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Design, Execution, and Management of Medical Device Clinical Trials, by Salah Abdel-aleem
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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
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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
level of understanding of the study by the attendees of the training (see Chapter 3 for more details on the study initiation visit).

**First Patient In**

This term means that the first patient is enrolled in the study after the subject met all study eligibility criteria. This is considered a key milestone in the clinical trial because it marks the actual initiation of patient enrollment in the study.

It is important to define in the study protocol the exact meaning of the phrase “enrolled subject or patient in the trial.” Does it means subjects who have met all eligibility criteria and have completed all baseline assessments, or does it refer to randomized subjects? Does it entail whether the investigational device has been implanted or will be implanted in the study subjects?

**Last Patient Out**

This term implies that last subject enrolled in the study has completed all study follow-up visits in accordance with the study protocol. Study follow-up visits range from several weeks or months (short term follow-up visits) to one year or longer (long-term follow-up visits). This event is also considered an important milestone in a clinical study because it designates the end of patient follows-up visits in the clinical trial.

**Study Close-Out**

The study close-out visit is completed once all subjects complete the follow-up visits, and once investigational device inventories are completed and copies of all CRFs are retrieved. For more details on this topic, see Chapter 3.

**Database Lock**

This term is used by data management personnel to indicate that all data for the study have been entered into the database and no additional patient data will be entered into the database after this date except data pertaining to the cleaning of the existing database. However, it should be noted that there are a few exceptions to the rule. For example, new significant data available to the study as well as long-term follow-up data can be entered into the database after it has been locked.
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Generation of Data Queries
All data queries for data inconsistency for the study that is entered into the database are generated on data correction forms (DCFs) or other forms and sent out to clinical study sites for clarification and correction. The study sites correct and clarify these data inconsistencies in the designated DCFs or CRFs, and send this information back to the sponsor. Copies of the corrected DCFs will be kept in patient clinical study files at the study sites and the sponsor files.

Database Cleaning
This process is conducted after receiving DCFs, or corrected CRFs from the study sites that contained data inconsistency, to clean up the data in the database. After the database cleaning the final data of the study are generated in form of various tables, charts, and figures in accordance with the statistical analysis plan (SAP).

Development of the Final Study Clinical Report
This represents the final task in the clinical study. The development of the final clinical report is a task that requires the input of several members on the clinical research team. The final study clinical report writing team typically consists of a report writing person, a biostatistician, and the clinical experts who have analyzed the clinical data. The final clinical report contains several sections, including a section on special procedures followed in the study to ensure the quality of the trial, analysis and discussion of patient baseline characteristics, study endpoints, and analysis of adverse events (for more detail on the content of this report, see Chapter 6).

Study Progress Reports
At least once a year the sponsor must provide reports to all reviewing IRB. For significant risk devices, the sponsor must also submit the progress report to the FDA.

A Template of an Outline of the FDA Annual Progress Report
An outline of the FDA annual progress report should include the following items:

1. Basic Elements
   • IDE number
• Device name and indication(s) for use
• Sponsor’s name, address, phone number, and fax
• Contact person

2. Study Progress
• Brief summary of the study progress in relation to the investigational plan
• Number of investigators/investigational sites (attach list of investigators)
• Number of subjects enrolled (by indication or model)
• Number of devices shipped
• Brief summary of results
• Summary of anticipated and unanticipated adverse effects
• Description of any deviations from the investigational plan by investigators (since last progress report)

3. Risk Analysis
• Summary of any new adverse information (since the last progress report) that may affect the risk analysis, such as preclinical data, animal studies, foreign data, and clinical studies
• Reprints of any articles published from data collected from this study
• New risk analysis, if necessary, based on new information and on study progress

4. Other Changes
• Summary of any changes in manufacturing practices and quality control (e.g., changes not reported in a supplemental application)
• Summary of all changes in the investigational plan not required to be submitted in a supplemental application

5. Future Plans
• Progress toward product approval, with projected date of PMA or 510(k) submission
• Any plans to change the investigation, such as to expand the study size or indications, to discontinue portions of the investigation, or to change manufacturing practices.

MANAGEMENT OF KEY CLINICAL TASKS AND ACTIVITIES

The project manager of the clinical study should use several tools to manage activities and track the progress of the tasks in the clinical
study (Microsoft Excel spread sheets, Microsoft Manager, etc.). The management of these studies includes tracking the progress of the project activities (project timeline), managing the human resources available for the project, and managing the study budget (payments for sites, CRO, consultants, materials, etc.).

Documents that are used to track the progress of these activities should include a description of each activity, a planned completion date, the actual completion date, and a comment section to show whether an activity is controlled by any other activity and/or to discuss why the completion of a particular activity has been delayed from its anticipated date. For example, selecting the PI and clinical sites for a study may require that the sponsor be able to share information about the proposed clinical study to potential clinical sites. This may necessitate signing a confidentiality agreement document by the PI in order to share confidential information with the investigator, and the development of the protocol synopsis (i.e., the protocol summary) to survey the level of interest of the investigator prior to the selection of the investigators and study sites. In addition certain activities should pass through several phases (e.g., the qualification and selection of the investigators, which starts with the evaluation of the potential investigators and ends with the final selection of those investigators).

EXAMPLE OF THE SPREAD SHEET FOR MANAGING CLINICAL STUDY ACTIVITIES

It is helpful to track the progress of the key clinical deliverables in spread sheet. It should be noted that some of these activities are tracked in different phases. For example, approval of a study may demand several rounds between the FDA or IRB and the sponsor. This process could start by giving the sponsor a conditional approval and end several months later with a final approval after the sponsor clarifies certain issues in the study. Therefore the tracking process should be set up to take into account all of the different phases of the activity (approval of the study protocol, approval of protocol amendments, etc.).

Tracking of items should include the planned date of activity, the actual completion date, and a comment section on each activity to list the reasons why particular activity has been delayed (see table 1.1).

THE CLINICAL RESEARCH TEAM

The clinical research team at, or representing, the sponsor consists of the following members:
### TABLE 1.1  Tracking of the Key Clinical Research Tasks and Activities

<table>
<thead>
<tr>
<th>Activity/Task</th>
<th>Planned Date</th>
<th>Completion Data</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol development</td>
<td></td>
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<tr>
<td>Protocol synopsis</td>
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<tr>
<td>ICF template</td>
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<tr>
<td>CRFs</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Qualification of potential sites</td>
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<td></td>
<td></td>
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<tr>
<td>Final selection of study sites</td>
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<tr>
<td>FDA approval for the study</td>
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<tr>
<td>Pre-IDE meeting</td>
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<tr>
<td>Final FDA approval</td>
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<tr>
<td>IRB approval for the study</td>
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<td>IRB submission</td>
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<tr>
<td>Final IRB approval</td>
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<tr>
<td>Study contract sign off</td>
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<tr>
<td>Investigational device shipment</td>
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<tr>
<td>Study initiation visit</td>
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<tr>
<td>First patient in</td>
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<tr>
<td>Last patient out</td>
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<tr>
<td>Close-out visit</td>
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<tr>
<td>All study CRFs in house</td>
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<tr>
<td>Database Lock</td>
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<tr>
<td>Study queries generation</td>
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<tr>
<td>Study queries out to clinical sites</td>
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<td></td>
<td></td>
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<tr>
<td>Response to queries received</td>
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<tr>
<td>Database cleaning</td>
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<td></td>
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<tr>
<td>Development of the final clinical report</td>
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<tr>
<td>Development of the annual progress report</td>
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</tr>
</tbody>
</table>

### Clinical Study Manager

This person is responsible for the following clinical tasks:

- Plan, manage, and execute clinical studies
- Plan the study timeline, budget, and resources
- Manage the development of the clinical protocol, ICF, CRFs, and other clinical materials
- Supervise and mentor study monitors
• Review monitoring reports
• Review the study adverse event reports
• Review clinical data

Clinical Research Associates (CRAs)
These personnel are responsible for the execution of the various activities in the study:

• Study setup and manage communications with clinical sites
• Prepare and execute of investigator meeting
• Conduct various study monitoring activities
• Write monitoring reports
• Review source documents for adverse events

Data Management Personnel
These personnel are responsible for managing the data of the study:

• Enter clinical study data into the study database
• Generate study tables and figures in accordance with the SAP and study protocol

Biostatistician
This person has the following responsibilities:

• Develop the Statistical Analysis Plan (SAP)
• Develop the statistics associated with the study’s endpoints and determine the sample size assumptions
• Participate in the development of the final clinical reports
• Ensure that the protocol and any amendments cover all relevant statistical issues clearly and accurately
• Review the CRFs to ensure that primary and secondary endpoints are collected and/or captured appropriately to satisfy analyses called for in the SAP, where applicable
• Work with clinical data manager to update study plan if the SAP changes and if those changes reflect changes to data collected during the conduct of the clinical research trial
**IRB Coordinator**

This person is responsible for the following activities:

- Coordinate IRB submissions
- Serve as contact person for communications
- Write responses to IRB

**Regulatory Specialist**

This person has the following activities:

- Review clinical protocols, ICF, and other clinical materials to ensure that these documents were developed in accordance with applicable regulations
- Coordinate FDA pre-IDE meeting
- Serve as a liaison between the sponsor and FDA
- Responsible for communicating responses to FDA questions regarding any particular submission to the FDA