# 1

# INTRODUCTION



Clinical trials are utilized in many clinical specialties to test the efficacy of a specific treatment or intervention in a group of patients/subjects, and inferences are then drawn about the use of the treatment in the general population. There are different types or phases of clinical trials, but they all have one common feature. The results that are reported at the end of the trial are only as good as the quality of the data collected and analyzed as part of the trial. A "good" result of a clinical trial is a result that provides the *correct* answers to the questions asked, not necessarily one that is positive or statistically significant.

Good data management practices are essential to any clinical trial, yet this area is one that can be neglected during the planning stages of a trial. This book discusses the various stages of the life of a trial from planning to analysis, and it focuses on the management of the data during each stage.

Clinical trials can be large or small; they can involve one clinical center or multiple centers. Multicenter trials allow more rapid accrual of patients to a trial, and therefore the answers to the questions being asked are available more quickly. The results of multicenter trials are also more easily generalized to the population as a whole because the trial includes patients from a variety of settings, rather than just a single site. Large multicenter trials usually have a Coordinating Center with a wide range of responsibilities, including input in trial design, quality control and computerization of trial data, interim and final analyses of the data, and preparation of a report on the results. The Coordinating

*Management of Data in Clinical Trials, Second Edition*, by Eleanor McFadden

Center may also develop systems to ensure timely flow of information among the people involved in the trial. In trials done at single centers, these functions are often the responsibility of the investigator who designs the study. Regardless of the size or complexity of a trial, detailed planning is essential, and the guidelines in this book have relevance to even the smallest clinical trial.

There is no one "correct" way to conduct a clinical trial. There are many different ways to organize a trial, and choices need to be made based on the environment and resources available. The system developed for conducting a specific trial should be based on intelligent decisions after reviewing the study requirements and available resources in great detail. Careful prospective planning is essential to ensure that the study runs smoothly, that all necessary data are collected in a timely way, that ongoing progress can be monitored to ensure patient safety, and that final results can be analyzed and published as soon as possible after the termination of the study. While everyone involved in clinical trials may think that their way of doing things is the best way, in reality a data management system is successful if, using available resources, it results in the collection of complete, timely accurate data that answers the scientific questions. All of us can learn from review of methods used by others, especially in this time of rapid change in the clinical trial environment.

## DEFINITION OF A CLINICAL TRIAL

Throughout this book, a clinical trial is defined as a trial involving the assessment of one or more regimens used in treating or preventing a specific illness or disease. The regimen may be curative, palliative, or preventive. There are other types of clinical studies, some involving the administration of questionnaires, surveys, or specific tests to subjects who fulfill certain requirements. These studies collect information on the subjects entered, but do not assess the efficacy of interventions. Many of the guidelines for therapeutic trials apply equally to these kinds of studies. For the most part, in this book, examples and terminology will refer to therapeutic trials, but parallels may be drawn for other types of studies.

## TYPES OF CLINICAL TRIALS

The design of a clinical trial depends on the objectives and the experimental treatment. Some trials involve comparisons with other treatment regimens, and other trials are designed to further knowledge about the effects and effectiveness of a specific treatment. There are four traditional types of therapeutic clinical trials:

### Phase I

Phase I trials are small noncomparative studies that test new therapies in humans, usually without therapeutic benefit to the patient. The objective of a Phase I study is to find the optimal dose or maximum tolerated dose (MTD) to use in further testing of the treatment. The MTD is defined as that dose which can be administered without inducing unacceptable side effects. Rapid reporting and assessment of all adverse events is therefore critical in any Phase I study. The study design will require that a specific number of patients be entered at a dose level. All adverse events for that dose level are assessed before deciding whether or not to escalate the dose. Dose escalation would be done if the adverse events are at an acceptable level. If accrual is rapid, the trial should be suspended to new accrual pending this evaluation of adverse events at one dose level before treating patients with a higher dose. Only the specified number of patients should be treated at each dose level, and additional patients should not be treated at the same or the higher dose level until the evaluation of adverse events is complete.

### Phase II

Phase II trials are noncomparative trials that assess the therapeutic activity of new treatments in humans. The objective is to identify promising new treatments that can then be moved into the next phase of testing in a larger population. As with Phase I studies, timely reporting of outcome data is critical. This will include assessments of treatment efficacy and treatment-related adverse events. Phase II trials can be randomized if two or more new treatments are available for testing in the same patient population, but statistical analysis of the data will usually not involve comparisons between the arms. Each arm is assessed independently for therapeutic activity according to the criteria defined in the protocol. Phase II trials usually have a fairly small accrual goal, and they often have a two-stage design where a preset number of patients is entered and assessed for positive outcome. If enough patients (as defined in the protocol) satisfy the criteria for therapeutic activity, additional patients are entered to complete the total accrual goal for the study.

### Phase III

Phase III trials are large studies with more than one treatment arm. They are comparative trials, with a comparison of one arm against another or against all others in the trial. Most Phase III trials involve a random assignment of treatment between a control arm and one or more experimental treatment arms. The control arm usually is the "current" standard care for a disease, and it could be an observation only without administration of any therapy. In some Phase III trials, the patient (and often the physician) is "blinded" to the treatment assignment and does not know what treatment the patient is receiving.

Usually the control arm for a blinded trial is a placebo treatment, which is identical in appearance to the medication that is being tested as the experimental treatment. Trials involving a placebo are feasible only when the experimental treatment arm does not cause severe or unusual side effects.

In Phase III trials, the randomization to one of the available treatments is done prospectively. There will be a mechanism in place for patients to be registered before starting treatment, and the treatment is assigned randomly using an algorithm defined by the study statistician. It is important to note that the treatment assignment is not controlled by the treating physician. Randomization raises practical and ethical issues that are discussed in more detail in Chapter 5. The benefits of randomization versus the use of historical control data for comparison of treatment effects is a subject of debate in the statistical literature and is not covered here. In this book, all discussions about Phase III trials refer to prospective, randomized trials.

### Phase IV

Phase IV trials are post-marketing surveillance trials for collecting additional information on short- and long-term side effects of treatment in the general population.

## DEVELOPMENT OF A CLINICAL TRIAL

A clinical trial goes through various stages from the development of the hypothesis to be tested, to the analysis of the results. In very broad terms, the three stages of a clinical trial are:

- Design and development
- Patient accrual and data collection
- Follow-up and analysis

In each of the three stages, consideration must be given to systems for managing the data. These three stages will be covered extensively in subsequent chapters, but this outline of each will provide the reader with a general overview of each stage.

### Design and Development

During the design and development stage of a trial, a protocol document is developed. The protocol contains critical information for the participants in the trial. Sections usually found in a protocol include:

- Scientific rationale for the trial
- Definition of the patient population

- Details of the treatment plan
- Criteria for assessment of effectiveness of the treatment(s)
- Other relevant administrative and scientific information.

This document becomes the rule book for the trial and ensures that the defined patient population will be treated in a uniform way. During this design and development phase, plans should also be made for systems that will allow monitoring of protocol compliance once patients are entered and treated on the trial.

In parallel with the development of the protocol, the data to be collected to answer the study objectives should be defined. Decisions need to be made about how the data are to be collected, whether on paper or electronically. Whichever is used, a format for the data capture forms or screens (or both) should be designed. When using paper forms, there is a need for systems for (a) distributing blank paper forms to the participating sites and (b) for returning completed forms in a timely way to the Coordinating Center. If data are captured electronically, hardware and software must be developed and fully tested and validated. If samples are being collected as part of the study (e.g., X rays, blood/tissue samples), mechanisms should be in place for shipping, receipt, and logging of samples. If the samples are sent to Reference Centers for review, communication systems need to be defined for rapid transmission of review results to the Coordinating Center (and to the sites if necessary).

The system used for patient registration is very important and needs to be planned and implemented prior to protocol activation. There are usually requirements to collect data that document compliance with regulations, or other administrative information that may be needed during the trial (such as names and contact details for key personnel). Decisions need to be made about how computers and other technology will be used, and all related systems have to be designed, written, validated, and implemented.

During this stage, documentation of study procedures should be developed. This documentation would include policies and procedures for the Coordinating Center and for participating sites. Developing timelines for the trial is a worthwhile exercise. This would include timelines for development, recruitment, follow-up, and analysis. While adjustments will almost certainly be required during the study, this does help with developing budgets and allocating resources. Having this in place will also identify any problem areas as the trial progresses.

This description is only a very broad overview of what must be tackled during the development stage. It is the most critical of the three stages because everything that happens after it hinges on the work done during development. The importance of the development stage cannot be overemphasized, and it is important whether the trial is a large, complex trial or a small simple trial. Activation of a study without proper systems in place can lead to inadequate and incomplete data and can compromise the integrity of the trial.

### Patient Accrual and Data Collection

After a trial has been activated, emphasis switches to patient registration, data collection, and quality control, and the systems for these should have been set up and fully tested during the design and development phase. There needs to be close monitoring of the trial to ensure that accrual rates are acceptable, that the eligibility requirements for the study are realistic, that regulatory requirements are being met, and that there are not unexpectedly high rates of adverse events being reported. Ongoing quality control of all data collected is done to check for consistency and completeness, and there should also be a system in place for ensuring that data are collected in a timely way. As well as routine ongoing monitoring of the study, interim statistical analyses should be done according to the design specified in the protocol. If the trial is being monitored by a Data Safety and Monitoring Committee, the ongoing reports need to be prepared for their meetings so that they can fulfill their responsibilities for reviewing safety and, when appropriate, treatment outcome data.

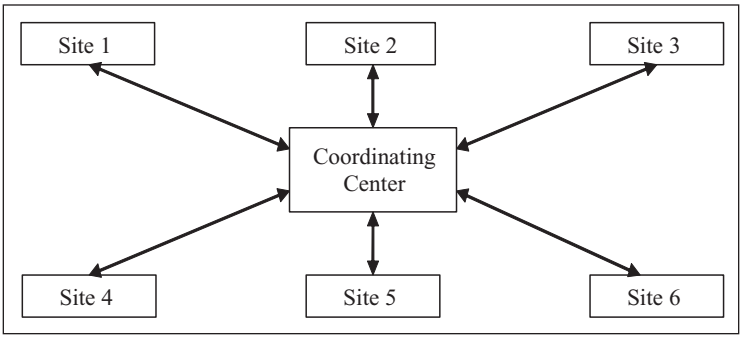
### Follow-Up and Analysis

Once the accrual goal for the study has been met and the trial is closed to further patient entry, it enters the follow-up stage. The duration of this stage depends on the study design and endpoints. Adequate time should be allowed for complete data to be submitted and for the data to mature sufficiently for the results to be meaningful. Disclosure of premature results can lead to erroneous conclusions about the efficacy of a treatment, so confidentiality is important. During this stage of the study, data should be cleaned thoroughly ready for final analysis. Any clinical review should also be completed, and once the final analysis is complete, electronic and paper files will be archived according to the requirements for the specific trial.

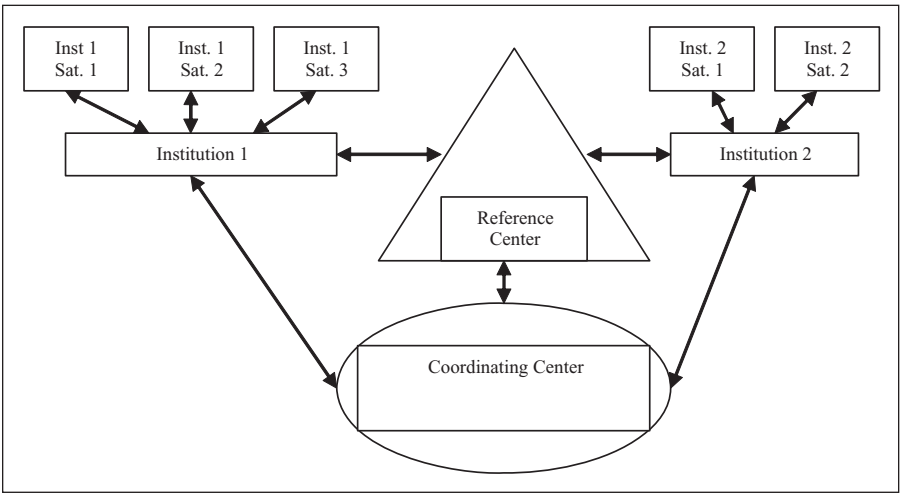
## COORDINATING CENTER

As mentioned previously, trials can involve multiple participating sites with a central Coordinating Center. Example 1.1 shows a common way for data to flow in such a study. All data flow from the participating sites directly to the Coordinating Center. Example 1.2 shows a more complex model where satellite sites send data to a main site from where it is forwarded to the Coordinating Center. Sites also send data to a Reference Center such as an X-ray reading facility, which forwards results to the Coordinating Center. However simple or complex the model used for information flow, the key is to have smooth transfer of information to all relevant parties in a timely way.

The Coordinating Center is responsible for the overall conduct of the trial and for ensuring that the trial is proceeding as planned, that all necessary systems and mechanisms are in place and functioning, that the protocol is




**Example 1.1.** Flow of Information through a Coordinating Center.




**Example 1.2.** Multicenter Trial with Satellite Institutions and a Reference Center.

being followed and necessary data are being submitted, and that all regulations are being met. Many of the key personnel for the trial are located at the Coordinating Center, and they are involved in all stages of the trial from development to analysis. The Coordinating Center is the main center for communications between all participants, so it must ensure that participants receive notification of changes to the protocol, changes to forms, patient safety updates, and any other critical information. The Coordinating Center would also be responsible for tracking data and materials collected for the trial. The systems become more complex when materials have to be sent to Reference Centers for review or processing. If this is required, decisions are made about whether the materials should be sent directly from the sites to the Reference Center (as in Example 1.2) or sent to the Coordinating Center and then forwarded from there. This may depend on the urgency of the review or the type of materials being collected. Direct transmission to the Reference Center is more efficient

but makes it more difficult for shipments to be tracked by the Coordinating Center. Quality control systems need to be developed and implemented at any reference Centers to ensure consistent and objective review of the materials.

In this book, the descriptions and procedures are described using the Coordinating Center model, although it is recognized that small trials can be done in a single location, with all functions of the Coordinating Center being carried out at that site by one or more people. The Coordinating Center is defined as the place where data forms are collected, quality control is done, and data are computerized and analyzed. The Coordinating Center responsibilities could be split between more than one organization. For example, one organization could be responsible for data management, while another one could be responsible for doing statistical analysis. The participating site or institution is defined as the place where patients are screened and entered into the trials and where source data are collected and transcribed onto case report forms.

Many clinical trials are sponsored and funded by pharmaceutical companies or government agencies. Besides providing financial support for the trial, the sponsoring organization may provide study drugs or other materials. The sponsoring organization may use its own personnel for the Coordinating Center, or it may contract this function to another organization. If contracted, the Coordinating Center acts as the agent of the sponsor in the conduct of the trial, although it the sponsor still maintains overall responsibility for ensuring that the trial is conducted properly. More details about the role of the Sponsor can be found in subsequent chapters, particularly with respect to international regulations.

## PERSONNEL

There are many people involved in the conduct of a large clinical trial, and all the relevant people play a role at the different stages of the trial. In different organizations and different areas of the world, varying titles are used for individuals who have the same basic responsibilities. For clarity, the following definitions apply in this text:

*Study Principal Investigator (PI).* The Study Principal Investigator develops the scientific concept to be tested and is usually a clinician. The PI takes responsibility for much of the ongoing conduct of the trial and may review some or all of the data from a clinical perspective. Other terms used for this person are Study Chair, Study Coordinator, and Clinical Coordinator. For some clinical trials, this role is filled by a Study Team, each with designated responsibilities.

*Statistician.* The statistician is involved in the design of the study and is responsible for calculation of the sample size and defining the statistical methodology that will be used in the trial and the analyses. The statistician prepares a Statistical Analysis Plan for the trial and, throughout the

study, is responsible for analysis of the trial data and monitoring the progress of the trial.

*Clinical Research Associate.* The Clinical Research Associate (CRA) is the person at the participating site who is responsible for completing the study case report forms (CRFs) and submitting them to the Coordinating Center. The CRA's responsibilities usually extend to other areas, such as patient registration/randomization, scheduling visits and tests, and preparing required regulatory submissions. The term CRA is most commonly used for this job description in the United States. In other parts of the world, the term Data Manager, Data Coordinator, or Research Coordinator are often used. CRAs should be involved to some degree in the design and pilot testing of case report forms, as well as in the evaluation of proposed systems and procedures. If software applications are to be used at the participating sites, CRAs should play a part in thoroughly testing the applications prior to the activation of the trial.

*Data Coordinator.* The Data Coordinator is responsible for quality control of data in the Coordinating Center. This person is also responsible for generating edit queries and data requests, for processing patient registrations, and for maintaining all study files. The Data Coordinator assists the Statistician in preparing data sets for analysis, and he or she is the primary contact with the trials personnel at the participating sites. For a small, single-center trial where there is no Coordinating Center, the person fulfilling this function may be the Clinical Research Associate, but because it is important to distinguish between the two roles, both titles are used in this book. Other titles used are Data Manager and Data Specialist. The Data Coordinator should be involved in the design of case report forms, review of the protocol document, and development and testing of the trials systems and procedures.

*Database Administrator.* The Database Administrator (DBA) is responsible for designing and setting up the trial database and for ongoing maintenance, including installation of software upgrades. The DBA also ensures the security and integrity of the database and is responsible for maintaining an adequate system for backup of all the electronic files and database(s).

*Systems Analyst.* The Systems Analyst is responsible for the design, development, testing, documenting, and validation of the trials software.

*Programmer.* The Programmer is responsible for writing and maintaining the computer programs under the direction of the Systems Analyst. The programmer will also be involved in testing and validating the software and in maintaining appropriate levels of documentation. In a clinical trials environment, there may be programmers for database-related applications and another team of programmers for statistical programming.

All the above individuals need to be involved in a clinical trial from the start. Sometimes several roles may be filled by one person, or several people may fill one role, but all areas need to be covered. This book focuses on the responsibilities of the Clinical Research Associate and the Data Coordinator in the design, conduct, and analysis stages of a clinical trial.

## TRAINING AND EDUCATION

It is important, especially for large Phase III multicenter trials, to establish a mechanism for initial training of all participants, and also for ongoing education. Training can be done by having participants attend a trials workshop, by video/webcast, by using written materials, or by a combination of these. Whatever mechanism is used, the primary goal should be to ensure that participants understand the protocol and the trial requirements. Once the trial us underway, continuing education can also be achieved by some or all of the above methods. A periodic trial newsletter to all participants can maintain interest in the trial, and it can update participants with any new information about the trial.

## REGULATIONS AND ETHICS

Most countries have regulations that govern the conduct of clinical research within that country, and it is essential that participants be aware of and comply with those regulations. If a Coordinating Center is running a trial involving several countries, they need to be aware of differences in regulations between the countries. The rights of a patient in a trial must be adequately protected, and it is important that those involved in running the trial understand and respect those rights. This includes the patient's right to withdraw from the trial at any time without jeopardy to their ongoing clinical care. The confidentiality of the patient must also be protected. In recent years, there has been important legislation in the United States and Europe covering the conduct of clinical trials and confidentiality of personal information. More details can be found in Chapter 8: Data Management and Good Clinical Practice.

## SUMMARY

For a clinical trial to be successful, it is important that there be detailed planning prior to activation. The design and planning stages of a trial are critical, and many aspects require careful consideration. While this planning stage is more critical for a large multicenter trial, it is also important for small trials being done in a single center. There are many things that can go wrong during

a trial, and unexpected things will happen, but with adequate planning and the appropriate resources, many problems can be avoided. It is also important to remember that there have been a lot of successful clinical trials, and there are well-established organizations with a great deal of experience in coordinating these trials. Before embarking on a clinical trial, there is much that can be learned from those organizations and from the literature.