outcome measure*. 2. The effect produced or assumed to be produced by a treatment in an individual patient. Usually assessed by measurements made before and after administration of the treatment in that individual.

treatment effects monitoring 1. Any process of reviewing accumulated *outcome data* for groups of *patients* in a *trial* as it proceeds to determine whether a designated treatment procedure should be altered or stopped. 2. The process of watching for *treatment effects* in an individual patient (term not ordinarily used in this context in this book).

treatment effects monitoring committee (TEMC) 1. A standing committee responsible for periodically reviewing accumulated data for evidence of adverse or beneficial *treatment effects* during the *trial* and for initiating recommendations for modification of a *study treatment*, including termination of the treatment when appropriate. 2. One of the *key committees* in the organizational structure of a *multicenter trial*. Usually composed primarily, if not exclusively, of individuals not directly involved in patient care or data collection in the trial.

treatment failure 1. Term sometimes used to characterize a *study patient* whose *study physician* has found it necessary to alter his *assigned treatment* because of the "failure" of the treatment to produce a desired effect. 2. A patient in a *clinical trial* who is no longer maintained on his assigned treatment, whether or not he continues under *follow-up*. (Usage note: Term not used in either context in this book.)

treatment and follow-up stage The fifth stage of a *clinical trial* in this book. Concerned with patient *treatment* and *follow-up* (see Chapter 3 and Appendix D).

treatment group The group of patients assigned to receive a specified *treatment*. See *study group*.

treatment interaction A situation in which the effect exerted by a *treatment* is influenced by the level, or presence or absence, of some other factor or condition not related to treatment (e.g., one would say there is a treatment-sex interaction if the *test-control treatment difference* is in one direction for males and in the other direction, or is of a different order of magnitude, for females).

treatment interaction effect The observed effect associated with a *treatment interaction*.

treatment lag The time required, or presumed to be required, for a treatment to exert its full effect.

treatment mask A condition or procedure that is imposed to keep someone from knowing the true identity of the *treatment assignment*.

treatment masking 1. A process in which *treatments* are administered so as to be *single-* or *double-masked*. 2. Any process that is designed to withhold information on *treatment assignment* from some individual or group of individuals in a *clinical trial*.

treatment monitoring *Treatment effects monitoring*.

treatment procedure The method of applying a particular *treatment* in a *clinical trial*.

treatment protocol A document that describes the *treatment procedures* used in a *clinical trial*.

treatment related bias A condition in which the nature of a reading, measurement, or classification recorded on a particular *patient* is influenced by the fact that the individual responsible for making the reading, measurement, or classification has knowledge of the patient's *treatment assignment*.

treatment side effect A by-product of treatment, either expected or unexpected, desired or undesired.

treatment structure The interrelationship of *treatments* used in a *clinical trial*, e.g., as characterized by treatments that are arranged in a *factorial structure*.

treatment trial A *trial* in which the *test treatment* consists of a procedure used for *treatment* of a specific disease or health condition. *Therapeutic trial*.

treatment unit The unit to which treatment is administered in a *clinical trial*. Usually *patient*, but the unit may be composed of multiple individuals, such as a family unit.

trial 1. *Clinical trial*. 2. Any tentative or experimental action done in order to obtain data for some judgment or conclusion.

triple-blind *Triple-masked* in this book. See *blind* for usage comment.

triple-blinded 1. *Triple-masked* in this book. See *blind* for usage comment. 2. Sometimes used in a jocular fashion (not in this book) to characterize a situation in which neither the patient, physician, nor statistician knows how the *trial* is designed or operated.

triple-blinded clinical trial *Triple-masked clinical trial*.

triple-mask *Triple-masked*.

triple-masked *Double-masked* plus masking for the individual (or group of individuals) who are responsible for *treatment monitoring*.

triple-masked clinical trial A *double-masked clinical trial* in which data analyses done for *treatment monitoring* are presented to the individual or group responsible for such monitoring in a way that conceals the identity of the *treatment groups*.

two-armed bandit A method of *outcome adaptive allocation* in which the *treatment assignment probability* for a particular treatment is a function of the observed *treatment difference* in *outcomes* of *patients* already *enrolled* in the *trial*. The motivation being to minimize the number of patients assigned to the inferior treatment (Robbins, 1952, 1956; Smith and Pyke, 1965; Zelen, 1969).

two-sided alternative hypothesis *Two-tailed alternative hypothesis*.

two-sided test (statistics) *Two-tailed test*.

two-tailed alternative hypothesis An alternative to the *null hypothesis* that specifies a range of permissible values that are symmetrically distributed about the null value (e.g., $H_0: \mu_1 = \mu_2$ versus $H_A: \mu_1 \neq \mu_2$). See *one-tailed alternative hypothesis* for opposing term.

two-tailed test (statistics) A statistical *test of significance* based on the null value of no difference versus the set of all alternative values (i.e., those that lie to the right and left of the null value).

type I error (statistics) The probability of rejecting the *null hypothesis* when it is true, usually denoted by the Greek letter α.

type II error (statistics) The probability of accepting the *null hypothesis* when it is false, usually denoted by the Greek letter β.

U

UGDP University Group Diabetes Program.

uncontrolled Not *controlled*.

uncontrolled clinical trial A *clinical trial* that does not involve a *control treatment*. In this book, any study that does not have a *control group* made up of patients treated and followed over the same time period as those in a *test-treated group*.

uncrossed treatments 1. A *treatment structure* not involving a *crossover design*. 2. *Nonfactorial treatment structure*.

uniform treatment allocation A scheme in which the *assignment probability* of any one *treatment group* is the same as for every other treatment group in a *trial*. See *equal treatment allocation*.

unmask To reveal the *treatment assignment* of an individual *patient* or group of patients to an individual or group of individuals associated with the *trial* (e.g., patients, *study physicians*, *treatment effects monitoring committee*) who have heretofore been denied this information.

unmasked trial *Nonmasked trial*.

unmasking The process of revealing a previously masked item of information, such as *treatment assignment*, to an individual or group of individuals in a *clinical trial*.

unrestricted allocation 1. Any system of *treatment allocation* that does not require the imposition of any restriction on the *assignment process*, over and above those implied with the *adaptive* or *fixed allocation* scheme used. 2. Use of *allocation schedules* within *clinics* in a multicenter trial, or *strata* within a clinic, but where there is no blocking within clinic or strata within clinic.

unrestricted allocation schedule An *allocation schedule* constructed using *unrestricted allocation*.

unrestricted random allocation Any *unrestricted allocation* scheme that uses a *random process* for generating *treatment assignments*.

unrestricted randomization The process of generating or issuing *treatment assignments* via an *unrestricted allocation schedule*.

unscheduled interim follow-up visit *Interim follow-up visit*.

USPHS United States Public Health Service.

V

VA Veterans Administration.

VA 43 *VACSP No. 43*.

VACSP Veterans Administration Cooperative Studies Program.

VACSP No. 43 Veterans Administration Cooperative Studies Program Number 43.

variable In this book, any trait, characteristic, test, measurement, or assessment that is recorded, or scheduled to be recorded, on *patients* enrolled, or to be enrolled, in a *clinical trial*.

VDT Video display terminal.

verification A process that is carried out to *verify* an item of information.

verify To confirm or substantiate an item of information recorded in a *data file* or keyed for entry into the *analysis database*.

visit *Clinic visit*.

W

WHO World Health Organization.

withdrawal 1. A technical term used to refer to the process of removing a specific individual from a *lifetable analysis* because of termination of *follow-up*, or because of the occurrence of an *event* that precludes further follow-up. 2. *Dropout* (not used in this context in this book).

writing team A team of *study investigators* who are appointed or designated to write a specified manuscript for presentation or publication.

B. Sketches of selected trials

B.1 Introduction
B.2 Methods
B.3 Results
Table B–1 List of trials sketched
Table B–2 Abstract summaries of trials sketched
Table B–3 Publication list of sketched trials
Table B–4 Summary tabulations from sketches
Table B–5 Sample sketch for the UGDP
Table B–6 Data coordinating centers for multicenter trials referenced in this book

B.1 INTRODUCTION

Table B–1 provides a list of the trials sketched in this Appendix. They are all multicenter trials, except the Physicians' Health Study (Sketch 1), and they all involve periods of follow-up of a year or longer. They represent seven different disease areas. The majority of the trials involve cardiovascular disease. The National Institutes of Health (NIH) serve as the sole source of support for 11 of the 14 trials, and they share funding responsibilities with a European foundation in the case of the International Reflux Study in Children. One of the other two trials was funded by the Veterans Administration and the other was funded by a pharmaceutical firm.

Eight of the trials involved tests of drugs, four involved surgical procedures, and one, the Hypertension Prevention Trial (HPT), involved testing diet modifications as preventive measures for hypertension. The remaining trial, the Multiple Risk Factor Intervention Trial (MRFIT), involved testing several different forms of intervention, all aimed at reducing known risk factors for heart disease.

The sketches are designed to:

- Acquaint readers with the design and operating features of some typical long-term trials
- Supplement information contained in the body of this book on some of the more frequently cited trials
- Provide a data resource for tabulations presented in chapters throughout the book

B.2 METHODS

The initial draft of each sketch was prepared by the senior author using:

- Published manuscripts produced from the trial (see Table B–3 for publication list)
- Basic design documents, such as original funding applications or requests for proposals
- Operational documents, such as manuals of operations, treatment protocols, data forms, etc.
- Personal communications with study personnel

Each sketch consisted of:

- An abstract summary of the trial
- A list of study publications
- Enumeration of the operating features of the trial

A copy of the draft sketch was sent to the chairman or vice-chairman of the study, director of the coordinating center or data coordinating center, or project officer for review. The date the review was completed (see item 33, Table B–4) was used as the cutoff date for information contained in the sketch and is considered the completion date for the sketch. Committee listing and membership information (items 27, 28, and 29, Table B–4) are as of this date for trials that had not yet entered the patient close-out stage. The committee structure is characterized as of the start of the close-out stage for trials that were already in this or in a later stage when the sketch was reviewed. Information on the steering committee and the committee responsible for treatment monitoring, as represented in items 28 and 29 of Table B–4, is based on data in the sketch (see Table B–5 for sample) and was collected on a supplementary form that was completed by the individual chosen to review the sketch.

B.3 RESULTS

Table B–2 contains the abstract summary of each trial sketched. Table B–3 lists official papers of the 14 study groups. Only papers appear-

ing in peer review journals or periodicals are listed. The list does not include:

- Papers published after the date in item 33, Table B–4
- Papers in preparation, submitted for publication but still under review, or accepted for publication but not yet published as of the date in item 33, Table B–4
- Abstracts or editorials concerning the study
- Papers published as part of a book, monograph, or the like, except where papers so published are part of a periodical indexed by the National Library of Medicine
- Reports published by the federal government
- Reports and documents placed on deposit at the National Technical Information Service or other similar repositories

The full list of publications is much more extensive than is shown in Table B–3 for some of the trials sketched, such as NCGS and CASS.

The author citations in Table B–3 are reproduced as supplied from the study, via the individual who reviewed the sketch, except for the exclusions listed above and minor editing. A comparison of citations in the table with those appearing in the body of the book will reveal differences. For example, named authors appear in the author field of citation 5.2 in Table B–3. The author designation in the body of the book for this citation is simply the National Cooperative Gallstone Study Group.

There are several reasons for the differences in the citations. First, it is not always clear how a paper should be listed from the arrangement of information in the masthead of the paper. Second, preference was given to corporate author designations when there was a choice between a conventional or corporate format in the body of the book. Use of corporate designations yielded shorter citations and made for a more logical grouping of related publications appearing in the combined bibliography (Appendix I) at the end of this book. Third, the listings in Table B–3 as supplied by the individuals selected to review the sketches were used to answer item 31.b in Table B–4. This was considered to provide the best basis for making the counts needed for that item.

Table B–4 contains summary tabulations derived from the sketches (See Table B–5 for sample sketch). The notes below relate to those tabulations. Table B–6 contains the name of the director of the data coordinating center or coordinating center and address of the center for all trials sketched, as well as the other multicenter trials referenced in this book.

Item number in Table B–4	*Comment*
1	• See Glossary for definition of type of trial.
2	• See Chapter 9 or Glossary for definition of fixed sample size design. All trials were of this type. None involved a sequential design.
3	• See Chapter 3 or Glossary for definitions of stages. The category *Completed* was checked if all funding for the trial had terminated by the date recorded in item 33.
5	• See Glossary for definitions.
6	• See Chapter 21.
7	• See Glossary for definitions of direct, indirect, and consortium awards.
8	• Start of funding taken as date of first award to any center in the trial. Awards issued simply for planning purposes were not counted in fixing the date. The ending date is the projected date for termination of all financial support for the trial. It is the termination date for completed trials.
9	• Number of clinics as of sketch completion for trials in the treatment and follow-up stage or earlier stage. Number of clinics entering the patient close-out stage for trials in that stage or beyond as of the sketch completion date given in item 33.
10	• See Glossary for definitions.
11.b	• Degree of coordinating center or data coordinating center director. Indicated as Bio (biostatistics), Epi (epidemiology), or Med (medicine).

Item number in Table B–4	*Comment*
11.c	• Answered *No* if the coordinating center or data coordinating center was financially and administratively independent of all other centers in the trial. Answered *Yes* if the center was funded through a clinical center in the trial or if it was under the administrative control of a clinic center director.
12, 13, 17	• See Glossary for definitions.
19.a	• See Chapter 14. Direct checked when potential study patients were identified and approached by study personnel, such as when patients are recruited from a primary care facility under the control of clinic investigators, or when patients are identified through special screening or direct mailings initiated by clinic personnel. Indirect checked if the initial contact is through some other agent or party outside the clinic, such as a referring physician, through review of records held by nonstudy physicians or at nonstudy hospitals, or via mass advertising compaigns initiated from the study and aimed at the general public.
19.b	• Month and year first patient was randomized.
19.c	• Month and year last patient was randomized. Projected date for trials still in the patient recruitment stage.
19.d	• Total number of patients enrolled (all treatment groups combined). Count at or before the date given in item 33.
20.a	• All 14 trials involved formal methods of randomization, as opposed to informal, nonrandom, or quasi-random methods, such as discussed in Chapter 8. All trials used patients as the randomization unit except one, the Macular Photocoagulation Study in which eyes served as the randomization unit.
20.b	• See Glossary for defninitions.
20.d	• The total number of allocation strata. Given by the product of the number of subgroups formed with each stratification variable. For example, a trial involving stratification by clinic (10 clinics), age (three levels), and sex would have $10 \times 3 \times 2 = 60$ allocation strata.
20.e	• See Chapter 10 and Glossary for definitions. Characterized as uniform if the allocation scheme was designed to yield equal numbers of assignments to the study treatments within a strata. Classified as nonuniform (denoted as *Nonuni* in the table) if this condition does not apply.
20.f	• Answered *Yes* if the allocations are blocked (see Chapter 10) to force the treatment assignments to satisfy a specified allocation ratio at various points during the patient enrollment process.
20.g	• Locus of control for the randomization classified as *Central* if release of individual assignments was triggered by written or telephone contact of clinic staff with staff of the coordinating center or data coordinating center (or staff of some other control center), or release was controlled via an on-site computer under the control of the coordinating center or data coordinating center. Control considered *Local* if clinic staff could obtain an allocation without use of an on-site computer controlled by the coordinating center or data coordinating center or without any contact with a coordinating center or other control facility.
21	• See Chapter 12 and Glossary for definitions. Regular follow-up visits do not include visits done simply for treatment application or adjustment.
22.a	• Recorded as the average length of follow-up or as a range. Anticipated values for trials that had not yet entered the patient close-out stage. Ranges recorded for trials in the close-out stage or beyond based on actual times of enrollment of the first and last patients entered into the study.
22.b	• Indicated as *NA* (not applicable) for trials still in the patient close-out stage or an earlier stage. Indicated as *None done* if trial is completed and no post-trial follow-up was done. The average length of follow-up provided or anticipated if post-trial follow-up was done or is under way.
24	• See Chapters 8 and 15.
26.a	• Original recruitment goal: That set when the trial was planned. Value recorded is as stated in the original design documents of the trial (e.g., original grant application, RFP, or RFA), or as reported in a study publication.

Item number in Table B-4	*Comment*
26.b	• The category *Sample size calculation* was checked if the goal was based on a sample size calculation with a specified level of type I and II error protection. The category *Pragmatic* was checked if a recruitment goal was set, but was based on practical considerations rather than on a formal sample size calculation.
26.c	• The number of patients recruited (all treatments combined). Listed as *NA* (not applicable) if recruitment not yet completed as of date in item 33.
26.d	• Answer based on information in published reports of results from the listed trials (see Table B-3 for list). The category *Not applicable* checked for trials that have yet to publish any results. The category *None required* checked for trials that produced a significant effect before patient recruitment was completed. The category *None stated* checked if the treatment effect observed was not considered to be significant by the authors of the report and the report contains no discussion of the rationale for the achieved sample size, or of the power provided to detect a specified treatment difference with the observed sample size and control event rate. The category *Sample size calculation* checked if the original recruitment goal was achieved and if the goal was the result of a sample size calculation made during or prior to the close of the patient recruitment stage. The category *Pragmatic* checked if recruitment was completed and the report contains a statement indicating the achieved sample was the result of practical considerations (i.e., was not the result of a formal sample size calculation). A check in both categories *Power calculation* and *Sample size calculation* indicates the report satisfied the requirements for both categories.
27	• See Chapter 23 and Glossary for definitions.
28.a, ii	• Patient care responsibilities? Answered *Yes* if chairman was responsible for treatment or care of any patients in the trial.
28.a, iii	• Recorded as *Self-appt* (self-appointed) in investigator-initiated trials where the chairman was designated on the initial application. Recorded as *E* (elected) if chairman was chosen by the investigative group after the trial was funded, either by acclamation or through a formal election. Recorded as *Appt* (appointed) if chairman was selected by the sponsor or the advisory-review committee of the trial.
28.a, iv	• Recorded as $\overline{WT}$ (without term) if the chairman, regardless of whether self-appointed, elected, or appointed, serves without term. Recorded as *Term* if chairman selected or appointed for a specified term less than the expected duration of the trial.
28.b, ii through iv	• See comments for 28.a, ii through iv.
28.c, i	• The study centers referred to in this item and in item 28.c, ii include clinical centers, as well as all resource centers. The number of members and their voting status is based on information supplied in study publications and as supplied from the study on a special form completed by the individual selected to review the sketch, as described in Section B.2.
28.d	• See Glossary for definitions of the positions listed. The positions denoted by items i through vi that were represented on the steering committee (SC) are marked *Yes*. *No* indicates that the position exists in the study, but that it is not represented on the SC. Positions that do not exist in the study are marked *NA* (not applicable). The positions represented by items vii and viii were marked *Yes* if individuals of the type indicated were on the SC, and were marked *No* if not.
28.e	• This item indicates the number of individuals elected to membership on the SC by some body of the study—generally the entire investigative body. The letter *T* following the number indicates election for a specified term. The letters $\overline{WT}$ indicate election without term.
29.a	• The committee scheduled to perform the treatment effects monitoring function for trials where monitoring is not yet under way. The actual committee performing that function for all other trials. See Glossary and Chapter 23.
29.b through f	• See comments for 28.a through e.
29.g	• The actual or planned number of meetings per year of the committee listed in item 29.a.

Item number in Table B-4	*Comment*
30	• See Chapter 23 for distinguishing features of communication models. Classifications made by author.
31.a	• Number from Table B-3.
31.b	• A paper was counted in the first category (corporate format) if the author field, as displayed in Table B-3, only contained the study name. It was counted in the second category (conventional format) if the author field only contained names of individual authors. It was counted in the third category (both formats) if the author field contained both the study name and the name of one or more authors.
32	• Item used to indicate the degree of involvement of the senior author of this book in the particular trials sketched.
33	• Taken as the date of review, as discussed in Section B.2.

Table B-1 List of trials sketched

Sketch number	*Study name*	*Acronym*	*Disease*	*Sponsor*
1	Physicians' Health Study	PHS	Cancer, cardiovascular	NIH
2	University Group Diabetes Program	UGDP	Diabetes	NIH
3	VA Cooperative Studies Program Number 43	VA 43	Diabetes	VA
4	Macular Photocoagulation Study	MPS	Eye	NIH
5	National Cooperative Gallstone Study	NCGS	Gallbladder	NIH
6	Coronary Drug Project	CDP	Cardiovascular	NIH
7	Aspirin Myocardial Infarction Study	AMIS	Cardiovascular	NIH
8	Persantine Aspirin Reinfarction Study	PARIS	Cardiovascular	Industry
9	Hypertension Detection and Follow-Up Program	HDFP	Cardiovascular	NIH
10	Multiple Risk Factor Intervention Trial	MRFIT	Cardiovascular	NIH
11	Coronary Artery Surgery Study	CASS	Cardiovascular	NIH
12	Program on the Surgical Control of Hyperlipidemia	POSCH	Cardiovascular	NIH
13	Hypertension Prevention Trial	HPT	Cardiovascular	NIH
14	International Reflux Study in Children	IRSC	Kidney	NIH and foundation

Table B-2 Abstract summaries of trials sketched

1. Physicians' Health Study (PHS)

The PHS is a randomized, double-masked, placebo-controlled clinical trial designed to test the value of regular use of aspirin on all cause and cardiovascular mortality after 4.5 years of follow-up, as well as beta-carotene on total cancer incidence in the last 2.5 years of the trial. Patients are randomly assigned to one of the four treatments listed below.

Treatment	*Dosage*
• Aspirin + beta-carotene: ASA + β	• One (325 mg) aspirin tablet every other day. One (30 mg) beta-carotene capsule on alternate days.
• Aspirin + beta-carotene placebo: ASA + $\bar{\beta}$	• One aspirin tablet every other day. One beta-carotene placebo capsule on alternate days.
• Aspirin placebo + beta-carotene: $\overline{\text{ASA}}$ + β	• One aspirin placebo tablet every other day. One beta-carotene capsule on alternate days.
• Aspirin and beta-carotene placebos: $\overline{\text{ASA}}$ + $\bar{\beta}$	• One aspirin placebo tablet every other day. One beta-carotene placebo capsule on alternate days.

Over 21,500 male physicians, 40 to 84 years of age at entry, are to be enrolled. Physicians volunteering to participate will receive their assigned medication via mail and will be asked to complete a short questionnaire first at 6-month and later at 1-year intervals after enrollment. The questionnaires will be collected by mail and will be used to assemble information on treatment adherence, treatment side effects, and morbidity. Participants are not required to make any clinic visits.

2. University Group Diabetes Program (UGDP)

The UGDP was a randomized, controlled, multicenter clinical trial designed to evaluate the effectiveness of long-term hypoglycemic drug therapy in preventing or delaying the vascular complications of diabetes. Only newly diagnosed, noninsulin dependent, adult-onset diabetics were eligible for enrollment. The study started patient enrollment in early 1961. All patient follow-up terminated in 1975. A total of 1,027 patients were enrolled and randomly assigned to one of the treatments listed below.

Treatment	*Dosage*
• Insulin variable: IVAR	• As much insulin (U-80 Lente Iletin or other insulins) per day as required to maintain "normal" blood glucose levels. Administered via subcutaneous injections.
• Insulin standard: ISTD	• 10, 12, 14, or 16 units of insulin (U-80 Lente Iletin) per day, depending on patient body surface. Administered via subcutaneous injections.
• Tolbutamide: TOLB	• 3 tablets per day, each containing 0.5 gms of tolbutamide.
• Phenformin: PHEN	• 1 capsule per day during first week of treatment, thereafter 2 capsules per day; 50 mg of phenformin per capsule.
• Lactose placebo: PLBO	• Number of tablets or capsules similar to those used for tolbutamide or phenformin treatments.

The tolbutamide and phenformin treatments were terminated in 1969 and 1971, respectively, because of lack of efficacy. The two insulin treatments were continued to the end of planned patient follow-up (1975), but were not judged to be any more effective than placebo medications in prolonging life or in delaying the onset and development of vascular complications.

3. VA Cooperative Studies Program Number 43 (VA 43)

The study is a long-term, randomized, double-masked, placebo-controlled clinical trial of aspirin and dipyridamole in diabetics with advanced vascular disease. The test treatment is a combination of aspirin and dipyridamole (one 325 mg tablet of aspirin and one 75 mg tablet of dipyridamole, three times per day). Patients assigned to placebo treatment received a prescription for a tablet schedule identical to that of the test-treated group. Patients in the trial had to have gangrene of the feet at enrollment or had to have had an amputation on one or both of their feet for gangrene in the last 12 months prior to enrollment. The study enrolled 231 patients. Recruitment was completed in May 1980. The study investigators plan to announce the results of the trial sometime in 1984.

Table B-2 Abstract summaries of trials sketched (*continued*)

4. Macular Photocoagulation Study (MPS)

The MPS is a multicenter study designed to assess the value of photocoagulation in eyes with choroidal neovascularization. The study consists of two sets of trials. The first was started in 1979 and focuses on the assessment of argon laser photocoagulation in eyes with leaking choroidal neovascular membranes that are between 200 and 2,500 microns from the center of the foveal avascular zone (FAZ). The second set of trials, started in 1982, involves use of krypton laser photocoagulation. This mode of treatment is restricted to eyes that were judged ineligible for argon laser photocoagulation because the choroidal neovascular membranes to be treated fell within 200 microns of the FAZ. Both studies involve three different types of eye diseases, as outlined below.

Type of eye disease	*Eligibility criteria*
• Senile macular degeneration (SMD)	• Neovascularization; visible drusen bodies as large or larger than those defined by standard MPS fundus photographs; age $\geq$ 50 at entry.
• Presumed ocular histoplasmosis (HISTO)	• Neovascularization; at least one atrophic scar (histo spot) in either eye; age $\geq$ 18 at entry.
• Idiopathic neovascular membrane (INVM)	• Neovascularization; no evidence of SMD or any other cause for neovascularization; no drusen bodies greater than those defined by standard MPS fundus photographs; no histo spots in either eye.

Eligible eyes in both sets of trials are randomly assigned to receive photocoagulation or no treatment. All patients are followed for changes in vision. The only results available from the trial through the date listed in item 33, Table B-4, relate to argon-treated SMD patients. Patient recruitment for that trial was terminated because of the apparent superiority of argon treatment. Of the SMD untreated eyes, 60% had reduced visual capacity by the eighteenth month of follow-up, compared with only 25% of the argon-treated SMD eyes.

5. National Cooperative Gallstone Study (NCGS)

The NCGS was a double-masked, randomized, controlled, trial designed to assess the efficacy and safety of chenodiol (chenodeoxycholic acid) for dissolution of radiolucent gallstones. The treatments are outlined below.

Treatment	*Dosage*
• High dose chenodiol: H	• 6 capsules per day, each containing 125 mg of chenodiol.
• Low dose chenodiol: L	• 6 capsules per day, each containing 62.5 mg of chenodiol.
• Placebo: P	• 6 capsules per day, each containing 3 mg of sodium cholate.

Nine hundred sixteen patients (not counting the 128 patients enrolled in a preliminary biopsy study) were enrolled, treated, and followed by the ten clinical centers participating in the trial. The percentages of patients with complete gallstone dissolution, after two years of treatment, as determined by radiographic metrology, were 13.5 for H, 5.2 for L, and 0.8 for P. Partial (over 50% dissolution) or complete dissolution occurred in 40.8% of H-treated patients, 23.6% of the L-treated patients, and 11.0% of the P-treated patients. Clinically significant hepatotoxicity requiring termination of the assigned treatment occurred in 3% of the H-treated patients and in 0.4% of the L-treated and P-treated patients.

Table B-2 Abstract summaries of trials sketched (*continued*)

6. Coronary Drug Project (CDP)

The CDP was a double-masked, randomized, controlled clinical trial designed to evaluate the efficacy of several different lipid-influencing drugs in prolonging the lives of men (aged 30 through 64 at entry) with a prior history of myocardial infarction. The treatments investigated are listed below.

Treatment	*Dosage per day**
• Low dose estrogen: ESG1	• 2.5 mg of mixed conjugated equine estrogen (Premarin®)
• High dose estrogen: ESG2	• 5.0 mg of mixed conjugated equine estrogen (Premarin®)
• Clofibrate: CPIB	• 1.8g of ethyl alpha parachlorophenoxy-isobutyrate (Atromid-S®)
• Dextrothyroxine: DT4	• 6.0 mg of dextrothyroxine (Choloxin®)
• Nicotinic acid: NICA	• 3.0 mg of nicotinic acid
• Placebo: PLBO	• 3.8g of lactose (placebo)

*Patients were required to take 9 capsules per day (3 capsules 3 times a day) to receive the specified dosage. They were started on 3 capsules per day. They were stepped to 6 capsules per day 1 month later and then to 9 capsules per day 1 month thereafter. They were then maintained on 9 capsules per day, except where contraindicated.

The study involved 55 clinics, a coordinating center, project office, central laboratory, ECG reading center, and drug procurement and distribution center. A total of 8,341 patients were enrolled. All patients were followed for a minimum of 5 years.

The two estrogen and dextrothyroxine treatments were discontinued during the course of the trial because of lack of efficacy. In addition, the clofibrate and nicotinic acid treatments, while continued to the end of the trial, did not show any evidence of efficacy. The 5-year mortality rates were 20.0, 21.2, and 20.9 per 100 population for CPIB, NICA, and PLBO, respectively.

7. Aspirin Myocardial Infarction Study (AMIS)

AMIS was designed to test the efficacy of aspirin in prolonging life in patients with a prior history of myocardial infarction. A total of 4,524 patients were enrolled and followed through the efforts of 30 clinical centers, a coordinating center, project office, central laboratory, ECG reading center, and drug procurement and distribution center. Patients assigned to aspirin treatment (ASA) received 1.0g of aspirin per day (two capsules per day, each containing 0.5g of aspirin). Patients assigned to the placebo treatment (PLBO) received a capsule schedule similar to that for aspirin-treated patients. Patients were followed for a minimum of 3 years.

The study failed to show any benefit for ASA treatment. In fact, the 3-year mortality rate for the ASA treatment group was higher than that for the PLBO treatment group (9.6 versus 8.8 per 100 population).

8. Persantine Aspirin Reinfarction Study (PARIS)

PARIS was an industry-sponsored randomized, controlled, clinical trial designed to test the efficacy of Persantine® (dipyridamole) and aspirin in prolonging lives of patients with an ECG-documented history of myocardial infarction (MI). The trial involved 2,026 patients. Clinics from both the United States and the United Kingdom participated. Patients were treated and followed for a minimum of 3 years. The treatments were as outlined below.

Treatment	*Dosage*
• Persantine® + Aspirin: PR + ASA	• 2 tablets, 3 times per day. 1 containing 75 mg of Persantine® and the other containing 324 mg of aspirin.
• Persantine® placebo + Aspirin: $\overline{PR}$ + ASA	• 2 tablets, 3 times per day. 1 containing 324 mg of aspirin and the other containing placebo medication.
• Persantine® placebo + Aspirin placebo: $\overline{PR}$ + $\overline{ASA}$	• 2 tablets, 3 times per day. Both containing placebo medication (starch, calcium phosphate, and microcrystalline cellulose).

There was no significant difference among the treatment groups in mortality. The percentages dead at the end of the study were 10.7, 10.5, and 12.8 for the PR + ASA, $\overline{PR}$ + ASA, and $\overline{PR}$ + $\overline{ASA}$ treatment groups, respectively. However, subgroup analyses of the data suggested the combination of Persantine® and aspirin may be beneficial in prolonging life, if used within a few months following an MI. This finding led to initiation of PARIS, Part II (not sketched).

Table B-2 Abstract summaries of trials sketched (*continued*)

9. Hypertension Detection and Follow-Up Program (HDFP)

The HDFP was a randomized, controlled, clinical trial of stepped care versus referred care for patients with hypertension. The study involved 14 clinics, a coordinating center, project office, central laboratory, ECG reading center, and a drug procurement and distribution center. A total of 10,940 men and women with a qualifying diastolic blood pressure (DBP) of 90 mmHg or higher were enrolled. Patients assigned to stepped care were treated at the study clinics by clinic personnel using a treatment protocol calling for stepped increases in the dosage of a prescribed medication or in the number of antihypertensive agents used in order to achieve desired BP reductions. Patients assigned to the referred care group were referred to their usual source of medical care for treatment.

Five-year mortality (all cause) was 17% lower for the stepped care group than for the referred care group (6.4 per 100 population for stepped care versus 7.7 per 100 population for referred care). The investigators concluded that the findings "indicate that the systematic effective management of hypertension has a great potential for reducing mortality for the large number of people with high BP in the population, including those with 'mild' hypertension."

10. Multiple Risk Factor Intervention Trial (MRFIT)

MRFIT was a randomized, controlled, clinical trial designed to assess the value of a multifactor intervention program aimed at reducing known risk factors for coronary heart disease (CHD). The three risk factors were elevated serum cholesterol, high blood pressure, and cigarette smoking. Only men aged 35 through 57 at entry, with no overt evidence of CHD, were eligible for enrollment. The 12,866 men enrolled were randomly assigned to either special intervention (SI) or usual care (UC). Those assigned to SI were placed on specific treatments for the risk factors present. A dietary approach was used for cholesterol reduction, antihypertensive drugs (plus weight reduction where appropriate) were used for blood pressure reduction, and a behavioral approach was used to achieve cessation or reduction of cigarette smoking. Participants assigned to UC were not given any care via study clinics for elevated blood pressure or advice on how to reduce cholesterol or cigarette consumption. However, hypertensives diagnosed via the study were referred to their usual source of care for treatment.

The trial completed participant recruitment in early 1976. Participants assigned to SI continued to be exposed to the required interventions until termination of follow-up in early 1982. The first report of findings appeared in late 1982. The report showed the interventions practiced on the SI-treated group to be effective in lowering blood pressure, cholesterol, and cigarette consumption. However, these reductions had virtually no effect on mortality. There was a slight but nonsignificant reduction in deaths from coronary heart disease (17.9 versus 19.3 per 100 population for the SI-treated versus the UC-treated groups). However, all cause mortality was slightly higher in the SI-treated group than in the UC-treated group (4.1 versus 4.0 per 100 population). Subgroup analyses presented in the 1982 publication raise the possibility that SI-treated men with hypertension and resting ECG abnormalities at entry may have fared worse than the corresponding UC-treated group of men.

11. Coronary Artery Surgery Study (CASS)

CASS is a multicenter study consisting of two components: A trial designed to assess the efficacy of coronary artery surgery in patients with proven coronary artery disease and a registry of consecutive patients undergoing coronary arteriography. The trial component involved 780 patients assigned to coronary bypass surgery or conventional medical therapy. The registry is made up of 24,959 patients, including randomized patients. Patients in both components are followed for mortality, as well as for various nonfatal cardiovascular events. The study involves 15 clinical centers, a coordinating center, project office, and ECG reading center. Results comparing surgical and medical treatment in the randomized portion of the study had not been published, as of the completion date for this sketch.

12. Program on the Surgical Control of Hyperlipidemia (POSCH)

POSCH is a randomized clinical trial designed to determine whether reducing cholesterol levels via partial ileal bypass, in patients with high cholesterol levels and a prior history of myocardial infarction (MI), is useful in prolonging life and mitigating atherosclerosis. Patients in the trial are randomly assigned to bypass surgery or regular medical care. Patient recruitment is scheduled to continue through May 1983 with the goal being to enroll 800+ patients. Follow-up is expected to continue for a minimum of 5 years after completion of recruitment. There are no publications containing treatment results, as of the date in item 33, Table B-4.

Table B-2 Abstract summaries of trials sketched (*continued*)

13. Hypertension Prevention Trial (HPT)

The HPT is a randomized, controlled, multicenter trial designed to assess the efficacy of different forms of dietary intervention in preventing the development of hypertension. Current funding is for the first stage of a possible two-stage effort. The first stage is designed to develop and test methods and procedures needed for the second stage and will involve 800 participants randomly assigned to the treatment groups indicated below. The second stage, if warranted by results from the first stage, may involve as many as 6,000 participants and is expected to start in 1985 or 1986.

Treatment	*Dietary goal*
High weight strata	
• Sodium restriction: Na	• Reduce sodium intake to ≤ 70 mEq per day.
• Sodium restriction and potassium supplementation: NaK	• Reduce sodium intake to ≤ 70 mEq per day and increase potassium intake to ≥ 100 mEq per day.
• Sodium restriction plus caloric restriction for weight reduction: NaCal	• Reduce sodium intake to ≤ 70 mEq per day and restrict calorie intake to bring body weight within normal limits.
• Caloric restriction for weight reduction: Cal	• Reduce calorie intake to bring body weight within normal limits.
• Control: Ct	• None.
Normal weight strata	
• Sodium restriction: Na	• Reduce sodium intake to ≤ 70 mEq per day.
• Sodium restriction and potassium supplementation: NaK	• Reduce sodium intake to ≤ 70 mEq per day and increase potassium intake to ≥ 100 mEq per day.
• Control: Ct	• None.

Only nonhypertensive individuals with diastolic blood pressures ≥ 78 mm Hg but < 90 mm Hg are eligible for enrollment in the first stage. Individuals who fall in the high weight strata, as determined by Quetelet's Index, are assigned to any one of the five treatments listed above. Individuals who are not considered to be overweight by this index are assigned either to the control treatment or to one of the two dietary treatments not involving caloric restriction.

The dietary goals stated above are pursued via a series of group counseling sessions in which individuals are shown how to shop, cook, and eat to achieve the desired goals. The counseling process will be maintained over the course of the trial. All participants will be followed for a period of 2 to 3 years for blood pressure changes.

14. International Reflux Study in Children (IRSC)

The IRSC is a randomized, controlled, clinical trial of surgical versus conventional medical treatment of vesicoureteral reflux (VUR) in children under the age of ten at entry. The study involves a multinational set of clinics directed by a steering committee with representatives from Europe and the United States. Data collection in the United States is supervised by a data center based in New York. Data collection in Europe is supervised by a data center based in Essen. The German data center will serve as the analysis center for the combined United States–European data set.

Grade III (European clinics only) and IV reflux patients are being enrolled and followed for evidence of renal scarring and measurement of renal growth. The trial has been under way for 3 years and is scheduled to continue for several more years. No results have been published as of the date in item 33, Table B-4.

Table B-3 Publication list of sketched trials

1. Physicians' Health Study (PHS)

None

2. University Group Diabetes Program (UGDP)

2.1 University Group Diabetes Program: A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. I: Design, methods and baseline characteristics. *Diabetes* 19(suppl 2): 747–783, 1970.

2.2 University Group Diabetes Program: A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II: Mortality results. *Diabetes* 19(suppl 2): 785–830, 1970.

2.3 University Group Diabetes Program: Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. III: Clinical implications of UGDP results. *JAMA* 218:1400–1410, 1971.

2.4 University Group Diabetes Program: Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. IV: A preliminary report on phenformin results. *JAMA* 217:777–784, 1971.

2.5 Prout TE, Knatterud GL, Meinert CL, Klimt CR: The University Group Diabetes Program: The UGDP Controversy: Clinical trials versus clinical impressions. *Diabetes* 21:1035–1040, 1972.

2.6 University Group Diabetes Program: A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. V: Evaluation of phenformin therapy. *Diabetes* 24(suppl 1):65–184, 1975.

2.7 University Group Diabetes Program: A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. VI: Supplementary report on nonfatal events in patients treated with tolbutamide. *Diabetes* 25:1129–1153, 1976.

2.8 University Group Diabetes Program: Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. VII: Mortality and selected nonfatal events with insulin treatment. *JAMA* 240:37–42, 1978.

2.9 Prout T, Knatterud G, Meinert C: The University Group Diabetes Program: Diabetes drugs: Clinical trial (letter). *Science* 204:362–363, 1979.

2.10 University Group Diabetes Program: Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. VIII: Evaluation of insulin therapy: Final report. *Diabetes* 31(suppl 5):1–78, 1982.

3. VA Cooperative Studies Program Number 43 (VA 43)

None

4. Macular Photocoagulation Study (MPS)

4.1 Macular Photocoagulation Study Group: Argon laser photocoagulation for senile macular degeneration. *Arch Ophthalmol* 100:912–918, 1982.

5. National Cooperative Gallstone Study (NCGS)

5.1 Croke G: Recruitment for the National Cooperative Gallstone Study. *Clin Pharmacol and Ther* 25:691–694, 1979.

5.2 Lachin JM, Marks JW, Schoenfield LJ; the NCGS Protocol Committee (Malcolm P. Tyor, Chairman, Peter H. Bennett, Scott M. Grundy, William G. M. Hardison, Lawrence W. Shaw, Johnson L. Thistle, Z. R. Vlahcevic) and the National Cooperative Gallstone Study Group: Design & methodological considerations in the National Cooperative Gallstone Study: A multicenter clinical trial. *Controlled Clin Trials* 2:177–229, 1981.

5.3 Lasser EC, Amberg JR, Baily NA, Varady P, Lachin J, Okun R, Schoenfield L: Validation of a computer-assisted method for estimating the number and volume of gallstones visualized by cholecystography. *Invest Radiol* 16:342–347, 1981.

5.4 Schoenfield LJ, Lachin JM, the Steering Committee (Baum RA, Habig RL, Hanson RF, Hersh T, Hightower NC, Jr., Hofmann AF, Lasser EC, Marks JW, Mekhjian H, Okun R, Schaefer RA, Shaw L, Soloway RD, Thistle JL, Thomas FB, Tyor MP), and the National Cooperative

Table B-3 Publication list of sketched trials (*continued*)

Gallstone Study Group: Chenodial (chenodeoxycholic acid) for dissolution of gallstones: The National Cooperative Gallstone Study. A controlled trial of efficacy and safety. *Ann Intern Med* 95:257–282, 1981.

5.5 Albers JJ, Grundy SM, Cleary PA, Small DM, Lachin JM, Schoenfield LJ, and the National Cooperative Gallstone Study Group: National Cooperative Gallstone Study: The effect of chenodeoxycholic acid on lipoproteins and apolipoproteins. *Gastroenterology* 82:638–646, 1982.

5.6 Fisher RL, Anderson DW, Boyer JL, Ishak K, Klatskin G, Lachin JM, Phillips MJ, and the Steering Committee for the National Cooperative Gallstone Study Group: A prospective morphologic evaluation of hepatic toxicity of chenodeoxycholic acid in patients with cholelithiasis: The National Cooperative Gallstone Study (NCGS). *Hepatology* 2:187–201, 1982.

5.7 Hofmann AF, Grundy SM, Lachin JM, Lan SP, Baum RA, Hanson RF, Hersh T, Hightower NC, Jr., Marks JW, Mekhjian H, Schaefer RA, Soloway RD, Thistle JL, Thomas FB, Tyor MP, and the National Cooperative Gallstone Study Group: Pretreatment biliary lipid composition in white patients with radiolucent gallstones in the National Cooperative Gallstone Study (NCGS). *Gastroenterology* 83:738–752, 1982.

5.8 Habig RL, Thomas P, Lippel K, Anderson D, Lachin J: Central laboratory quality control in the National Cooperative Gallstone Study. *Controlled Clin Trials* 4:101–123, 1983.

5.9 Lachin JM, Schoenfield LJ, and the National Cooperative Gallstone Study Group: Effects of dose relative to body weight in the National Cooperative Gallstone Study: A fixed-dose trial. *Controlled Clin Trials* 4:125–131, 1983.

5.10 Phillips MJ, Fisher RL, Anderson DW, Lan SP, Lachin JM, Boyer JL and the Steering Committee for the National Cooperative Gallstone Study Group. Ultrastructural evidence of intrahepatic cholestasis before and after chenodeoxycholic acid (CDCA) therapy in patients with cholelithiasis: The National Cooperative Gallstone Study (NCGS). *Hepatology* 3:209–220, 1983.

5.11 Schoenfield LJ, Grundy SM, Hofmann AF, Lachin JM, Thistle JL, Tyor MP, for the National Cooperative Gallstone Study: The National Cooperative Gallstone Study viewed by its investigators. *Gastroenterology* 84:644–648, 1983.

6. Coronary Drug Project (CDP)

6.1 Coronary Drug Project Research Group: The Coronary Drug Project: Initial findings leading to modifications of its research protocol. *JAMA* 214:1303–1313, 1970.

6.2 Coronary Drug Project Research Group: The Coronary Drug Project: Findings leading to further modifications of its protocol with respect to dextrothyroxine. *JAMA* 220:996–1008, 1972.

6.3 Coronary Drug Project Research Group: The prognostic importance of the electrocardiogram after myocardial infarction: Experience in the Coronary Drug Project. *Ann Intern Med* 77:677–689, 1972.

6.4 Coronary Drug Project Research Group: The Coronary Drug Project: Design, methods and baseline results. *Circulation* 47(suppl I): I-1—I-50 (plus appendixes), 1973.

6.5 Coronary Drug Project Research Group: The Coronary Drug Project: Findings leading to discontinuation of the 2.5-mg/day estrogen group. *JAMA* 226:652–657, 1973.

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6.8 Coronary Drug Project Research Group: Left ventricular hypertrophy patterns and prognosis: Experience post-infarction in the Coronary Drug Project. *Circulation* 49:862–869, 1974.

6.9 Coronary Drug Project Research Group: The prognostic importance of premature ventricular complexes in the late post-infarction period: Experience in the Coronary Drug Project. *Acta Cardiol* (suppl 18):33–53, 1974.

6.10 Coronary Drug Project Research Group: The Coronary Drug Project. Clofibrate and niacin in coronary heart disease. *JAMA* 231:360–381, 1975.

6.11 Coronary Drug Project Research Group: Reply to letter from D. J. Gans. *JAMA* 234:22–23, 1975.

Table B-3 Publication list of sketched trials (*continued*)

6.12 Coronary Drug Project Research Group: Aspirin in coronary heart disease. *J Chronic Dis* 29:625–642, 1976.

6.13 Coronary Drug Project Research Group: Serum uric acid: Its association with other risk factors and with mortality in coronary heart disease. *J Chronic Dis* 29:557–569, 1976.

6.14 Coronary Drug Project Research Group: The prognostic importance of plasma glucose levels and of the use of oral hypoglycemic drugs after myocardial infarction in men. *Diabetes* 26:453–465, 1977.

6.15 Coronary Drug Project Research Group: Gallbladder disease as a side-effect of drugs influencing lipid metabolism: Experience in the Coronary Drug Project. *N Engl J Med* 296:1185–1190, 1977.

6.16 Coronary Drug Project Research Group: The Coronary Drug Project: Implications for clinical care. *Primary Care* 4:247–253, 1977.

6.17 Coronary Drug Project Research Group: The Coronary Drug Project Aspirin Study: Implications for clinical care. *Primary Care* 5:91–95, 1978.

6.18 Coronary Drug Project Research Group: The natural history of myocardial infarction in the Coronary Drug Project: Long-term prognostic importance of serum lipid level. *Am J Cardiol* 42:489–498, 1978.

6.19 Coronary Drug Project Research Group: Clofibrate and gallbladder disease (letter). *N Engl J Med* 298:461, 1978.

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6.21 Coronary Drug Project Research Group: Reply to editorial by L. Carlson (letter). *Atherosclerosis* 30:239–241, 1978.

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6.24 Coronary Drug Project Research Group: Influence of adherence to treatment and response of cholesterol on mortality in the Coronary Drug Project. *N Engl J Med* 303:1038–1041, 1980.

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6.26 Coronary Drug Project Research Group: Practical aspects of decision making in clinical trials: The Coronary Drug Project as a case study. *Controlled Clin Trials* 1:363–376, 1981.

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7. Aspirin Myocardial Infarction Study (AMIS)

7.1 Aspirin Myocardial Infarction Study Research Group: A randomized, controlled trial of aspirin in persons recovered from myocardial infarction. *JAMA* 243:661–669, 1980.

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7.3 Wasserman AG, Bren GB, Ross AM, Richardson DW, Hutchinson RG, Rios JC: Prognostic implications of diagnostic Q waves after myocardial infarction. *Circulation* 65:1451–1455, 1982.

8. Persantine Aspirin Reinfarction Study (PARIS)

8.1 Persantine Aspirin Reinfarction Study Research Group: Persantine Aspirin Reinfarction Study: Design, methods, and baseline results. *Circulation* 62(suppl II):II-1—II-42, 1980.

Table B-3 Publication list of sketched trials (*continued*)

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9. Hypertension Detection and Follow-Up Program (HDFP)

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Table B-3 Publication list of sketched trials (*continued*)

9.19 Hypertension Detection and Follow-Up Program Cooperative Group: The effect of treatment on mortality in "mild" hypertension—Results of the Hypertension Detection and Follow-Up Program. *N Engl J Med* 307:976-980, 1982.

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10. Multiple Risk Factor Intervention Trial (MRFIT)

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11. Coronary Artery Surgery Study (CASS)

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Table B-3 Publication list of sketched trials (*continued*)

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Table B-3 Publication list of sketched trials (*continued*)

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12. Program on the Surgical Control of Hyperlipidemia (POSCH)

12.1 Buchwald H, Moore RB, Varco RL: Maximum lipid reduction by partial ileal bypass: A test of the lipid-atherosclerosis hypothesis. *Lipids* 12:53-58, 1977.

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12.4 Moore RB, Buchwald H, Varco RL, and the Participants in the Program on the Surgical Control of the Hyperlipidemias: The effect of partial ileal bypass on plasma lipoproteins. *Circulation* 62:469-476, 1980.

12.5 Buchwald H, Fitch L, Moore RB: Overview of randomized clinical trials of lipid intervention for atherosclerotic cardiovascular disease. *Controlled Clin Trials* 3:271-283, 1982.

Table B-3 Publication list of sketched trials (*continued*)

12.6 Buchwald H, Moore RB, Matts JP, Long JM, Varco RL, Campbell GS, Pearce MB, Yellin AE, Blankenhorn CH, Holmes WL, Smink RD Jr, Sawin HS Jr and the participants in the Program on the Surgical Control of the Hyperlipidemias: A status report. *Surgery* 92:654–662, 1982.

12.7 Buchwald H, Moore RB, Rucker RD Jr, Amplatz K, Castaneda WR, Francoz RA, Pasternak RC, Varco RL, and the POSCH Arteriography Review Panel: Clinical angiographic regression of atherosclerosis after partial ileal bypass. *Atherosclerosis* 46:117–128, 1983.

13. Hypertension Prevention Trial (HPT)

None

14. International Reflux Study in Children (IRSC)

14.1 International Reflux Study Committee: Medical versus surgical treatment of primary vesicoureteral reflux: A prospective International Reflux Study in Children. *J Urol* 125:227–283, 1981.

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Table B-4 Summary tabulations from sketches

Item	*Acronym and sketch no.*															*Freq.*
	PHS 1	*UGDP* 2	*VA43* 3	*MPS* 4	*NCGS* 5	*CDP* 6	*AMIS* 7	*PARIS* 8	*HDFP* 9	*MRFIT* 10	*CASS* 11	*POSCH* 12	*HPT* 13	*IRSC* 14	
1. Type of trial															
Therapeutic		✓	✓	✓	✓	✓	✓	✓	✓		✓	✓		✓	11
Prophylactic	✓									✓			✓		3
2. Type of design															
Fixed sample	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	14
3. Stage															
Initial design															0
Protocol development															0
Patient recruitment	✓			✓					✓				✓		3
Treatment and follow-up											✓	✓		✓	3
Patient close-out										✓					0
Termination			✓		✓										3
Post-trial follow-up						✓			✓						2
Completed		✓					✓	✓							3

Table B–4 Summary tabulations from sketches (*continued*)

Item	Acronym and sketch no. PHS 1	UGDP 2	VA43 3	MPS 4	NCGS 5	CDP 6	AMIS 7	PARIS 8	HDFP 9	MRFIT 10	CASS 11	POSCH 12	HPT 13	IRSC 14	Freq.
4. Funding source															
NIH	✓	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	12
VA			✓												1
Industry								✓							1
Private foundation														✓	1
5. Funding type															
Grant	✓	✓		✓		✓		✓				✓	✓	✓	8
Contract					✓		✓		✓	✓	✓				5
Neither			✓*												1
6. Mode of initiation															
Investigator	✓	✓	✓	✓								✓	✓	✓	7
Sponsor							✓	✓	✓	✓	✓				5
Sponsor–investigator					✓	✓									2

Table B–4 Summary tabulations from sketches (*continued*)

Item	Acronym and sketch no. PHS 1	UGDP 2	VA43 3	MPS 4	NCGS 5	CDP 6	AMIS 7	PARIS 8	HDFP 9	MRFIT 10	CASS 11	POSCH 12	HPT 13	IRSC 14	Freq.
7. Mode of fund dispersal															
Direct to individual centers	NA	✓	✓	✓		✓	✓			✓	✓				7
Indirect via a consortium award	NA				✓			✓				✓		✓	4
Direct to some centers indirect to others	NA								✓				✓		2
8. Funding date															
Start	Sept 1981	Sept 1960	Oct 1976	Jan 1979	June 1973	Mar 1965	Oct 1974	April 1974	June 1971	June 1972	May 1973	June 1973	Sept 1981	July 1979	–
End	Dec 1986	April 1982	Oct 1983	Dec 1986	Oct 1983	April 1984	Nov 1979	Sept 1980	June 1985	June 1985	May 1988	Not set	Aug 1986	Not set	–
9. Clinics															
No. in U.S. (incl P.R.)	NA	12	11	12	10	53	30	16	14	22	13	4	4	18	–
No. outside U.S.	NA	0	0	0	0	0	0	4	0	0	1	0	0	8	–
Total no.	NA	12	11	12	10	53	30	20	14	22	14*	4	4	26	–

Table B–4 Summary tabulations from sketches (*continued*)

Item	Acronym and sketch no.														
	PHS 1	*UGDP* 2	*VA43* 3	*MPS* 4	*NCGS* 5	*CDP* 6	*AMIS* 7	*PARIS* 8	*HDFP* 9	*MRFIT* 10	*CASS* 11	*POSCH* 12	*HPT* 13	*IRSC* 14	*Freq.*
10. Resource centers															
Data coord. center	NA	NA	1	NA	1	NA	NA	NA	NA	NA	NA	NA	1	NA	3
Trt. coord. center	NA	NA	1	NA	1	NA	NA	NA	NA	NA	NA	NA	1	NA	3
Coord. center	1	1	NA	1	NA	1	1	1	1	1	1	1	NA	1*	11
Project office	1	1	1	1	1	1	1	0	1	1	1	1	1	1*	13
Central laboratories	1	2	2	0	2	1	1	1	1	1	0	1	1	0	11
Reading centers	0	1	0	1	3	1	1	1	1	2	1	2	1	2*	12
Quality control center	0	0	0	0	0	0	0	1	0	1	0	0	0	0	2
Procurement and distribution center	0	0	1	0	0	1	1	1	1	1	0	0	0	0	6
Total no.	3	4	6	3	8	5	5	5	5	7	3	5	5	4*	14
11. Coord. center or data coord. center															
a. Location															
School of public health									✓	✓	✓		✓		4
School of medicine	✓	✓		✓		✓	✓					✓		✓	7
Other teaching inst.					✓										1
Nonteaching inst.			✓					✓							2

Table B–4 Summary tabulations from sketches (*continued*)

Item	Acronym and sketch no.														
	PHS 1	*UGDP* 2	*VA43* 3	*MPS* 4	*NCGS* 5	*CDP* 6	*AMIS* 7	*PARIS* 8	*HDFP* 9	*MRFIT* 10	*CASS* 11	*POSCH* 12	*HPT* 13	*IRSC* 14	*Freq.*
11. CC or data CC (cont'd)															
b. Primary degree of director	MD (Epi)	PhD (Bio)	PhD (Bio)	MSc (Bio)	ScD (Bio)	PhD (Bio)	PhD (Bio)	MD (Epi)	ScD (Bio)	PhD (Bio)	PhD (Bio)	EdD (Bio)	PhD (Bio)	MD (Med)	11 Bio
c. Affiliation with other study centers															
Yes	NA				✓*			✓*				✓*	✓*	✓*	5
No	NA	✓	✓	✓		✓	✓		✓	✓	✓				8
12. Type of treatment design															
Noncrossover	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	14
13. Type of treatment structure															
Simple		✓	✓	✓	✓	✓	✓		✓	✓	✓	✓		✓	11
Partial factorial								✓					✓		2
Full factorial	✓														1

Table B–4 Summary tabulations from sketches (*continued*)

Item	Acronym and sketch no.														
	PHS 1	*UGDP* 2	*VA43* 3	*MPS* 4	*NCGS* 5	*CDP* 6	*AMIS* 7	*PARIS* 8	*HDFP* 9	*MRFIT* 10	*CASS* 11	*POSCH* 12	*HPT* 13	*IRSC* 14	*Freq.*
14. Study treatments															
No. of test treatments	3	3	1	2	2	5	1	2	1	1	1	1	4	1	–
No. of control treatments	1	2	1	1	1	1	1	1	1	1	1	1	1	1	–
Total no. of study trts.	4	5	2	3	3	6	2	3	2	2	2	2	5	2	–
15. Type of test treatment															
Drug	✓	✓	✓		✓	✓	✓	✓	✓	✓					9
Surgery				✓							✓	✓		✓	4
Behavior change										✓			✓		2
16. Type of control treatment															
Placebo pills	✓	✓	✓		✓	✓	✓	✓							7
Standard med. trt.		✓							✓	✓	✓	✓		✓	6
No treatment				✓						✓			✓		3

Table B–4 Summary tabulations from sketches (*continued*)

Item	Acronym and sketch no.														
	PHS 1	*UGDP* 2	*VA43* 3	*MPS* 4	*NCGS* 5	*CDP* 6	*AMIS* 7	*PARIS* 8	*HDFP* 9	*MRFIT* 10	*CASS* 11	*POSCH* 12	*HPT* 13	*IRSC* 14	*Freq.*
17. Level of trt. masking															
None		✓		✓					✓	✓	✓	✓	✓	✓	8
Single-masked															0
Double-masked	✓	✓	✓		✓	✓	✓	✓							7
18. Patients studied															
Males	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	14
Females		✓		✓	✓		✓	✓	✓		✓	✓	✓	✓	10
Children														✓	1
Adults	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		13
19. Patient recruitment															
a. Primary mode of contact															
Direct	✓	✓	✓		✓	✓	✓	✓	✓	✓			✓		10
Indirect			✓	✓	✓					✓	✓	✓		✓	7

Table B–4 Summary tabulations from sketches (*continued*)

Item	Acronym and sketch no. PHS 1	UGDP 2	VA43 3	MPS 4	NCGS 5	CDP 6	AMIS 7	PARIS 8	HDFP 9	MRFIT 10	CASS 11	POSCH 12	HPT 13	IRSC 14	Freq.
19. Patient recruitment (cont'd)															
b. Start of enrollment	Mid 1982	Feb 1961	Mar 1977	Mar 1979	Sept 1976	Mar 1966	May 1975	April 1975	Feb 1973	Nov 1973	Aug 1975	Sept 1975	Sept 1982	Jan 1980	--
c. End of enrollment	Mid 1983	Feb 1966	May 1980	Not set	June 1978	Oct 1969	Aug 1976	Sept 1976	May 1974	Feb 1976	May 1979	June 1983	Oct 1983	Not set	--
d. Total no. enrolled	17,350	1,027	231	756	916	8,341	4,524	2,026	10,940	12,866	780	838	235	260*	--
20. Method of randomization															
a. Type															
Fixed allocation ratio	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	13
Number adaptive					✓										1
b. Stratification variables															
Clinic	Na	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	13 Yes
Disease state or type	No	No	Yes	Yes	No	Yes	No	No	Yes	No	Yes	Yes	No	Yes	7 Yes
Demographic characteristics	Yes Age	No	No	No	No	No	No	No	No	No	No	No	No	Yes Age,sex	2 Yes
Other	No	No	No	No	No	No	No	No	No	No	No	Yes*	Yes Wt	No	2 Yes
c. Total no. of variables controlled	1	1	2	2	1	2	1	1	2	1	3	4	2	4*	--

Table B–4 Summary tabulations from sketches (*continued*)

Item	Acronym and sketch no. PHS 1	UGDP 2	VA43 3	MPS 4	NCGS 5	CDP 6	AMIS 7	PARIS 8	HDFP 9	MRFIT 10	CASS 11	POSCH 12	HPT 13	IRSC 14	Freq.
20. Randomization (cont'd)															
d. Total no. of allocation strata	7	12	20	36	10	106	30	20	42	22	66	48	8	216*	--
e. Allocation ratio	Uniform	Non-uni	Uniform	Uniform	Uniform	Non-uni	Uniform	Non-uni	Uniform	Uniform	Uniform	Uniform	Uniform	Uniform	11 Uni
f. Blocking in strata															
Yes	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	13
No					✓										1
g. Locus of control															
Central	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	13
Local									✓						1
h. Method of release															
From control center to clinic via phone		✓		✓	✓					✓	✓	✓		✓*	7
From control center to clinic via sealed schedule			✓			✓	✓	✓						✓*	5
From clinic via self-administered schedule									✓						1
From clinic via on-site micro-computer													✓		1
From control center direct to patient	✓														1

Table B–4 Summary tabulations from sketches (*continued*)

Item	Acronym and sketch no. PHS 1	UGDP 2	VA43 3	MPS 4	NCGS 5	CDP 6	AMIS 7	PARIS 8	HDFP 9	MRFIT 10	CASS 11	POSCH 12	HPT 13	IRSC 14	Freq.
21. Data collection schedule															
a. Baseline clinic visits	NA*	2	2	1	2	3	3	2	2	3	1	2	3	1–2	--
b. Regular follow-up clinic visits/year	NA*	4	4	2	3–6*	3	3	3	0–3*	1*	2	1	2	1	--
22. Length of follow–up (yrs.)															
a. During trial	4.5	9.5–14.5	3–6	2+	2	5–8	3–4+	3–4+	5–6.5	6–8	4–8	⩾5	⩾2	Not set	--
b. Post-trial	NA	2	NA	NA	NA	6+	None done	None done	3	2–4	NA	NA	NA	NA	--
23. Primary outcome															
Deaths all causes	√	√				√	√	√	√		√	√			8
Deaths from specified cause			√							√					2
Other				√*	√*								√*	√*	4

Table B–4 Summary tabulations from sketches (*continued*)

Item	Acronym and sketch no. PHS 1	UGDP 2	VA43 3	MPS 4	NCGS 5	CDP 6	AMIS 7	PARIS 8	HDFP 9	MRFIT 10	CASS 11	POSCH 12	HPT 13	IRSC 14	Freq.
24. Method of follow–up close–out															
Common calendar date		√	√			√	√	√	√	√	√	√	√		10
Common period of follow–up					√										1
Not yet specified	√			√										√	3
25. Data entry															
a. Primary entry site															
CC or data CC	√	√	√	√	√	√	√	√	√	√		√		√	12
Clinic											√		√		2
b. Primary mode of entry															
Direct from forms	√	√	√	√	√	√	√	√	√	√	√	√	√	√	14
Indirect from code sheets prepared from forms															0
26. Sample size specification															
a. Original recruitment goal (all trts. combined)	21,500	1,000	456	522*	900	8,379	4,250	2,000	10,500	11,000	1,500	1,000	800	250*	--

Table B–4 Summary tabulations from sketches (*continued*)

Item	PHS 1	UGDP 2	VA43 3	MPS 4	NCGS 5	CDP 6	AMIS 7	PARIS 8	HDFP 9	MRFIT 10	CASS 11	POSCH 12	HPT 13	IRSC 14	Freq.
	Acronym and sketch no.														
26. Sample size (cont'd)															
b. Rationale for original recruitment goal															
Sample size calculation	✓		✓	✓	✓	✓	✓		✓	✓	✓	✓		✓	11
Pragmatic		✓						✓					✓		3
c. Achieved sample size															
All trts. combined	NA	1,027	231	236*	916	8,341	4,524	2,026	10,940	12,866	780	NA	NA	NA	–
d. Published rationale for achieved sample size															
Not applicable	✓		✓								✓	✓	✓	✓	6
None required				✓											1
None stated															0
Power calculation		✓			✓			✓		✓					4
Sample size calculation						✓	✓		✓	✓					4
Pragmatic		✓													1

Table B–4 Summary tabulations from sketches (*continued*)

Item	PHS 1	UGDP 2	VA43 3	MPS 4	NCGS 5	CDP 6	AMIS 7	PARIS 8	HDFP 9	MRFIT 10	CASS 11	POSCH 12	HPT 13	IRSC 14	Freq.
	Acronym and sketch no.														
27. Committees represented															
Steering committee	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	14 Yes
Executive committee	No	Yes	Yes	No	No	No	No	No	No	Yes	Yes	No	Yes	No	5 Yes
Treatment effects monitoring committee	Yes	No	NA	Yes	Yes	Yes	NA	Yes	Yes	NA	NA	Yes	Yes	Yes	9 Yes
Advisory review committee	No	Yes	NA	No	Yes	Yes	NA	Yes	Yes	NA	NA	Yes	Yes	No	7 Yes
Advisory review & treatment effects monitoring comm.	NA	NA	Yes	NA	NA	NA	Yes	NA	NA	Yes	Yes	NA	NA	NA	4 Yes
No. of other committees	2	10	2	1	7	11	8	1	8	8	4	3	3	0	–
Total no. of committees	4	13	5	3	10	14	10	4	11	11	7	6	6	2	–
28. Steering committee															
a. Chairman															
i. Primary degree	MD	MD	MD	MD	MD	MD	MD	MD	MD	MD	MD	MD	MD	MD	14 MD
ii. Patient care responsibilities	No	Yes	No	Yes	No	No	No	No	Yes	No	No	Yes	Yes	Yes	6 Yes
iii. Elected or appointed	Self-appt	E	E	Self-appt	Self-appt	Appt	Appt	Appt	E	Appt	Appt	Self-appt	E	E	5 E
iv. Term of office	WT	WT	WT	WT	WT	WT	WT	WT	WT	WT	WT	WT	WT	WT	14 WT

Table B–4 Summary tabulations from sketches (*continued*)

Item	Acronym and sketch no. PHS 1	UGDP 2	VA43 3	MPS 4	NCGS 5	CDP 6	AMIS 7	PARIS 8	HDFP 9	MRFIT 10	CASS 11	POSCH 12	HPT 13	IRSC 14	Freq.
28. Steering committee (cont'd)															
b. Vice-chairman															
i. Primary degree	MPH	NA	NA	NA	NA	MD	MD	MD	MD	MD	NA	NA	MD	MD	7 MD
ii. Patient care responsibilities	No	NA	NA	NA	NA	Yes	Yes	Yes	No	No	NA	NA	Yes	Yes	6 Yes
iii. Elected or appointed	Appt	NA	NA	NA	NA	Appt	Appt	E	E	Appt	NA	NA	E	E	4 E
iv. Term of office	WT	NA	NA	NA	NA	WT	WT	WT	WT	WT	NA	NA	WT	WT	8 WT
c. Membership															
i. From study centers															
Voting	7	26	14	12	14	14	11	9	19	39	17	6	10	10	–
Nonvoting	4	1	0	0	1	0	7	0	0	0	2	0	2	0	–
Total	11	27	14	12	15	14	18	9	19	39	19	6	12	10	–
ii. From outside study centers															
Voting	5	0	0	1	2	1	0	2	0	0	0	0	0	0	–
Nonvoting	0	0	0	0	0	0	0	1	0	0	0	0	1	0	–
Total	5	0	0	1	2	1	0	3	0	0	0	0	1	0	–

Table B–4 Summary tabulations from sketches (*continued*)

Item	Acronym and sketch no. PHS 1	UGDP 2	VA43 3	MPS 4	NCGS 5	CDP 6	AMIS 7	PARIS 8	HDFP 9	MRFIT 10	CASS 11	POSCH 12	HPT 13	IRSC 14	Freq.
28. Steering committee (cont'd)...															
c. Membership (cont'd)															
iii. Total															
Voting	12	26	14	12	16	15	11	11	19	39	17	6	10	10	–
Nonvoting	4	1	0	1	1	0	7	1	0	0	2	0	3	0	–
Total	16	27	14	13	17	15	18	12	19	39	19	6	13	10	–
d. Positions represented on committee															
i. Study chairman	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	14 Yes
ii. Vice-chairman	Yes	NA	NA	NA	NA	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	8 Yes
iii. CC or data CC director	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	14 Yes
iv. Clinic directors	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes*	Yes	Yes	13 Yes
v. Project officer	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	No	Yes	No	10 Yes
vi. Clinic coordinators	NA	No	No	Yes	No	No	Yes	No	No	Yes	No	Yes	No	No	4 Yes
vii. Nonhealth professional	No	No	No	No	No	No	No	No	No	No	No	No	No	No	0 Yes
viii. Lay representative	No	No	No	No	No	No	No	No	No	No	No	No	No	No	0 Yes

Table B–4 Summary tabulations from sketches (*continued*)

Item	Acronym and sketch no. PHS 1	UGDP 2	VA43 3	MPS 4	NCGS 5	CDP 6	AMIS 7	PARIS 8	HDFP 9	MRFIT 10	CASS 11	POSCH 12	HPT 13	IRSC 14	Freq.
28. Steering committee (cont'd)															
e. No. of members elected	0	0	0	0	0	4,T	5,T	0	0	4,$\overline{WT}$	0	0	0	0	–
29. Treatment effects monitoring committee															
a. Responsible group															
Trt. effects monitoring comm	√			√	√	√		√	√			√	√	√	9
Advisory review & trt. effects monitoring comm			√				√			√*	√				4
Steering committee		√													1
b. Chairman															
i. Primary degree	MD (Epi)	MD (Med)	MD (Med)	PhD (Bio)	MD (Med)	PhD* (Bio)	MD (Med)	MD* (Epi)	MD (Epi)	MD (Med)	MD (Med)	MD (Epi)	PhD (Bio)	PhD (Bio)	10 MD
ii. Patient care responsibilities	No	Yes	No	No	No	No*	No	No*	No	No	No	No	No	No	1 Yes
iii. Elected or appointed	Appt	E	E	Appt	Appt	Appt*	Appt	Appt*	E	Appt	Appt	Appt	E	Appt	10 Appt
iv. Term of office	$\overline{WT}$	$\overline{WT}$	$\overline{WT}$	$\overline{WT}$	$\overline{WT}$	$\overline{WT}$*	$\overline{WT}$	$\overline{WT}$*	$\overline{WT}$	$\overline{WT}$	$\overline{WT}$	$\overline{WT}$	$\overline{WT}$	$\overline{WT}$	14 $\overline{WT}$

Table B–4 Summary tabulations from sketches (*continued*)

Item	Acronym and sketch no. PHS 1	UGDP 2	VA43 3	MPS 4	NCGS 5	CDP 6	AMIS 7	PARIS 8	HDFP 9	MRFIT 10	CASS 11	POSCH 12	HPT 13	IRSC 14	Freq.
29. Treatment effects monitoring committee (cont'd)															
c. Vice-chairman															
Primary degree	NA	NA	NA	NA	NA	MD* (Epi)	NA	MD* (Epi)	NA	NA	NA	NA	NA	NA	2 MD
Patient care responsibilities	NA	NA	NA	NA	NA	No*	NA	No*	NA	NA	NA	NA	NA	NA	2 No
Elected or appointed	NA	NA	NA	NA	NA	Appt*	NA	Appt*	NA	NA	NA	NA	NA	NA	2 Appt
Term of office	NA	NA	NA	NA	NA	$\overline{WT}$*	NA	$\overline{WT}$*	NA	NA	NA	NA	NA	NA	2 $\overline{WT}$
d. Membership															
i. From study centers															
Voting	1	26	0	0	0	11	0	5	5	0	2	0	7	0	–
Nonvoting	1	1	4	6	7	0	1	0	2	2	0	2	0	4	–
Total	2	27	4	6	7	11	1	5	7	2	2	2	7	4	–
ii. From outside study															
Voting	3	0	4	5	5	5	7	3	6	7	11	8	0	4	–
Nonvoting	0	0	0	0	0	0	0	1	0	0	0	1	0	0	–
Total	3	0	4	5	5	5	7	4	6	7	11	9	0	4	–

Table B–4 Summary tabulations from sketches (*continued*)

Item	Acronym and sketch no. PHS 1	UGDP 2	VA43 3	MPS 4	NCGS 5	CDP 6	AMIS 7	PARIS 8	HDFP 9	MRFIT 10	CASS 11	POSCH 12	HPT 13	IRSC 14	Freq.
29. Treatment effects monitoring committee (cont'd)															
d. Membership (cont'd)															
iii. Total															
Voting	4	26	4	5	5	16	7	8	11	7	13	8	7	4	–
Nonvoting	1	1	4	6	7	0	1	1	2	2	0	3	0	4	–
Total	5	27	8	11	12	16	8	9	13	9	13	11	7	8	–
e. Positions represented on committee															
i. Study chairman	No	Yes	Yes	Yes	Yes	Yes	Yes*	Yes	Yes	Yes*	Yes	Yes	Yes	Yes	13 Yes
ii. Vice-chairman	No	NA	NA	NA	NA	Yes	No	No	Yes	Yes*	NA	NA	Yes	Yes	5 Yes
iii. CC or data CC director	No	Yes	Yes	Yes	Yes	Yes	Yes*	Yes	Yes	Yes*	Yes	Yes	Yes	Yes	13 Yes
iv. Clinic directors	NA	Yes	No	Yes*	No	Yes*	No	No	Yes	No	No	No	Yes	Yes	6 Yes
v. Project officer	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes*	Yes	Yes	Yes	13 Yes
vi. Clinic coordinator	NA	No	No	No	No	No	No	No	No	No	No	No	No	No	0 Yes
vii. Nonhealth professional	No	No	No	Yes	No	No	No	No	No	No	Yes	No	No	No	2 Yes
viii. Lay representative	No	No	No	NA	No	No	No	No	Yes	No	No	No	No	No	1 Yes

Table B–4 Summary tabulations from sketches (*continued*)

Item	Acronym and Sketch no. PHS 1	UGDP 2	VA43 3	MPS 4	NCGS 5	CDP 6	AMIS 7	PARIS 8	HDFP 9	MRFIT 10	CASS 11	POSCH 12	HPT 13	IRSC 14	Freq.
29. Treatment effects monitoring committee (cont'd)															
f. No. of members elected	0	0	0	0	0	0	0	0	0	0	0	0	0	0	–
g. Meetings per year	2	2	2	2	2	2	2	2	2	2	2	3	2	2	–
30. Type of communications model															
Sponsor directive							√		√	√	√				4
Sponsor nondirective	√	√	√	√	√	√		√				√	√	√	10
31. Study publications															
a. No. of publications	0	10	0	1	11	29	3	2	24	10	31	7	0	2	130
b. Method of authorship															
Papers with corporate format alone	0	8	0	1	0	29	1	2	6	2	0	0	0	2	51
Papers with conventional format alone	0	2	0	0	3	0	1	0	8	8	29	3	0	0	55
Papers with both formats	0	0	0	0	8	0	1	0	10	0	2	4	0	0	24

Table B-4 Summary tabulations from sketches (*continued*)

Item	Acronym and sketch no.														
	PHS 1	*UGDP* 2	*VA43* 3	*MPS* 4	*NCGS* 5	*CDP* 6	*AMIS* 7	*PARIS* 8	*HDFP* 9	*MRFIT* 10	*CASS* 11	*POSCH* 12	*HPT* 13	*IRSC* 14	*Freq.*
32. *Author participation in trial*															
None	√						√	√		√					4
Member of CC		√				√							√		3
Member of trt. monitoring or advisory review committee			√	√	√				√		√	√		√	7
33. *Date sketch completed*	Mar 1983	April 1983	April 1983	May 1983	Mar 1983	April 1983	Mar 1983	Mar 1983	May 1983	May 1983	Mar 1983	May 1983	Mar 1983	Mar 1983	–

Notes for Table B-4

Item 5
- (VA 43) Technically, VA Cooperative studies are part of the VA intramural research program.

Item 9
- (CASS) Fourteen clinics participated in the registry component of the study. However, only 10 of the clinics randomized patients.

Item 10
- (IRSC) The structure involves separate data centers for the United States and European portions of the study. The two centers feed results to the study coordinating center located in Germany. The project office noted is for the United States portion of the study. The European portion has no corresponding office. The two reading centers are for X-ray determination of reflux grade and renal scarring. One center reads films generated by U.S. clinics and the other center reads films generated by the European clinics.

Item 11.c
- (NCGS) The data coordinating center receives its funding via a consortium award to the institution housing the study chairman.
- (PARIS) Coordinating center also responsible for dispersing funding to participating clinics.
- (POSCH) Coordinating center receives its funding via consortium award to the chairman of the study (also director of the Minnesota clinic).
- (HPT) Data coordinating center funds the central laboratory and food coding center of the HPT.
- (IRSC) Institution housing the coordinating center also houses a clinic in the study.

Item 19.d
- (IRSC) Grade IV reflux patients.

Item 20.b
- (POSCH) Cholesterol level and plasma lipoprotein type was used for stratification, in addition to clinic and level of coronary vessel disease.

Item 20.c and 20.d
- (IRSC) The two halves of the study used different stratification procedures. The number recorded is for the U.S. portion of the study. It used clinic (18), age (3 levels), sex, and renal scarring (2 levels), creating a potential for 216 allocation strata.

Item 20.h
- (IRSC) Method of release via phone for U.S. portion and via sealed envelope for European portion.

Item 21.a and 21.b
- (PHS) No clinic visits required (see abstract summary in Table B-2).

Item 21.b
- (NCGS) Visits at 1, 2, and 3 months after randomization for dosage adjustment and data collection and at 6, 9, 12, 16, 20, and 24 months after randomization for regular follow-up visits.
- (HDFP) Stepped care patients seen at least once every four months. Referred care patients seen at the end of 1, 2, 4, and 5 years of follow-up.
- (MRFIT) Participants assigned to special intervention visited the clinic on a regular basis for administration of the required interventions. All participants seen once per year for outcome assessment.

Item 23
- (MPS) Vision change using a standard visual acuity test.
- (NCGS) Gallstone dissolution.

- (HPT) Blood pressure change.
- (IRSC) Renal growth and scarring.

Item 26.a

- (MPS) Stated recruitment goals: 522 in SMD argon trial, 736 in HISTO argon trial, and 212 in SMD krypton trial. No goal set for INVM in the argon trial or for INVM or HISTO in the krypton trial.
- (IRSC) Goal for reflux grade IV patients. No goal set for grade III.

Item 26.c

- (MPS) The only trial with published results at the time the sketch was completed.

Item 28.d.iv

- (POSCH) The chairman of the study is the only clinic director represented.

Item 29.a

- (MRFIT) Originally the study had separate advisory-review and treatment effects monitoring committees. The latter committee was disbanded in 1977. Its functions were assumed by the advisory-review committee at that time.

Item 29.b and 29.c

- (CDP) The treatment effects monitoring committee was headed by co-chairmen. See items 29.b and 29.c for information on the two individuals.
- (PARIS) The treatment effects monitoring committee was headed by co-chairmen. See items 29.b and 29.c for information on the two individuals.

Item 29.e

- (MPS) The clinic director represented on the committee was also chairman of the study.
- (CDP) The only clinic director represented on the committee was also the vice-chairman of the study.
- (AMIS) The study chairman and director of the coordinating center attended meetings of the committee, but were not official members of the committee.
- (MRFIT) The chairman and vice-chairman of the study and the director of the coordinating center were present at meetings of the committee, but were not official members of the committee.
- (CASS) The project officer was present at meetings of the committee, but was not an official member of the committee.

Table B-5 Sample sketch for the UGDP

1. **General**
   a. *Official name:* University Group Diabetes Program
   b. *Official acronym:* UGDP
   c. *Sketch number:* 2
   d. *Type of trial:* Therapeutic
   e. *Type of design:* Fixed sample size design
   f. *Stage:* Completed
2. **Funding**
   a. *Source:* Public: National Institute of Arthritis, Metabolism and Digestive Diseases (now the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases), Bethesda, Maryland
   b. *Type:* Grant
   c. *Mode of initiation:* Investigator-initiated
   d. *Mode of fund dispersal to centers:* Direct
   e. *Start of funding:* September 1960
   f. *End of funding:* April 1982
3. **Clinics: 12 (including one in Puerto Rico)**
4. **Resource centers**
   a. *Types of centers represented*
      - Coordinating center
      - Reading center
      - Central laboratories (2)
   b. *Coordinating center*
      - *Study name:* Coordinating Center (Baltimore)
      - *Director:* Genell Knatterud, Ph.D. (Christian R. Klimt, M.D., Dr. P.H., through 1977)
      - *Affiliations with other centers:* None
      - *Address:* University of Maryland, School of Medicine, Baltimore, Maryland
   c. *Reading center*
      - *Study name:* ECG Reading Center
      - *Director:* Henry Blackburn, M.D. (Cardiology)
      - *Affiliations with other centers:* Lipid Laboratory and ECG Reading Center both under the direction of Henry Blackburn. There was a clinic at Minnesota as well, but it was organizationally and administratively independent of these two resource centers.
      - *Address:* University of Minnesota, School of Public Health, Minneapolis, Minnesota
   d. *Central Laboratory*
      - *Study name:* Lipid Laboratory (Minnesota)
      - *Director:* Henry Blackburn, M.D. (Cardiology)
      - *Affiliations with other centers:* Lipid Laboratory and ECG Reading Center both under the direction of Henry Blackburn. There was a clinic at Minnesota as well, but it was organizationally and administratively independent of the two resource centers.
      - *Address:* University of Minnesota, School of Public Health, Minneapolis, Minnesota
   e. *Central laboratory*
      - *Study name:* Lipid Laboratory (Morgantown)
      - *Director:* Margaret J. Albrink, M.D. (Medicine)
      - *Affiliations with other centers:* None
      - *Address:* West Virginia University Medical Center, Morgantown, West Virginia
5. **Project office**
      - *Study name:* Liaison Office
      - *Project Officer:* Keatha K. Krueger, Ph.D.

Table B-5 Sample sketch for the UGDP (*continued*)

- *Affiliations with other centers:* None
- *Address:* National Institute of Arthritis, Metabolism, and Digestive Diseases (now the National Institute of Arthritis, Diabetes, Digestive, and Kidney Diseases), Bethesda, Maryland

6. Treatments

a. *Type of treatment design:* Noncrossover

b. *Type of treatment structure:* Simple

c. *Test treatments*

i. Number: 3

ii. Mode of intervention: Drug

iii. Treatment description: See abstract summary

d. *Control treatments*

i. Number: 2

ii. Type of treatment administered: Placebo pills or capsules, or standard dose of insulin via injections

iii. Treatment description: See abstract summary

e. *Level of masking:* Oral hypoglycemic agents administered double-masked. Two insulin treatments administered in unmasked fashion.

7. Patient characteristics

a. *Eligibility criteria:* Adult-onset diabetes diagnosed within 12 months prior to enrollment.

b. *Demographic characteristics:* 20–79 years of age at entry. Mean age: 52.7, 71% female, 54% white.

8. Patient recruitment

a. *Mode of initial patient contact:* Direct from primary care clinics

b. *Start of patient enrollment:* February 1961

c. *End of patient enrollment:* February 1966

d. *Total number of patients randomized:* 1,027

9. Method of randomization

a. *Type:* Fixed allocation ratio

b. *Stratification variable:* Clinic

c. *Total number of allocation strata:* 12 (1 per clinic)

d. *Allocation ratio:* 1:0:1:1:1 for TOLB, PHEN, ISTD, IVAR, and PLBO, respectively, for 6 clinics not administering phenformin and for first 32 patients in the Boston clinic. Ratio of 1:3:1:1:1 was used in the 5 clinics using phenformin and after enrollment of the 32nd patient in the Boston clinic.

d. *Blocking constraints:* After every 16th allocation for the 1:0:1:1:1:1 allocation ratio and after every 14th allocation for the 1:3:1:1:1 allocation ratio.

f. *Locus of control:* Central

g. *Method of release:* Coordinating center, usually via telephone. By letter if time permitted.

10. Data collection schedule

a. *Baseline:* 2 examinations about 1 month apart

b. *Follow-up:* Examinations at 3-month intervals after enrollment

c. *Post-trial follow-up:* Some by individual clinics (see reference citation 2.10, Table B-3, for details)

11. Length of patient follow-up

a. *During the trial:* Minimum: 9.5 years. Maximum: 14.5 years.

b. *Post-trial:* 2 years. See comment for item 10.c.

12. Outcome

a. *Primary:* Death

b. *Secondary:* Nonfatal vascular complications, especially those affecting the eyes, heart, kidney, or peripheral vascular system.

13. Treatment effects monitoring

a. *Frequency:* Twice a year in conjunction with semiannual investigator meetings.

Table B-5 Sample sketch for the UGDP (*continued*)

b. *Approach:* Data reports prepared by the coordinating center; reviewed by investigative group.

14. Method of close-out:

Common close-out date. Close-out examinations performed over a 3-month period, with separation completed by August 1975.

15. Data entry

a. *Site of entry:* At the coordinating center

b. *Primary mode of entry:* Direct from the data forms

16. Sample size specification

a. *Original recruitment goal:* 200 per treatment group

b. *Rationale for the original recruitment goal:* Pragmatic

c. *Achieved sample size:* 200+ per treatment group. Total of 1,027 patients assigned to the 5 treatment groups.

d. *Published rationale for achieved sample size:* Power argument as stated in reference citation 2.10, Table B-3.

17. Organizational structure

a. *Committees*

i. *Key committees*

- Steering Committee
- Executive Committee
- Advisory-Review Committee

ii. *Standing subcommittees of the Steering Committee*

- Analysis Coordination Committee
- Eye Committee
- Heart Committee
- Kidney Committee
- Medical Technology and Quality Control Committee
- Mortality Committee
- Peripheral Vascular and Neurological Committee
- Statistical Committee
- Clinic Review Committee
- Editorial Review Committee

b. *Steering Committee*

- *Name:* Investigative Group
- *Chairman:* Max Miller, M.D., Case-Western Reserve University, Cleveland, Ohio
- *Affiliations with other centers:* Director of one of the clinics in the trial.
- *Number of members:* 26
- *Membership representation:* 2 voting members from each of the 12 clinics and the coordinating center.

c. *Executive Committee*

- *Name:* Executive Committee
- *Chairman:* Max Miller, M.D., Case-Western Reserve University, Cleveland, Ohio
- *Affiliations with other centers:* Director of one of the clinics in the trial.
- *Number of members:* 9
- *Membership representation:* Study chairman, director of the coordinating center, plus 2 other coordinating center representatives, plus 3 elected members from the study clinics (3-year terms), the project officer, and the chairman of the advisory-review committee.

d. *Advisory-Review Committee*

- *Name:* Advisory-Review Board (appointed in 1971)
- *Chairman:* Thomas Chalmers, M.D., Mount Sinai School of Medicine, New York, New York
- *Affiliations with other centers:* None
- *Number of members:* 9
- *Membership representation:* Members appointed by the National Institute of Arthritis, Metabolism, and Digestive Diseases without term. Members included study chairman and director of the coordinating center. No other member had any affiliation with the trial.

Table B-5 Sample sketch for the UGDP (*continued*)

18. Study publications

a. *Number of papers published:* 10 (See Table B-3)

b. *General method of authorship:* Corporate, with writing committee indicated.

19. Information sources used for completion of sketch

- Published papers
- UGDP manual of operations

20. Author's involvement in trial

- Deputy director of coordinating center from start of study to mid-1979

21. Person reviewing sketch

- *Name:* Genell L. Knatterud, Ph.D.
- *Position in study:* Director of Coordinating Center

22. Date sketch completed

April 12, 1983

Table B-6 Data coordinating centers for multicenter trials referenced in this book

Study name and acronym	*Data coordinating center director*	*Address*
1. Anturane Reinfarction Trial (ART)	Sidney H. Kane, M.D.	Ciba-Geigy Corporation Pharmaceutical Division Summit, New Jersey 07901
2. Aspirin Myocardial Infarction Study (AMIS)	William F. Krol, Ph.D.	Maryland Medical Research Institute 600 Wyndhurst Avenue Baltimore, Maryland 21210
3. Beta Blocker Heart Attack Trial (BHAT)	C. Morton Hawkins, Sc.D.	School of Public Health University of Texas 1100 Holcombe Blvd. Houston, Texas 77025
4. Coronary Artery Surgery Study (CASS)	Lloyd D. Fisher, Ph.D.	School of Public Health University of Washington 1107 NE 45th Street Seattle, Washington 98105
5. Coronary Drug Project (CDP)	Paul L. Canner, Ph.D.	School of Medicine University of Maryland 600 Wyndhurst Avenue Baltimore, Maryland 21210
6. Diabetes Control and Complications Trial (DCCT)	John M. Lachin, Sc.D.	Department of Statistics The George Washington University 7979 Old Georgetown Road Bethesda, Maryland 20814
7. Diabetic Retinopathy Study (DRS)	Genell L. Knatterud, Ph.D.	School of Medicine University of Maryland 600 Wyndhurst Avenue Baltimore, Maryland 21210
8. Early Treatment of Diabetic Retinopathy Study (ETDRS)	Genell L. Knatterud, Ph.D.	School of Medicine University of Maryland 600 Wyndhurst Avenue Baltimore, Maryland 21210
9. Eastern Cooperative Oncology Group (ECOG)	Marvin Zelen, Ph.D.	School of Public Health Harvard University 44 Binney Street Boston, Massachusetts 02115
10. Hypertension Detection and Follow-Up Program (HDFP)	C. Morton Hawkins, Sc.D.	School of Public Health University of Texas 1100 Holcombe Blvd. Houston, Texas 77025
11. Hypertension Prevention Trial (HPT)	Curtis L. Meinert, Ph.D.	School of Hygiene and Public Health The Johns Hopkins University 615 North Wolfe Street Baltimore, Maryland 21205
12. International Mexilitene Placebo Antiarrhythmic Coronary Trial (IMPACT)	Jean-Pierre Boissel, M.D.	Dept. Unite de Pharmacologie Clinique Hopital Cardiologique B.P. Lyon Montchat 69394 Lyon Cedex 3 France
	Christian R. Klimt, M.D.	Maryland Medical Research Institute 600 Wyndhurst Avenue Baltimore, Maryland 21210

Table B-6 Data coordinating centers for multicenter trials referenced in this book (*continued*)

Study name and acronym	*Data coordinating center director*	*Address*
13. International Reflux Study in Children (IRSC)	Tytti Tamminen, M.D.	University Children's Hospital Hufelandstrabe 55 Essen, West Germany D-4300
	Robert Weiss, M.D.	Albert Einstein College of Medicine 1825 Eastchester Road New York, New York 10461
14. Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT)	O. Dale Williams, Ph.D.	School of Public Health University of North Carolina Chapel Hill, North Carolina 27514
15. Macular Photocoagulation Study (MPS)	Barbara S. Hawkins, M.Sc.	The Wilmer Ophthalmology Institute The Johns Hopkins University 550 North Broadway Baltimore, Maryland 21205
16. Multicenter Investigation for Limiting Infarction Size (MILIS)	W. Kenneth Poole, Ph.D.	Research Triangle Institute Research Triangle Park, North Carolina 27709
17. Multiple Risk Factor Intervention Trial (MRFIT)	Marcus O. Kjelsberg, Ph.D.	School of Public Health University of Minnesota Minneapolis, Minnesota 55455
18. National Cooperative Dialysis Study (NCDS)	Edmund G. Lowrie, M.D.	School of Public Health Harvard University 721 Huntington Avenue Boston, Massachusetts 02115
19. National Cooperative Gallstone Study (NCGS)	John M. Lachin, Sc.D.	Department of Statistics The George Washington University 7979 Old Georgetown Road Bethesda, Maryland 20814
20. Persantine Aspirin Reinfarction Study (PARIS)	Christian R. Klimt, M.D., Dr. P.H.	Maryland Medical Research Institute 600 Wyndhurst Avenue Baltimore, Md 21210
21. Physicians' Health Study (PHS)	Charles Hennekins, M.D.	Department of Medicine Harvard Medical School 55 Pond Avenue Boston, Massachusetts 02146
22. Program on the Surgical Control of Hyperlipidemia (POSCH)	John M. Long, Ed.D.	School of Medicine University of Minnesota Minneapolis, Minnesota 55455
23. University Group Diabetes Program (UGDP)	Genell L. Knatterud, Ph.D.	School of Medicine University of Maryland 600 Wyndhurst Avenue Baltimore, Maryland 21210
24. Veterans Administration Cooperative Studies Program No. 43 (VA 43)	Stephen F. Bingham, Ph.D.	Veterans Administration Medical Center Perry Point, Maryland 20801

C. Year 1980 clinical trial publications[1]

C.1 PAPERS REVIEWED (113)

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19. Cross FS, Long MW, Banner AS, Snider DE, Jr: Rifampin-isoniazid therapy of alcoholic and nonalcoholic tuberculosis patients in a U.S. Public Health Service cooperative therapy trial. *Am Rev Respir Dis* 122:349–353, 1980.

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D. Activities by stage of trial

This appendix lists the activities and functions required for each stage of a trial. The stages are (see Chapter 3):

I. Initial design stage
II. Protocol development stage
III. Patient recruitment stage
IV. Treatment and follow-up stage
V. Patient close-out stage
VI. Termination stage
VII. Post-trial follow-up stage (optional)

The time at which certain activities are started will vary from trial to trial. This should be recognized if this outline is used as a management tool in planning activities for a specific trial. Activities listed in one stage in this schedule may not begin until the following stage in an actual trial.

I. INITIAL DESIGN STAGE

A. Design specifications

Specify the initial design features concerning:

1. Purpose and rationale of trial
2. Number and type of test treatments
3. Number and type of control treatments
4. Level and method of masking
5. Primary and secondary outcomes
6. Type and frequency of observations
7. Required number of patients based on a sample size calculation for a specified outcome, type I and II error, length of follow-up, and projected treatment differences to be detected
8. Estimate of number of clinical centers required based on the sample size calculation
9. Number and type of other centers, e.g., coordinating center(s), central laboratory, and reading center(s)
10. Patient eligibility and exclusion criteria
11. Population(s) from which patients are to be selected
12. Stratification varibles to be used in randomization
13. Patient safeguard procedures
14. Projected timetable for the trial
15. Approach to patient close-out, i.e., fixed closing date versus fixed follow-up interval

B. Organizational structure

1. Develop general guidelines concerning:
   a. Desired qualities of the study chairman and members of the steering, advisory-review, and treatment effects monitoring committees
   b. Terms of office of study chairman and members of key committees
   c. Method of selection of study chairman and members of key committees
   d. Voting rules for key committees
2. Outline responsibilities of the steering, advisory-review, and treatment effects monitoring committees
3. Establish key elements of overall organizational structure of the trial
4. Outline meeting schedule for key committees
5. Specify functions/duties of the coordinating center(s)
6. Outline general plans for paper writing and authorship procedures

C. Patient recruitment, treatment, and data collection procedures

1. Develop methods for patient recruitment and procedures for randomization

2. Outline data collection procedures
3. Develop a timetable for testing and finalization of data collection forms
4. Determine specifications for drugs to be evaluated, including methods for bottling, labeling, and distributing drugs (if a drug trial)
5. Outline main elements of the treatment protocol

D. Data processing and analysis

1. Outline data processing and database management procedures
2. Develop a timetable for implementation of database management procedures
3. Outline general data analysis plans
4. Outline plans for quality control of data collection and processing activities

E. Other activities

1. Perform literature review to identify pertinent background information on the study treatment, including review of safety and efficacy data
2. Prepare and submit funding proposal
3. Submit research plan and draft consent statement to local institutional review boards (IRBs) for preliminary approvals

II. PROTOCOL DEVELOPMENT STAGE

A. Patient recruitment and care

1. Identify source of patients
2. Write treatment protocol
3. Determine recruitment goals for individual clinics
4. Develop detailed patient eligibility and exclusion criteria
5. Establish permissible time windows for prerandomization and follow-up examinations
6. Establish protocol for management of clinical conditions known or suspected to be related to the disease or therapy under study
7. Establish procedures for monitoring the clinical management of individual patients
8. Develop patient information and consent procedures
9. Generate the treatment allocation schedule and write description of the methods used to generate the schedule
10. Develop publicity schemes needed to facilitate patient recruitment

B. Data processing and analysis

1. Develop procedures for data interface between clinics and the data center
2. Specify contents of data collection forms
3. Draft and test data collection forms
4. Submit forms to appropriate study body for review and approval
5. Develop data management systems, including data collection, processing, editing, and correction procedures
6. Initiate development of data system and test computer programs required for:
   a. Verifying patient eligibility
   b. Issuing treatment allocations
   c. Keying, inventorying, editing, and updating study data
7. Write study handbook and manual of operations. Include sections on:
   a. Informed consent procedures and methods for safeguarding patient rights
   b. Recruitment and randomization procedures
   c. Patient follow-up procedures
   d. Procedures for data collection and processing
   e. Study organizational structure
8. Outline procedures for monitoring the randomization process
9. Review data storage, backup, and security procedures

C. Training and communication

1. Develop and implement training and certification procedures for key study staff, especially staff at the clinical centers responsible for data collection
2. Acquaint staff of all participating centers with the following:
   a. Design and methods of the trial
   b. Importance of integrity in data collection
   c. Need for data security
   d. Study organization
   e. Performance and treatment monitoring procedures to be employed
3. Initiate regularly scheduled meetings of:
   a. Study investigative group
   b. Steering committee
   c. Other study committees
4. Consider distribution of newsletters at periodic intervals to inform staff of participating centers of study progress and procedural changes
5. Develop study address directory and procedures for maintaining same
6. Outline communication channels and ground rules for center-to-center communication
7. Identify center(s) responsible for coordinating study communications
8. Develop and initiate clinic site visiting procedures in order to:
   a. Identify and correct problems in patient recruitment
   b. Review administration of study procedures
   c. Identify and correct possible deficiencies in data collection methods
9. Develop procedures for dealing with requests for study information originating outside the study

D. Quality assurance

1. Develop procedures for monitoring and reviewing performance of participating centers in the trial
2. Outline content of performance monitoring reports concerning data collection and data quality
3. Mock up data tables needed for performance monitoring
4. Develop documentation procedures for:
   a. Treatment allocation
   b. Reporting primary and secondary outcomes
   c. Classification of primary outcome
   d. Modification of data collection instruments and procedures
   e. Data management and forms revision
   f. Informed consent
   g. Modifications of study handbooks and manuals of operations
5. Specify mechanisms for monitoring adequacy of documentation

E. Treatment monitoring

1. Outline content of treatment effects monitoring reports
2. Establish timetable for treatment monitoring and generation of treatment monitoring reports

F. Authorship

1. Establish authorship policies for study papers and for ancillary studies
2. Establish review procedures for study papers
3. Establish methods for review and approval of presentations made by members of the investigative group on behalf of the study

G. Management

1. Outline study policy concerning:
   a. Informed consent, including minimum standards for the

consent process and mechanisms to be used to monitor clinics for adherence to those standards
b. Responsibilities for patient care
c. Data security, including specification of mechanisms to be used to protect computer data files against loss or destruction
d. Access to study data by investigators in the study; by people outside the study
e. Rights of patients to privacy and confidentiality
f. Collection and storage of study records
g. Review and approval of ancillary studies performed by study investigators
h. Communications with persons outside the study, including the news media, regarding study design and results
i. National and local publicity
j. Dissemination of study results to study patients; to study staff
k. Acquisition of liability insurance for participating centers and investigators
l. Nature and extent of follow-up of dropouts

2. Develop guidelines and procedures required to:
   a. Decide when to terminate a treatment because of adverse or beneficial effects
   b. Modify the general design specifications of the trial
3. Create treatment effects monitoring committee or some other body to monitor for treatment effects
4. Establish system for making work priority assignments for the data center and other resource centers in the trial
5. Designate the group responsible for dissemination of study information and results to the lay and scientific communities
6. Develop safeguards to protect against premature disclosure of study results to parties outside the study

H. Other activities

1. Develop projected budget and staffing requirements for the trial
2. Order study drugs and initiate packaging, labeling, and distribution procedures (if a drug trial)
3. Recruit staff at participating centers
4. Develop informational brochures, official study name, logo, etc.
5. Obtain Investigational New Drug Application (INDA) if required by the Food and Drug Administration (FDA)
6. Negotiate specialized contracts or agreements, such as study liability insurance, equipment contracts, etc.
7. Designate official repository for study documents, i.e., minutes of meetings, performance and treatment effects monitoring reports, completed data collection forms, etc.
8. Print and distribute essential materials, such as recruitment materials, forms, study handbooks and other manuals
9. Create necessary committees, beginning with the steering committee
10. Review and refine general design specifications
11. Evaluate preparedness of all centers to initiate patient recruitment and follow-up

III. PATIENT RECRUITMENT STAGE

A. Treatment and patient care

1. Establish liaison with appropriate medical and lay societies to facilitate patient recruitment
2. Establish channels for patient referral
3. Initiate local and national publicity campaigns for patient recruitment when appropriate
4. Inform local referring physicians of aims of study and of limits of study responsibility regarding patient care
5. Provide clinical centers with patient information brochures
6. Review progress in patient recruitment
7. Project time requirements for completion of patient recruitment based on recruitment performance
8. Establish date for termination of patient recruitment and inform patient referral sources of date

B. Data processing and analysis

1. Implement procedures for monitoring the treatment allocation process
2. Initiate and maintain procedures for collecting and processing study data and related materials (e.g., ECGs and fundus photographs)
3. Verify that incoming baseline data forms document patient eligibility for the trial
4. Initiate data editing procedures to provide checks for accuracy and consistency within and across forms
5. Establish and maintain monitoring procedures to identify deficiencies in data collection and data processing
6. Establish procedures to be followed in maintaining adherence to the examination schedule
7. Define responsibilities of clinical centers and of data center for locating patients lost to follow-up
8. Define responsibility of clinical centers in maintaining contact with dropouts
9. Review data storage, backup, security, and integrity procedures in all participating centers

10. Identify topics for analysis and methods to be used for analysis
11. Outline quality control procedures for data analyses
12. Complete final editing of recruitment and entry data

C. Training and communication

1. Maintain training and certification procedures for staff of participating centers
2. Continue site visits to participating centers
3. Initiate regular meetings of the treatment effects monitoring committee
4. Continue to hold regularly scheduled meetings of:
   a. Study investigative group
   b. Steering committee
   c. Other study committees
5. Initiate, if appropriate, preparation of a newsletter to inform staff of study progress and procedural changes
6. Consider central preparation and local distribution of newsletter for study patients
7. Update and distribute study address directory at periodic intervals

D. Quality assurance

1. Initiate external monitoring and review procedures for all centers in the trial, e.g., clinical centers, data center, central laboratory, reading centers, etc.
2. Review adequacy of the randomization procedure
3. Prepare periodic reports summarizing performance of clinical centers with regard to patient recruitment
4. Prepare reports summarizing:
   a. Adherence to study protocol
   b. Adherence to data collection and patient examination schedule
   c. Data quality

d. Data collection activities at clinical centers
e. Data processing activities at the data center
f. Activities at other resource centers

5. Review documentation standards and monitor adequacy of documentation for:
a. Treatment allocation procedures
b. Reporting of major events
c. Classification of cause of death or other major events
d. Informed consent procedures
e. Modification of data collection forms
f. Modification of study protocol
g. Data management and data analysis procedures

E. Treatment monitoring

1. Develop analytic techniques and computer programs needed to monitor study data for evidence of adverse or beneficial treatment effects
2. Begin generating treatment monitoring reports

F. Authorship and publications

1. Establish paper writing teams and schedules
2. Review and, if necessary, revise guidelines for authorship
3. Write paper(s) on design and methods of the study
4. Establish procedures for distribution of published papers to the study group
5. Distribute at periodic intervals updated listings of study publications and presentations to all participating investigators

G. Management

1. Review and, if necessary, revise:
a. Informed consent procedures
b. Guidelines on patient care
c. Guidelines on study publicity
d. Guidelines on data access, security, backup, and storage
2. Continue to review and assign priorities to activities carried out by the data center and other key resource centers in the trial
3. Initiate periodic review of study committee structure; dissolve nonfunctional committees
4. Develop patient close-out strategy

H. Other activities

1. Print and distribute data collection forms and related materials needed for follow-up examinations
2. Initiate reporting procedures with FDA (if trial involves INDA)
3. Establish a central resource of data slides on study design and findings for use by study investigators in making presentations concerning the trial
4. Implement procedures for documenting important events in the trial that may effect data quality

IV. TREATMENT AND FOLLOW-UP STAGE

A. Treatment and patient care

1. Monitor and report adverse treatment effects
2. Review procedures for monitoring and evaluating the clinical management of individual patients

B. Data processing and analysis

1. Continue procedures for maintaining adherence to follow-up visit schedule, including special procedures for patients classifed as inactive or lost to follow-up
2. Review and expand data edit procedures to provide checks for consistency within and across forms, including forms used for prerandomization visits
3. Review and expand, if necessary, monitoring procedures to identify deficiencies in data collection and processing
4. Initiate central coding procedures, if required, for cause of death or other primary outcome variables
5. Revise data collection forms as necessary
6. Reproduce and distribute data collection forms as needed
7. Develop and test data collection forms and data management systems required for patient close-out stage
8. Prepare to process data collected at close-out visit(s)
9. Revise data management procedures as appropriate
10. Monitor patient adherence to assigned treatment

C. Training and communications

1. Continue site visits to participating centers to:
a. Review administration of study procedures
b. Identify and correct the problems in data collection and processing
2. Continue to hold regularly scheduled meetings of:
a. Study investigative group
b. Steering committee
c. Treatment effects monitoring committee
d. Other study committees
3. Continue to publish newsletter (if initiated):
a. To inform study investigators of study progress and procedural changes
b. To inform study patients of study progress
4. Continue (modify if necessary) certification procedures for staff of participating centers
5. Update and distribute revised study handbooks and manuals of operations
6. Continue to update and distribute study address directory, mailing labels, forms (when necessary), etc.
7. Communicate with personnel of all participating centers concerning timetable and procedures for close-out stage, especially in the use of new data collection forms or techniques

D. Quality assurance

1. Review and revise study quality assurance procedures as appropriate
2. Continue to prepare monitoring reports summarizing:
a. Adherence to study protocol
b. Adherence to data collection and examination schedule
c. Quality of data generated
d. Data collection activities at clinical centers
e. Data processing activities at the data center
3. Continue periodic review of adequacy of documentation for:
a. Reporting of primary and secondary outcomes
b. Classification of causes of death or other major outcomes
c. Modification of data collection forms
d. Modification of study protocol
e. Ongoing data management procedures

E. Treatment monitoring

1. Revise data analysis and reporting procedures required to monitor study results for evidence of adverse or beneficial treatment effects
2. Initiate procedures for review and implementation of protocol modifications recommended by the treatment effects monitoring committee

F. Authorship and publications

1. Paper writing activities:
a. Establish and activate writing teams

b. Develop papers on study findings
c. Develop papers on natural history and ancillary studies

2. Draft paper containing main study conclusions
3. Prepare stand-by press release for use in the event study findings appear in the news media prior to publication in a scientific journal
4. Continue procedures for distribution of published papers to study investigators
5. Update and distribute listing of study publications to study investigators

G. Management

1. Review and, if necessary, revise study guidelines concerning:
   a. Patient care
   b. Inquiries from outside the study regarding study design or study results
   c. Rights of access to study data
   d. Informed consent procedures
   e. Information sources to be used in classification of major events
2. In the event of a major protocol change or in preparation for close-out discuss and establish procedures for:
   a. Informing patients of close-out
   b. Informing referring physicians of close-out
   c. Developing special data collection forms for close-out
   d. Developing special patient consent forms for post-trial follow-up (if planned)
3. Develop detailed patient close-out procedures
4. Establish timetable for close-out activities, including timetable for termination of funding for data collection at participating clinical centers
5. Recommend procedures to be followed at clinical centers in termination of patient follow-up
6. Prepare special informational material to be dispensed to patients at the close-out examination
7. Develop plan to monitor for possible adverse effects associated with treatment in the close-out stage
8. Review data storage, backup, security, and integrity procedures
9. Review and revise organizational structure of the trial
10. Continue making priority assignments for data analysis activities

H. Other activities

1. Continue procedures for distribution of study drugs during the follow-up phase
2. Continue FDA reporting procedures (if trial involves INDA)
3. Reproduce and distribute data collection forms to be used during close-out stage
4. Review timetable for remainder of study and prepare request for additional funding (if necessary)
5. Update central repository of data slides for use by study investigators in making study presentations

V. PATIENT CLOSE-OUT STAGE

A. Treatment and patient care

1. Initiate procedures for unmasking treatment assignments, when masking is involved
2. Monitor for adverse effects due to treatment termination (if appropriate)
3. Inform the study investigators of study results and their implications for patient care
4. Formulate treatment recommendations to be made to patients on close-out
5. Inform patients of study results and recommended future treatment
6. Inform patients' primary care physicians of study results
7. Update patient identifying information to facilitate post-trial follow-up
8. Inform patients of plans for post-trial follow-up (if any) and of methods to be used to maintain contact with them after termination of regular follow-up
9. Request data center to prepare summaries of accumulated follow-up data needed by clinic personnel when reviewing care needs of individual patients and for facilitating transfer of pertinent data to primary care physicians
10. Effect transfer of patient care responsibilities to appropriate sources
11. Document that all active patients have been informed of study results

B. Data processing and analysis

1. Perform final edit of accumulated study data. Identify items that need review or corrections
2. Initiate special search procedures to locate patients classified as lost to follow-up for final data analysis
3. Develop and carry out data analyses that summarize study findings, including results from the close-out process

C. Quality assurance

1. Prepare final reports summarizing:
   a. Adherence to study protocol
   b. Adherence to data collection and examination schedule
   c. Quality of data generated
   d. Performance of all participating

D. Treatment monitoring

1. Prepare final report on treatment effects

2. Hold final meeting of treatment effects monitoring committee
3. Monitor close-out process to ensure adherence to indicated procedures for separation of patients from the trial

E. Authorship and publications

1. Write and submit for publication paper(s) summarizing study results
2. Supply advance copy of paper(s) on results to participating clinics for distribution to staff and referring physicians
3. Establish coordinated approach to dissemination of information to the medical public in conjunction with publication of study results, including press releases, if needed
4. Develop paper writing and analysis plans for termination stage of study, including procedures for review of papers prepared in that stage
5. Develop mechanism for support of travel and work of writing teams and leadership committees during termination stage
6. Develop mechanism for distribution of papers published during termination stage
7. Update and distribute list of publications to study investigators

F. Management

1. Develop plans and policies for:
   a. Disposition of equipment purchased with study funds
   b. Disposition of unused study drugs and other supplies
   c. Disposition of centrally stored study materials, such as frozen serum specimens, ECGs, fundus photographs
   d. Disposition of patient medical records and materials accumulated at clinical centers in a manner consistent with local statutes

e. Final disposition of study data on completion of the termination stage

2. Review study organizational structure and propose revisions for termination stage
3. Review timetable for termination stage and develop plans for additional funding (if necessary)
4. Develop plans for disengaging study investigators and related staff from the trial

G. Other activities

1. Update central repository of data slides for use by study investigators in making presentations of study findings
2. Update and distribute address directory

VI. TERMINATION STAGE

A. Treatment and patient care

1. Verify that all clinics have complied with close-out procedures (e.g., verify that all patients have been informed of study results, have been taken off their assigned treatment, and have had care responsibilities transferred)
2. Review and revise, if necessary, conclusions of the study after completion of final data analysis

B. Data processing and analysis

1. Complete final edit procedures and create final data file
2. Prepare data listings or data tapes (disks) needed by writing teams
3. Update backup tapes and repository listings of data files

C. Authorship and publications

1. Implement plans for support of travel and work of writing teams and leadership committees remaining in operation in termination stage
2. Implement plan for authorship and review of manuscripts prepared during termination stage
3. Distribute copies of finished papers to study investigators
4. Distribute updated list of study publications to participating investigators

D. Management

1. Establish policy on type and amount of data to be made available outside the study structure during and after the termination stage
2. Establish approach for dealing with inquiries regarding the study and the study results
3. Establish study stewardship body after termination of the trial

E. Repository

1. Establish a suitable repository for all study materials to be retained beyond the termination stage, such as:
   a. Patient medical records
   b. Completed data forms
   c. Associated records, such as ECGs and fundus photographs
   d. Serum samples, biopsy slides, etc.
2. Establish a central repository for patient identifying and locator information
3. Store computer data files and backup copies

F. Other activities

1. Dispose of unused study drugs (if any)
2. Complete phase-out of study personnel
3. Dissolve all remaining study committees, except for stewardship committee
4. Submit final report to FDA (if trial involved INDA)
5. Inform IRB of completion of study
6. Prepare final version of data slides for use by study investigators in presenting results of the trial
7. Maintain communications with participating investigators

VII. POST-TRIAL FOLLOW-UP STAGE (optional)

A. Preparatory steps

1. Re-establish contact with clinics to:
   a. Inform them of the proposed follow-up
   b. Update address directory
   c. Address special procedural and ethical questions posed by the follow-up
2. Assemble roster of patients to be followed
3. Outline approach to be used in the follow-up and the amount of data to be collected
4. Obtain IRB approval for the proposed follow-up study

B. Follow-up

1. Initiate mechanisms to establish patient contact
2. Implement special procedures to locate patients who do not respond to initial contact or who cannot be located
3. Update patient identifying and locator information
4. Assemble data collected from the post-trial follow-up

C. Data analysis and publication

1. Link added follow-up data with existing patient files
2. Carry out analyses to summarize post-trial follow-up results
3. Prepare manuscript summarizing results

D. Other activities

1. Store updated patient identifying and location information for future follow-up
2. Distribute a copy of any manuscript(s) produced to study investigators

E. Sample consent statements

E.1 Consent statement for the Macular Photocoagulation Study (MPS): Senile Macular Degeneration Study
E.2 Consent statement for the Persantine Aspirin Reinfarction Study (PARIS)
E.3 Consent statement for the Hypertension Prevention Trial (HPT)

Table E-1 Content checklist for sample consent statements

This appendix contains consent statements from three of the multicenter trials sketched in Appendix B:

- Macular Photocoagulation Study (MPS): Senile Macular Degeneration Study
- Persantine Aspirin Reinfarction Study (PARIS)
- Hypertension Prevention Trial (HPT)

The statements used by the individual clinics may have differed. All clinics could expand on information contained in the prototype statements, but could not delete or abridge information.

Table E-1 provides a content analysis of the three statements. The checklist is based on Table 14-4. None of the statements covered all of the items in the checklist. The MPS statement had the largest number of content deficiencies—16. There were 9 noted for the PARIS and 7 for the HPT statements.

The last line in Table E-1 gives the reading grade level of the text, derived using a scoring system developed by McLaughlin (1969). The PARIS statement had the highest reading level. It also contained language designed to speak for the patient (e.g., as in use of the phrase *I understand*)—a defect largely avoided in the other two statements.

E.1 CONSENT STATEMENT FOR THE MACULAR PHOTOCOAGULATION STUDY (MPS): SENILE MACULAR DEGENERATION STUDY

Macular degeneration is a major cause of visual loss in the U.S. It results from aging changes that affect the pigment cells and small blood vessels behind the retina. There is a familial tendency. No form of treatment is known to be effective.

Sometimes, a progressive deterioration of the pigment cells results in a slow reduction in vision. At other times, a break in the membrane behind the retina permits a blood vessel to grow through and leak fluid and/or blood beneath the retina and into the retina causing a rather sudden loss of vision.

Photographs taken after fluorescein dye injection locate the position of the leaking blood vessel. The closer this vessel is to the center of the retina, the greater the threat to vision. If the vessel is somewhat removed from the center, it may be possible to close the vessel with the laser and prevent further growth and further bleeding. If the vessel is directly central, laser treatment is not recommended.

Prior to laser treatment, numbing medication is given to prevent discomfort and motion of the eye. Rarely, this injection may cause some swelling behind the eye and some visual loss.

Possible complications of laser treatment include bleeding, retinal wrinkling, pigment loss, and damage to the center of the retina which may cause vision to be worse than before treatment. It is important to recognize, however, that each of these problems can occur without the use of the laser.

At present, it is not known whether your chances of maintaining good central vision are better with or without laser treatment, and your doctor has agreed to participate in a randomized trial to find an answer to this question. If your eye is eligible and if you agree to participate, you will be assigned in random fashion to a treatment group or to a non-treatment group. Randomization is similar to flipping a coin so that there is one chance in two of being treated or not treated with the laser. This provides an opportunity to balance the risks and benefits of laser treatment.

There is another important benefit. Patients with a second eye at risk have much to gain from participation since we anticipate the results of this study may provide information that will help the ophthalmologist with the management of the second eye.

Table E-1 Content checklist* for sample consent statements

Topic	*MPS*	*PARIS*	*HPT*
General descriptive and design information			
• Disease or condition to be studied	✓	✓	✓
• Type of people to be studied	✓	✓	✓
• Length of follow-up	—	—	✓
• Method of follow-up	—	—	✓
• Description of data collection procedures and schedule	—	—	✓
Treatment procedures described			
• Test treatment	✓	✓	✓
• Control treatment	—	✓	✓
• Method of treatment administration	✓	✓	✓
• Method of treatment assignment	✓	✓	✓
• Treatment masking	NA	✓	NA
• Rationale for choice of treatment	—	✓	✓
• Alternative treatments	—	✓	NA
Risk-benefit information detailed			
• Nature of treatment side effects	✓	✓	—
• Risk-benefit of test treatment	✓	✓	—
• Risk-benefit of control treatment	—	—	NA
• Potential side effects of test treatment	✓	✓	—
• Potential side effects of control treatment	✓	NA	NA
• Risk-benefit of special procedures to be performed	✓	NA	NA
Patient responsibilities and safeguards			
• Patient follow-up responsibilities detailed	—	✓	✓
• Provisions for protecting patient from prolonged denial of a beneficial treatment or exposure to a harmful treatment detailed	—	✓	—
• Safeguards for protecting patient's right to privacy detailed	—	—	✓
• Patient's right to withdraw from trial stated	✓	✓	✓
• Statement of right to have questions answered before enrollment provided	—	✓	✓
• Types of information that will not be disclosed during trial detailed	—	—	—
• Policy on care and payment for study related injuries detailed	—	—	✓
• Statement of where and how personal identifiers will be used	—	—	✓
• Amount and type of information provided to patient during trial indicated	—	✓	—
• Amount and type of information provided to patient at end of trial indicated	—	—	—
SMOG grade	12	14	12

*A checkmark indicates the item was covered. A dash indicates it was not. NA indicates not applicable.

Results of the study will be analyzed regularly; and any significant findings will be made known to the patient, especially findings which would alter the management of either eye.

To be certain that the physician will be able to locate all patients in case there are important study findings, we ask you for the names of relatives and others who may be contacted in case the patient cannot be located at some future date.

My signature below indicates that I understand all of the above and agree to participate in this program. I recognize that I am under no obligation to join this study, that I am free to withdraw at any time, and that neither failure to join nor withdrawal will prejudice the medical care which I receive at the Johns Hopkins Medical Institutions.

Patient's Signature _____

Doctor's Signature _____

Witness _____

Date _____

E.2 CONSENT STATEMENT FOR THE PERSANTINE ASPIRIN REINFARCTION STUDY (PARIS)

I agree to permit Dr. _____ and the study physician to treat me, _____, with Persantine (dipyridamole) and/or aspirin (acetylsalicylic acid) or placebo (inactive substance) for coronary heart disease. It has been explained to me that some studies have shown that aspirin may produce favorable results in the treatment of heart attacks and blood clot disorders by affecting the function of the blood platelets (the small cells in the blood that are necessary to keep blood from clotting [sic]). There is also some indication that the addition of Persantine may enhance these effects. However, at present there are no clear-cut data showing that people having one heart attack will not have another heart attack if they are given drugs which change platelet function. This study is designed to test the possibility that these drugs may help to prevent a recurrent heart attack.

It has been further explained to me that all of the persons participating in this study will be assigned at random to one of the following three groups. Neither I nor my physician will know to which group I belong.

1. One group will be given aspirin. Along with aspirin this group will receive a placebo pill (inactive substance) resembling the second drug, Persantine. Persons in this group will take 325 mg of aspirin three times a day.
2. A second group in this study will take aspirin and Persantine. Persons in this group will take 325 mg of aspirin and 75 mg of Persantine three times a day.
3. The third group will be what is called the control group. Those selected at random for this group will be given two placebos, that is, pills appearing like the other drugs in the study but with no active medication in them. This group will be compared with the other groups to see if there is a difference between the groups taking medication and the group taking placebos.

I understand that aspirin may cause stomach irritation or a bleeding tendency. No one who has had a personal sensitivity or history of significant problems taking aspirin will be asked to participate. I also understand that Persantine may cause lightheadedness or dizziness as a result of lowered blood pressure. I understand that there are no data in humans to suggest that its long-term use will lead to the development of any serious illness. Studies are in progress to determine whether or not this drug has any potential to cause tumors in animals. Should information become available suggesting any adverse effects, I understand that I would immediately be notified by the study physicians and that any such measures deemed necessary for the protection of my health would be carried out promptly. I also understand that if I should have any reactions to the medication during the study, I should notify the study physician so that appropriate treatment could be carried out promptly.

I understand that the reason for the placebo group is that there is always a chance, in fact a reasonable possibility, that the drugs may be ineffective and may cause some side effects which outweigh any beneficial effects. It has been explained to me that if at any point during this study it becomes evident that patients on one treatment are not doing as well as the patients on the other treatments, they will be switched to one of the superior treatments.

It has also been explained to me that there are other methods of possible prevention of recurrent heart attack including diet, weight reduction, exercise programs, drug control of high blood pressure, cessation of smoking, various types of heart surgery, or use of anticoagulants which reduce the clotting ability of blood without affecting blood platelets. I understand that all of these forms of treatment, with the exception of anticoagulant drugs which cannot be given together with PARIS medications, are available to me with the advice of my personal physician. I also understand that I must avoid taking aspirin and aspirin-containing drugs during my participation in this study.

I have read and have understood the foregoing explanation and I fully understand the program of study. I also understand that my participation in this study is of great value to me and to others like myself who have coronary disease and have survived a heart attack. I have had an adequate chance to ask questions and I may ask questions at any time while the study is in progress. I voluntarily consent to participate, or to continue my participation, in this study and to treatment with these drugs or placebo. I understand that I may withdraw my consent and discontinue my participation in the study at any time.

Witness: _____
Signature

Address: _____
Street

_____
City State Zip Code

Signed: _____
Patient or person authorized to consent for the patient

Address: _____
Street

_____
City State Zip Code

Today's Date: _____
Month Day Year

Source: Reference citation 375. Reprinted with permission of the American Heart Association, Inc., Dallas, Texas.

E.3 CONSENT STATEMENT FOR THE HYPERTENSION PREVENTION TRIAL (HPT)

The Hypertension Prevention Trial (HPT) is designed to help us determine whether or not people can avoid high blood pressure through a change in diet. Only volunteers who are not being treated for hypertension and who do not now have elevated blood pressure are eligible for the study. The main aim is to determine if people can make, and then maintain, the diet changes proposed. Each person will be studied for at least two years. The amount of change in blood pressure will be observed over that time period. The specific diets to be studied are:

- *Low-sodium diet*—participants assigned to this diet will be asked to reduce the amount of foods they eat which contain high levels of sodium. Sodium is a mineral required by the human body in small amounts. The most common source of sodium is table salt (sodium chloride).
- *Low-sodium and high potassium diet*—participants assigned to this diet will be asked to reduce the amount of high-sodium foods in their diet and also increase their use of foods which are high in potassium. Potassium is also a mineral required by the human body. The most common sources of potassium are fresh fruits and vegetables.
- *Weight loss diet*—participants assigned to this diet will be asked to reduce body weight by eating less and through increased exercise.
- *Weight loss and low-sodium diet*—participants assigned to this diet will be asked to lose weight by eating less, increasing exercise, and to reduce consumption of high-sodium foods.

People entering the study will be placed in one of two weight groups. Approximately half the people enrolled are expected to fall into each of the two groups. People in the higher weight group will be assigned to one of the above diets, or to no diet change. Those in the lower weight group will be assigned to one of the two diets above that do not involve a weight loss, or to no diet change.

The specific diet you will be asked to follow depends on an assignment made by the Data Coordinating Center located in Baltimore, Maryland. The assignment is made using a chance

procedure, like rolling dice, but carried out with a computer. Hence, neither we nor you know in advance the group to which you will be assigned.

Everyone taking part in the study will need to return to the clinic for blood pressure measurement, every six months after enrollment. A 24-hour food record and overnight urine collection will be required prior to each of these visits. An electrocardiogram and a blood sample will be drawn once a year.

Participants assigned to a diet group will need to make more frequent visits to the clinic to receive instructions on how to make necessary diet changes. As a rule, these visits will be organized as group instruction sessions. Each session will last about one and one-half hours. The schedule will be:

- One session a week for the first ten weeks after enrollment
- Six additional sessions during the rest of the first year
- A minimum of four sessions in the second year, and in each year thereafter so long as the study continues

Entry into the study is voluntary. If you do decide to enroll we will keep in contact with you for the duration of the study. We may even wish to maintain written or telephone contact with you after the study is finished.

You are not obligated to continue in the study if you change your mind about participating later on. Withdrawal from the study will in no way affect any care or treatment you are receiving from other clinics in the University. However, anyone who drops out after enrollment reduces the scientific value of the study. Hence, you should not enroll if you are uncertain about the value of the study or if you know now that you cannot fulfill the study requirements. If you do decide to drop out, we will contact you by telephone or letter about once a year.

Data, including peronal information such as name and address, will be stored in a computer at the Clinic and at the Data Coordinating Center in Baltimore. All personal information is confidential and available only to study personnel. No reports will be presented or published which reveal your identity.

There will be no charge to you for any of the study procedures or clinic visits. The examination procedures used in this study are not intended for individual medical diagnosis or care. If you have any medical problems that come to our attention, we will refer you to proper sources of care.

The University has no general provision for compensation in the event of physical injury resulting from research studies. In the unlikely event that injury should occur, medical treatment is available, but may not be provided free of charge.

We believe the risks associated with participation in this trial are small. The diets being studied are consistent with general nutritional recommendations. The tests and procedures are standard and in common use.

If you are satisfied with the explanation of the Hypertension Prevention Trial and wish to take part in it, please sign below. Please do not sign until you have had all questions concerning the study and your participation in it answered to your satisfaction.

Participant

Name (print) _____

Signature _____ Date _____

Witness

Name (print) _____

Signature _____ Date _____

Should you have any complaint after enrollment, you may contact the HPT Clinic Director, or the University Human Volunteers Office. The Human Volunteers Office should be contacted if you desire to make the complaint without knowledge of the clinic staff.

Clinic Director:	Harry J. Jones, M.D. 684 North Fox Street Any Town, MD 47150 Phone: 872-8420
Human Volunteers Office:	Jane V. Moore, M.D. 7844 East 5th Street Any Town, MD 47150 Phone: 962-7741

CLINIC STAFF: *Please make a copy of the signed consent form for the participant*

F. Data items and forms illustrations

F.1 Item numbering
F.2 Items that indicate presence or absence of a finding or condition
F.3 Unnecessary words
F.4 Double negatives
F.5 Compound questions
F.6 Comparative evaluations
F.7 Inverted meaning of a yes reply
F.8 Presence versus absence of a condition
F.9 Time references
F.10 Direction of response
F.11 Leading questions
F.12 Vertical versus horizontal response lists
F.13 Unit specifications
F.14 Precision specifications
F.15 Calculation items
F.16 Instruction items
F.17 Age and birthdate items
F.18 Reminder and documentation items
F.19 Full-page versus two-column layout
F.20 Layout for SKIP items
F.21 Instructional information
F.22 Unformatted responses
F.23 Formatted responses
F.24 Layout for check positions
F.25 Field designations and precoded responses

This appendix contains illustrations referenced in Chapter 12. Many of the items are taken from study forms as used in a clinical trial or an epidemiological study and are exact photo reproductions of the items except for the reductions necessary to fit the format of this book. Others have been retyped as they appeared except for minor differences in type style and spacing (these are labeled as facsimiles). Some of the items have been contrived (labeled as such) to illustrate specific points not covered by actual examples.

The categorization of an illustration as satisfactory or unsatisfactory relates to the point considered. A satisfactory classification in one context may be unsatisfactory in another.

F.1 ITEM NUMBERING

F.1.1 Unnumbered items (Unsatisfactory; photo reproduction)

Study No.: _____

Date of Record Rev.: ___/___/___ (mo.) (day) (yr.)

Name of Reviewer: _____

Name of Hospital: _____

Name of Patient: _____

Address: _____

Telephone No.: _____

Name in Which listed: _____

History No.: _____

Soc. Sec. Number: _____

Medicare Number: _____

Insurance Number: _____

Date of Birth: ___/___/___ (mo.) (day) (yr.)

Age: _____

F.1.2 Numbered items (satisfactory; photo reproduction)

2. LAST NAME		3. OPD NO.	4. HOSPITAL NO.	5. SPECIAL NO.
6. FIRST NAME	7. MIDDLE	8. MAIDEN		COMPLETE ONLY IF NEEDED BY HOSPITAL
9. ADDRESS (Street and Number)	(City, Zone and State)		10. TELEPHONE NO.	11. EDC
12. DATE REGISTERED Mo. Day Year	13. DATE FORM INITIATED Mo. Day Year	14. FIRST DAY LMP Mo. Day Year	15. DATE OF BIRTH Mo. Day Year	16. AGE
17. MARITAL STATUS ☐S 1 ☐M 2 ☐CL 3 ☐W 4 ☐D 5 ☐SEP. 6		18. RACE ☐W 1 ☐N 2 ☐OR 3 ☐PR 4 ☐Other 5		19. WEEKS OF GESTATION
20. PATIENT STATUS ☐Clinic 1 ☐Private 2	21. SAMPLING FRAME PATIENT SELECTED FOR STUDY ☐Based on 1 Systematic Sampling ☐Based on 2 Special Sampling (Specify)		NOT SELECTED FOR STUDY ☐Based on 7 Sampling Design ☐For Other Reasons 8 (Specify below)	

F.1.3 Comment

Item numbering is mandatory if the respondent is required to skip certain items. However, it is useful even when skips are not required. The numbers serve as convenient references for data editing and processing.

F.2 ITEMS THAT INDICATE PRESENCE OR ABSENCE OF A FINDING OR CONDITION

F.2.1 (Unsatisfactory; photo reproduction)

15. GENERAL MEDICAL HISTORY: Have you ever had any of the following conditions?
For each yes in column 1, please fill in columns 2 to 7.

Condition	(1) Check if yes	(2) First occurrence (Yr.)	(3) First seen by physician (Yr.)	(4) Treated currently (yes or no)	(5) Current or most recent physician and/or clinic (Name & address)
Cataracts					
Any other eye problems (specify)					
Heart trouble of any kind					
Stroke					

F.2.2 (Unsatisfactory; photo reproduction)

15. Could you list all the pets (types of animals) you/_____ had?
Index Subject

A. Pet	B. Did you have close contact with this pet? e.g., did he sit on your lap, sleep on your bed?	C. If YES, Ask D - G: Was this pet ever sick prior to your/ Index Subject's hospitalization/ physician visit in ____ - ____? Month Year			D. Could you tell me the name of the disease?	E. What year was this pet sick?	F. Could you tell me the name and location of the veterinarian who treated this pet?
		YES	NO	UNK			

F.2.3 (Satisfactory; photo reproduction)

13. Has a doctor ever told you that you had ASK (a-c) FOR EACH OF THE FOLLOWING:	(A) IF YES ASK (B-C) YES	NO	UNK	(B) IF YES At what age?	(C) IF YES TO (A): Were you hospitalized? YES	NO	UNK
Varicose veins							
Phlebitis (Inflammation of veins usually in arms or legs)							
Repeated Vaginal Infections (more than 3/year)							
Repeated Pelvic and/or Uterine (female) Infections							
Venereal Disease							
Stroke							
High Blood Pressure							
Heart Disease (Specify:)							
Anemia (poor blood)							

F.2.4 (Satisfactory; photo reproduction)

a. Have you ever been pregnant? NO ☐ YES ☐ b. How many times? _____

(If yes, please complete table below listing all pregnancies, beginning with the first pregnancy. Include miscarriag

(If no, go to page 18)

Pregnancy order: No.	Child's first name	Date pregnancy ended or date of birth	Residence during pregnancy, list all if more than one (No. of mos. in each)	Physician and/or hospital (Name & address)	Pregnancy outcome and no. of months pregnant*
1.					
2.					
3.					
4.					

F.2.5 Comment

F.2.1 is deficient in that it allows the respondent to skip conditions that are absent. This design can lead to ambiguous results, especially when none of the conditons are checked. There is no way in such cases to know if the entire item was overlooked or if it was left unanswered because none of the conditions were present.

F.2.2 is defective in that it provides no indication of what the index subject is to do when the answer to the lead question is "No." Taken literally, a "No" reply means the respondent is unable to list *all* his pets. Further, the time period to which the question refers is unclear. Is the intent to list all pets the index subject has ever had or only those for some specified time period? Presumably the entire set of questions is to be skipped for an index subject reporting no pets, creating the same ambiguity as cited for F.2.1.

The items shown in F.2.3 and F.2.4 avoid this problem by requiring an answer even if the condition is absent. Example F.2.3 requires a "Yes," "No," or "Unknown" answer for each disease condition listed; example F.2.4 has a lead question that, if checked "No," allows the respondent to skip the rest of the item.

F.3 UNNECESSARY WORDS

F.3.1 (Unsatisfactory; facsimile)

Would you please tell me about how much income you and your family will get during 1971, January through December? I mean your total family income - before taxes from all sources.

1. Under $3,999
2. $4,000 - $7,999
3. $8,000 - $11,999
4. $12,000 - $15,999
5. $16,000 - $24,999
6. Over $25,000

F.3.2 (Satisfactory; contrived from F.3.1)

Please indicate your total, before tax, family income for 1971.

1. Under $3,999
2. $4,000 - $7,999
3. $8,000 - $11,999
4. $12,000 - $15,999
5. $16,000 - $24,999
6. Over $25,000

F.3.3 Comment

F.3.1 contains unnecessary words that are not helpful, and perhaps even confusing, particularly since the question simply refers to income and the "clarifying" remark following the question refers to total family income. F.3.2 conveys the same meaning as F.3.1, but with fewer words.

It is easy to find examples of items with unnecessary words. An economy of words cannot be achieved without a considerable investment of time and effort in the development, review, and testing processes involved in constructing forms.

F.4 DOUBLE NEGATIVES

F.4.1 (Unsatisfactory; facsimile)

05:38. In the past week, did you have any injuries or accidents that didn't cause you to cut down on your normal activities?

0 NO 1 YES

F.4.2 (Unsatisfactory; contrived)

The answers to items 28 thru 32 have been reviewed by a nutritionist and they do not disqualify the candidate from enrollment.

( ) Yes ( ) No

F.4.3 (Unsatisfactory; contrived)

Since your stroke are you (check one)

( ) Unable to walk
( ) Barely unable to walk
( ) Able to walk fairly well
( ) Able to walk normally

F.4.4 (Satisfactory; contrived from F.4.1)

In the past week did you have any accidents or injuries?

0 NO 1 YES

If yes,

Did they cause you to cut down on your normal activities?

0 NO 1 YES

F.4.5 (Satisfactory; contrived from F.4.2)

Were items 28 through 32 reviewed by a nutritionist?

( ) Yes ( ) No

If Yes,

Do the answers qualify the candidate for enrollment in the study?

( ) Yes ( ) No

F.4.6 (Satisfactory; contrived from F.4.3)

Since your stroke are you (check one)

( ) Unable to walk
( ) Barely able to walk
( ) Able to walk fairly well
( ) Able to walk normally

F.4.7 Comment

F.4.1 is almost impossible to comprehend in this form. Compare it with the reworded version in F.4.4.

F.4.2 is difficult to understand because it consists of two parts and a double negative phrase, "do not disqualify." The reworded version in F.4.5 divides the question into two parts and eliminates the use of the double negative.

Example F.4.3 uses two negative terms, "barely" and "unable." F.4.6 avoids the confusion created by their use.

F.5 COMPOUND QUESTIONS

F.5.1 (Unsatisfactory; contrived)

The answers to items 28 thru 32 have been reviewed by a nutritionist and they qualify the participant for enrollment.

( ) Yes ( ) No

F.5.2 (Unsatisfactory; facsimile)

_____MONTH _____YEAR

Why did you see a doctor? I mean, what was wrong with you?

00 ROUTINE CHECK-UP (GENERAL HEALTH)
01 ROUTINE CHECK-UP FOR PREGNANCY
02 JUST DIDN'T FEEL GOOD
03 RECEIVING TREATMENT FOR ILLNESS, SPECIFY ILLNESS:
_____
_____

04 RECEIVING TREATMENT FOR INJURY OR ACCIDENT?
SPECIFY WHAT WAS WRONG. _____
_____

05 RECEIVING TREATMENT BECAUSE RESPONDENT WAS A VICTIM
OF CRIME. SPECIFY. _____
_____

06 OTHER, SPECIFY _____
_____

F.5.3 (Satisfactory; contrived from F.5.1)

Were items 28 thru 32 reviewed by a nutritionist?

( ) Yes ( ) No

If Yes,

Do the answers qualify the candidate for enrollment in the study?

( ) Yes ( ) No

F.5.4 (Satisfactory; contrived from F.5.2)

Why did you see a doctor?

00 ROUTINE CHECK-UP (GENERAL HEALTH)
01 ROUTINE CHECK-UP FOR PREGNANCY
02 JUST DIDN'T FEEL GOOD
03 RECEIVING TREATMENT FOR ILLNESS, SPECIFY ILLNESS:
_____

F.5.5 Comment

The question in F.5.1 requires two conditions to be met in order to check "Yes." Technically, a "No" could mean either that the list of questions was not reviewed by a nutritionist or that one or more of the answers disqualified the candidate from enrollment. The confusion is eliminated in F.5.3 by first asking if a nutritionist reviewed the listed items and then making the second question conditional on a "Yes" reply to the first question.

F.5.2 is unsatisfactory because the two questions require different responses. The reasons for going to a doctor may not relate to what is actually wrong. The confusion is avoided by deleting the second "clarifying" question, as in example F.5.4.

F.6 COMPARATIVE EVALUATIONS

F.6.1 Unstated standard

F.6.1.1 (Unsatisfactory; contrived)

Do you get more exercise now?

( ) Yes ( ) No

F.6.1.2 (Satisfactory; contrived from F.6.1.1)

Do you get more exercise now than you did before your illness?

( ) Yes ( ) No

F.6.2 Undefined standard

F.6.2.1 (Unsatisfactory; contrived)

Do you have any major diseases?

( ) Yes ( ) No

F.6.2.2 (Better; contrived from F.6.2.1)

Do you have any major diseases, such as cancer or heart disease?

( ) Yes ( ) No

F.6.2.3 (Satisfactory; contrived from F.6.2.2)

Do you have any of the following diseases? (Check as many as apply):

( ) Cancer
( ) Heart disease
( ) Diabetes
( ) Arthritis
( ) Other (specify)
_____

F.6.3 Positive versus negative standards

F.6.3.1 (Unsatisfactory; contrived)

Are you shorter than your mother?

( ) Yes ( ) No

F.6.3.2 (Satisfactory; contrived from F.6.3.1)

Are you taller than your mother?

( ) Yes ( ) No

F.6.3.3 (Unsatisfactory; contrived)

Would you say you are in worse health than you were a year ago?

( ) Yes ( ) No

F.6.3.4 (Satisfactory; contrived from F.6.3.3)

Would you say you are in better health than you were a year ago?

( ) Yes ( ) No

F.6.4 Comment

Items requiring a comparative assessment should indicate the standard for the comparison. Question F.6.1.1 is confusing because there is no specification of the time period over which the comparison is to be made. F.6.1.2 specifies a reference point for the assessment.

Care should be taken to avoid the ambiguity of an undefined term, such as in F.6.2.1. F.6.2.2 provides a general indication of what is meant by "major" disease. F.6.2.3 is even more explicit in this regard.

Comparative statements should be cast in positive terms, since they are generally easier to understand than corresponding statements cast in negative terms (e.g., F.6.3.2 and F.6.3.4 versus F.6.3.1 and F.6.3.3).

F.7 INVERTED MEANING OF A YES REPLY

F.7.1 (Unsatisfactory; contrived)

Patient does not use (answer a through c):

	Yes	No
a. Insulin	( )	( )
b. Oral hypoglycemic agents	( )	( )
c. Digitalis	( )	( )

F.7.2 (Satisfactory; contrived from F.7.1)

Patient uses (answer a through c):

	Yes	No
a. Insulin	( )	( )
b. Oral hypoglycemic agents	( )	( )
c. Digitalis	( )	( )

F.7.3 Comment

F.7.1 requires the respondent to check "Yes" if the patient does not use an indicated drug. The question is less confusing if the use of a drug requires a "Yes" reply, as in F.7.2.

F.8 PRESENCE VERSUS ABSENCE OF A CONDITION

F.8.1 (Unsatisfactory; contrived)

Are you free of heart disease?

( ) Yes ( ) No

F.8.2 (Satisfactory; contrived from F.8.1)

Has a doctor ever told you that you have heart disease?

( ) Yes ( ) No

F.8.3 Comment

F.8.1 requires an affirmative response to indicate the absence of a condition. In a sense, the question is impossible to answer since there is no way to know if one is free of heart disease.

Item F.8.2 is stated in positive terms and avoids the problem of F.8.1 by relying on an operational definition of heart disease.

F.9 TIME REFERENCES

F.9.1 Time point references

F.9.1.1 Present time point (Satisfactory; facsimile)

9. (AAW) Are you presently taking any drugs prescribed by a physician?

( )$_1$ Yes ( )$_2$ No

F.9.1.2 Time frame defined in terms of a specified calendar date (Satisfactory; photo reproduction)

9. Approximately what was your weight in _____? (2 YEARS PRIOR TO REF. DATE) _____ POUNDS (_____ KG) UNKNOWN ☐

10. Approximately what was your weight in _____? REFERENCE DATE _____ POUNDS (_____ KG) UNKNOWN ☐

F.9.1.3 Time frame specified in terms of a defined event (Satisfactory; contrived)

Were you taking any prescription drugs when you had your last MI?

( )$_1$ Yes ( )$_2$ No

F.9.2 Time interval references

F.9.2.1 Time interval defined by two events (Satisfactory; facsimile)

110. Did your doctor advise you not to take the pill or IUD between the start of your periods and your first pregnancy?

YES, IUD ☐

YES, PILL ☐ ASK: What were the reasons? _____

NO ☐ UNKNOWN ☐

F.9.2.2 Time interval defined as period from last study examination to present (Satisfactory; photo reproduction)

8) Since the patient's last completed follow-up visit, has he had any of the following (answer each question):

	Yes	No
A) Cardiac asthma?	( )	( )[45]
B) An obvious stroke?	( )	( )[46]
C) Weakness or paralysis of any part of his body?	( )	( )[47]

F.9.2.3 Time interval defined as entire "study period" (Satisfactory; facsimile)

List all in-patient admissions during study period (for any diagnosis, to this hospital only).

Identify with a check the admission selected for review sample	Date of Admission Month	Day	Year	Date of Discharge Month	Day	Year
1st						
2nd						
3rd						
4th						
5th						
6th						

If Study Admission is the First in the Study Period, give most Recent Date of Hospitalization (this hospital only) before Study Period: _____ **None** ☐

F.9.2.4 Time interval defined from some calendar time to present (Satisfactory; photo reproduction)

18. PHYSICIAN OR CLINIC VISITS SINCE 1950

Please list all physician and/or clinic visits since 1950 other than routine employment exams.

Physician and/or clinic (Name & address)		Date (Mo. & yr.)	Specialty

F.9.2.5 Time interval from present to recall limit (Satisfactory; photo reproduction)

16. Could you please tell me a few things about each time you were x-rayed? Start with the first x-ray you remember, and then tell me about later ones. (ASK A-F)

(A) What part of the head was x-rayed? skull, tonsils, sinuses, etc.)	(B) In what year was this done?	(C) In what hospital or doctor's office was this done? NAME ADDRESS	(D) Why was the x-ray taken?	(E) About how many films were taken?

F.9.3 Comment

The examples in F.9.1 all refer to some point in time—the present, a calendar date, or the date on which a defined event occurred. The examples in F.9.2 are for defined time intervals. The interval in F.9.2.1 is defined by two events—the start of menstruation and first pregnancy. A common frame of reference for follow-up studies is illustrated in F.9.2.2 where the respondent is required to cover the time period from the last follow-up visit to the present visit. The time frame in F.9.2.3 is the entire "study period." This mode of reference is useful only when it is clear what is meant by the phrase. Example F.9.2.4 covers a time interval from 1950 to the time of the interview. The interval in F.9.2.5 is defined by the limits of a respondent's recall.

F.10 DIRECTION OF RESPONSE

F.10.1 Mixed disease categorization (Unsatisfactory; contrived)

Is the patient (answer each question):

	Yes	No
Hypertensive?	( )	( )
Euglycemic?	( )	( )
Obese?	( )	( )
Hyperlipidemic?	( )	( )

F.10.2 Mixed attitude expression (Unsatisfactory; facsimile)

How often did you feel _____ (READ CHOICES)

		NOT AT ALL (0)	ONCE (1 TIME)	SEVERAL TIMES (2-3 TIMES)	OFTEN (3+ TIMES)
03:43	Pleased about having accomplished something?	0	1	2	3
44.	Proud because someone complimented you on something you had done?	0	1	2	3
45.	Depressed or very unhappy?	0	1	2	3
46.	Bored?	0	1	2	3
47.	Particularly excited or interested in something?	0	1	2	3
48.	Downcast and dejected?	0	1	2	3

F.10.3 Comment

The difficulty with F.10.1 arises from the mixture of disease and nondisease states. This problem could be corrected by replacing "euglycemic" with "diabetic" in the check list.

F.10.2 includes a mix of positive and negative states of mind. The first two items are phrased in positive terms. The next two are stated in negative terms. Intermixing of this sort is ill-advised unless there are good reasons for doing so (e.g., to keep a respondent from automatically checking the same category for all items without thinking).

F.11 LEADING QUESTIONS

F.11.1 (Leading; contrived)

Do you still have allergies to ragweed?

( ) ( )
Yes No

F.11.2 (Not leading; contrived)

Have you ever had allergies to ragweed?

( ) ( )
Yes No

If Yes,

Do you still have them?

( ) ( )
Yes No

F.11.3 Comment

F.11.1 not only leads the patient but assumes he has had an allergy to ragweed in the past. As written, there is no way to answer the question if the patient has never had ragweed allergies. F.11.2 avoids the problem by beginning with a general question that determines whether the patient has ever had ragweed allergies before inquiring about current allergies.

F.12 VERTICAL VERSUS HORIZONTAL RESPONSE LISTS

F.12.1 Horizontal lists

F.12.1.1 (*Unsatisfactory; photo reproduction*)

Sex and Race: (check) ☐ WM; ☐ WF; ☐ NWM; ☐ NWF; ☐ OM; ☐ OF

F.12.1.2 (*Unsatisfactory; photo reproduction*)

11. How many times a week do you eat each of the following foods?
Fish ____; Meat ____; Poultry ____; Eggs ____; Cheese ____; Butter or margarine ____;
Breads & cereals ____; Potatoes ____; Rice ____; Vegetables ____; Green salads ____;
Fruits and fruit juices ____; Sweet desserts ____; Candy ____

F.12.1.3 (*Unsatisfactory; photo reproduction*)

16. Check the reactions at test sight 7-14 days after application.
☐ **0. None** ☐ **1. Erythema** ☐ **2. Edema** ☐ **3. Vesicles/oozing**
☐ **4. Bulla/denudation** ☐ **5. Delayed flare**

F.12.1.4 (*Unsatisfactory; photo reproduction*)

22. RADIATION THERAPY: Have you ever had any treatments with radium, cobalt 60, cobalt bomb radic
☐ NO ☐ YES ☐ DON'T KNOW If yes, please complete the table below: (Start with most r

F.12.1.5 (*Satisfactory; contrived from F.12.1.4*)

RADIATION THERAPY: Have you ever had any treatments with radium, cobalt 60, cobalt bomb radio is
☐ NO ☐ YES ☐ DON'T KNOW If yes, please complete the table below: (Start wi

F.12.1.6 (*Satisfactory; contrived*)

Are you taller than your mother?

( ) ( )
Yes No

F.12.1.7 (*Unsatisfactory; photo reproduction*)

14. How often do you use the following types of medicine?

Aspirin, Bufferin	Never ☐	Occasionally ☐	Frequently ☐
Vitamin pills	Never ☐	Occasionally ☐	Frequently ☐
Sleeping pills	Never ☐	Occasionally ☐	Frequently ☐
Tranquilizers	Never ☐	Occasionally ☐	Frequently ☐
Laxatives	Never ☐	Occasionally ☐	Frequently ☐
Anti-acid medicine	Never ☐	Occasionally ☐	Frequently ☐

F.12.1.8 (*Satisfactory; photo reproduction*)

16. How often do you experience:

	Never	Occasionally	Frequently
Sensation of heart beating (except after exercise)	☐	☐	☐
Insomnia	☐	☐	☐
Sense of exhaustion (except after exercise)	☐	☐	☐
Periods of alternating gloom and cheerfulness	☐	☐	☐
Periods of being particularly self-conscious	☐	☐	☐

F.12.2 Vertical lists

F.12.2.1 (*Satisfactory; facsimile*)

(AAW) How would you characterize your ethnic origin? (Use HPT flashcard 01)

( )1 White
( )2 Black
( )3 Hispanic
( )4 Oriental
( )5 Other (Specify)

_____

F.12.2.2 (*Satisfactory; facsimile*)

(AAW) What is the combined income of all members of your household? (Use list below to categorize candidates response). (Use HPT flashcard 03)

( )0 < $5,000
( )1 5 thru 10,999
( )2 11 thru 15,999

( )3 16 thru 20,999
( )4 21 thru 25,999
( )5 26 thru 35,999

( )6 36 thru 45,999
( )7 46 thru 55,999
( )8 55,000 and over
( )9 declines to answer

F.12.2.3 (*Satisfactory; contrived from F.12.1.3*)

Check the reactions at test sight 7-14 days after application.

|__| 0. None
|__| 1. Erythema
|__| 2. Edema
|__| 3. Vesicles/oozing
|__| 4. Bulla/denudation
|__| 5. Delayed flare

F.12.2.4 (*Satisfactory; contrived*)

Does the patient have any of the following diseases? (Check all that apply.)

( )1 Diabetes
( )2 Cancer
( )3 Hypertension
( )4 Heart disease
( )0 None of the above

F.12.3 Comment

A list that is horizontally arrayed requires less space than one that is vertically arrayed (e.g., compare F.12.1.3 and F.12.2.3). However, vertical layouts are generally less confusing than horizontal layouts to use (compare items in F.12.2 with those in F.12.1). The main difficulty with the examples in F.12.1 stems from the confusion the respondent is likely to have in locating the proper check space. Items F.12.1.2 and F.12.1.4 are especially defective in this regard. The uniformity of spacing makes it difficult for the respondent to decide whether the check space for the response is in front of or behind the designated reply.

A horizontal layout is acceptable for short lists. However, even in such instances it is important to use a layout, as in F.12.1.5 and F.12.1.6, that makes it easy to associate a response with the appropriate check space. The association is not obvious for F.12.1.1 and F.12.1.4 and only moderately so for F.12.1.7.

The amount of space provided for making a check in a vertical list should be adequate to avoid the confusion that can result if the check is not registered squarely in the center of the check space. For example, the vertical separations in F.12.2.3 are better than those in F.12.1.7 and F.12.1.8.

F.13 UNIT SPECIFICATIONS

F.13.1 Time units

F.13.1.1 (*Unsatisfactory; contrived*)

a. Date of patient's next appointment?

Mo__ - Day__ - Yr__

b. Time of patient's next appointment?

F.13.1.2 (*Satisfactory; facsimile*)

Time and date of BP measurement

a. Time of day __ __ : __ __ AM PM

b. Date: Mo__ - Day__ - Yr__

F.13.2 Laboratory units

F.13.2.1 (*Unsatisfactory; photo reproduction*)

14. Laboratory Tests:	YES	NO	NR	DAY (if menstruating day of cycle)	DATE	RESULTS OF TEST
Serum prolactin	—	—	—			
LH	—	—	—			
Estradiol	—	—	—			

F.13.2.2 (*Fair; photo reproduction*)

If a check mark was placed after item 20-R, answer items A through E below relative to the episode which resulted in a diagnosis of myocardial infarction:

A) Highest SGOT recorded (state units): .. _____ 55
If not done, check here: ..... (STOP)

B) Highest LDH recorded (state units): .... _____ 56
If not done, check here: ..... ( )

C) Highest sedimentation rate recorded (mm/hr): ..... _____ 57

If not done, check here: ..... ( )

F.13.2.3 (*Satisfactory; contrived from F.13.2.1*)

Laboratory Tests:	YES	NO	NR	DAY (if menstruating day of cycle)	DATE	RESULTS OF TEST	UNITS
Serum prolactin	—	—	—				
LH	—	—	—				
Estradiol	—	—	—				

F.13.3 Height-weight units

F.13.3.1 (*Unsatisfactory; photo reproduction*)

Height: _____ NR ☐

Weight: _____ NR ☐

F.13.3.2 (*Satisfactory; facsimile*)

13. Ht (shoes off): __ __ inches

14. Wt (outdoor garments and shoes off): __ __ _ lbs.

F.13.4 Unconventional units (Unsatisfactory; photo reproduction)

1) Results for the FIRST 90 minute collection period.

a) Serum creatinine determination. The blood sample for this determination should be taken at the start of the FIRST 90 minute collection period. Record the results in mg./ml. Carry the accuracy of the determinations four (4) places beyond the decimal point, e.g., 0.0185 mg./ml. Record the readings from both aliquots.

SERUM A
Aliquot 1_____mg./ml.
Aliquot 2_____mg./ml.

b) Urine creatinine concentration for the FIRST collection period. Record results in mg./ml. Carry the accuracy of the determinations three (3) places beyond the decimal point, e.g., 0.155 mg/ml. Record the readings from both aliquots.

URINE A
Aliquot 1_____mg./ml.
Aliquot 2_____mg./ml.

F.13.5 Comment

F.13.1.1 does not specify how time is to be recorded—on a 24-hour basis or on a 12-hour basis. If the latter, there will be ambiguity in the information supplied unless the respondent indicates AM or PM. F.13.1.2 avoids this difficulty by requiring the respondent to indicate AM or PM.

The unit of measurement should be part of the item, as in F.13.3.2 and F.13.4, when measurements are to be made using a specified unit. The item should provide space for recording the unit of measurement when it is not specified (e.g., as in F.13.2.3). The format for F.13.2.3 is better in this regard than for F.13.2.2. Items F.13.2.1 and F.13.3.1 are defective because they do not provide an indication of the unit of measurement.

The illustration in F.13.4 is taken from a form used in the University Group Diabetes Program (UGDP). Creatinine determinations are typically recorded in 100mg/ml. The UGDP form required recordings in mg/ml. The requirement resulted in a large number of recording errors.

F.14 PRECISION SPECIFICATIONS

F.14.1 Dashed lines with decimal points (Satisfactory; facsimile)

Height: __ __ . __ __ inches
Weight: __ __ __ . __ pounds

F.14.2 Boxes with decimal points (Satisfactory; contrived)

Height: ☐☐ . ☐ inches
Weight: ☐☐☐ . ☐ pounds

F.14.3 Hatched line with indication of required precision (Satisfactory; contrived)

Systolic blood pressure ☐☐☐ mmHg

F.14.4 Solid line with written indication of required precision (Satisfactory; facsimile)

Blood pressure (record to nearest even number)
Diastolic _____ mmHg
Systolic _____ mmHg

F.14.5 Solid line with no indication of required precision (Unsatisfactory; facsimile)

Height _____ inches
Weight _____ lbs.

F.14.6 Comment

F.14.1 indicates the required precision through use of a series of dashed lines and decimal points. This format is preferred to those illustrated in F.14.2 and F.14.3 for reasons indicated in Section 12.6.8.2. The main problem with F.14.1 is that it requires more precision than is attainable with ordinary body height and weight measurements.

A format involving use of a solid line with no indication of required precision, such as illustrated in F.14.5, should be avoided if possible. The instructions for the item should indicate the desired precision if this format is used, as in F.14.4.

F.15 CALCULATION ITEMS

F.15.1 Bad examples

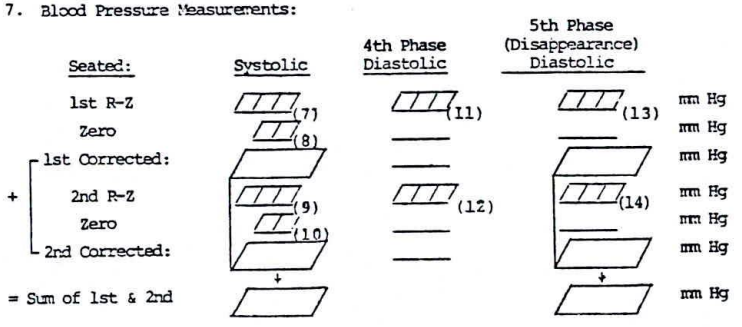
F.15.1.1 Blood pressure measurement (Facsimile)

INITIAL MEASUREMENT (Record 3 measurements)
☐☐☐ ☐☐☐ 1. ___/___
SBP DBP 2. ___/___
(AVERAGE OF 3 READINGS) 3. ___/___

SECOND MEASUREMENT (Record 3 measurements)
☐☐☐ ☐☐☐ 1. ___/___
SBP DBP 2. ___/___
(AVERAGE OF 3 READINGS) 3. ___/___

F.15.1.2 Blood pressure measurement (Photo reproduction)

7. Blood Pressure Measurements:



F.15.1.3 Cholesterol readings (Photo reproduction)

5) Serum cholesterol (recorded in mg. per cent). Determination made at the University of Minnesota on the basis of two .1 mL aliquots taken at both the initial and final examinations. When aliquots have been taken place a check in the appropriate parentheses at the right and record the date taken below.

Initial taken ____ ____ ____ ____
Mo. Day Yr.

Final taken ____ ____ ____ ____
Mo. Day Yr.

Both "I" aliquots taken ( ) Both "F" aliquots taken ( )

→		← Avg. →	←
I - F →			← Diff.
Overall →			← Avg.

Reserved for Recording Reading

F.15.1.4 Oscillometric readings (Photo reproduction)

1) Record the oscillometric readings for the RIGHT leg, for the two sites indicated.

a) Two inches below the lower margin of the patella ____ mm.

b) Two inches above the apex of the internal malleolus ____ mm.

2) Record the oscillometric readings for the LEFT leg, for the two sites indicated.

a) Two inches below the lower margin of the patella ____ mm.

b) Two inches above the apex of the internal malleolus ____ mm.

3) Total of all four readings on PRESENT examination (1a+1b+2a+2b) ____ mm.

4) Total of all four readings on PREVIOUS examination (1a+1b+2a+2b) ____ mm.

5) Item 4 — Item 3 ____ mm.

6) Item 5 ÷ Item 4 ____

F.15.1.5 Activity assessment (Photo reproduction)

ACTIVITY (1)	Did you perform this activity? No (2)	Yes (3)	For Clinic Personnel Use Only: Month of Activity Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec	Average number of times per month	H
SECTION A: Walking and Miscellaneous																
Walking for Pleasure and/or to Work																
Using Stairs When Elevator is Available																
Cross Country Hiking																
Back Packing																
Mountain Climbing																

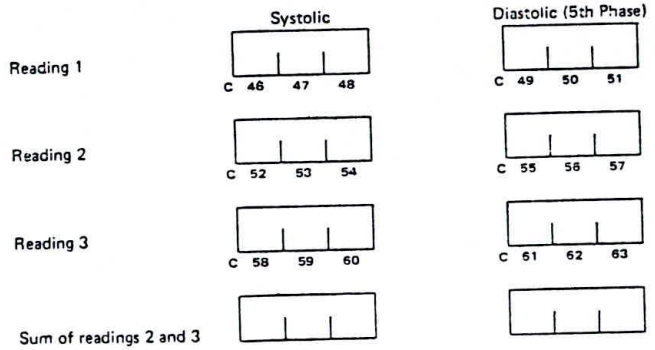
F.15.2 Good examples

F.15.2.1 Blood pressure measurement (Facsimile)

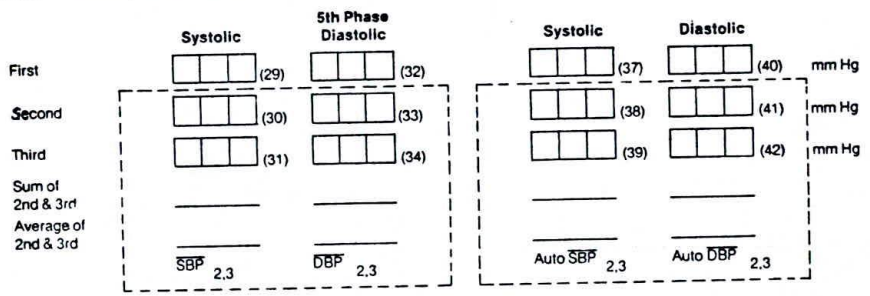
RZ BP measurements

Reading	BP in mmHg SBP	DBP
1st RZ		
a. Reading	___ ___	___ ___
b. Zero value	___	___
c. a-b	___ ___	___ ___
2nd RZ		
d. Reading	___ ___	___ ___
e. Zero value	___	___
f. d-e	___ ___	___ ___
Avg RZ		
g. Sum (c + f)	___ ___	___ ___
h. Avg (g ÷ 2)	___ ___	___ ___

F.15.2.2 Blood pressure measurement (Photo reproduction)



F.15.2.3 Blood pressure measurement (Photo reproduction)



F.15.2.4 Pulse (Photo reproduction)

28. Standard Pulse ☐☐ (28) beats/30 secs.

x2 = _____ beats/minute

F.15.3 Comment

F.15.1.1 is bad because there is no space for calculating the average systolic and diastolic blood pressures. F.15.1.2 has a confusing layout as well as a shortage of work space. The three blood pressure examples in Section F.15.2 avoid the problems of F.15.1.1 and F.15.1.2.

F.15.1.3 is defective because of the absence of any work space for performing the additions, subtractions, and divisions required for the item. As written, the operation must be done on scratch paper. A vertical layout, such as displayed in F.15.2.1, would be required to enable the respondent to use the form to make and record intermediate calculations needed to complete the item.

The layout in F.15.1.4 could be improved by providing work space for the required additions and by having item 4 appear above item 3 to facilitate the subtraction required in item 5.

The layout of F.15.1.5 is not well suited for the averaging process, since users would almost certainly have to copy the data from the item onto a separate worksheet to perform the required additions and divisions.

F.16 INSTRUCTION ITEMS

F.16.1 STOP items

F.16.1.1 Eligibility STOP item (Satisfactory; facsimile)

13. Ht (shoes off): ___ Inches

14. Wt (outdoor garments and shoes off): ___ lbs.

15. Q.I. = Wt/Ht^2 (use HPT Chart 11)

0. ____ lbs/in^2

16. Q.I. <0.0500 lbs/in^2

( ) Yes 1 (stop) No 2*

F.16.1.2 Temporary STOP item (Satisfactory; facsimile)

24. Serum specimen for central laboratory determinations collected?

( ) Yes 1 (stop) No 2*

* Remove by drawing required blood.

F.16.2 SKIP item (Satisfactory; facsimile)

6. (AAW) Have you ever had your blood pressure measured before your first visit here?

( ) Yes 1 ( ) No 2

If No, go to item 7.

If Yes, answer a and b

F.16.3 Comment

See Section 12.5.8 for discussion of STOP and SKIP items.

F.17 AGE AND BIRTHDATE ITEMS

F.17.1 (Satisfactory; facsimile)

9. (AAW) What is the month, day and year of your birth?

___ Mo - ___ Day - ___ Yr

10. (AAW) What was your age at your last birthday?

___

11. (DA) Does the birthdate fall within the interval defined below?

( ) Yes 1 (stop) No 2

Candidate must be 25 or older but 49 or less at the time of registration to be eligible for enrollment into the HPT. Permissible birthdates for visits completed in 1982 are (use month and day recorded in item 8):

___ Mo - ___ Day - 3 2 Yr

thru

___ Mo - ___ Day - 5 7 Yr

F.17.2 Comment

See Section 12.5.10.

F.18 REMINDER AND DOCUMENTATION ITEMS

F.18.1 Reminder items

F.18.1.1 Time window check (Facsimile)

5. Time window check

a. Date of BL 1 (item 20b, Form 01CP)

__Mo__ - __Day__ - __Yr__

b. Is this visit at least 7 days after the date in item a.

( ) Yes 1 (stop) No 2*

* Candidate should be rescheduled to remove this stop condition.

F.18.1.2 Procedure reminder (Facsimile)

24. Serum specimen for central laboratory determinations collected?

( ) Yes 1 (stop) No 2*

* Remove by drawing required blood.

F.18.2 Documentation items (Facsimile)

32. Form reviewed by:

a. Name: _____

b. HPT Cer. No. __ __ - __ __

c. Date: __Mo__ - __Day__ - __Yr__

33. Data entered by:

a. Name: _____

b. HPT Cer. No. __ __ - __ __

c. Date: __Mo__ - __Day__ - __Yr__

F.18.3 Comment

See Section 12.5.13.

F.19 FULL-PAGE VERSUS TWO-COLUMN LAYOUT

F.19.1 Full-page layout

F.19.1.1 (Unsatisfactory; photo reproduction)

1. When were you born? ___/___/___ (MONTH DAY YEAR)

2. Were you born in the U.S.? ☐ No ☐ Yes
IF YES, in what state? _____

3. Sex: ☐ Male ☐ Female

4. Race: ☐ White ☐ Black ☐ Hispanic ☐ Asian ☐ American Indian ☐ Other_____

5. Please circle the highest grade in school you have completed:
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 16+

6. Have you smoked at least 100 cigarettes (five packs) in your entire life? ☐ No ☐ Yes IF YES
a) How old were you when you first started regular smoking?_____years old
b) On the average of the entire time you smoked, how many cigarettes did you smoke per day?_____cigarettes per day
c) Did you ever stop smoking cigarettes for a year or more, and then start again? ☐ No ☐ Yes, stopped for____years
d) Do you smoke cigarettes now?
☐ No IF NO, how old were you when you stopped? _____years old
☐ Yes IF YES, how many cigarettes a day do you smoke now?_____cigarettes
e) Do you (or did you) inhale? ☐ No, rarely ☐ Yes, usually
f) Do you (or did you) smoke filter cigarettes ☐ No, rarely ☐ Yes, usually
g) Did you ever smoke cigarettes which you rolled yourself? ☐No ☐ Yes, for_____years

7. Have you ever smoked a pipe regularly? ☐ No ☐ Yes IF YES
a) How old were you when you started regular pipe smoking?_____years old
b) On the average of the entire time you smoked, how much pipe tobacco did you smoke? _____pipefuls per_____ (day or week)
c) Did you ever stop smoking a pipe for a year or more and then start again? ☐ No ☐ Yes, stopped for_____years
d) Do you smoke a pipe now?
☐ No IF NO, how old were you when you stopped?_____years old
☐ Yes IF YES, how much tobacco do you smoke now?_____pipefuls per_____ (day or week)

8. Have you ever smoked cigars regularly? ☐ No ☐ Yes IF YES
a) How old were you when you started regular cigar smoking?_____years old
b) On the average of the entire time you smoked, how many cigars did you smoke?_____cigars per_____ (day or week)
c) Did you ever stop smoking cigars for a year or more, and then start again? ☐ No ☐ Yes, stopped for_____years
d) Do you smoke cigars now?
☐ No IF NO, how old were you when you stopped?_____years old
☐ Yes IF YES, how many cigars do you smoke per day or per week? _____cigars per_____ (day or week)

F.19.1.2 (*Satisfactory; photo reproduction*)

PART III: Clinical Findings.

		Yes	No	Not possible to test
1) Is the femoralis artery palpable?	Right leg	( )	( )	( )
	Left leg	( )	( )	( )
2) Is the dorsalis pedis artery palpable?	Right foot	( )	( )	( )
	Left foot	( )	( )	( )

PART IV: Oscillometric Examination. The upper margin of the cuff for the knee measurement should be placed two (2) inches below the lower margin of the patella. The lower margin of the cuff for the ankle reading should be placed two (2) inches above the apex of the internal malleolus. The patient should be reclining and the knee unflexed with the ankle in a neutral position. If a particular reading cannot be taken because the site is missing or the patient has a lesion in the area of the site of the measurement, please indicate this by writing "Not Possible" in the space reserved for recording the measurement. Record the results in mm.

1) Record the oscillometric readings for the RIGHT leg, for the two sites indicated.

a) Two inches below the lower margin of the patella _____ mm.

b) Two inches above the apex of the internal malleolus _____ mm.

2) Record the oscillometric readings for the LEFT leg, for the two sites indicated.

a) Two inches below the lower margin of the patella _____ mm.

b) Two inches above the apex of the internal malleolus _____ mm.

F.19.2 Two-column layout

F.19.2.1 *Right-hand justification for response boxes* (*Satisfactory; photo reproduction*)

Item 6 continued:

C) How much exertion would it typically take to precipitate such an episode (check only one)?
- Walking at less than ordinary pace (1)[25]
- Walking at an ordinary pace (2)
- Walking hurriedly or up hill, or climbing stairs (3)
- Not related to exertion (4)

D) Can excitement, emotion, or meals precipitate such an episode? (Yes) (No)[26]

E) Does rest typically relieve such an episode?
- Not at all (1)[27]
- After more than 10 minutes (2)
- In less than 10 minutes (3)
- Rest not used (4)

F) Does nitroglycerin typically relieve such an episode?
- Not at all (1)[28]
- After more than 10 minutes (2)
- In less than 10 minutes (3)
- Nitroglycerin not used (4)

G) What has been the longest duration of such an episode?
- Less than 10 minutes (1)[29]
- 10 to 30 minutes (2)
- More than 30 minutes (3)

H) Have any of the episodes been such that rest or nitroglycerin did *NOT* bring relief in the typical manner? (Yes) (No)[30]

I) Did the patient get medical attention in connection with any episode of pain, aching, etc., during this period? (Yes) (No)[31]

If *NO*, proceed to item 6-J.

If *YES*, please give the place where such medical information may be found:

_____

Then avail yourself of this information and answer items i through viii below. (If medical attention was obtained on more than one occasion, answer the questions in connection with the most serious of the episodes.)

Item 6-I continued:

ii) Any evidence of shock? (Yes) (No)[33]

iii) Arrhythmia? (Yes) (No)[34]

iv) Leucocytosis? (Not Done) (Yes) (No)[35]

If *YES*, what was the highest recorded value (cells/mm³)? _____

v) Elevated sedimentation rate? (Not Done) (Yes) (No)[36]

If *YES*, what was the highest recorded value (mm/hr)? _____

vi) Abnormal SGOT? (Not Done) (Yes) (No)[37]

If *YES*, what was the highest recorded value (state units)? _____

vii) Abnormal LDH? (Not Done) (Yes) (No)[38]

If *YES*, what was the highest recorded value (state units)? _____

viii) ECG evidence of a new myocardial infarction?
- ECG not done (1)[39]
- Negative (2)
- Suggestive (3)
- Definite (4)

J) Did any of the episodes since the last completed follow-up visit result in a diagnosis of:

	Suspect	Yes	No
i) Myocardial infarction?	(3)	(1)	(2)[40]
ii) Acute coronary insufficiency?	(3)	(1)	(2)[41]
iii) Angina pectoris?	(3)	(1)	(2)[42]

7) Has the patient required nitroglycerin since his last completed follow-up visit? (Yes) (No)[43]

F.19.2.2 Left-hand justification for response boxes (Satisfactory; photo reproduction)

12. If death was not witnessed, what is the estimated time between when the patient was last known to be alive and the death? 47

[1] ≤ 1 minute
[2] 1–4 minutes
[3] 5–29 minutes
[4] 30–59 minutes
[5] 1–24 hours
[6] > 24 hours
[7] Unknown
[8] Death witnessed

PART V: Pathology Noted on Autopsy

13. Was an autopsy performed? 48

[1] Yes
[2] No

Were there findings of the following? (Check each Item)

Yes	No	Inadequate Information		
[1]	[2]	[3]	A. Esophagitis	49
[1]	[2]	[3]	B. Gastritis	50
[1]	[2]	[3]	C. Superficial gastric erosion(s)	51

13. (Continued)

Yes	No	Inadequate Information		
[1]	[2]	[3]	M. Other non-neoplastic renal pathology	
[1]	[2]	[3]	N. Malignant neoplasm	
[1]	[2]	[3]	O. Benign neoplasm	
[1]	[2]	[3]	P. Recent acute myocardial infarction	
[1]	[2]	[3]	Q. Old myocardial infarction or scar	
[1]	[2]	[3]	R. Rupture of myocardium	
[1]	[2]	[3]	S. Myocardial aneurysm	
[1]	[2]	[3]	T. Recent coronary occlusion by thrombosis or embolism	
[1]	[2]	[3]	U. Recent coronary occlusion by hemorrhage into plaque	
[1]	[2]	[3]	V. Pulmonary embolism	

F.19.3 Comment

The layout for F.19.1.1 is confusing and cluttered. The lack of a standard location for check spaces adds to the confusion. The layout in F.19.1.2 is cleaner. It requires more page space but makes the response positions of the items easier to locate than in F.19.1.1.

The two-column layout in the examples shown in F.19.2 makes more efficient use of page space than is the case in F.19.1.2. The examples in F.19.2 differ with regard to location of check positions; either arrangement is acceptable.

F.20 LAYOUT FOR SKIP ITEMS

F.20.1 Arrows and pointers

F.20.1.1 (Unsatisfactory; photo reproduction)

1 ☐ yes ——→
2 ☐ no ↓

2. Did you personally request the diet information from your physician? 1 ☐ yes 2 ☐ no
3. Please summarize the food changes your physician advised you to make.
CC USE 1☐
4. For each item below indicate whether it was for that reason that the physician asked you to follow the special diet.
a. Diabetes 1 ☐ yes 2 ☐ no
b. Overweight 1 ☐ yes 2 ☐ no
c. High Blood Pressure 1 ☐ yes 2 ☐ no
d. High Blood Fat or Cholesterol 1 ☐ yes 2 ☐ no
e. Food Allergy 1 ☐ yes 2 ☐ no
f. Ulcer 1 ☐ yes 2 ☐ no
g. Other 1 ☐ yes 2 ☐ no
Specify _____
5. Were you given printed instructions describing the special diet? 1 ☐ yes 2 ☐ no
6. Was the special diet explained to you by the physician or his staff?

1 ☐ yes ——→
2 ☐ no ↓

7. Check the following people who explained the diet to you.
a. Physician 1 ☐ yes 2 ☐ no
b. Nurse 1 ☐ yes 2 ☐ no
c. Dietitian or Nutritionist 1 ☐ yes 2 ☐ no
d. Other Staff 1 ☐ yes 2 ☐ no
Specify _____

8. How well did you understand the diet changes the physician advised you to make? (Check one)
1 ☐ Very well. I understood what changes to make
2 ☐ Fairly well. I understood some of the changes required but had further questions
3 ☐ Not very well. I didn't know what changes to make

9. Have you started making the diet changes the physician advised you to follow?

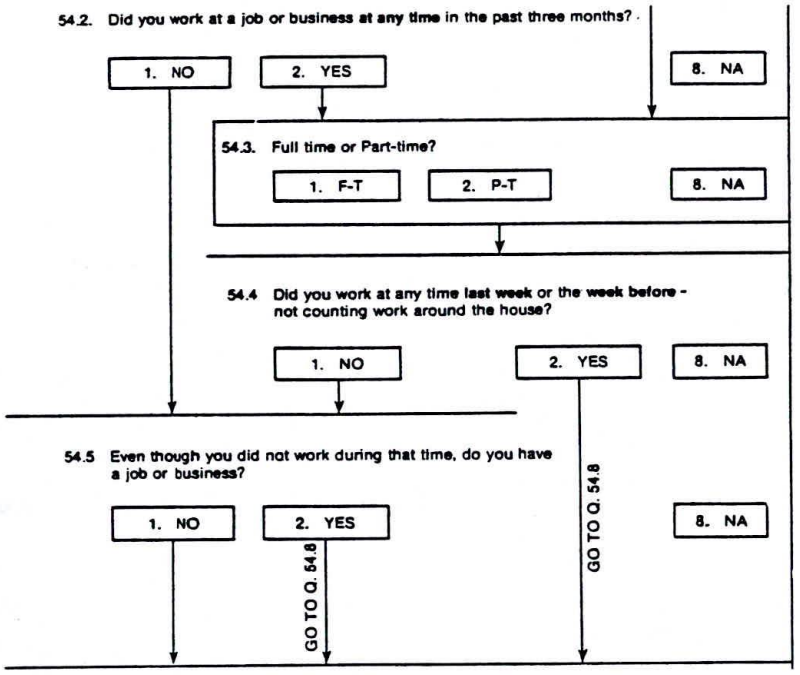
1 ☐ yes ——→
2 ☐ no ↓

10. Approximately how long has it been since you started making these diet changes?
1 ☐ less than one month
2 ☐ one-three months
3 ☐ four-six months
4 ☐ seven-nine months
5 ☐ ten-twelve months
6 ☐ more than twelve months

11. In general, how closely have you been following this diet during the past year?
1 ☐ have changed eating habits consistent with diet and very rarely go off diet
2 ☐ follow diet most of the time
3 ☐ have not been able to stick to the diet consistently

Continue with question 12.

F.20.1.2 (Unsatisfactory; photo reproduction)



F.20.1.3 (Satisfactory; photo reproduction)

7. Have you ever smoked a pipe regularly? ☐ No ☐ Yes IF YES

a) How old were you when you started regular pipe smoking?_____years old
b) On the average of the entire time you smoked, how much pipe tobacco did you smoke?_____pipefuls per_____ (day or week)
c) Did you ever stop smoking a pipe for a year or more and then start again? ☐ No ☐ Yes, stopped for_____years
d) Do you smoke a pipe now?
☐ No IF NO, how old were you when you stopped?_____years old
☐ Yes IF YES, how much tobacco do you smoke now?_____pipefuls per_____ (day or week)

8. Have you ever smoked cigars regularly? ☐ No ☐ Yes IF YES

a) How old were you when you started regular cigar smoking?_____years old

F.20.1.4 (Satisfactory; photo reproduction)

If the shipyard worker is DECEASED

a. Date of Death: ___ Mo ___ Day ___ Year
b. Place of Death: ___ City ___ State
c. Cemetery: ___ Name ___ City ___ State
d. Cause of Death: ___

Please GO TO PAGE 3 (YELLOW FORM) and answer the questions ABOUT THE DECEASED

F.20.2 SKIP or GO TO items

F.20.2.1 (Satisfactory; facsimile)

9. (AAW) Are you presently taking any drugs prescribed by a physician?

( ) Yes 1 (stop) No 2

If No, go to Item 10, Page 4

If Yes, answer items a thru d

F.20.2.2 (Satisfactory; photo reproduction)

11. Have you ever had any surgery or operations, even minor ones such as tonsillectomy?

YES ☐ ASK Q. 12 NO ☐ SKIP TO Q. 13 UNKNOWN ☐ SKIP TO Q. 13

IF YES, ASK:

12. Could you tell me:

(A) What type of surgery?	YES	NO	UNK	IF YES, ASK B, C: (B) How old were you at the time?	(C) Were you hospitalized? YES	NO	UNK
Tonsillectomy							
Appendectomy							
*Hysterectomy (removal of uterus)							
*Removal of ovaries							

F.20.3 Comment

The layouts for F.20.1.1 and F.20.1.2 are cluttered. Those for F.20.1.3 and F.20.1.4 are better.

The illustrations in F.20.2.1 and F.20.2.2 involve use of GO TO or SKIP instructions in place of arrows or pointers. Arrows and pointers have more visual impact than GO TO or SKIP instructions, but they add to the clutter of the form, as seen in F.20.1.1 and F.20.1.2. GO TO or SKIP instructions are preferable to arrows or pointers when the form involves a lot of skips on the same page or when the skips are to other pages of the form.

F.21 INSTRUCTIONAL INFORMATION

F.21.1 Shading or highlighting (Photo reproduction)

PLEASE COMPLETE THE ONE SECTION BELOW WHICH APPLIES TO YOU.

If you ARE the person named above

Did you ever work in a shipyard?

1 ☐ YES Please GO TO PAGE 3 and complete the yellow form. Skip page 2.

0 ☐ NO Please RETURN THIS QUESTIONNAIRE in the enclosed envelope so we can correct our records and prevent another mailing to you. Do not complete the remainder of this questionnaire.

If you ARE NOT the person named above

☐ Please check box and COMPLETE PAGE 2 of the white form.

THIS SURVEY IS AUTHORIZED UNDER THE DOE ORGANIZATION ACT PL 95-91. OMB NO. 1901-0250 EXP. DATE 9/30/84

F.21.2 Boxes

F.21.2.1 Boxed instructions for entire form (Photo reproduction)

```
Complete this form for all candidates who remain eligible after BL 1.
Proceed immediately to Form 04CP once this form is completed.

Answers to questions with boxed |__| item numbers must be reviewed by an
HPT physician. Questions preceded by (AAW) are to be asked as written; those
preceded by (SAW) are to be shown as written using HPT flashcards. Questions
preceded by (DA) are to be answered using information from previous items.
```

F.21.2.2 Boxed instructions for specific item (Photo reproduction)

14. BL 2 Appointment:

a. Time of day: __ __ : __ __ AM PM

b. Day of week: _____

c. Date: __Mo__ - __Day__ - __Yr__

```
NOTE: Date in item 14 must be at
least 7 days after date in item
20b on Form 01CP
```

15. Candidate given:

( )1 Appointment card
( )1 Participant reminder form
( )1 Informed consent material
( )1 Material introducing HPT
( )1 Other (specify):

_____

F.21.3 Comment

Instructional information contained on a form should be identified. This is done via reverse image printing, pointers, and use of a different print font in F.21.1. Boxes are used to set off instructional material in F.21.2.

F.22 UNFORMATTED RESPONSES

F.22.1 (Unsatisfactory; photo reproduction)

34	IS THERE A PREVIOUS HISTORY OF STROKE? 1. ____YES 2. ____NO 3. ____UNKNOWN
35	IF YES, MONTH ____ DAY ____ YEAR ____ UNKNOWN
36	IF THERE WAS A CEREBROVASCULAR DISEASE DIAGNOSIS: APPROXIMATE DATE OF ONSET: MONTH ____ DAY ____ YR. ____ DATE UNKNOWN ____ NO STROKE
37	ACTIVITY AT ONSET OF STROKE ____ UNKNOWN ____ NO STROKE
38	PLACE AT ONSET OF STROKE ____ UNKNOWN ____ NO STROKE
39	APPROXIMATE HOUR OF ONSET OF STROKE ____ UNKNOWN ____ NO STROKE

F.22.2 (Satisfactory; photo reproduction)

2) Has the patient been hospitalized at any time since his last quarterly examination? . . . ( ) Yes ( ) No

If YES, give the date, duration and reason for each hospitalization in the space below.

DATE	DURATION (Days)	REASON

F.22.3 (Satisfactory; facsimile)

7. Did the participant die in a hospital?

( )1 Yes ( )2 No ( )3 Unk

If Yes, give the name and address of the hospital and attending physician.

a. Name and address of hospital.

b. Name and address of attending physician.

F.22.4 Comment

There is not enough vertical space between lines in F.22.1. There should be at least ¼" of separation between lines, as in F.22.2, or the form should provide a boxed space of adequate size, as in F.22.3, when handwritten responses are required.

F.23 FORMATTED RESPONSES

F.23.1 Boxes (Photo reproduction)

3. *INTERVIEWER ASK:* Do you wish to have the results of your tests sent to your physician?
   1 ☐ YES 33 2 ☐ NO → GO TO QUESTION 12

4. ☐☐ 34 *Title*

5. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ 16 *First Name*

6. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ 51 *Last Name*

7. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ 71 *Clinic/Building*

8. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ 95 *Street Address*

9. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ 120 *City*

10. ☐☐ 140 *State*

11. ☐☐☐☐☐☐☐☐☐ 142 *Zip Code*

F.23.2 Hatched lines (Photo reproduction)

Social Security Number ☐ Social Security Number unavailable

C 62 63 64 C 65 66 C 67 68 69 70

PUNCH C62-70 all 0's if SS unavail.

NOW I WOULD LIKE TO ASK YOU A FEW QUESTIONS ABOUT WHERE YOU HAVE LIVED FOR THE PAST FEW YEARS

F.23.3 Comment

See Section 12.6.8.

F.24 LAYOUT FOR CHECK POSITIONS

F.24.1 Varied order for yes-no responses (Unsatisfactory; photo reproduction)

7. At least once a week, do you engage in any regular activity akin to brisk walking, jogging, bicycling, etc. long enough to work up a sweat?
   ☐ No
   ☐ Yes ____ How many times per week?_____ Activity _____

SOCIAL AND DIETARY HABITS

9. Do you smoke CIGARETTES now? ☐ No ☐ Yes How many CIGARETTES per day? _____
   Do you drink COFFEE now? ☐ No ☐ Yes How many CUPS per day? _____
   Do you drink TEA now? ☐ No ☐ Yes How many CUPS per day? _____
   Do you drink MILK now? ☐ No ☐ Yes How many GLASSES per day? _____ *(1 glass = 8 oz.)*

12. When eating meat, do you avoid eating the fat? Yes ☐ No ☐

13. Do you often add salt to your food? Yes ☐ No ☐; Pepper? Yes ☐ No ☐;
    Catsup, mustard, or spices? Yes ☐ No ☐; Mayonnaise or salad oil? Yes ☐ No ☐

F.24.2 Scattered check positions (Unsatisfactory; photo reproduction)

3. Long leg sitting (knees <90° flex) with arm support R/L
   (I) without arms support ___ time
   weight distribution —symmetrical —more on L/R
   hips abd —neutral; pelvis:thigh ✂ ___ | pelvis:thigh ✂ ___
   hip rotation ___ neutral | w/knees pass. ext. to ___
   trunk ___ erect ___ kyphosis ___ lateral flexion R/L
   shoulders ___ elevated ___ retracted ___ protracted
   head ___ erect ___ cradled ___ lateral flexion R/L
   LE's ___ relaxed ___ fixing in flexion ___ tonic extension knees
   UE support ___ forward R/L ___ lateral R/L ___ posterior R/L
   shifts weight to ___ L ___ recovers ___ R ___ recovers
   ___ ant ___ recovers ___ post ___ recovers
   ___ diag back L ___ recovers
   ___ diag back R ___ recovers

F.24.3 Scattered check positions (Photo reproduction)

25. When was the last time you smoked that much? ___/___ (MONTH YEAR) UNKNOWN ☐

26. About how many cigarettes per day did you smoke 2 years ago? _____ UNKNOWN ☐

27. Did you smoke cigarettes a year ago? YES ☐ ASK Q. 28 NO ☐ SKIP TO Q. 32 UNKNOWN ☐ SKIP TO Q. 29

IF YES, ASK:

28. About how many cigarettes did you smoke a year ago? _____ UNKNOWN ☐

29. Was there ever any period of time when you stopped smoking?

YES ☐ ASK Q. 30-31 NO ☐ SKIP TO Q. 34 UNKNOWN ☐ SKIP TO Q. 34

F.24.4 Inadequate check space (Photo reproduction)

SCHOLARLY QUALITY OF PROGRAM FACULTY

1. ( ) DISTINGUISHED
2. ( ) STRONG
3. ( ) GOOD
4. ( ) ADEQUATE
5. ( ) MARGINAL
6. ( ) NOT SUFFICIENT FOR DOCTORAL EDUCATION

0. ( ) DON'T KNOW WELL ENOUGH TO EVALUATE

FAMILIARITY WITH WORK OF PROGRAM FACULTY

1. ( ) CONSIDERABLE FAMILIARITY
2. ( ) SOME FAMILIARITY
3. ( ) LITTLE OR NO FAMILIARITY

EFFECTIVENESS OF PROGRAM IN EDUCATING RESEARCH SCHOLARS/SCIENTISTS

1. ( ) EXTREMELY EFFECTIVE
2. ( ) REASONABLY EFFECTIVE
3. ( ) MINIMALLY EFFECTIVE
4. ( ) NOT EFFECTIVE

0. ( ) DON'T KNOW WELL ENOUGH TO EVALUATE

CHANGE IN PROGRAM QUALITY IN LAST FIVE YEARS

1. ( ) BETTER THAN FIVE YEARS AGO
2. ( ) LITTLE OR NO CHANGE IN LAST FIVE YEAR
3. ( ) POORER THAN FIVE YEARS AGO

0. ( ) DON'T KNOW WELL ENOUGH TO EVALUATE

F.24.5 Unsatisfactory list layout (Photo reproduction)

18. Please check Marital Status: NEVER MARRIED ☐1 MARRIED ☐2 SEPARATED ☐3 (55)
DIVORCED ☐4 WIDOWED ☐5

19. How many GRADES of school, including College, did you complete? _____ grades(56-57)

20. Are you under treatment for high blood pressure? YES ☐1 NO ☐2 (58)

21. How many hours has it been since your last meal? _____ hours (59)

F.24.6 Satisfactory list layout (Contrived from F.24.5)

Please check marital status:

( )1 Never married
( )2 Married
( )3 Separated
( )4 Divorced
( )5 Widowed

F.24.7 Excessive white space (Contrived from F.24.8)

Hepatobiliary Pathology on Autopsy (check one or more)

1. No autopsy ( )
2. Normal liver ( )
3. Hepatitis ( )
4. Fatty metamorphosis ( )
5. Cirrhosis ( )
6. Congestion ( )
7. Nonspecific changes ( )
8. Gall stones ( )
9. Other findings (please specify): ( )

F.24.8 Eye lines (Photo reproduction)

Hepatobiliary Pathology on Autopsy (check one or more)

1. No autopsy ..... ( )
2. Normal liver ..... ( )
3. Hepatitis ..... ( )

4. Fatty metamorphosis ..... ( )
5. Cirrhosis ..... ( )
6. Congestion ..... ( )

7. Nonspecific changes ..... ( )
8. Gall stones ..... ( )
9. Other findings (please specify): ..... ( )

F.24.9 Eye lines and blocking (Contrived from F.24.8)

Hepatobiliary Pathology on Autopsy (check one or more)

1. No autopsy ..... ( )
2. Normal liver ..... ( )
3. Hepatitis ..... ( )

4. Fatty metamorphosis ..... ( )
5. Cirrhosis ..... ( )
6. Congestion ..... ( )

7. Nonspecific changes ..... ( )
8. Gall stones ..... ( )
9. Other findings (please specify) ..... ( )

F.24.10 Blocked list (Facsimile)

10. (AAW) Have you taken any of these caffeine containing, non-prescription drugs in the last month? (Use HPT Chart 13 as a flash card if you wish)

( )1 Anacin
( )1 Appedrine
( )1 Bromoquinine

( )1 Coryban D
( )1 Dexatrim
( )1 Dristan

( )1 Excedrin
( )1 Midol
( )1 Nodoz

( )1 Permathene - 12
( )1 Prolamine
( )1 Triaminicin
( )1 Vanquish

F.24.11 Comment

The layout in F.24.1 is confusing because of the variation in the position of the Yes-No check spaces. In question 7 the No is above the Yes. In question 9 Yes follows No. The order is reversed in questions 12 and 13.

Items F.24.2 and F.24.3 are both examples of layouts with scattered locations for check positions. Contrast these layouts with those shown for illustrations F.24.6 through F.24.10.

The parentheses for recording checks are too small and there is not enough separation between the lines in F.24.4. The lack of line separation can cause confusion when data from completed forms are keyed. A slight error in placement of a check can cause the item to be keyed incorrectly.

F.24.5 is included to illustrate the importance of layout in a list of items. The format in the example can be expected (as was the actual case) to result in an understatement of the number of people married. Unless one is careful, the first space will be used to denote a married individual because of where the word *Never* appears. The problem could be avoided with a single-column vertical layout as shown in F.24.6, or with better spacing or different placement of the check boxes.

F.24.6 through F.24.10 involve lists with vertical layouts. The layout in F.24.7 requires the respondent to identify the item to be checked on the left hand side of the page and then locate the check space on the right hand side of the page without any lines to aid the eye. Eye lines should be used, as in F.24.8 and F.24.9, when the list and check spaces are separated. Blocking, as illustrated in F.24.9, also helps to avoid confusion in locating the proper check space. Placement of the check space to the left of the item, as shown in F.24.10, avoids the need for eye lines.

F.25 FIELD DESIGNATIONS AND PRECODED RESPONSES

F.25.1 Field designations (Satisfactory; photo reproduction)

III. FAMILY HISTORY

		Age if Living	Age at Death	Cause of* Death
20. Father		145-46	147-48	149
21. Mother		150-51	152-53	154
22. Brother(s)	A	155-56	157-58	159
	B	160-161	162-63	164
	C	165-66	167-68	169
	D	170-71	172-73	174
	E	175-76	177-78	179
23. Sister(s)	A	180-81	182-83	184
	B	185-86	187-88	189
	C	190-91	192-93	194
	D	195--96	197-98	199
	E	200-01	202-03	204

24. Comments: _____

_____

*Causes of Death:

1 - Coronary Heart Disease (Heart Attack)
2 - Stroke
3 - Hypertensive Heart Disease
4 - Cancer
5 - Other Heart Disease (specify) _____
6 - Other Disease (specify)
_____
7 - Accident or trauma
8 - Unknown
9 - Old Age

F.25.2 Precoded responses

F.25.2.1 (Satisfactory; photo reproduction)

10. Which choice below would help you lose the most weight?
(Circle one.)

Jogging 1 mile. 01
Walking 3 miles. 02
Refusing one piece of cherry pie. 03
Refusing one 12-ounce soda 04

11. Read each statement below and then circle the number to the right of the statement that best describes how YOU feel. If you STRONGLY AGREE with a statement, circle number 1. If you STRONGLY DISAGREE, circle number 5. Try not to circle 3 unless you are really unsure of how you feel.

(Circle one number on each line.)

	Strongly Agree	Agree	Unsure	Disagree	Strongly Disagree
a. My health is directly affected by the actions I take every day	.01	.02	.03	.04	.05
b. I am doing all I can to keep myself healthy	.01	.02	.03	.04	.05
c. People can't do anything to reduce their chances of having a heart attack	.01	.02	.03	.04	.05
d. I am not concerned about preventive health measures	.01	.02	.03	.04	.05
e. I just go on doing the things that make me less healthy even when I know I shouldn't	.01	.02	.03	.04	.05

F.25.2.2 (Photo reproduction)

8) In your best judgment (based on a capsule count and/or any other information or impressions obtained from the patient at this visit), what percentage of the capsules of ALLOCATED medication (i.e., from bottles 1-30) prescribed since Initial Visit 3 has the patient actually taken?

At least 80% ..... (1) 15
At least 60% but less than 80% ..... (2)
At least 40% but less than 60% ..... (3)
At least 20% but less than 40% ..... (4)
Less than 20% ..... (5)

F.25.2.3 (Facsimile)

29. (AAW) Who usually prepares the meals you eat at home? (Use list below to categorize response)

( )1 Candidate alone
( )2 Spouse or partner, alone
( )3 Someone else, alone

( )4 Candidate and spouse or partner
( )5 Candidate and someone else
( )6 Other (specify)

_____

F.25.3 Comment

The numbers appearing in items 20 through 23 in F.25.1 correspond to field designations for the data entry process. The numbers appearing in F.25.2.1, in the parentheses in F.25.2.2, and next to the parentheses in F.25.2.3, correspond to defined codes for designated fields.

G. Sample manual of operations, handbook, and monitoring report

G.1 Introduction
G.2 Table of contents of the National Cooperative Gallstone Study Clinic Manual of Operations (July 1975 version)
G.3 Listing of pages in the Hypertension Prevention Trial Handbook (April 7, 1983 version)
G.4 Sample tables from Macular Photocoagulation Study Treatment Monitoring Report (January 31, 1982)
G.5 Listing of tables in the final Treatment Effects Monitoring Report of the Persantine Aspirin Reinfarction Study (October 15, 1979 Database)

G.1 INTRODUCTION

The sample documents contained herein were provided by the Hypertension Prevention Trial (HPT), Macular Photocoagulation Study (MPS), National Cooperative Gallstone Study (NCGS), and Persantine Aspirin Reinfarction Trial (PARIS). All four trials are sketched in Appendix B.

G.2 TABLE OF CONTENTS OF THE NATIONAL COOPERATIVE GALLSTONE STUDY CLINIC MANUAL OF OPERATIONS (July 1975 Version)

PART I Introduction

Chapter 1. Background and Development (2 pages)

Chapter 2. Objectives and Study Design (3 pages)
- 2.1 Study Objectives
- 2.2 Study Design
- 2.3 Treatment Schedule
- 2.4 Interim Monitoring

Chapter 3. Organization (7 pages)
- 3.1 Introduction
- 3.2 The Coordinating Center and Its Units
- 3.3 The Steering Committee and Sub-Committees
- 3.4 The Advisory Board

Chapter 4. Policy Matters (19 pages)
- 4.1 Introduction
- 4.2 Informed Consent
- 4.3 Blinding and Breaking of the Code
- 4.4 Ancillary Studies and the Disclosure of Ancillary Study Results
- 4.5 Blinding Ancillary Study Investigators
- 4.6 Protocol Changes During the Trial
- 4.7 Evaluation of Treatment Center Performance
- 4.8 Phase III
- 4.9 Sharing Costs

Chapter 5. Patient Recruitment (10 pages)
- 5.1 Introduction
- 5.2 Mechanism of Referral
- 5.3 Patient Recruitment Sources
- 5.4 Editorials and Newsletters

PART II Evaluation and Follow-Up

Chapter 6. Patient Eligibility and Exclusion Criteria (10 pages)
- 6.1 Introduction
- 6.2 Eligibility Criteria

Chapter 7. Randomization and Drug Packaging (10 pages)
- 7.1 Introduction
- 7.2 Master Randomization List
- 7.3 Drug Packaging and Distribution
- 7.4 Randomization
- 7.5 Parallel Ancillary Studies
- 7.6 Local Access to the Treatment Code

Chapter 8. Drug Administration (13 pages)
- 8.1 Introduction
- 8.2 Project Physician
- 8.3 Treatment Center Pharmacist

Chapter 9. Dosage Level Adjustment (5 pages)
- 9.1 Introduction
- 9.2 Initial Stabilization
- 9.3 Dosage Level Re-Adjustment
- 9.4 Assignment to Known Placebo
- 9.5 Reinstatement of Assigned Therapy

Chapter 10. Schedule and Description of Patient Visits (18 pages)
- 10.1 Introduction

10.2 Evaluation Visit
10.3 Randomization Visit
10.4 Follow-up Visits
10.5 Interim Visits

Chapter 11. Dropouts and Withdrawals (3 pages)
11.1 Introduction
11.2 Dropouts and Withdrawals
11.3 Missed Visit Form
11.4 Reinstatement of Dropouts
11.5 Transfers
11.6 Tracking Procedures

Chapter 12. Management of Illness (15 pages)
12.1 Introduction
12.2 Medical Staff and Responsibilities
12.3 Summary of Clinical Management Procedures
12.4 Management of Gastrointestinal disorders
12.5 Management of Hepato-Biliary Disorders
12.6 Management of Any Other Illness Possibly Related to Bile Acid Feeding

Chapter 13. Permanent Cessation of Therapy (3 pages)
13.1 Introduction
13.2 Permanent Cessation of Therapy
13.3 Death of a Patient
13.4 Biological Specimens

PART III Procedures

Chapter 14. Radiological Procedures (5 pages)
14.1 Introduction
14.2 Patient's Preparation
14.3 Obtaining the X-Ray
14.4 Development of Film
14.5 Non-Visualizing Gallbladder
14.6 Reading the X-Ray
14.7 Dissolution of Gallstones
14.8 Handling and Storage

Chapter 15. Determination of Gallstone Volume and Number (4 pages)
15.1 Introduction
15.2 Visual Reading
15.3 Computer Assisted Reading

Chapter 16. Procedures for Duodenal Intubation (6 pages)
16.1 Introduction
16.2 Preparation
16.3 Duodenal Intubation
16.4 Shipment of Specimens
16.5 Processing of Specimens
16.6 Supplies

Chapter 17. Procedures for Liver Biopsies (5 pages)
17.1 Introduction
17.2 Preparation
17.3 Performing the Biopsy
17.4 Treatment Center Pathology Laboratory
17.5 Central Morphology Laboratory

Chapter 18. Procedures for Electrocardiogram (1 page)
18.1 Introduction
18.2 Performing the ECG

Chapter 19. Collection and Handling of Laboratory Specimens (16 pages)
19.1 Introduction
19.2 Preparation
19.3 Urine
19.4 Blood and Serum
19.5 Shipment of Specimens
19.6 Processing of Specimens
19.7 Supplies

Chapter 20. Laboratory Evaluations and Tests (6 pages)
20.1 Introduction
20.2 Required Tests
20.3 Test Result Ranges

Chapter 21. Medication Procurement and Handling (8 pages)
21.1 Introduction
21.2 Capsule Formulation
21.3 Capsule Requirements
21.4 Ordering
21.5 Manufacture
21.6 Shipping

Chapter 22. Treatment Center Procedures (6 pages)
22.1 Introduction
22.2 Scheduling Visits
22.3 Visit Procedures
22.4 Preparing for a Patient Visit
22.5 Checking Forms
22.6 Medical Records
22.7 Other Responsibilities

PART IV Data Handling and Analysis

Chapter 23. Completion and Mailing of Forms (11 pages)
23.1 Introduction
23.2 Forms Supplies
23.3 Patient Identification

23.4 Completing Forms
23.5 Batching and Mailing
23.6 Receipt of Forms
23.7 Treatment Center Enquiry

Chapter 24. Data Management Procedures (9 pages)
24.1 Introduction
24.2 Eligibility Evaluation
24.3 Data Entry
24.4 Randomization Processing
24.5 Editing
24.6 Update Procedures
24.7 Form Revision
24.8 Back-Up and Security

Chapter 25. Endpoints and Statistical Analyses (9 pages)
25.1 Introduction
25.2 Evaluation of Treatment
25.3 Final Statistical Analyses
25.4 Intermediary States
25.5 Interim Statistical Analyses

Chapter 26. Publicity and Publications (4 pages)
26.1 Introduction
26.2 Press Releases and Interviews
26.3 Presentations and Publications
26.4 Review of Presentations and Publications

G.3 LISTING OF PAGES IN THE HYPERTENSION PREVENTION TRIAL HANDBOOK (April 7, 1983 Version)[1]

1. Background

- Abbreviations
- Definitions (3 pages)
- Proposed time schedule
- HPT objectives
- Specific aims and operational tasks of Stage 1
- HPT landmark dates
- Design and operating synopsis for Stage 1
- Projected distribution of participants for Cohorts 1, 2, and 3 combined
- Minimal detectable treatment-control difference
- Test cohort distribution of participants by treatment assignment
- Anticipated distribution of participants by treatment group for Cohorts 1, 2, and 3 combined (2 pages)
- Identification numbers
- Document numbering scheme (3 pages)
- HPT numbered documents (2 pages)

2. Organization

- HPT centers
- HPT bodies
- Investigative Group specifications (IG)
- Steering Committee specifications (SC)
- Executive Committee specifications (EC)
- Quality Assurance Committee specifications (QAC)
- Intervention Methods Committee specifications (IMC)
- Laboratory Committee specifications (LC)
- Treatment Effects Monitoring and Analysis Committee specifications (TEMAC)
- Policy Advisory Board specifications (PAB)
- HPT participating centers
- HPT functions by centers
- Steering Committee and Executive Committee composition
- Policy Advisory Board composition
- HPT meetings
- Steering Committee rules
- HPT Committee structure

3. Enrollment

- Major HPT inclusion and exclusion criteria
- HPT Chart 05: Exclusion conditions by form and item number (2 pages)
- HPT Chart 06: Baseline Visit 1 exclusion drugs (2 pages)
- HPT recruitment approaches
- Number of persons to be covered in recruitment mailing
- Randomization features
- HPT consent and enrollment procedures (2 pages)

4. Weight strata

- HPT weight strata
- HPT Chart 07: Minimal BL 1 body weight required for classification in the high (H) weight stratum
- HPT Chart 15: BL 1 body weight exclusion limit for a Quetelet's Index ≥ 0.0500
- HPT Chart 11: Quetelet's index by height and weight

1. Each line in the listing represents a page in the Handbook, except where indicated.

5. Intervention

- HPT Stage I study treatments
- HPT Chart 13: Time schedule for intervention contacts
- Required forms and procedures for intervention contacts
- HPT Chart 16: Intervention documents list

6. Data schedule

- Forms list
- Charts list
- Flashcards list
- Required forms and related documents for data collection visits (2 pages)
- HPT Chart 18: HPT data collection examination schedule (2 pages)
- HPT procedures by data collection visit
- Blood pressure measurement
- Height measurement
- Weight measurement
- Blood collection
- Blood processing for serum collection
- Upper right arm girth measurement
- Skinfold thickness measurement
- Electrocardiogram (ECG)
- 24-hour food record collection
- 24-hour food record processing
- 24-hour food record review and mailing
- Urine collection
- Urine processing

7. Time constraints

- Cohort specifications
- Time window specifications for baseline visits
- Time window specifications for follow-up visits
- HPT Chart 13: Time schedule for intervention contacts

8. Assurance procedures

- Quality assurance procedures
- Certification and recertification schedule
- Equipment inspection and maintenance schedule
- Clinic certification and recertification
- Personnel certification and recertification
- BP observer certification and recertification specifications
- Center director certification and recertification specifications
- Clinic coordinator certification and recertification specifications
- Data entry operator certification and recertification specifications
- Dietary interventionist certification and recertification specifications
- Food record documentor certification and recertification specifications
- Laboratory technician certification and recertification specifications
- ECG technician certification and recertification specifications
- Skinfold observer certification and recertification specifications
- Study physician certification and recertification specifications
- Wt-Ht observer certification and recertification specifications
- General inspection and maintenance procedures
- Standard BP manometer inspection procedure
- Standard BP manometer maintenance procedure
- Random zero BP manometer inspection procedure
- Random zero blood pressure manometer maintenance procedures (2 pages)
- Scale inspection procedure
- Scale maintenance procedure
- Skinfold caliper inspection procedure
- Room thermometer inspection procedure

9. Policy matters

- Design and data separation principles
- HPT policy prohibitions
- HPT document access policy
- HPT publicity policy
- HPT authorship policy
- HPT presentation and publication policy
- HPT ancillary study policy
- HPT abstract submission clearance policy (2 pages)
- HPT external presentation clearance procedure
- HPT manuscript clearance procedure
- HPT distributed data analysis policy

10. Miscellaneous

- Medical management principles
- Clinic supply procedures
- Document storage and distribution
- Center to center communications ground rules (2 pages)
- Exercise and diet preparation for BL 1, 2, 3, IE and all FUs
- Data rounding rules
- Data entry and correction procedures
- Data documentation assurance

G.4 SAMPLE TABLES FROM MACULAR PHOTOCOAGULATION STUDY TREATMENT MONITORING REPORT (January 31, 1982 Report)

Full report available via the National Technical Information Service, Springfield, VA, accession no. PB83-168-179.

Available information* by assignment, SMD study, 01-31-82

	Untreated			*Treated*		
Visit	*Completed*	*Missed*	*Delinquent†*	*Completed*	*Missed*	*Delinquent†*
Initial visit	111	—	—	113	—	—
Treatment visit	—	—	—	113	—	—
Post-treatment (6-weeks)	—	—	—	106	—	—
Follow-up 01 (3 months)	97	1	3	100	0	1
Follow-up 02 (6 months)	81	3	0	81	1	2
Follow-up 03 (12 months)	52	0	1	53	0	0
Follow-up 04 (18 months)	23	0	0	18	2	0
Follow-up 05 (24 months)	10	0	1	10	0	1
Follow-up 06 (30 months)	0	0	0	2	0	0
All follow-up visits	263	4	5	264	3	4
All visits	374	4	5	596	5	5

*The numbers in this table reflect clinic forms received and entered at the coordinating center.

†Delinquent visits (visits for which the time window has expired, but no form has been received in the coordinating center).

Change in visual acuity from initial visit (IV) to specified follow-up visits (FV), SMD study

	Untreated	*Treated*	
Distribution of change from IV to FV01:			
> 1.5 lines better	4 (4.1)	16 (16.0)	
< 1.5 lines change	45 (46.4)	57 (57.0)	
1.5–3.5 lines worse	23 (23.7)	9 (9.0)	
3.5–5.5 lines worse	15 (15.5)	4 (4.0)	
5.5–7.5 lines worse	8 (8.2)	6 (6.0)	
> 7.5 lines worse	2 (2.1)	8 (8.0)	
Total eyes	97	100	
Distribution of change from IV to FV02:			
> 1.5 lines better	4 (4.9)	16 (19.8)	
< 1.5 lines change	22 (27.2)	38 (46.9)	
1.5–3.5 lines worse	18 (22.2)	13 (16.0)	
3.5–5.5 lines worse	13 (16.0)	1 (1.2)	p = 0.06
5.5–7.5 lines worse	8 (9.9)	6 (7.4)	
> 7.5 lines worse	16 (19.8)	7 (8.6)	
Total eyes	81	81	
Distribution of change from IV to FV04:			
> 1.5 lines better	2 (8.7)	0 (0.0)	
< 1.5 lines change	5 (21.7)	11 (61.1)	
1.5–3.5 lines worse	2 (8.7)	1 (5.6)	
3.5–5.5 lines worse	1 (4.3)	2 (11.1)	p = 0.06
5.5–7.5 lines worse	5 (21.7)	0 (0.0)	
> 7.5 lines worse	8 (34.6)	4 (22.2)	
Total eyes	23	18	
Distribution of change from IV to LAST FV after FV01:			
> 1.5 lines better	7 (8.3)	14 (17.1)	
< 1.5 lines change	16 (19.0)	33 (40.2)	
1.5–3.5 lines worse	14 (16.7)	8 (9.8)	
3.5–5.5 lines worse	9 (10.7)	15 (18.3)	p = 0.00003
5.5–7.5 lines worse	13 (15.5)	3 (3.7)	
> 7.5 lines worse	25 (29.8)	9 (11.0)	
Total eyes	84	82	

Number of patients with selected baseline characteristics, SMD study

	Untreated	*Treated*		*Untreated*	*Treated*
Study Eye			**Diabetes**		
Right	66 (59.5)	60 (53.1)	No	105 (94.6)	109 (96.5)
Left	45 (40.5)	53 (46.9)	Yes or ?	6 (5.4)	4 (3.5)
Sex			**Hypertension**		
Male	63 (56.8)	46 (40.7)	None	23 (20.7)	16 (14.2)
Female	48 (43.2)	67 (59.3)	BP > 140/80 or on medication	88 (79.3)	95 (84.1)
Race			**Cigarette use**		
Caucasian	111 (100.0)	113 (100.0)	Little or none	84 (75.7)	86 (76.1)
Black	0 (0.0)	0 (0.0)	> 10 per day	27 (24.3)	27 (23.9)
Other	0 (0.0)	0 (0.0)	**Aspirin use**		
Histo belt resident			< 4 per week	87 (78.4)	79 (69.9)
Never	54 (48.6)	57 (50.4)	4–28 per week	22 (19.8)	27 (23.9)
Ever	57 (51.4)	56 (49.6)	> 28 per week	2 (1.8)	7 (6.2)
Presently	38 (34.2)	38 (33.6)			

G.5 LISTING OF TABLES IN THE FINAL TREATMENT EFFECTS MONITORING REPORT[2] OF THE PERSANTINE ASPIRIN REINFARCTION STUDY (October 15, 1979 Database)

Section 1. Patient follow-up

- Status of patients by treatment group
- Number and percentage missed visits by treatment group and follow-up visit

Section 2. Fatal and nonfatal events

- Number and percentage dead by treatment group and cause of death (15 pages)
- Percentage dead by selected baseline characteristics and treatment group (4 pages)
- Percentage of patients with specified nonfatal events as reported on follow-up visit forms by treatment group (3 pages)
- Number and percentage of patients with specified nonfatal events as classified by the Mortality and Morbidity Committee by treatment group
- Percentage of patients with de novo and recurrent angina by specified baseline characteristics and treatment group (2 pages)
- Percentage of fatal and nonfatal events by treatment group (6 pages)
- Number and percentage fatal and nonfatal events as classified by the Mortality and Morbidity Committee by treatment group
- Plot of Z-values for observed differences in proportion of deaths and critical boundaries for $\alpha = 0.05$ (2 pages)
- Plot of Z-values for observed differences in proportion of coronary deaths or definite MIs and critical boundaries
- Plot of Z-values for observed differences in proportion of deaths or definite MIs and critical boundaries for $\alpha = 0.05$ (2 pages)
- Percentage of selected fatal and nonfatal events by clinic and treatment group (7 pages)
- Cumulative fatal and nonfatal event rates and number of patient intervals by treatment group and months of follow-up (5 pages)
- Lifetable plots by treatment groups of:
  - Death—all causes
  - Coronary death
  - Sudden coronary death
  - Definite nonfatal MIs
  - Fatal or nonfatal pulmonary coronary death or definite MI
  - Fatal or nonfatal pulmonary embolism or thrombophlebitis
  - Death—all causes or definite MI
  - Cardiovascular (CV) death or any CV event, new angina excluded
  - Death—all causes or any CV event, new angina excluded
  - New angina
  - CV death or any CV event
  - Death—all causes or any CV event
- Percentage of patients hospitalized by reason and treatment group, all follow-up visits combined
- Percentage of patients hospitalized for specified symptoms by treatment group, all follow-up visits combined

Section 3. Adherence and side effects

- Percentage distribution of patients by adherence level and follow-up visits (2 pages)
- Percentage distribution of patients by number of tablets prescribed and follow-up visits
- Percentage of patients with non-compliance as defined by the urine salicylate and urine dipyridamole tests by follow-up visit and treatment group (3 pages)
- Percentage of patients with non-compliance as defined by the urine salicylate and urine dipyridamole tests by follow-up visit and treatment group, excluding patients on zero prescription (3 pages)
- Percentage of patients with non-compliance as defined by the urine salicylate and urine dipyridamole tests by clinic, follow-up visit and treatment group (10 pages)
- Percentage of all possible tablets taken, by clinic and treatment group, all follow-up visits combined
- Percentage of all possible tablets taken, by follow-up visit and treatment group, all clinics combined
- Percentage of patients with reduced level of adherence by reason and treatment group, all follow-up visits combined (2 pages)

2. Supplied by Persantine Aspirin Reinfarction Study Coordinating Center, April 1983.

- Percentage of patients complaining of specific types of problems by treatment group, all follow-up visits combined
- Percentage of patients with reduced prescription by reason and treatment group, all follow-up visits combined
- Number of side effects forms submitted, by clinic and treatment group
- Percentage of patients with side effects forms by reason and by treatment group, all follow-up visits combined (2 pages)
- Mean urine salicylate and percent of patients with urine salicylate level above 10 mg/100 ml by visit and treatment group
- Percentage of patients with positive dipyridamole test for specified visits by treatment group
- Percentage of patients using or prescribed specific types of medication since entry, by follow-up visit and treatment group (2 pages)

Section 4. Laboratory and clinical findings

- Percentage of patients reporting specified symptoms by treatment group, all follow-up visits combined
- Percentage of patients with one or more laboratory or clinical measurements outside given limits by treatment group, all follow-up visits combined (2 pages)
- Percentage of patients with one or more laboratory or clinical measurements outside given limits by treatment group, all follow-up visits combined excluding patients outside the limits at baseline (2 pages)
- Distribution of changes from baseline to first annual visit of laboratory measurements by treatment group (5 pages)
- Distribution of changes from baseline to second annual visit of laboratory measurements by treatment group (5 pages)
- Distribution of changes from baseline to third annual visit of laboratory measurements by treatment group (5 pages)
- Distribution of changes from baseline to fourth annual visit of laboratory measurements by treatment group (5 pages)
- Percentage of patients with changes from baseline to third anual visit in systolic blood pressure and fasting glucose by selected baseline characteristics and treatment group (4 pages)

Section 5. Non-study drug usage

- Percentage of patients using non-study medications by treatment group, all follow-up visits combined (2 pages)
- Percentage of patients using acetaminophen or dextropropoxyhene hydrochloride, by follow-up visit

H. Budget summary for Hypertension Prevention Trial Data Coordinating Center

Table H-1 DCC ceiling support levels as specified in NHLBI Notice of Grant Award

Table H-2 Projected allocation of funds by budget category and year of study

Table H-3 Projected staffing pattern by year of study, in full-time equivalents (FTEs)

Table H-4 Projected travel expenses by year of study

Table H-5 Other DCC expenses by year of study

Table H-6 DCC percent allocation of funds, excluding nonDCC related costs

Table H-7 Cost of DCC, relative to total projected HPT cost

The tables in this Appendix are from documents prepared by the Hypertension Prevention Trial (HPT) Data Coordinating Center (DCC). See Sketch 13, Appendix B, for design details. The ceiling support levels reported in Table H-1 correspond to actual values recorded in the Notice of Grant Award from the National Heart, Lung, and Blood Institute (August 17, 1981). The total direct cost figures in Table H-2 are from tables prepared by the DCC in a rebudgeting process, prior to the award. Final negotiations led to a modest reduction in the funds awarded for each of the five years, thereby accounting for small discrepancies in the total direct costs in Table H-2 compared to Table H-1.

Table H-1 DCC ceiling support levels as specified in NHLBI Notice of Grant Award

	Time period covered		
Study year	*Start*	*End*	*Ceiling DCC support level*
01	Sept. 1, 1981	Aug. 31, 1982	$ 297,120
02	Sept. 1, 1982	Aug. 31, 1983	$ 524,963
03	Sept. 1, 1983	Aug. 31, 1984	$ 590,080
04	Sept. 1, 1984	Aug. 31, 1985	$ 636,524
05	Sept. 1, 1985	Aug. 31, 1986	$ 551,670
Total			2,600,357

Table H-2 Projected allocation of funds by budget category and year of study

	Year of study				
Category	*01*	*02*	*03*	*04*	*05*
1. Personnel*	$136,224	$198,441	$224,148	$237,596	$251,851
2. Consultant	5,750	5,750	5,750	5,750	5,750
3. Equipment	8,660	500	550	605	731
4. Supplies	4,250	4,800	5,450	6,200	6,750
5. Travel (Table H-4)	34,000	35,750	41,140	45,258	32,252
a. DCC-related	17,000	17,050	16,940	18,618	11,728
b. NonDCC-related	17,000	18,700	24,200	26,640	20,524
6. Other expenses (Table H-5)	112,610	284,136	317,920	346,029	258,648
a. DCC-related	49,666	72,182	98,003	118,884	121,775
b. NonDCC-related	62,944	211,954	219,917	227,145	136,873
7. Total direct costs	301,494	529,377	594,958	641,438	555,982

*Includes salaries as well as cost of fringe benefits.

Table H-3 Projected staffing patterns by year of study, in fulltime equivalents (FTEs)*

	Year of study				
Study position†	*01*	*02*	*03*	*04*	*05*
A. Professional					
✓ DCC director	0.20	0.20	0.20	0.20	0.20
✓ DCC deputy director	0.20	0.20	0.20	0.20	0.20
✓ Senior statistician	0.20	0.20	0.20	0.20	0.20
✓ Junior statistician	0.15	0.40	0.40	0.40	0.20
✓ Physician coinvestigator	0.05	0.10	0.10	0.10	0.10
✓ Nutritionist	0.10	0.10	0.10	0.10	0.10
✓ Research associate	0.50	0.50	0.50	0.50	0.50
✓ Research associate	0.10	0.20	0.20	0.20	0.20
✓ DCC coordinator	1.00	1.00	1.00	1.00	1.00
Senior programmer	1.00	1.00	1.00	1.00	1.00
Junior programmer	—	0.50	0.50	0.50	0.50
Assistant programmer	0.20	0.50	0.75	0.75	0.75
Total professional FTEs	3.70	4.90	5.15	5.15	4.95
B. Support					
Secretary	0.50	1.00	1.00	1.00	1.00
Secretary	0.20	0.50	0.75	0.75	0.75
Clerk-typist	0.65	0.65	0.65	0.65	0.65
Administrator	0.15	0.15	0.15	0.15	0.15
Administrator	0.10	0.10	0.10	0.10	0.10
Total support FTEs	1.60	2.40	2.65	2.65	2.65
C. Total FTEs	5.30	7.30	7.80	7.80	7.60

*The corresponding table submitted to the NHLBI contained actual projected salaries for each person or position listed.

†Positions preceded by the symbol ✓ had a named individual listed in the application. Those not so identified were designated in the proposal as TBA (to be appointed).

Table H-4 Projected travel expenses by year of study*

	Study year				
Type of travel	*01*	*02*	*03*	*04*	*05*
A. Travel for DCC staff					
1. Advisory-Review Committee:					
Person meetings/year	2	2	2	2	2
Cost	$ 1,000	$ 1,100	$ 1,210	$ 1,332	$ 1,466
2. Steering Committee:					
Person meetings/year	6	6	6	4	4
Cost	$ 3,000	$ 3,300	$ 2,420	$ 2,664	$ 1,466
3. Executive Committee:					
Person meetings/year	2	2	2	2	2
Cost	$ 1,000	$ 1,100	$ 1,210	$ 1,332	$ 1,466
4. Standing subcommittees:					
Person meetings/year	2	2	2	2	2
Cost	$ 1,000	$ 1,100	$ 1,210	$ 1,332	$ 1,466
5. Treatment Effects Monitoring Committee:					
Person meetings/year	3	3	6	6	3
Cost	$ 1,500	$ 1,650	$ 3,630	$ 3,996	$ 2,199
6. Training sessions for clinic personnel:					
Person sessions/year	3	3	3	3	0
Cost	$ 1,500	$ 1,650	$ 1,815	$ 1,998	0
7. Clinic site visits:					
Person site visits/year	12	8	4	4	0
Cost	$ 6,000	$ 4,400	$ 2,420	$ 2,664	0
8. Professional meetings:					
Person meetings/year	4	5	5	5	5
Cost	$ 2,000	$ 2,750	$ 3,025	$ 3,300	$ 3,665
Total DCC travel	$17,000	$17,050	$16,940	$18,618	$11,728
B. Travel for non-DCC staff					
1. Executive Committee:					
Person meetings/year	4	6	6	6	6
Cost	$ 2,000	$ 3,300	$ 3,630	$ 3,996	$ 4,398
2. Standing subcommittees:					
Person meetings/year	6	6	6	6	6
Cost	$ 3,000	$ 3,300	$ 3,630	$ 3,996	$ 4,398
3. Treatment Effects Monitoring Committee:					
Person meetings/year	6	6	12	12	6
Cost	$ 3,000	$ 3,300	$ 7,260	$ 7,992	$ 4,398
4. Food Record Coding Center personnel:					
Person trips/year	4	4	4	4	2
Cost	$ 2,000	$ 2,200	$ 2,420	$ 2,664	$ 1,466
5. Study consultants:					
Person trips/year	14	12	12	12	8
Cost	$ 7,000	$ 6,600	$ 7,260	$ 7,992	$ 5,864
Total other travel	$17,000	$18,700	$24,200	$26,640	$20,524
C. Total travel (Sum of parts A and B)	$34,000	$35,750	$41,140	$45,258	$32,252

*Costs calculated assuming $500 per person trip in year 01 and increased by 10% each year thereafter.

Table H-5 Other DCC expenses by year of study

Item	*Study year* 01	02	03	04	05
A. Johns Hopkins (JHU)					
1. Computing time	$ 11,000	$ 19,500	$ 30,000	$ 41,000	$ 41,000
2. Intelligent terminals					
a. JHU central terminal	7,212	7,933	8,726	9,599	10,559
b. Satellite terminals (8)	27,072	59,560	65,520	72,072	44,592
3. CRT workstation terminals (2)	3,000	3,300	3,630	3,992	4,392
4. Word processor	7,200	7,920	8,712	9,588	10,548
5. Telecopier	840	924	1,016	1,118	1,230
6. Telephone line charges	1,000	1,200	1,400	1,550	1,000
7. Photocopying	3,800	4,400	4,820	5,162	5,636
8. Data entry services	1,500	2,500	4,500	4,500	4,000
9. Forms printing	3,500	2,000	2,000	1,000	0
10. Manuscript page charges	0	0	1,000	4,000	6,000
11. Postage	750	900	1,100	1,200	600
12. Microfilming	0	250	400	550	700
13. Bank vault rental	300	400	475	550	625
14. Books and journals	150	200	250	300	300
15. Equipment maintenance	400	500	550	600	650
16. Central Laboratory	3,869	48,265	48,463	49,958	13,739
17. Food Record Coding Center	2,340	63,577	54,789	49,342	13,563
18. Study insurance	19,490	21,439	23,583	25,941	28,536
Total JHU	93,423	44,768	260,934	282,022	187,670
B. Maryland Medical Research Institute (MMRI)					
19. Computing time	1,500	5,000	10,000	12,500	15,000
20. Word processor	1,080	3,960	6,534	7,191	7,911
21. Telephone line charges	400	600	800	900	800
22. Photocopying	800	1,000	1,200	1,400	1,600
23. Postage	200	300	400	500	600
24. Microfilming	0	0	100	200	300
25. Bank vault rental	0	100	150	175	200
26. Books and journals	150	200	250	300	350
27. Space rental	1,500	1,650	1,800	2,000	2,200
28. MMRI overhead	13,557	26,558	35,752	38,841	42,017
Total MMRI	19,187	39,368	56,986	64,007	70,978
C. Total (Sum of parts A and B)	112,610	284,136	317,920	346,029	258,648

Table H-6 DCC percent allocation of funds, excluding nonDCC related costs*

Category	*Study year* 01	02	03	04	05
Personnel	63.1	67.7	65.0	62.2	64.1
Equipment	4.0	0.2	0.2	0.2	0.2
Supplies	2.0	1.6	1.6	1.6	1.7
Travel	7.9	5.8	4.9	4.9	3.0
Other expenses	23.0	24.6	28.4	31.1	31.0
Total	100.0	100.0	100.0	100.0	100.0
Total cost after exclusions	$215,800	$292,973	$345,091	$381,903	$392,835

*Excluding costs for consultants (line 2, Table H-2), nonDCC travel (Part B of Table H-4), Central Laboratory, Food Record Coding Center, and study insurance (lines 16-18, Table H-5). Also excluded are costs for seven of the eight terminals (line 2b, Table H-5) and overhead payments to MMRI (line 28, Table H-5).

Table H-7 Cost of the DCC relative to total projected HPT cost

	Study year 01	02	03	04	05	*Total 5-year cost*
a. Projected dollar cost, all HPT centers combined*	879,966	2,054,880	1,597,509	1,671,896	1,541,713	7,745,964
b. DCC dollar cost (from Table H-6)	215,800	292,973	345,091	381,903	392,835	1,628,602
c. DCC cost as percentage of line a	24.5%	14.3%	21.6%	22.8%	25.5%	21.0%

*Based on totals derived from summary prepared prior to actual award. Funded totals differ only slightly from those cited above.

I. Combined bibliography

This appendix contains a listing of all citations appearing in this book, except those in Appendixes B and C. The citations are arranged in chronologic order by first author. Journal abbreviations correspond to those used by the National Library of Medicine in *Index Medicus* and MEDLINE. The numbers and letters appearing in the right-hand margin correspond to chapters and appendixes in which the citations appear.

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The index contains an entry for each person or corporate entity represented in a bibliographic citation, even if that author's name does not appear on the page cited (e.g., when the number of the reference is cited or the author is not the first author on papers involving three or more authors). A superscript asterisk next to the page cited in the index is used to denote citations of the latter type. All author listings have a minimum of two page listings, at least one of which refers to a page in the Combined Bibliography (pages 430 through 451). Names of persons that appear in the text only as authors are listed as they appear in the Combined Bibliography (i.e., last name followed by initials). The person's first (or second) name is used if the heading contains citations related to the person in a context other than as an author.

Sixty-six of the authors represented are corporate entities. Corporate names related to bibliographic citations from multicenter trials contain the name of the study and end with the term *group* or *research group*. Listings with these terms in parentheses—for example, as in Coronary Drug Project (CDP) (Research Group)—include references to the study itself as well as to papers produced on its behalf.

The terminology conventions discussed in Chapter 1 (pages 8 and 9) and reflected in comments throughout the Glossary (Appendix A) have been followed in constructing this index. Page designations for definitions appear in italics, the majority of which refer to pages in the Glossary (pages 281 to 308).

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