CHAPTER THIRTEEN

Study Initiation

This chapter discusses a number of activities that must be completed before a study site can begin enrolling subjects. Topics include: study initiation documents, financial disclosure, investigator meetings, study initiation meetings, investigator study files and grants and contracts. CRAs are very involved in these activities and need to have a thorough understanding of them.

Study Initiation Documents

Before a trial can begin, a number of documents must be collected for each site. Most of these are required by FDA regulations, although some sponsors may require their own additional documents. Both the sponsor and the investigator must have copies of each document; usually, the originals are kept at the investigator's site while copies are sent to the sponsor. It is recommended that the CRA also keep copies of most of them, in case one is misplaced or disappears and needs to be replaced during the study. The documents listed below are what a sponsor must have before the trial may start. Note that most sponsors will not ship the study drug before receiving all of the documents.

- Signed, IRB-approved protocol and any amendments.
- IRB-approved informed consent, preferably containing an IRB-approved stamp.
- IRB approval letter, verifying approval of both the protocol and consent document.
- IRB approval of advertising and subject recruitment materials including subject compensation, if applicable.
- Signed, completed FDA 1572 form (Statement of Investigator). (Note: for device studies, the 1572 is not used. The sponsor obtains a signed agreement from the investigator that includes statements similar to those on the 1572.)

- Financial disclosure forms for the investigator and any other study personnel listed on the 1572 form.
- Appropriate CVs of everyone listed on the 1572 form.
- Current laboratory certification and laboratory normal ranges.
- Signed contract or letter of agreement (not required by regulation, but required by most sponsors).

Some sponsors have specific employees whose primary responsibility is to collect and maintain these documents, while in other companies the CRAs gather the documents for their sites. The CRA is the person who visits the site, so he or she will probably be involved in the collection and maintenance of documents even if another internal group has primary responsibility.

The document that generally takes the longest time to receive is the IRB approval letter. This is the only document not under the direct control of the investigator. The IRB may have approved the study, but until the investigator receives written notification it is not official. The CRA may need to encourage the investigator to keep contacting the IRB, as some are slow to issue approval letters.

Most sponsors will not ship the study drug until all the documents have been received. Note that some companies do ship the case report forms and other non-drug supplies before receiving all the documents in an effort to speed up the process, while others wait and ship everything only after documentation is complete.

Financial Disclosure

In 1998, the FDA published the final rule for financial disclosure.[1] This requirement became effective in 1999 and applies to any study of a drug, biologic or device that is used to support a marketing application. The regulation requires that sponsors certify the absence of certain financial interests of clinical investigators, disclose these financial interests or certify that the information was impossible to obtain. If a sponsor does not do this, the FDA may refuse to file the application. A full description of the requirements is found in 21 CFR 54, which is included in Appendix G.

Disclosable financial arrangements, as taken from the FDA's "Guidance for Industry: Financial Disclosure for Investigators," are:

> *(a) Compensation affected by the outcome of clinical studies means compensation that could be higher for a favorable outcome than for an unfavorable outcome, such as compensation that is explicitly greater for a favorable result or compensation to the investigator in the form of an equity interest in the sponsor of a covered study or in the form of compensation tied to sales of the product, such as a royalty interest.*

(b) Significant equity interest in the sponsor of a covered study means any ownership interest, stock options or other financial interest whose value cannot be readily determined through reference to public prices (generally, interests in a non-publicly traded corporation), or any equity interest in a publicly-traded corporation that exceeds $50,000 during the time the clinical investigator is carrying out the study and for one year following completion of the study.

(c) Proprietary interest in the tested product means property or other financial interest in the product including, but not limited to, a patent, trademark, copyright or licensing agreement.

(f) Significant payments of other sorts means payments made by the sponsor of a covered study to the investigator or the institution to support activities of the investigator that have a monetary value of more than $25,000, exclusive of the costs of conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical investigator is carrying out the study and for one year following the completion of the study.[2]

Financial disclosure became an issue with small biotech companies in their start-up phases. Sometimes investigators and companies had closely tied financial interests, which lead to a conflict of interest in the testing of potential new products.

A financial interest in a company or product does not mean that an investigator cannot be involved in a trial; it simply means that all parties must be aware of the potential for conflict of interest. The sponsor will want to evaluate the potential for bias based on an investigator's financial interest before deciding whether or not to use that investigator. The FDA will do the same when reviewing an NDA.

Financial disclosure applies to all of the people listed on FDA form 1572 for a study, plus their spouses and dependent children. This is a good reason to not list unnecessary people on the 1572 form.

Financial disclosure information must be collected at the start of the study. Any changes that result in exceeding the threshold(s) must be reported during the course of the study and for one year following its completion. There is no required form for the collection of this information from the investigator. Consequently, sponsors develop their own forms and ways of collecting and maintaining this information.

Financial disclosure information must be reported to the FDA on FDA forms 3454 (certification of absence of financial interest) or 3455 (disclosure of financial interest). These forms are submitted as a part of the NDA.

Although not popular with investigators or sponsors, financial disclosure information is required to be collected, and usually CRAs are involved in its collection. Because of their involvement, it is recommended that CRAs read