INTRODUCTION

“A properly planned and executed clinical trial is a powerful experimental technique for assessing the effectiveness of an intervention” (1, p. 2). This paper will discuss the issues related to the proper planning and execution of a multicenter clinical trial. The importance of a detailed protocol and manual of operations should not be underestimated. The fundamental principles are relatively simple, but the implementation of some of these principles is not as obvious as it may seem at first glance. Meticulous attention to details during planning is a good investment. If investigators have not participated in the planning or management of a clinical trial, they may be surprised about the amount of time required for planning to assure that there are comparable and good-quality data collected from all participating sites.

There are several useful texts on clinical trials (1–3). One of the first books on clinical trials was written by Hill (4) and covers some basic principles. Guidance may also be obtained from the experience of others. Controlled Clinical Trials and Statistics in Medicine frequently publish descriptions of individual clinical trial designs and individual reports on clinical trial methods. These journals also publish supplements with the proceedings of meetings and workshops on various topics related to the conduct of clinical trials. All of these reports can be of extraordinary value in making decisions with respect to design and data management issues.

“Unless these rules and regulations are well kept...difficulties arise in the final analysis of the results” (5, p. 281). This paper will also present methods for ascertaining whether the rules and regulations (that is, the procedures described in the study protocol and the manual of operations) are being followed. One principle that underlies the degree of success that will be achieved in conducting a multicenter trial depends upon all investigators agreeing that the primary question is important, has not been answered, and can be answered by the proposed design.

The emphasis of this paper is on the conduct of multicenter trials, but many of the issues are also relevant for single-center studies. The differences between single and multicenter trials have been described in detail by Meinert (3).

Study timetable

The major activities for a clinical trial are often described by phase. The first phase after funding has been obtained is devoted to preparing the required study documents, that is, the study protocol; the manual of operations; and the necessary study forms, including the informed consent form; obtaining Institutional Review Board approval in each participating institution; establishing the study organization; and developing the data management system in the coordinating center. The second phase is the period of patient recruitment and collection of baseline data. The third phase is for follow-up data collection. The last phase includes closeout of all sites, data analysis, and preparation of publications. This paper has been organized by activity rather than by phase, since the conduct of the trial involves activities that cover all of the phases.

STUDY ORGANIZATION

Each multicenter clinical trial has groups that are responsible for the screening, recruitment, and follow-up of study participants and central units, including a coordinating center (or there may be a clinical coordinating center and data coordinating center). Studies involving study medications will have a drug distribution center. There may also be central laboratories and/or reading centers that receive and process study specimens or materials, such as angiograms, electrocardiograms, or fundus photographs. For convenience, in this paper, clinical groups are referred to as “clinical sites.” The group responsible for assisting with the design and taking responsibility for data collection, processing, and analysis is referred to as the “coordinating center.” The persons responsible for study activities are referred to as “investigators.” Those enrolled and followed in a trial are referred to as “participants.”

A multicenter trial requires an administrative structure that includes a study chairman (sometimes referred to as Principal Investigator of the study) and committees that have responsibility for planning and for operational decisions during the course of the trial. Special committees may be established to implement the editorial policy (publications and presentations committee) and to review study performance (quality-control committee). Other committees are established as needed. A steering committee of all investigators usually serves as the governing body of the trial. A small group (study chairman, a few clinical site investigators, representatives of all central units, and the sponsor)
may have conference calls as frequently as once or twice a month to oversee study activities. An independent data and safety monitoring board should be established. This group should consist of investigators who have expertise relevant to the study but who are not participating in it; the group has the responsibility for reviewing the accumulating data to ensure the safety of the participants to determine whether the data provide evidence of treatment differences that warrant protocol changes and to assess the performance of all of the participating units to assure that the study continues to be feasible and will be successful in accomplishing the designated study goals.

**STUDY COMMUNICATION**

An efficient, studywide communication system is required for all phases of the study. The coordinating center has responsibility for establishing this communication system, or if there is a clinical coordinating center and a data coordinating center, these two groups will share responsibility. Coordinating center staff should ascertain the resources each group has to send and receive information as each clinical site and central unit are identified. This information is used to select the most cost-effective way to communicate with all sites. An address directory should be prepared, distributed, and revised at regular intervals by the coordinating center staff. This directory should include what might be called “contact information,” that is, the persons designated within each of the central units to be contacted for specific issues. All queries, whether sent by e-mail, facsimile transmission, or verbal transmission by telephone, should be responded to promptly, and if appropriate, the decision should be forwarded to all study personnel. The distribution of this information is best accomplished by use of numbered memos. It has also been helpful to ask the Principal Investigator of each participating site to identify one person who will be responsible for distributing study information to all personnel at that site. Copies of each document should be sent to at least two persons at each site: the Principal Investigator and the person designated to distribute information.

A studywide website can be established and used to post the protocol, manual of operations, study forms, numbered memos, minutes, frequently asked questions, announcement of meetings and conference calls, and materials that have been used at training sessions. The instructions for printing these study documents should also be provided to the participating sites. The coordinating center has the responsibility for distributing hard copies of the protocol, manual of operations, and study forms as well as the numbered memos.

Meetings of all investigators are valuable to keep the investigators and, if possible, other clinic personnel informed about the status of the study; these meetings also provide an opportunity for all investigators to participate in the studywide decisions and to share information concerning recruitment and other issues relevant to the conduct of the trial. If study funds are not available to support investigator meetings, these can be scheduled at the time of national meetings that these investigators are likely to attend. This limits the resources required for setting up such a meeting to the cost of the room and audiovisual equipment. For example, for the studies of patients with myocardial infarction, meetings have been scheduled at the same time as the those of the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. This allows the investigators who are attending these meetings to connect with the other investigators and study leadership at least once a year.

The study leadership should establish a system for responding to important questions in a timely way, and the coordinating center should assure that these decisions are transmitted promptly to all appropriate groups.

A monthly study newsletter is an effective method of informing the investigators of study progress and future plans. The newsletter should also include acknowledgment of the best performing sites with respect to recruitment and data quality during specified time intervals.

**STUDY PROTOCOL**

The study protocol should describe all of the basic features of the research plan. A model table of contents for a protocol is given in table 1. The first chapter should provide the background, rationale, and significance of the study. This chapter should also include a description of any prior studies, as well as pilot studies conducted by the investigators that establish the feasibility of the planned trial. The chapter on the aims and objectives of the study should include the rationale for the study design and the population to be studied. The description of the study objectives should specify the primary question and the primary response variable as well as the secondary questions and response variables. If appropriate, subgroup hypotheses should be specified. The criteria for inclusion and exclusion of participants should be described in detail. The complexity of eligibility criteria has a direct relation to data quality. The phase of development of the agent or procedure under study may influence the definitions of the participants to be studied. Treatments with unknown benefit-to-risk profiles may require recruitment of a narrowly defined population while confirmatory trials would focus on broader groups. Some entry criteria may be confirmed centrally prior to the enrollment of the participant, or eligibility may be evaluated after participants are enrolled to ascertain whether any protocol violations have occurred. Having too many criteria or too complex criteria will lead to increased likelihood of ineligibility of the enrolled participants because of random error or the inability of the investigators to comply with the protocol. Procedures for providing orientation to eligible participants and the informed consent procedures should be detailed. The chapter describing the treatments to be studied should include a summary of known adverse reactions and how to manage side effects. A chapter on standard medical care for the participants is also needed. The procedures for screening and performing baseline and follow-up examinations as well as the follow-up visit schedule should be specified. The chapter on statistical considerations should provide a description of the statistical design; the statistical rationale for the planned study size, including
TABLE 1. Model study protocol—table of contents

I. Background, rationale, and preliminary studies

II. Aims and objectives

III. Design
   A. Overview
   B. Screening and enrollment (inclusion and exclusion criteria)
   C. Treatments and control group
   D. Primary and secondary outcome variables
   E. Participant visit schedule
   F. Measurement and data collection
   G. Standard medical care
   H. Study timetable

IV. Statistical considerations
   A. Planned study size
   B. Randomization procedures
   C. Interim data analysis plan
   D. Final analysis plan

V. Participant orientation and informed consent

VI. Study organization
   A. Participating units
   B. Study administration

VII. Policy matters
   A. Training in human subject research
   B. Conflict-of-interest policy
   C. Editorial policy
   D. Participant privacy
   E. Ancillary studies

VIII. Quality assurance
   A. Training and certification
   B. Adherence aids
   C. Performance monitoring
   D. Performance reports
   E. Site visits

IX. Data collection and processing
   A. Data entry
   B. Inventory of forms and study materials
   C. Data editing
   D. Database
   E. Backup procedures

X. Special study procedures

adjustments for dropouts and crossovers; the procedures for randomization; and planned data analyses, both interim and final. The latter should include the analytic approaches to be used for both primary and secondary response variables. There should be a chapter on quality assurance procedures and one on study organization, with a description of the participating units and the administrative committee structure. The chapter on policy matters should review the requirements for training investigators in human subject research; conflict-of-interest policy; the publication policy, including authorship; and the plans to maintain participant privacy.

MANUAL OF OPERATIONS

Most clinical trials need a manual of operations or a procedures manual as well as a protocol. Some large and simple clinical trials may require only a protocol, which would contain the description of data collection procedures and definitions. Instructions for completing each item on each of the study forms may be included in the manual of operations or prepared as separate documents and distributed with the study forms. The manual of operations should provide study definitions and an explicit description of each of the data collection procedures. For example, if fundus photographs are to be obtained, the kind of camera, the position of the camera, the lighting, the lens setting, the time of exposure, the type of film, the views of the fundus required, and other details should be outlined in the manual. The study leadership organizing the trial and other persons who know what factors should be considered and how these details should be specified should be responsible for drafting appropriate sections of the manual. The manual should be written in excruciating detail; illustrations and diagrams may help to clarify certain aspects of the procedures. All study procedures should be tested to ensure that the description is clear and unambiguous. The table of contents for a procedures manual for a clinical trial of participants who have had a myocardial infarction is given in table 2.

STUDY FORMS

Data collection should be limited to the items essential for the study goals and should be practical to collect (3, pp. 119–37; 6; 7). When planning data collection, it helps to keep in mind that there is a cost associated with collecting each bit of information. There is not only the cost of collecting the information but also the expenditure in time for the participant as well as the expense of processing and analysis, and in addition, there is the danger that collecting information on secondary variables may interfere with collecting the data on the major response variables. After all of the potential variables that might be considered for data collection both at baseline and during follow-up are listed, each one should be examined to confirm that it is essential for the study goals and that staff time will be available to collect the data.

Baseline variables are collected for two reasons: to confirm the eligibility of the participants and to assess the comparability of the participants assigned to each of the treatment groups. Variables that are collected during the course of follow-up serve a different purpose. The data for the primary and secondary response variables are used to evaluate treatment effects; information on expected and unexpected side effects or toxic reactions should also be obtained. Some information is usually collected during follow-up to monitor adherence to treatment and may include interviews with the participants concerning compliance, pill counts, and reasons the dosage was reduced or the medication stopped.

General principles of form design should be followed (3, pp. 119–37; 6). The format of answers should be consistent within a form and across all forms. The items should be arranged in a logical order in accordance with the expected
clinical site procedures and in a manner that will make them easy to complete accurately. A question should be formulated so that, whenever possible, nonresponses will not be assumed to represent answers. The use of write-in responses is discouraged.

It is recommended that all forms be pretested prior to initiation of participant recruitment. Pretesting of forms before recruitment starts has the advantage of ascertaining that each question is unambiguous, has appropriate answers (multiple choice question), and has specified the correct number of digits to be recorded for responses that are numerical. Pretesting also provides an efficient way for study personnel to become familiar with the forms.

Review of each study form with the investigators at planning meetings and pretesting of study forms are good investments to avoid form revisions later, but these steps may not eliminate the need to revise one or more forms. Unless there are major problems, revisions should not be made until clinical sites have had at least 3 months of experience with the forms so that all (or, at least, most) problems can be identified and only one revision is required. Major revisions of study forms are costly to implement; thus, every effort should be made to avoid any revisions after recruitment of participants begins. The implications of form revisions for data processing and analyses will be discussed in a later section.

VISIT SCHEDULES

The same consideration that is given to the decision to collect individual items should be given to the specification of the frequency of data collection of each item (3, pp. 119–37; 7). The factors that should be considered in establishing the time interval between visits and the total duration of follow-up are dependent on 1) study goals, 2) the frequency of visits required for dispensing and managing study medication and appropriate medical care, 3) the costs of each visit, and 4) frequency that is convenient for the participant and will also maintain contact. In many studies of participants with coronary disease, the visit schedule is every 3 or 4 months; in some cases, some follow-up information is collected only at 12-month intervals. Although a 4-month schedule may be appropriate for clinical management, it is questionable whether data collection every 4 months is really necessary for the evaluation of treatment efficacy and safety (7). Information concerning the best time interval to maintain contact with participants is lacking.

Canner (7) suggested that the frequency of data collection on known or suspected adverse treatment effects differs depending on whether the information is to be collected for the purpose of documenting treatment effects or whether the information is needed for individual participant monitoring. He emphasized the importance of adequate collection of baseline information to assess whether the treatment groups are comparable and to identify prognostic factors. He also suggested that information designed to understand the mechanism of treatment or natural history of the condition under study might better be collected in ancillary studies.

TRAINING OF STUDY PERSONNEL

The goals and content of the planned training activities should be included in the protocol or manual of operations. Training sessions of all investigators prior to the start of participant recruitment and as a part of the investigators’ meetings and site visits during the trial are good investments. As part of the training procedures, study personnel may be asked to complete procedures and study forms for nonparticipants. They also may be required to pass an “open book” examination on the protocol before they are eligible to complete study procedures on enrolled or potential participants. In other situations, the investigators or clinical site personnel may be required to document their experience, for example, to provide information on the number of angioplasties performed each year and the complication rates for these procedures (Appendix).

The Diabetic Retinopathy Study (DRS) is one of the first for which formal training programs were conducted prior to the start of participant recruitment and during the trial; these programs included orientation to the study as a whole and detailed explanations of the procedures for which the people would have responsibility for during the trial. There were special training programs for visual acuity examiners, for fundus photographers, and for the ophthalmologists who would screen and treat participants.

In a more recent study, Power Point (Microsoft Corp., Redmond, Washington) slides have been put on the trial’s website, and training sessions for new study personnel have been conducted by conference call. Training of new personnel during the course of the trial may also be conducted by a trained staff member at the clinical site or at investigator meetings.

DATA COLLECTION AND PROCESSING

Data entry may be performed by clinical site personnel or by coordinating center personnel. The choice depends on the system that is adopted for data entry. There are advantages and disadvantages to each of the systems that have been utilized by multicenter studies. The early clinical trials relied on completion of the study forms at the clinical site; the forms were mailed to the coordinating center and processed by staff trained in data entry procedures. Optical character recognition techniques were used in place of keying for some forms in some trials. Systems that use facsimile transmission and optical character recognition have been developed. “Distributed data entry systems” have been used; this type of system calls for each clinical site to have identical microcomputers with the software for data entry installed and also mandates substantial amount of coordinating center staff time to set up and maintain. Major revision of study forms requires reinstallation of the appropriate software on each of the clinical site computers. Alternatives to the distributed data entry system are the use of e-mail systems or Internet interactive systems for data entry. Each of these types of data entry systems requires specific hardware and software and training of personnel. An e-mail system can include some editing as the forms are keyed; that is, codes
that are inappropriate for a given item are not accepted, and numeric values outside specified ranges are not accepted. An Internet system may incorporate substantially more edits than an e-mail system during data entry. The more editing that occurs the slower the data entry process is, but there is the advantage that it is likely that forms processed in this way will have responses that are appropriate, and thus, the number of edit queries that will be sent to a clinical site for submitted forms will be reduced. The choice of system depends on the complexity of the study forms, available resources both in the clinical site and the coordinating center, and consideration of the cost of personnel time required for data entry and for maintaining the data entry system. The procedures available for data entry vary from keying the data into a microcomputer or terminal at the time of data collection (interview or examination) to keying from completed study forms after data collection.

The advantages of performing data entry at the clinical site are the possibility that the time between data collection and data entry may be reduced and that those responsible for data collection may also perform data entry and, therefore, are less likely to make errors as a result of illegible responses. In addition, these persons may query other clinic personnel, check the source documents, or have other information available to confirm the answers.

Independent double data entry procedures with the two keyings compared electronically have been shown to reduce errors but also increase costs (8–10). With a distributed data entry system and single keying, coordinating center staff should request a sample of forms at specified intervals to check on the data entry performance of clinical site personnel and to assure that the error rate for single keying remains close to that achieved with double data entry. The same guidelines for adopting double data entry should be applied to keying of forms within the coordinating center. The quality-control program should identify any systematic problems to be corrected and should also identify the most cost-effective method of data processing.

### RANDOMIZATION PROCEDURES

One of the most important aspects of any clinical trial is the method of randomization. The process should be conducted...
so that each treatment assignment is issued for a specific eligible participant in such a way that the investigator cannot anticipate what the next treatment assignment might be. The simplest procedure would be to use a table of random numbers or toss a coin to allocate each participant to each of the treatment groups to be studied, without any other constraints.

In practice, such a simple randomization is usually not used. A common approach is to generate a separate randomization schedule for each of the clinical sites and within the clinical site to have some blocking so that, after a fixed number of participants enrolled, there will be equal numbers assigned to each of the treatment groups. If this strategy is used, it is recommended that the size of the blocks also be randomly determined by considering the demographics and eligibility characteristics are reported before the allocation is issued. Such a system should require that certain demographic and eligibility characteristics are reported before the allocation is issued. It is also a good idea to obtain some confirmation that the appropriate treatment was implemented immediately after the allocation was issued. This can be accomplished by requesting that a copy of the treatment allocation be returned to the coordinating center with a copy of one of the labels taken from the kit or bottle(s) assigned to the participant or other appropriate information on treatment for other types of intervention, such as surgical procedures.

The issue of whether to stratify on other participant characteristics is somewhat controversial (2, pp. 66–89; 3, pp. 90–112). If there is very good evidence that a given participant characteristic is predictive of the outcome to be studied in the trial, it is probably worthwhile to consider stratification, but if there will be at least 40 participants within a site, there is a reasonable chance of achieving balance without stratification.

The other aspect of randomization that must be considered is how clinical sites will obtain each randomization. The use of a central procedure that includes some verification that the participant is eligible before the allocation is issued for a specific participant is preferred over the use of sealed envelopes. Many large-scale studies are now using automated voice-response systems that are available 24 hours a day 7 days a week to provide treatment assignments. Such a system should require that certain demographic and eligibility characteristics are reported before the allocation is issued. It is also a good idea to obtain some confirmation that the appropriate treatment was implemented immediately after the allocation was issued. This can be accomplished by requesting that a copy of the treatment allocation be returned to the coordinating center with a copy of one of the labels taken from the kit or bottle(s) assigned to the participant or other appropriate information on treatment for other types of intervention, such as surgical procedures.
of the study medication also have to be considered. A larger supply of medications is needed, and more study medication will not be used if one number is assigned to each participant in each clinical site.

In studies evaluating drug therapy, it is usually possible to prepare placebos that look like the medications under study and to make all active agents look alike, so the study medication may be administered in such a way that the participant does not know which treatment he or she is receiving. In addition, the treating physician does not know which treatment has been assigned to the participant being treated or examined. This approach is referred to as “double masked” or “double blinded.” Some studies of surgical procedures have had sham procedures so that the participant would not know the treatment assignment.

If it is not possible to administer study treatments in a double-masked fashion, other steps should be taken to avoid bias in the assessment of the primary response variable. In the DRS, the primary response variable was best-corrected visual acuity. Every effort was made to assure that the visual acuity examiners who were responsible for performing refraction and measuring best-corrected visual acuity did not know which eye had been treated and did not have access to information on refraction and the visual acuity levels at prior visits. This procedure was used to assure that the visual acuity examiner who provided the information for the primary endpoint could obtain these measurements in an objective manner. This approach was accomplished by having another staff member greet the study participant on arrival at the clinic and inquire about the participant’s well-being and any problems with respect to visual status. This staff member would then remind the participant not to discuss visual status with the visual acuity examiner until after the visual acuity measurements had been obtained. Any bias on the part of the participant with respect to visual status was counteracted by the visual acuity examiner coaxing the participant to continue reading smaller and smaller lines, guessing if necessary, until at least two letters were missed on one line during the examination of each eye.

In some studies, the reported events (such as myocardial infarction) with appropriate documentation may be classified by persons who do not have information on the assigned treatment. In other studies, the primary response variable may be based on readings of materials such as ambulatory electrocardiograms or coronary angiograms made in a central reading center by personnel who do not have information on the assigned treatment or clinical outcomes for the participants.

PATIENT RECRUITMENT

Strategy

Recruitment of the required number of study participants in the time period specified in the protocol is a major challenge for all clinical site investigators. Each of these investigators should develop a recruitment strategy based on some preliminary information concerning the number of potential participants who would be available in the clinic population or a registry or, if participants are to be recruited from the hospital admission population, the investigator should have the number of admissions for a period of time prior to the initiation of recruitment and some information about the characteristics of these admissions. This information is necessary to assess whether a given clinical site has the potential to recruit the required number of participants within a given time period. Mass mailings have been used by some trial investigators to contact large numbers of persons; this strategy involves identifying appropriate target groups for which addresses may be obtained. The appropriate strategy depends on the target population for the trial. Each investigator should have a recruitment strategy and should make some effort to evaluate the success of the various approaches to identify and enroll participants. In a multicenter study, the investigators should share information on the success or lack of success of a given strategy in their clinical site. However, a recruitment strategy that is effective for one target population may not be appropriate for another, and a strategy that works in one clinical site may not work in others. A summary of the literature of research on patient recruitment for clinical trials is a useful reference on recruitment issues (11). A recent report compares costs and yields of hospital- versus community-based strategy for one trial (12).

Clinical site investigators should encourage their colleagues to refer potentially eligible participants to the investigator. The investigator can achieve this collaboration by making presentations at grand rounds and sending letters to potential collaborators or referring physicians outlining the objectives of the study, specifying the inclusion and exclusion criteria, and describing the treatments under study. Information from some studies has indicated that, although the total number of participants referred may be smaller than from other sources of recruitment, referral generally has a higher yield than other sources (13). Frequent reminders that the study is still in the recruitment phase are also required.

Recruitment reports by clinical site should be prepared at least every month, and information concerning the status of recruitment should be shared with all clinical sites to generate a healthy competition among the clinical sites to maintain study goals. If a clinical site consistently demonstrates an inability to recruit participants, consideration should be given to discontinuing that site.

Information on the screening process and the reasons participants may be declared ineligible during the course of screening is helpful in determining whether one or two exclusion criteria are the primary reasons participants are not eligible for the study. In some studies, review of these tabulations has resulted in modification of the inclusion or exclusion criteria to expand the number of participants eligible for the study and, thus, increase the yield of persons enrolled from among those screened.

Screening

Scheduling of more than one prerandomization visit may be necessary in some circumstances to establish eligibility. Requiring at least two screening visits has the advantage that some information concerning the participant’s ability to understand procedures and to comply with scheduled visits is assessed by the response to the instructions given at the
time of the first visit. These visits may be separated by a few days or weeks, depending on why two visits are scheduled. Some studies have asked participants to take placebo medication or a very low dose of study medication as another way to assess compliance prior to enrollment.

Informed consent

The study consent form provides the potential participant a description of the study objectives, overview of the design of the study, description of the study treatments, benefits and risks of treatments, benefits and the risks of participating in the study, and alternatives to participating in the study. A checklist of items to be covered on the consent form is given on the Office for Human Research Protection website (14). Some suggestions concerning the format of the consent form are presented in table 3.

The leadership of the study should prepare a model study consent form. The Principal Investigator of each clinical site can use the model form or modify it, but the revised form must contain all of the information required. Information can be added if it is required by the investigator’s Institutional Review Board, but it cannot be omitted. Long and complicated forms should be avoided, and the consent forms should be evaluated to ensure that they are at approximately the seventh or eighth grade reading level. As part of the consent process, it is helpful to have a brochure describing the study that the potential participant may take to review with family and friends.

TABLE 3. Central review of consent forms—checklist

<table>
<thead>
<tr>
<th>I. Content</th>
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<tbody>
<tr>
<td>A. General</td>
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<tr>
<td>1. Nature of research project</td>
</tr>
<tr>
<td>2. Background</td>
</tr>
<tr>
<td>3. Purpose of trial</td>
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<tr>
<td>4. Eligibility for trial</td>
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<tr>
<td>5. Procedures/conditions of participation</td>
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<tr>
<td>6. Duration of follow-up</td>
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<tr>
<td>7. Risks/benefits</td>
</tr>
<tr>
<td>8. Alternatives to participating in the research project</td>
</tr>
<tr>
<td>9. Confidentiality statement</td>
</tr>
<tr>
<td>10. Individual to contact to answer questions</td>
</tr>
<tr>
<td>11. Right to refuse or withdraw</td>
</tr>
<tr>
<td>12. Signature and date (participant)</td>
</tr>
<tr>
<td>13. Signature and date (Principal Investigator)</td>
</tr>
<tr>
<td>14. Signature and date (witness)</td>
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<tr>
<td>15. Statement participant will receive a copy of the signed form</td>
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<tr>
<td>16. Explanation concerning compensation and costs</td>
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<tr>
<td>17. Explanation of compensation for research-related injury (physical, psychological, social, financial, or otherwise)</td>
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<table>
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<tr>
<th>B. Project specific</th>
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</thead>
<tbody>
<tr>
<td>1. Enrollment procedure</td>
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<tr>
<td>2. Study visits</td>
</tr>
<tr>
<td>3. Biomedical specimens</td>
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<tr>
<td>4. Specimens for repository and future tests</td>
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<tr>
<td>5. Audiotaping interviews</td>
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<table>
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<tr>
<th>II. Form preparation</th>
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</thead>
<tbody>
<tr>
<td>A. Name of institution</td>
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<tr>
<td>B. Page numbers</td>
</tr>
<tr>
<td>C. Space for initials on each page</td>
</tr>
<tr>
<td>D. Institutional Review Board period of approval</td>
</tr>
<tr>
<td>E. Reading level</td>
</tr>
<tr>
<td>F. Section headings</td>
</tr>
<tr>
<td>G. Consistent pronouns</td>
</tr>
<tr>
<td>H. Grammatical and typographic errors</td>
</tr>
<tr>
<td>I. Date of form</td>
</tr>
</tbody>
</table>

| III. Recommendations |

Baseline data

Data collected at prerandomization visits and the randomization visit are usually considered as baseline data. The data collected at these visits are required to assess the participant’s eligibility and to collect information on variables that may affect prognosis. These visits are also important to explain the purpose of the study, to obtain consent and issue the treatment assignment, and to initiate study treatment.

Follow-up data

Compliance

In drafting the protocol, consideration should be given to incorporating approaches that will increase the likelihood that the study participants will return for follow-up visits and will take the prescribed study medication. A simple regimen of medications to be taken once a day is more likely to be followed than regimens that require taking medications several times a day or taking several types of medications. The manual of operations should describe the treatment schedule for dose adjustments and how to handle known side effects. It should specify the frequency of follow-up examinations for regular checkups, for the resupply of study medications, and for monitoring side effects. Enrolling only participants who followed instructions for the screening visits will increase the likelihood that participants will adhere to the study protocol.

Participants may be sent reminders by mail or telephoned about upcoming appointments. Some investigators involve family members to help the participants continue taking the study medication as well as returning for visits. Special methods of dispensing the medication or other ways of providing reminders of the schedule for taking study medication, such as magnets for the refrigerator, may be helpful for participants.

The coordinating center should prepare reports by clinical site on a regular basis about the number of participants who are not taking any study medication, the reasons they are not taking medication, and estimates of the percent of prescribed medication that is taken, based on pill counts. In some cases, it is possible to perform tests on either blood or urine to detect the presence of active medication or metabolites. Measurement of salicylate levels in urine was used as one indicator of compliance in a study of aspirin (15). In studies that involve the assessment of surgical procedures, such as angioplasty or photocoagulation for diabetic retinopathy, the pre- and postangiograms or fundus pho-
Handling dropouts, withdrawals, and missed visits

It is, of course, obvious that the best way to handle dropouts, withdrawals, and missed visits is to prevent these occurrences. Some steps that have led to improving compliance were outlined by Probstfield et al. (16, 17). A key feature of this approach is the management of participants who show signs of dropping out of the study. These participants should be contacted by a senior study investigator because this conveys the sense of how important the participants are to the study and may increase their willingness to return for follow-up visits. As part of the discussion with the participants, the investigator can negotiate with them on the parts of the study they are willing to complete. This approach may result in patients agreeing to return to complete only the examination for the primary endpoint of the study. For example, in the DRS, participants could have only the visual acuity examination and not have fundus photographs taken if the latter procedure was uncomfortable.

Withdrawal or discontinuation of study medication, for whatever reason, does not mean that follow-up should be discontinued; in fact, participants should be encouraged to return for scheduled visits unless they ask not to be contacted. The number and percent of participants who withdraw from the study or have missed two consecutive visits should be reported at regular intervals by clinical site. If possible, an attempt should be made to maintain some contact with participants, even if they are not willing to return for visits, so that information on vital status will be available on all participants. Efforts should be made to minimize the number of participants who may take active medication of the same type or that is identical to the study medications so that participants assigned to active medication do not take higher doses of the study medication and so that the participants in the control group are not taking the active study medication.

In spite of such efforts, it is recognized that some participants will not have all of the data available for all follow-up visits. Analysis approaches should be developed to account for the missing data. Data can be missing at random (not dependent upon the outcome), they could be missing because of the occurrence of an adverse event related to the primary endpoint (informative censoring), or the participant could have died, preventing the primary endpoint from being observed. If death is not the primary outcome, the approach for handling these missing observations should be defined during planning. The value for a single missed visit for an endpoint such as visual acuity can be estimated by averaging the values obtained at the visit before and the one after the missed visit. In the Asymptomatic Cardiac Ischemia Pilot Study (18), patients who died or who had a myocardial infarction or revascularization procedure not specified by study protocol before the follow-up visit at which the primary endpoint (presence of ischemia on an ambulatory electrocardiogram) was to be obtained were declared to have ischemia present on that follow-up visit. In the Post Coronary Artery Bypass Graft Trial (19), the primary outcome was the per patient percentage of patent grafts at baseline that had substantial progression on the follow-up angiogram. In that study, all participants who died were regarded as having occluded grafts at the time of death.

All deviations from the ideal protocol should be reported, and all participants randomized should be analyzed in the group to which they were assigned regardless of the overall adherence to treatment or compliance with study protocol. A report from the Coronary Drug Project Research Group indicated the difficulties in interpretation if the treatment results are analyzed only for patients who adhered to the assigned treatment regimens (20). The analysis of the Coronary Drug Project data showed that such findings are unreliable and potentially misleading.

DATA MANAGEMENT SYSTEM

The coordinating center is responsible for designing, implementing, and maintaining a data management system to process data from the clinical sites and core laboratories and/or reading centers. The main functions of the data management system are 1) receipt and inventory of clinical site data, 2) interface with core laboratories or reading centers, if appropriate, 3) editing the data, 4) preparing protocol adherence aids, and 5) data extraction for analyses related to research objectives. Study forms received from the clinical sites, whether they arrive by regular mail, e-mail, Internet, or facsimile transmission, should be electronically inventoried promptly. Each record in the inventory should contain the form number; the participant’s identification number; and other identifiers such as initials or name code, visit number, examination date, date form received, and other information pertinent to the status of the material being processed. The inventory process should provide an initial review of submitted forms and materials. If there are problems with the participant’s identification or visit date, the clinical site should be contacted to assist in resolving the problem.

Each form should also be evaluated by a central edit program after inventory and data entry. This edit should include checks for completeness, internal consistency, consistency with previous data from the same participant, numeric values outside of specified limits, illegal codes, illegible responses, and adherence to the treatment protocol. Any edit queries should be sent in a timely manner to the clinical site. Corrections received in response to the edit queries should be entered through data entry screens either at the clinical site or at the coordinating center. There should be an audit file that includes the old and the new values for any field and the date of correction. Any forms that are corrected should then be reedited in the same manner as in the first edit. Complete reediting of corrected forms should avoid the necessity of reediting the entire database at the end of the study.

The study form data should be kept in the format that corresponds to the study form revision number in the database. The data for all form revisions for a specific form should
also be organized in one table in the study database. All data on the latest revision that are common to all form revisions should be mapped to the same locations in that table. New fields have to be generated for observations that do not exist on previous forms. These new fields should be given a null value for all forms not containing the new fields. Similarly, fields deleted in the form revision should be given null values in all future records after implementation of a revision of a study form. Insertion and deletion of fields from a form results in missing data, and thus, such changes should be made judiciously.

Knowledge of the location and status of materials (such as blood specimens, ambulatory electrocardiograms, or angiograms) is one of the primary goals of the interface of the data management system in the coordinating center with any core laboratory or reading center participating in the trial. The procedures for tracking the receipt of materials between these central units and the clinical sites should be developed and implemented during the planning phase. For example, at the beginning of each month, the central unit should send the coordinating center a list of the materials received in the previous month. This inventory can then be compared with the coordinating center records of the materials sent to this central unit. The clinical site should be contacted to resolve any discrepancies.

**MONITORING CLINICAL SITES**

Coordinating center staff should implement a number of procedures to assure the timely collection of complete and accurate data. These procedures are designed to prevent errors, detect problems so that they can be corrected, and have information to describe the quality of the data.

**Adherence aids**

To assist the clinical site staff in completing follow-up of participants, the data management system should be used to generate the following protocol adherence aids: 1) appointment schedules for enrolled participants; 2) a list of follow-up visits expected in the next month, itemizing the forms and materials required; 3) a list of forms delinquent according to the appointment schedule and events reported; and 4) a list of participants who have missed two consecutive visits. The delinquent list is used to report to the clinical site staff those forms associated with the required follow-up data collection and reports of materials that have not yet been received at the coordinating center. Clinical site staff are required to account for the performance of each expected procedure or study form or to document why the procedure was not performed or why the form is not available.

**Performance reports**

Comprehensive performance reports should be prepared at regular intervals to summarize the performance of individual sites as well as that of the study as a whole. Some of the performance characteristics to be included in these reports are patient recruitment, extent of patient follow-up, adherence to treatment, completion of data forms, study visits identified as delinquent, data entry errors, number of edit queries, and findings from data audits. Each performance report should be reviewed to obtain a global impression of whether one site is or several sites are performing at a level below that of the majority of sites. The performance of the best person or clinical site in a study can be used to establish goals for all other staff and clinical sites.

**Site visits**

Another important component of a monitoring program is a well-planned site visit (21). If fiscally feasible, annual site visits to each clinical site and to each central unit, including the coordinating center, should be scheduled. The first site visit should be scheduled shortly after patient recruitment has started in a clinical site. If possible, the site visit team should include the study chairman or vice chairman, a Principal Investigator, and a coordinator from another clinical site and representatives from the sponsor and the central units, including the coordinating center. There should be a planned agenda. The investigator of the site should be notified in advance of the materials to be available for the site visit.

Each visit should include auditing of participant records. Auditing involves comparison of study form data with source documents; there should also be a comparison of the study form data with printouts of data from the coordinating center computer database. These materials should be compared to check on protocol compliance as well as accuracy of transcripts and proper record keeping. Consent forms for all enrolled participants should be reviewed to confirm that the forms used were approved by the institution’s Institutional Review Board and were properly completed.

Other items to be covered in a site visit are 1) strategies of recruitment and special success or problems in recruitment, 2) participant retention and adherence to follow-up, 3) any difficulties encountered with study forms or other aspects of the study protocol, and 4) review of any special issues or inspection of any special equipment to check on calibration. Review of other selected procedures, such as preparation of specimens or performance of angiography, should be part of the site visit as appropriate for the trial. Study record files should be inspected.

A site visit report should be prepared promptly, and each report should include recommendations and be sent to the Principal Investigator of the site with a request that he or she provide a response indicating how each of the recommendations will be implemented.

**Statistical investigations**

Coordinating center staff should use statistical techniques to examine the data for patterns that may be indicative of errors (21, 22). Comparison of descriptive statistics among the sites of a multicenter trial may show that one site differs remarkably from all others. Comparison of values across time for individual study participants may also identify problems with data. These investigations might identify a
single, outlying value or might indicate too little variation over time. Measures of variability as well as those of central tendency should be examined. In addition, the relation of several variables should be evaluated. An unusual statistical characteristic of the data is not sufficient to conclude that there is a problem in data collection, but it may indicate that some investigation is warranted.

MONITORING CENTRAL UNITS

Drug distribution center

The samples from each drug-labeling session should be taken and assayed to confirm that the drug-labeling process was correct. At periodic intervals during the course of the trial, it is also useful to collect from each clinical site a few samples that have been returned by the participants at follow-up visits; these samples can also be assayed to confirm that the drug-labeling system has been implemented correctly.

Central laboratories or reading centers

Both internal and external quality-control programs should be specified for central laboratories and reading centers. The internal quality-control procedures often include replicate values obtained from aliquots of the same laboratory specimens or repeat readings. During site visits to the core laboratory or reading center, the site visit team should review the internal quality-control reports. The reports should also be requested at regular intervals by the coordinating center staff for review either in the coordinating center or by the study’s designated quality-control committee. Coordinating center staff should develop procedures to submit blinded duplicate specimens or materials to the central unit for measurements to ascertain the accuracy of evaluations. The external program may include submission of known standards for analysis or readings. These procedures should be performed over the course of the trial to detect secular trends. The manual of operations should outline the methods that are planned as well as the expected level of agreement that would meet the requirements of the trial. If the reports indicate problems, action should be taken to ascertain the source of the problems and to take appropriate steps to correct them. The extent of the quality-control program should be determined on the basis of the effect variability of evaluations will have on the outcome variables.

Coordinating center

The success of any clinical trial depends on the assurance of quality in all units, including the coordinating center. The importance of proper inventory, processing, storage, and analyses of the data is obvious. Sometimes less attention has been paid to monitoring the performance of the coordinating center than to the other units. Internal review procedures should provide an evaluation of all aspects of data handling and analysis. In addition to the internal monitoring procedures, the coordinating center should be subjected to outside review and site visits.

A detailed procedures manual describing all aspects of the data entry (if performed centrally), inventory, and database management procedures should be prepared. This manual serves as a guide for evaluation of the procedures and for assessing adherence to these procedures. The philosophy in preparing these manuals should be that each procedure is described in sufficient detail that it would be possible for someone unfamiliar with the study to perform the tasks by using the written description.

An internal review committee composed of study members from other studies in the coordinating center may take responsibility for reviewing the description of the procedures before they are implemented as well as for reviewing and approving any changes in the procedures during the course of the trial. This review team should operate in a fashion akin to a team of auditors or bank examiners.

For testing of the computer edit programs, a set of study forms should be prepared with errors and inconsistencies. The edit programs should be run on these test forms until all of the major problems identified by these test cases are corrected before any edit queries are sent to the clinical sites. The edit programs should then be run on a few forms received from the clinical sites and the edit output carefully checked. If that test indicates that there are no problems, the edit programs can become part of the usual maintenance procedure.

Analysis programs can be checked by preparing hand tabulations of small subgroups of participants. It is also helpful to have two persons perform the same analyses after they have prepared their own data files and programs. When the statistical reports are being reviewed, comparing counts and the number of participants treated and completing each visit with recruitment tables generated for that cutoff date may identify problems. A second check is to generate frequency distributions of all variables that are included in the report. These procedures identify out-of-range values, possible keying errors, and errors in the conversion of the forms from one revision to the most recent version. A third check is a review of listings of certain variables. In some studies with distributed data entry, staff at certain clinical sites can be asked to process the data by using the distributed system and then duplicate certain analyses as a check on the coordinating center. In one study, a separate data audit group was established to monitor certain aspects of the coordinating center activities.

CLOSEOUT

A recent issue of Controlled Clinical Trials had several reports on closeout issues (24–29). Planning for closeout should begin at least a year before the first participant is scheduled to have the last follow-up visit. If the study is stopped before the planned end, this schedule will have to be accelerated. The investigators should decide early in the planning phase whether additional procedures are to be performed at the last follow-up visit of each study participant.

Clinical site activities

Clinical site personnel should make special efforts to contact all participants and to ask them to return for a final visit.
At the last follow-up visit, any required examinations should be performed, and the participants should be thanked for their participation in the trial. They should be reminded how important and valued their contributions have been. If appropriate, participants and their physicians should be told whether each participant was assigned to placebo or active medication. They should also be told that once study results are known, they will receive a summary by mail, telephone contact, or an invitation to participate in a group session. Contact information needed to reach the participant should be verified and updated. If appropriate, summaries of any clinically relevant data obtained during follow-up should be prepared for distribution to the participant’s physician.

All supplies of study medication should be destroyed or returned to the drug distribution center. Appropriate steps to have secure and accessible storage space for all study records should be implemented.

**Coordinating center activities**

Coordinating center staff should plan to complete the processing of study materials and responses to edit queries within 2–3 months of the conclusion of participant follow-up; that schedule will require that any reedit of study data is performed as participants complete the debriefing visit and that processing of responses to edit queries is completed as they are received. Coordinating center staff should also initiate special procedures to locate participants classified as lost to follow-up if the clinical site investigator requests assistance in locating participants who have stopped returning for regularly scheduled visits during the course of the study. Applications can be submitted to the National Death Index to obtain information on vital status. The Social Security system can be accessed by Internet to obtain information on participants registered with the system.

A major activity during the closeout period will be the preparation of data analysis for planned study manuscripts and presentations. The writing teams for major topics should be identified before the closeout period begins if these manuscripts are to be submitted to a journal shortly after the completion of follow-up of participants.

In federally supported studies, coordinating centers are required to prepare a public-access data set and accompanying documentation for submission to the program office (30). These data sets should be prepared while maintaining participant confidentiality; thus, no information should be included that would identify an individual participant. All dates should be converted to time from study entry, and other information should be omitted if such information has any possibility of identifying a participant.

All study materials as well as the study database and the analyses file should be maintained for at least 3 years. In some cases, the sponsor may request that this information be available for longer periods of time.

**SUMMARY**

In preparing to undertake a clinical trial, it may be helpful to keep in mind Fredrickson’s description of clinical trials (31):

“Field trials are indispensable. They will continue to be an ordeal. They lack glamour, they strain our resources and patience, and they protract the moment of truth to excruciating limits. Still, they are among the most challenging tests of our skills. I have no doubt that when the problem is well chosen, the study is appropriately designed, and that when all the populations concerned are made aware of the route and the goal, the reward can be commensurate with the effort. If, in major medical dilemmas, the alternative is to pay the costs of perpetual uncertainty, have we really any choice?”

**REFERENCES**

19. The Post Coronary Bypass Graft Trial investigators. The


Angioplasty Operator Certification for Lead Interventionalist

> Enrolling Center Name: ____________________________________________

> PTCA Site Names if more than one or different from above

(1) __________________________ (2) __________________________ (3) __________________________

PI: ____________________________________________________________

Lead Interventionalist Name (if not PI): ________________________________

Participating CENTER qualifying certification:

________ Number of annual coronary interventional cases (not less than 150 cases per year)

________ Number of annual diagnostic coronary cases (not less than 500 cases per year)

Availability of at least 3 different guidewires incorporating variable tip stiffness characteristics and hydrophilic coatings. Yes _____ No _____

Cardiac surgical back-up Yes _____ No _____

Criteria for certification of lead interventionalist - Answer all questions:

(A) Coronary Angiography in-hospital complication (death, MI, CVA) rate <0.5% during the past calendar year. Yes _____ No _____

(B) Non-emergent coronary interventional volume >75 per year. Yes _____ No _____

(C) Non-emergent angioplasty success rate >95% Yes _____ No _____

(D) In-hospital angioplasty complication rate:

death, Q wave MI or emergency CABG <2% in the past year for non-emergent procedures. Yes _____ No _____

(E) Implantation of >50 coronary stents, after training, per certified operator with the above success and complication rates. Yes _____ No _____

(F) Cumulative total of interventional cases must be ≥500.

State volume or approximate Yes _____ No _____

PI / Lead Interventionalist (Sign) ____________________________

Printed Name

Department or Division Chief (Sign) ____________________________

Printed Name

Date ________________ Date ________________

UPON COMPLETION FAX TO

Accepted by Clinical Coordinating Center:

Date ________________ Signature ____________________________