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A Systematic Approach to Protocol Deviation Management at the Clinical Research Site

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Noncompliance with clinical research protocol requirements can put the integrity of data in jeopardy and the safety of human subjects at risk. It can also lead to regulatory trouble for both study sponsors and clinical investigators. Sponsors and investigators thus have a shared interest in reducing protocol deviations as much as possible.

Protocol deviation management is an essential part of any site's clinical research compliance program. The clinical research team must understand the process for identifying protocol deviations and taking effective corrective and preventive actions (CAPAs). In doing so, sites can minimize the effect of deviations and avoid future instances of protocol noncompliance.

Systematic deviation management includes early identification of deviations, trending the occurrence of deviations over time, determining the root cause of deviations and implementing effective corrective and preventive actions. A collaborative effort between sponsors and investigative sites on these activities is key to the successful reduction of study risks. This article describes how sites can effectively manage protocol deviations and provides an overview of the sponsor's role in managing clinical trial risks.

Deviation Identification

Investigators should not intentionally deviate from the protocol without first gaining approval from the institutional review board (IRB) and obtaining agreement from the sponsor. The exception to this rule is when the deviation is necessary to eliminate an immediate risk to human subjects.

However, most deviations occur unintentionally and without the research team noticing it. As a result, identifying deviations after the fact is a routine and important activity. Members of the clinical research team should feel empowered to identify deviations expeditiously after they occur and must not wait until the end of the study to document deviations, when it is too late to take action. Most deviations are easily identified during data entry and query resolution, if not sooner. Sites can also benefit from the expertise and critical eye of clinical monitors in identifying deviations.

Deviation Documentation and Trending

Good Clinical Practice (GCP) requires sites to document and explain deviations from the protocol. To do so, record details of each unique deviation in a single system for each study. Sponsors may provide a mechanism for tracking deviations, such as entry into the study's electronic data capture system. Strengthen your site's compliance program by compiling deviation details into a single sitewide system that allows you to trend deviations across studies in addition to following sponsor reporting requirements.

The tracking process starts when a deviation is identified and continues until completion of any CAPAs. For each deviation, record the deviation type, description, dates of occurrence

and identification, whether it occurred at the site or subject level, the visit type, the date of IRB notification (if applicable) and details of any corrective or preventive actions taken. Recording this level of detail will allow you to trend and analyze deviations over time.

The occurrence of multiple similar deviations over time may reflect a larger pattern of noncompliance. For example, multiple deviations for missed visits may reflect an issue with the scheduling system. A good rule of thumb is to take a deeper dive when a third deviation of the same kind occurs, such as three missed visits or three missed assessments.

Root Cause Analysis

Root cause analysis is a systematic process often used in science and engineering to discover the root cause of a problem. It can help you find a way to prevent problems before they occur so you do not have to put out fires after they happen. For example, if your car breaks down, you can address the problem by taking the bus, but you would be addressing only the symptoms rather than the underlying cause of the problem. A root cause analysis looks beyond the symptoms to identify where systems or processes failed.

For clinical studies, a root cause analysis should be performed for all important protocol deviations (also called "protocol violations"). The sponsor and IRB usually define important deviations. Important deviations are those that could have a significant impact on human subjects' protection or data integrity and commonly include informed consent issues, eligibility violations and investigational product dosing errors.

Also consider performing a root cause analysis when you have encountered the three-of-a-kind rule described above. You may be able to break the trend if a common root cause applies to each of the similar deviations.

The Five Whys method is a simple technique for root cause analysis. Asking "why" multiple times allows you to identify and fix the true root cause of a deviation, instead of implementing CAPAs that are ineffective because they do not address the underlying problem. Five is not a magic number — continue asking "why" until you run out of answers.

To illustrate use of the Five Whys method, consider the example of a broken-down car. Your mechanic might proceed as follows:

- Why did the car break down?
  The brakes didn't work.
- Why did the brakes not work?
  The brake fluid was low.
- Why was the brake fluid low?
  Nobody checked the level and refilled it.
- Why didn't anyone check the level and refill it?
  Everyone at the shop assumed someone else had done it.
- Why did everyone have this assumption?
  The shop's standard procedures for vehicle maintenance did not clearly identify who is responsible for this task.

By asking "why" five times, the root cause of the problem — an inadequate vehicle maintenance procedure — can now be addressed.

Using this same technique in a clinical trial example, imagine how it might help you resolve a trend of missed study visits by addressing systematic issues with your site's scheduling system, rather than only addressing the superficial symptoms by calling subjects to reschedule their visits.

Corrective and Preventive Actions

Corrective actions address the current deviation, for example, re-consenting a subject who signed the wrong version of the consent form or rescheduling a missed visit. Corrective actions also include documenting the deviation and, if required, reporting to your IRB. Some deviations cannot be corrected, but the earlier a deviation is identified the more likely you can do something to mitigate it and prevent future occurrences.

Preventive actions attempt to ensure that a deviation does not occur again. The best preventive actions build quality into the process by revising a procedure or creating a study tool, such as a checklist or worksheet. You may need to ask the sponsor to clarify or correct the protocol or other study instructions. Your preventive action plan should include retraining study personnel on any revised processes or new tools but retraining alone is seldom sufficient to address the root cause.

Define a measure and timeframe for success to determine whether a preventive action plan has been effective. For instance, to monitor your action plan for deviations associated with missed visits, monitor the outcome of the next three or more required visits to confirm they were completed as required by the protocol. Did your corrective action plan work? If not, you may need to reexamine the root cause of the problem and modify your plan accordingly.

Proceduralize Deviation Management

Create a standard operating procedure (SOP) that defines responsibilities for deviation management and reporting, the process for tracking and trending deviations, and when and how to perform a root cause analysis and implement CAPAs. Train all research staff on the new SOP.

Documentation

Detailed documentation of deviations and CAPAs will be critical in an audit or FDA inspection. You want the auditor or investigator to feel confident that you have sufficiently addressed past deviations and have a reliable process in place for addressing and minimizing future deviations.

The Study Sponsor’s Role

Starting in the study planning stage, ICH E6(R2) GCP requires sponsors to identify risks to critical study processes and study data and to evaluate these risks based on likelihood, detectability and impact on subject safety and data integrity. Sponsors then establish key quality indicators (KQIs) and quality tolerance thresholds. Study events that exceed the risk threshold should trigger an evaluation to determine if action is needed. In this way, sponsors can proactively manage risk and address protocol noncompliance.

Sponsors monitor protocol compliance in a way similar to what is recommended here for sites and contact sites when risk thresholds have been exceeded. While sites can follow the sponsor’s lead when determining a protocol deviation’s risk to data integrity and patient safety, they should also proactively manage deviations as they occur and not rely solely on the sponsor to initiate deviation evaluations and CAPAs.

Conclusion

Sponsors and investigators have a shared responsibility to reduce clinical trial risks that could affect the protection of human subjects and integrity of the data. Sites have primary

responsibility for their own protocol compliance and are responsible for evaluating and addressing compliance issues that occur at their sites, while sponsors are responsible for managing overall study risks and compliance with the protocol across sites. Working together to develop effective CAPAs not only helps the site with protocol deviation management but can also improve studywide compliance when root cause analysis identifies problems that affect other sites as well.

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