CHAPTER FOURTEEN

Study Monitoring

This chapter will discuss the CRA's main activity: study monitoring. Previous chapters discussed the importance of a good protocol, case report forms, investigator selection, investigator meetings and startup and initiation meetings in producing high-quality clinical trials. Without good study monitoring, however, the best preparation will not produce a high-quality study. Poor study monitoring is probably the largest single contributor to inferior study quality.

A good CRA can produce good studies under a variety of circumstances, with investigators and protocols of varying quality. On the other hand, a poor CRA will almost always generate a substandard study, regardless of the quality of the protocol and experience of the investigator. Good CRA site monitoring and management are essential for good studies.

The Monitoring Plan

The game plan used in athletics is a strategy that the coach and players develop before each game and includes what needs to be done to maximize the chance of winning. It changes for each game because the conditions, circumstances and opposition are different each time. So it is with monitoring. No two study sites are the same, even if they are following the same protocol. A CRA should spend some time putting together a monitoring plan (or familiarize themselves with the monitoring plan created by the study project manager), including both general and specific information for each site. The primary components addressed in this plan are: how the study will be monitored, how often monitoring visits/remote monitoring visits should occur and specific activities to be performed.

How to Monitor

How to monitor a study in the field (meaning you must travel from your company/home office to the study site) requires considerable thought. Almost all

field monitoring requires regular visits to the site by the CRA throughout the period of the study. On very rare occasions, an extremely simple, low-risk study might be monitored almost exclusively by telephone except for the startup and closeout visits.

Over the last several years, more sponsors/CROs have adopted a risk-based monitoring model for clinical trials conduct. The risk-based element targets critical study endpoint or influential visit data for review, based on risk analysis of the protocol and data. The risk-based model includes alternative monitoring practices as opposed to traditional, 100% on-site routine monitoring visits conducted at specific time intervals. These alternatives include centralized or remote monitoring of critical endpoints and data (via EDC or source documents/CRFs uploaded by site staff to a shared drive or transmitted electronically), and on-site review of targeted, critical visit data and source documents in lieu of 100% CRF/source document review (such as targeted review of drug administration and accountability data, inclusion/exclusion criteria, study endpoints, adverse event or safety reporting). This can occur in between or in lieu of some on-site monitoring visits.

Alternative site management practices such as email correspondence, teleconference and video conference provide opportunities for consistent training, site management and dissemination of information to ensure better oversight of the investigational site study performance and data collection practices.

Risk-based monitoring specific to central/remote monitoring of eCRFs and source documents will be reviewed later in this chapter.

A CRA must determine how to integrate telephone, email, fax and regular mail communications into a monitoring strategy. This will differ for different programs and sites. It will depend on the technologies available, both sponsor and site SOPs and personal preferences at both the site and the sponsor company. In monitoring, like any business, many problems can be traced back to a lack of communication, inappropriate communication and/or unclear communication. Consistent and effective communication strategies should have a high priority in your monitoring plan.

The intensity of monitoring will vary across studies and among sites. Must or should the CRA be present while the site is seeing study subjects? Will the CRA have any interaction with study subjects? In early phase I studies, the CRA may be required to be present during all or part of a subject's treatment. Therefore, the CRA must determine how long he or she will need to be there and make appropriate arrangements.

Sometimes a CRA is the sole monitor for a site, while at other times the CRA will comonitor with other company CRAs. Establishing who will monitor requires consideration of the sponsor's SOPs for field monitoring, the complexity of the protocol, the condition being studied, the experience of the investigator and his or her staff and the training and experience of the CRA.

The CRA's overall monitoring plan should remain fairly consistent, but the strategy for individual sites may change considerably during the course of the study, depending on many factors such as study conditions, protocol changes, site status and performance.

Frequency of Monitoring Visits

A key determination in a monitoring plan is the frequency with which the CRA will visit each site. There are a number of factors that must be considered in making this decision:

- Complexity of the protocol.
- Disease being evaluated.
- Experience of the investigator/staff.
- Number of study subjects enrolled at the site.
- Rate of enrollment.
- Site performance.
- Site performance (clean data vs. data discrepancies, protocol deviations, noted findings during monitoring visits).
- CRA experience and effectiveness.

The protocol dictates the conduct of the study by establishing the procedures that subjects must undergo and their frequency. The more activities required during a study visit, the more monitoring will be required. The disease being studied also dictates the frequency of visits. For example, if the CRA is monitoring an infectious disease study, the course of therapy will probably be complete for each subject in about 10 days. This requires a different frequency of visits than a cholesterol-lowering study with a treatment period of one or two years.

All sites should be visited soon after the first subject or two are enrolled just to be sure the site understands and is correctly following protocol procedures (industry standard is that the first monitoring visit occurs within one to two weeks of the first study patient enrolled at a site). Catching and solving problems early will save a lot of extra work as the study progresses. (See more about this in Chapter 18, Quality Management.) A critical benefit to central or remote monitoring of source documents or EDC is the ability for CRAs to review preliminary study visit data entry by sites, early on in a trial, (before the first monitoring visit) to proactively determine site trends in protocol deviations, GCP non-compliance or eligibility/enrollment discrepancies. This expedites preventative action and can potentially lower incidence of corrective action. The rate of enrollment will also affect monitoring frequency. Generally speaking, the more subjects a site has, the more frequently the CRA will have to visit. The faster a site enrolls and the more data generated, the more frequently the site will need monitoring.

The CRA should visit a site regularly even though enrollment may be slow or non-existent. Slow subject enrollment may indicate a lack of enthusiasm on the part of site personnel regarding the study. In that case, a bit of CRA encouragement may help, which will probably involve visits. Site personnel often view frequent visits by the CRA as an indication of the importance of their study to the sponsor. Not only that, but seeing the CRA walk through