DESIGN, EXECUTION, AND MANAGEMENT OF MEDICAL DEVICE CLINICAL TRIALS

SALAH ABDEL-ALEEM

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DESIGN, EXECUTION, AND MANAGEMENT OF MEDICAL DEVICE CLINICAL TRIALS
Dedication

For my mother, Farha, my loving wife, Maro, and my sons Omar, Tarek, and Yussuf. Your support has been truly inspirational.
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# LIST OF ABBREVIATIONS

<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse event</td>
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<tr>
<td>ACE</td>
<td>Angiotensin converting enzyme</td>
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<td>ANDA</td>
<td>Abbreviated new drug application</td>
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<tr>
<td>ARR</td>
<td>Absolute risk reduction</td>
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<tr>
<td>BMS</td>
<td>Bare metal stent</td>
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<tr>
<td>CBER</td>
<td>Center for Biologics Evaluation and Research (FDA)</td>
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<tr>
<td>CDHR</td>
<td>Center for Devices and Radiological Health (FDA)</td>
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<tr>
<td>CDER</td>
<td>Center for Drug Evaluation and Research (FDA)</td>
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<tr>
<td>CE marking</td>
<td>A mandatory European marking for certain product groups to indicate conformity with the essential health and safety requirements set out in European directives</td>
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<tr>
<td>CFR</td>
<td>Code of federal regulation</td>
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<td>CMS</td>
<td>Centers for Medicare and Medicaid Services</td>
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<td>CRA</td>
<td>Clinical research associate</td>
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<td>CRFs</td>
<td>Case report forms</td>
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<td>CRPAC</td>
<td>Clinical research policy analysis and coordination</td>
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<td>CRO</td>
<td>Clinical research organization</td>
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<tr>
<td>CLI</td>
<td>Critical limb ischemia</td>
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<td>DCFs</td>
<td>Data correction forms</td>
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<tr>
<td>DES</td>
<td>Drug eluting stent</td>
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<tr>
<td>DOB</td>
<td>Date of birth</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
<td>--------------------------------------------------</td>
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<tr>
<td>DOD</td>
<td>Date of death</td>
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<tr>
<td>DSMB</td>
<td>Data safety monitoring board</td>
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<tr>
<td>EC</td>
<td>Ethics committee</td>
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<tr>
<td>ELA</td>
<td>Excimer laser atherectomy</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FWA</td>
<td>Federal wide assurance</td>
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<tr>
<td>LACI</td>
<td>Laser angioplasty for critical limb ischemia</td>
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<tr>
<td>LOI</td>
<td>Letter of intent</td>
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<tr>
<td>GCP</td>
<td>Good clinical practice</td>
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<td>GMDN</td>
<td>Global medical device nomenclature</td>
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<tr>
<td>HDE</td>
<td>Humanitarian device exemption</td>
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<tr>
<td>HIPAA</td>
<td>Health Insurance Portability Accountability Act</td>
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<td>HUD</td>
<td>Humanitarian use device</td>
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<tr>
<td>ICF</td>
<td>Informed consent form</td>
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<tr>
<td>IDE</td>
<td>Investigational device exemption</td>
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<tr>
<td>IND</td>
<td>Investigational new drug</td>
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<tr>
<td>IRB</td>
<td>Institutional review board</td>
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<tr>
<td>NDA</td>
<td>New drug application</td>
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<tr>
<td>NIH</td>
<td>National Institute of Health</td>
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<tr>
<td>NSR</td>
<td>Nonsignificant risk</td>
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<tr>
<td>MACE</td>
<td>Major adverse cardiac events</td>
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<td>MI</td>
<td>Myocardial infarction</td>
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<tr>
<td>OHRP</td>
<td>Office of Human Research Protection</td>
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<tr>
<td>OPC</td>
<td>Objective performance criteria</td>
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<tr>
<td>PAD</td>
<td>Peripheral artery disease</td>
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<tr>
<td>PI</td>
<td>Principal investigator</td>
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<tr>
<td>PMA</td>
<td>Premarket approval</td>
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<tr>
<td>PTA</td>
<td>Percutaneous transluminal angioplasty</td>
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<tr>
<td>RAS</td>
<td>Renin-angiotensin system</td>
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<tr>
<td>RRR</td>
<td>Relative risk reduction</td>
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<tr>
<td>SAE</td>
<td>Serious adverse event</td>
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<tr>
<td>SAP</td>
<td>Statistical analysis plan</td>
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<tr>
<td>SFA</td>
<td>Superficial femoral artery</td>
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<tr>
<td>SR</td>
<td>Significant risk</td>
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<tr>
<td>SOP</td>
<td>Standard operating procedures</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>SSN</td>
<td>Social security number</td>
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<tr>
<td>TASC</td>
<td>TransAtlantic Inter-Societal Consensus</td>
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<tr>
<td>TLR</td>
<td>Target lesion revascularization</td>
</tr>
<tr>
<td>TVR</td>
<td>Target vessel revascularization</td>
</tr>
<tr>
<td>UADE</td>
<td>Unanticipated adverse device effect</td>
</tr>
<tr>
<td>WHC</td>
<td>Weighted historic control</td>
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Clinical trial tasks and activities are widely diverse and require certain skill sets and educational backgrounds to both plan and execute. Among the various requirements needed for conducting clinical trials are management and communication skills, the ability to develop different clinical scientific and administrative documents (e.g., study protocols, case report forms, statistical analysis plans, final clinical reports, clinical standard operating procedures, and investigator brochures), and adequate monitoring experience. This book is designed to benefit people who work in the field of clinical research, specifically, although not limited to, clinical scientists, clinical managers, biostatisticians, clinical research associates, data management personnel, and clinical coordinators. Developed as a training manual, this book provides professionals with both an in-depth and broad range of knowledge of clinical research tasks and activities that will enable them to execute these tasks and activities successfully.

Specifically, this book provides a comprehensive review on the following topics:

- An overview of clinical trial tasks and activities starting with the preparation of clinical study materials and selection of clinical sites and ending with the completion of the final clinical study report
- A review of the FDA and ICH regulations applicable to medical devices
• A brief introduction of the use of biostatistics for sample size determination and study endpoints
• An outline and discussion of the final clinical study report
• Adverse event definitions, classifications, reporting, and analysis
• Challenging issues and obstacles in designing clinical studies
• Investigator-initiated clinical trials
• A review of clinical research bioethics

While this book is intended to serve as a training manual for professionals working with medical device clinical trials, several of these tasks are also applicable to drugs and biologics trials. Throughout this book practical examples compiled from previous clinical trial experiences are discussed in a sequential manner as they occurred in the study, starting from the development of the clinical protocol, progressing to selection of clinical sites, and ending with the completion of the final clinical report study.

After reading this book, the reader will be able to understand the function and responsibilities of each member of the clinical research team. In addition, the reader will acquire a comprehensive understanding of regulations, good clinical practices (GCP), and clinical standard operating procedures (SOP), which cover medical device clinical development and can be applied to everyday clinical operations for conducting and monitoring clinical trials. By nature, the subject material of this book is expansive. Certain topics, such as the international regulations of clinical trials, were considered beyond the scope of this project and are only briefly discussed. This book focuses on the FDA regulations of the United States. International regulations, although important, were considered to be outside the scope of this project. Notwithstanding, select references to international regulations, especially those in which the sponsor plans to include international sites as part of the FDA study, have been included. Finally, this book is not intended to discuss the statistical principals of clinical trial design in depth, but rather provide a simple approach in order to enable the reader to understand main terms, statistical procedures, sample size determination, study hypothesis, among other things.

The first four chapters of this book discuss clinical trial tasks and activities and instruct the reader how to perform these activities. This portion of the book provides an overview of tasks and definitions as well as instruction on managing and tracking the progress of these tasks. A presentation of the functions and responsibilities of every member of the clinical team is discussed in the first chapter to assist
the reader to understand the integrative clinical tasks and activities required for the completion of a clinical study and how to manage these activities effectively. Chapter 2 discusses a manual of procedures on how to develop key documents required for clinical trials. Instructions and practical examples are given in this chapter on developing the clinical protocol, case report forms (CRF), clinical standard operating procedures (SOP), informed consent form (ICF), instructions for use (IFU), study regulatory binder, and other clinical forms required for the trial. The instructions for these documents include the thought process in developing the document, an outline of the content of each document, and actual examples of some of these documents such as CRF and clinical SOP. In this chapter, there is a discussion of methods and procedures used to ensure the quality and integrity of the data of a trial, such as selection of investigators, design of randomized blind study, the use of case report forms, institutional review board/ethical committee (IRB/EC), use of core laboratories, study committees, monitoring procedures/monitoring plan, defining protocol deviations, and defining study record retention and study reports. In continuation with the instructions for tasks and activities of clinical research, Chapter 3 provides a detailed discussion of the qualification and selection of study investigators and study sites. This chapter also includes discussions of the different types of study visits by the sponsor such as study initiation visit, interim monitoring visits, and study close out visits. The responsibilities of the study monitors are discussed in accordance with the type of site visit. At the end of this chapter, a presentation and examples of study monitoring reports are discussed.

The following chapters in the book, Chapters 4 through 6, are designed to cover the safety and effectiveness outcome of the study and statistical methods used to determine the outcome of the trial. In Chapter 4, a presentation of the definition of adverse events is discussed in accordance with the FDA and ICH guidelines. Chapter 4 is devoted to the definition of adverse events, serious adverse events, and unanticipated adverse device effects in accordance with the FDA and ICH guidelines. Also in this chapter, guidance is given to the investigator on the potential anticipated adverse events, what information needs to be reported about each adverse event, and the timeline for reporting different types of adverse events, as well as to whom they will report these adverse events. This chapter further defines what types of adverse events need be reported throughout the follow-up visits, after the completion of the research procedure. The analysis of adverse events as specified in the statistical analysis plan (SAP) is discussed. A definition is provided for what is considered a device-related adverse event,
serious adverse event, unanticipated device adverse effect, and the grading of the severity or strength of adverse events. Chapter 5 provides a brief discussion of the statistical methods used in a clinical study and the statistical analysis plan (SAP). An outline and the contents of the SAP are discussed, followed by a brief discussion of statistical methods used in a clinical study, such as determination of the study sample size and power of a study. Instructions and recommendations are given in this chapter on how to eliminate or minimize the bias in a clinical trial. After reading this chapter, the reader will become familiar with simple statistic procedures and terms used for clinical studies. However, it should be noted that this chapter is not intended to provide detailed statistic analysis methods and procedures for clinical studies. Chapter 6 is devoted to discussing the final study clinical report. This activity is considered one of the most important activities in the clinical study, and enough time and resources should be assigned to complete this task because the FDA acceptance of a clinical study is largely dependent on this activity. This chapter starts with an outline of the final clinical report and then discusses each item in this outline. This chapter includes discussions of other important items in the report, such as missing data analysis, examination of data across study sites, and subgroup analysis.

Chapter 7 presents key FDA regulations applicable to medical devices, such as premarket notification using 510 (K), investigational device exempt (IDE), premarket application (PMA), and humanitarian device exemption (HDE). Regulations regarding combination products (e.g., drug eluting stent and drug delivery systems) are also reviewed in this chapter. Other FDA regulations have impact on the development of clinical tasks, and the chapter includes activities such as FDA-sponsor meetings (e.g., pre-IDE meetings), institutional review board (IRB) functions and responsibilities, special study committees (e.g., data safety monitoring board, clinical event adjudication, and steering committees), the HIPAA privacy rule, and bioresearch monitoring. It should be noted that this book is focused on the US medical device regulations of the FDA, and international regulations, although important, are largely deemed beyond the scope of this book.

Chapter 8 reviews some challenging issues in designing clinical studies, such as the selection of historic control as the control group of the trial and the conduct of superiority versus noninferiority trial. This chapter also presents the data analysis of two PMA studies that used the historic control approach in its clinical studies. This chapter ends with recommendations for studies that use historic control and requirements of this control.
Chapter 9 provides a brief presentation of the investigator-sponsored clinical trials, particularly on the logistics of these studies. There is an increasing body of evidence that suggests an increased number of these trials, particularly in academic institutions funded by federal sources or private industry. Unlike clinical studies sponsored by biopharmaceutical or medical device companies, the sponsor of investigator-initiated research is usually an academic institution or private group of investigators. The sponsor of the study is usually responsible for the financial support, protocol development, product provision, conduct, and management of the study.

Chapter 10 presents the bioethics principles that were developed after World War II, such as the Declaration of Helsinki, and the Belmont Report. Special ethical concerns in clinical trials, such as regarding the use of placebo group in clinical research, are discussed as well.

A glossary of important clinical and statistical terms used in clinical research is presented in Chapter 11 of this book to get the reader familiar with the clinical and statistical terms used.

In summary, this book is intended to provide valuable information for clinical scientists (biostatisticians and clinical data analysis experts)—who develop and execute scientific clinical tasks, such as clinical protocols, statistical analysis plan (SAP), and final clinical protocol reports—as well as research associates—who manage and monitor clinical sites. Additionally, this book is a valuable resource for clinical managers needing to develop an integrative vision of all clinical research activities in order to plan and execute clinical studies effectively.

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AN OVERVIEW OF CLINICAL STUDY TASKS AND ACTIVITIES

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      and the Study of Advertising Materials 5
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Last Patient Out 7
Study Close-Out 7
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The Clinical Research Team 10
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KEY CLINICAL STUDY TASKS AND ACTIVITIES

This chapter provides an overview of the clinical tasks and activities that are required for planning and executing clinical studies. Usually all of the clinical activities are completed in a pivotal clinical study (an adequate size confirmatory study to demonstrate the safety and effectiveness of the investigational product); however, in some observatory clinical trials some of these steps may be reduced or eliminated altogether. The diversity and complexity of these tasks may require a clinical team that consists of people of certain skill sets (e.g., clinical managers, clinical scientists, biostatisticians, data management personnel, and clinical research associates) in order to complete these activities successfully. This chapter presents an overview of the key clinical deliverables (the details of each sub-activity task are discussed in the following chapters), such as, the development of the clinical protocol includes other sub-activity tasks, such as the development of the protocol synopsis, detailed study procedures, statistical section, administrative section, and finally the entire protocol. The clinical tasks and activities are arranged in this chapter in a sequential manner as they occur in the clinical study, starting with the development of the study clinical protocol and ending with the completion of the final clinical report. In this introductory chapter, methods of management of the clinical tasks by study managers are presented. In addition a presentation of the different members of the clinical team and their role and responsibilities is discussed in this chapter. In summary, this chapter will help the reader to keep an integrative view of all key tasks and activities required for a clinical studies and how to manage these activities effectively. At the end of this chapter the reader should get familiar with all clinical tasks as well as the order of these tasks required for a clinical study.

The following is a list of the key clinical deliverables for a clinical study:

1. Development of the clinical protocol and study materials
2. Qualification and selection of the clinical investigators and study sites
3. FDA approval for the study if required
4. IRB approval of the protocol, informed consent form (ICF), and advertising materials
5. Study research contract
6. Study initiation visit
7. First patient in (first patient enrollment)
8. Last patient out (last patient completed last follow-up visit)
9. Study close-out
10. Database lock (all data for the study are entered into the database)
11. Generation of data queries
12. Database cleaning
13. Development of the final study clinical report
14. Study progress reports

DISCUSSION OF KEY TASKS AND ACTIVITIES

Development of the Clinical Protocol and Study Materials

Development of the clinical protocol is one of the earliest activities in a clinical study. The clinical protocol considered one of the most important documents for the study, as it describes the background, purpose, objectives, design, and procedures for the study. Enough time and resources should be given to the process of developing the clinical protocol. Each section in the protocol should be clearly written to avoid confusion and misinterpretation. The protocol is also a dynamic document in the sense that it can be revised or amended, even after starting the study, if there is a need to clarify or modify certain procedures.

The development of the clinical protocol may require effort from several clinical research staff members working at or for the sponsor of the study and may also require input from leading clinical researchers in each area of research. Clinical experts and key researchers can provide valuable information on the proposed patient population, study endpoints, and its measurements, and the experimental procedures of the trial. Once the clinical protocol is established, templates for other clinical materials, such as the case report form and the informed consent form template, are developed in accordance with it.

The creation of protocol synopsis (protocol summary) is the first step in developing the clinical protocol. This document is usually a few pages long and includes the study title, purpose, patient selection criteria (inclusion or exclusion criteria), endpoints, and experimental procedures. This document can be used in the early preparation phase of the trial to communicate the proposed study with the potential clinical investigators.
The following study details should be clearly explained and discussed in the clinical protocol:

- Basis for sample size calculation and anticipated power of the study
- How patients are recruited and randomized to groups (this is illustrated in patients enrollment flowchart)
- Define patient selection criteria (this is defined by setting up specific inclusion/exclusion criteria)
- Methods of blinding
- Planned subgroups and interim analysis
- Study special committees (e.g., Data Safety Monitoring Board, Clinical Event Adjudication Committee, and Steering Committee)
- Data quality assurance procedures

For more on the process of development of the clinical protocol, see Chapter 2: “The Development of the Clinical Protocol, Case Report Forms, Clinical Standard Operating Procedures, Informed Consent Form, Regulatory Study Binder, and Other Clinical Materials.”

Qualification and Selection of Investigators and Clinical Sites

Potential clinical investigators and clinical sites should be carefully selected in the preparation for the study. The selection of the principal investigator (PI) and study sites is discussed in Chapter 3. The process of qualifying and selecting investigators and clinical sites can be summarized as follows:

- To ensure the confidentiality of the product and study information, a Confidentiality Agreement is usually signed by the potential investigator prior to exchanging information about the study or the study product.
- The study sponsor representative contacts the potential investigators and sends out the protocol synopsis to find out if they are interested in participating in the study.
- The sponsor may schedule a qualification visit to further evaluate interested investigators and their clinical sites for adequacy for the proposed trial.
- After the final selection process is completed, a letter is sent out to these investigators informing them whether or not they were selected for the study.
FDA Approval for the Study (If Required)

If the product is determined to present significant risk and the study is conducted under, for example, an IDE (Investigational Device Exemption), the sponsor must obtain FDA approval for the study prior to conducting the research. This may also require early discussion with the FDA about the proposed study to ensure that the FDA finds it acceptable. The discussion between the FDA and the sponsor usually focuses on the selection of the patient population, the indication for the treatment, study endpoints, and study procedures. Communication between the FDA and the sponsor is initiated by the sponsor requesting a pre-IDE meeting with the FDA. For more details on this process, see section under FDA-Sponsor Meetings in Chapter 7. Additionally, the sponsor may want to invite clinical experts to participate in this meeting if their participation is essential in highlighting certain clinical issues pertaining to the proposed study to the FDA. Early communication between the study sponsor and the FDA is highly encouraged to prevent any confusion about the planned study between the sponsor and the FDA. The sponsor should feel confident that the FDA agrees with the proposed study design (patient population, indication, study endpoints, and study procedures).

Institutional Review Board/Ethics Committee (IRB/EC) Approval of the Protocol, the Informed Consent Form (ICF), and the Study of Advertising Materials

IRB/EC must approve the study protocol, informed consent form, and study advertising materials. If the study is conducted under the IDE process, a majority of the reviewing IRBs require the FDA approval prior to their review and approval. A summaries of the role and responsibility of the IRB are presented in Chapters 2 and 7. Certain clinical sites use local IRB; other sites use central IRB. Enough time should be given to get the IRB approval, particularly in sites that use local IRB. The preparation of the study and the approval of the local IRB could take two to three months. The central IRB approval is usually obtained in less time.

Study Research Contract

A signed research contract between the sponsor and the study site or research investigator must be completed prior to initiating the study. Enough time should be given to complete this activity especially when
dealing with academic sites, which tend to take longer time than private clinical sites.

The research contract includes the following points:

- The name, title, and address of the parties involved
- Responsibilities of the principal investigator (PI)
- Subject injury reimbursement
- Payments to the clinical sites and the terms of payment
- Schedule of payments
- Deliverables required for payments
- Indemnification
- Publication policy

The research contract is a legally binding agreement involving four main points:

- Offer: From pharmaceutical/medical device company as the sponsor
- Acceptance: By institution and investigator
- For services and results: By institution and investigator
- In exchange for money: From sponsor to conduct the research/trial

The structure and template of the research contracted are presented in Chapter 2.

**Study Initiation Visit**

The sponsor conducting the study initiates a visit to train the principal investigator and the research team at the clinical site on the protocol, the investigational product, study procedures, and good clinical practice (GCP) issues, including the responsibilities of the principal investigator and research team in the reporting of adverse events, and obtaining consent of study subjects. This visit is typically conducted following FDA and IRB approval for the study, and the investigational product is received at the site. It is preferred that the visit be scheduled as close as possible to the enrollment of the first subject in the trial. During this training the sponsor should use various presentation and device models to describe and give details of the study. The sponsor representative(s) conducting this visit should file the name and title of every attendee of this training in the study training log. In certain studies the sponsor may want to administer a quiz at the end of this visit to ensure an adequate