White paper

Clinical CAPA: Embedding Quality into Clinical Research

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Introduction

The primary objective of any clinical trial is to determine the clinical safety and efficacy of an investigational product. One critical component of obtaining conclusive data is to conduct a high quality trial. Managing quality in a clinical trial must begin long before the first patient is enrolled and continue through the completion of the clinical study report (CSR). Management of quality in clinical consists of multiple factors and tools working together to control and insure quality throughout the life of a trial. One such tool is the use of clinical corrective actions and preventative actions (Clinical CAPA) when certain deviations or quality concerns arise. Although there are no current mandatory regulatory requirements for a company to implement a Clinical CAPA process, managing clinical quality using corrective and preventative actions is not new to clinical. The International Conference for Harmonization (ICH) released guidelines for Good Clinical Practice (GCP) as a scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. This guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as other countries and health organizations. Although much of the oversight of a clinical trial falls on the shoulders of the Institutional Review Board (IRB), the sponsor or CRO is responsible for insuring that all of the documentation and information regarding the procedures of the clinical trial are in place.

Although most companies do not have a formal clinical CAPA process they do have quality control and quality assurance processes embedded into their clinical management plans. A good clinical quality plan does not rest solely on a CAPA process; it requires quality procedures to be in place in order to identify necessary actions prior to, during and after a CAPA is executed. Additionally, a complete quality plan includes criteria for evaluating when a CAPA is or is not necessary.

The Cornerstones of Quality in Clinical Research

There are three independent areas of quality that make up a complete quality plan for any organization: Quality Assurance, Quality Control, and Risk Management. Although these three areas work closely together they should not be merged or mistaken for each other as they provide a checks-and-balances approach to managing quality. An effective quality plan must start with defining the ideal desired level of quality in all areas of the clinical trial process. Using that ideal threshold, processes can then be established and put into place to ensure that these standards are met and define who is responsible for executing and ensuring these quality procedures.

Corrective Actions (CA) and Quality Control (QC)

Quality Controls are procedures put in place to insure that the results are as expected. After executing procedures, and if inconsistencies are found, actions can be taken to rectify the issues. Examples of quality control are monitoring visits, audits, documentation of findings and corrective actions/preventative actions (CAPAs).

Corrective actions can be taken without the need for a preventative action or formally filing a CAPA. A number of factors may impact the decision to simply correct an action and take no further action; factors such as risk, impact, severity, and frequency of the event.

Often immediate action must be taken to correct an issue that is identified in order to continue with the study. For example, a monitor is conducting a site interim monitoring visit and finds that an investigator has placed the investigational product on a window sill in direct light when product storage instructions state that the product should be stored in a dry cool place or possibly refrigerated. The monitor inquires how long the product has been there and requests that it be placed in a proper storage location. The corrective action in this example is the proper placement of the product in order to rectify the issue immediately, a decision that must be made as to the magnitude of the issue. Is this an isolated case of an investigator not following directions? Is this occurring at other sites? Could it be that proper instructions for product storage were not highlighted in the protocol or training materials? These are the types of questions that must be considered when deciding if an issue or deviation should be escalated to a CAPA.

Preventative Action (PA) and Quality Assurance (QA)

Quality Assurance consists of procedures and standards that outline what must be done, when and by whom. This is used to insure that tasks are done correctly and consistently as required. In many ways quality assurance plays the same role as preventative actions. Examples of quality assurance are standard operating procedures (SOPs), protocols, and training materials.

Preventative Actions are actions taken to reduce risk and prevent noncompliance. These preventative actions can be made before an issue occurs or in response to a finding or issue. Risk, however, often drives the decision of whether or not to take a preventative action after an issue has been identified. If a compliance issue is found to be infrequent or evaluated as minimal risk, a decision can be made to simply correct the immediate issue, document it for record-keeping purposes, but not take further action to prevent it from happening again.

In the example given earlier, an investigator is found to be improperly storing investigational product; if the monitor finds that a trend is occurring and that a number of various sites are found to be improperly storing the product, a preventative action may be taken to amend training materials or the protocol to include an emphasis on storage and retrain study staff across all sites. Doing so would make the immediate correction of the issue the corrective action (CA) and the amending of training materials and request for retraining as the preventative action (PA). If the monitor finds that the improper storage of the product is an isolated case or occurs infrequently, then immediate corrective action to close out the issue and document that action may suffice. In the example stated the risk of not storing the product properly could have negatively impacted the product, making it unsafe or ineffective and could compromise the findings of the entire study.

Risk Management

Risk management is the task of identifying, measuring, and prioritizing the impact of the uncertainty of various variables throughout a clinical trial. For example, a protocol that contains complex tests and procedures has a higher risk of noncompliance than one that contains basic testing and exam procedures. The complexity may increase likelihood of errors as well as delays in the event that a facility requires a third-party lab to conduct some of the test.

Risk can further be minimized through extensive screening and selection process of clinical sites to participate in a clinical trial. There are a number of ways a study owner can reduce risk at the clinical site level both before selecting a site as well as during the clinical trial. A few examples are listed in Table 1.

Table 1 Risk Areas for Clinical Site Selection

Risk Area	Benefit
Investigator Qualification	Expertise and experience can lead to increased quality of results and early detection of complications should they arise.
Site Qualification	Selecting a site with proper facilities and equipment (i.e., lab, pharmacy, CT Scan), can increase visibility, accountability as well as reduce delays.
Past Audit History	Past experience with a site and the frequency of issues and audit results should be a factor in prioritizing the use of a site since past history is a good indicator of future results.
Study Staff Training	Properly trained staff can significantly reduce errors in data and in execution of procedures.
Study Information Location	Easy access to essential study documents for reference as needed can increase quality and compliance as well as reduce likelihood of assumptions being made.

A strong risk management plan should include being able to predict issues before they occur. However, this is often easier said than done. To this end, it is important that quality assurance procedures be customized to each individual study's nuances and unique procedures. For example, a study that requires a specific demographic of study participants that is narrow in scope should require a particular focus on this area during site monitoring visits and when the sites are audited. Oversight in this area can result in numerous patients being enrolled in the study that should not have been and put both the patients and the overall study at risk.

The quality of clinical research results can be significantly impacted by lack of training, inadequate facilities, incomplete data entry, missed doses and test, improper patient enrollment, and so much more. The roles of the individuals monitoring and auditing the study activities are critical to managing risk and proactively putting processes and checks in place to reduce risk of noncompliance. One way to do this is to clearly define roles and responsibilities of the sponsor, the clinical research organization (CRO), and the investigator.

Roles and Responsibilities of Quality

Communication and clearly defined ownership of responsibility play a significant role in managing quality and risk in a clinical trial. Whether a sponsor is managing a clinical trial or outsourcing some or all clinical management tasks to a CRO, defining responsible parties for different aspects of the clinical trial is something that should be communicated thoroughly to all study staff. This delegation of responsibility and roles can be further assisted though the use of process oriented applications that distribute tasks to the appropriate parties as processes progress throughout the life of a trial. Many tools also provide the ability to quickly track and trend different aspect of a trial to measure failure or success and manage risk. A clinical trial is made up of various responsibilities such as training, site qualification, site initiation, monitoring visits, patient enrollment, adverse event reporting, and so much more. The higher the number of people involved in a clinical study, the higher the probability that there will be misunderstandings and miscommunications around roles and responsibilities increasing the likelihood of non-compliance.

Sponsor and CROs

Communication and clearly defined roles and responsibilities between the sponsor and the CRO are critical to the overall quality of a clinical trial. The sponsor as the owner of the clinical trial for the investigation product holds the primary responsibility for the trial. According to the ICH HARMONISED TRIPARTITE GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R1), Section 5.1.1, "The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s)." This means that the sponsor must ensure that all parties involved in the trial are performing their duties appropriately through well-documented quality control, such as the use of SOPs, and verifying the quality through quality assurance procedures such as monitoring, audits, and documentation of deviations and CAPAs. Even if the clinical trial duties are outsourced to a CRO in whole or in part, the responsibility of quality of the clinical trial still falls upon the sponsor as indicated in section 5.2.1: "A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control." This does not, however, mean that the CRO holds no responsibilities for quality. As partners, the sponsor and CRO must work together to come to an agreement of duties and responsibilities, as well as agree on which procedures and documents will be followed, such as the use of SOPs. It is important that all aspects of a clinical trial and its responsibilities are clearly defined and that everyone is aware of who is responsible for those duties. As part of a contract between a sponsor and CRO, information should be stated regarding what aspects will be held by the sponsor, and which will be delegated to the CRO. This information should include the areas of responsibility (i.e., adverse event reporting, patient enrollment, product supply), name of the individual, and contact information. This collection of information should then be shared with all support staff at the sponsor, CRO, and investigator sites. This type of open communication and transparency will decrease delays and increase accountability for quality.

Clinical Investigators

In 2009 the Food and Drug Administration (FDA) released a guidance titled "Investigator Responsibilities – Protecting the Rights, Safety and Welfare of Study Subjects." In this guidance, the FDA outlines clearly that investigators have the responsibility to inform and protect study participants, ensure the integrity of the data collected, and report any concerns and deviations. The guidance goes on further to outline what is appropriate delegation of duties to other staff, as well as expectations for training. It is also the responsibility of the investigator to report any safety concerns and deviations in the study.

Is a Deviation a Violation?

It is important to note that the FDA and the International Conference on Harmonization (ICH) do not distinguish between "deviations" and "violations." In fact, in the FDA Inspectional Manual the term "Protocol Deviation" is defined as "A protocol deviation/violation that is generally

an unplanned excursion from the protocol that is not implemented or intended as a systematic change."
Therefore a deviation should be an exception and "not implemented or intended as a systematic change." It is also important to note that the FDA is well aware that no clinical study is free of deviation, but how those deviations are handled, documented, and closed is what the FDA is concerned with. If a deviation is required it is important that the following steps be taken:

1. Investigate the issue and identify the root cause.
2. If possible correct the problem immediately.
3. Assess and document the risk, impact, severity and frequency of the event.
4. Close out issue or escalate the issue to CAPA.

To CAPA or not to CAPA

Good Clinical Practices (GCP) dictate that a protocol deviation must be thoroughly documented and explained by a sponsor and reported to the sponsor if found by a CRO. Documentation alone of the finding is not enough. Researchers should also document what will be done to correct and prevent reoccurrence of the issue. One of the challenges of a quality management plan for clinical studies is deciding when to use a CAPA and when not to.
For example, a clinical monitor during an interim visit finds that the investigational product needing refrigeration is stored in a non-refrigerated environment at one particular site. The immediate action may result in the disposal of the current product on site, replacement with new product, and a label placed on the product stating clearly that it must be stored in a refrigerated environment. The corrective action in this example is to replace the product that may be compromised. The preventative action is to label the product with the instructions so as to make the refrigeration requirement more obvious. The corrective action rectified the immediate issue at the site in question. However, it did nothing to analyze if this is a systemic problem occurring at other sites and what the impact is on patient safety. The preventative action has helped to minimize the risk of the event occurring again at this site, but it does nothing to reduce the risk of it occurring at other sites. As part of a risk management plan, the decision should be made as to whether the impact of reoccurrence of this issue warrants the effort of labeling the product across all sites. Risk to patient safety due to administration of product that was not refrigerated properly may play a significant role in making that decision. If the clinical monitor simply told the investigator to refrigerate the product verbally and took no further action, it would be impossible to track and trend the issue and analyze what the impact on patient safety or even efficacy of the outcome for the study, as lack of refrigeration may have impacted the potency of the product.

Incorporating Quality Solutions into Clinical Processes

Technology can play a significant role in implementing a clinical quality management system. Quality Management Systems (QMS) provide essential functionality to facilitate compliance with Good Clinical Practices (GCP) requirements throughout a clinical trial. It is essential that a quality solution provide a holistic approach to managing all areas of quality in a clinical trial, including but not limited to:

1. Document Management: GCP Essential Documents & Trail Master File (TMF)
2. Site Management: Qualification Information, etc.
3. Training Management
4. Audit Management
5. Process Management: Monitoring, Deviations, CAPA
6. Risk Management: Analytics, Risk Analysis

An organization that implements a robust QMS that utilizes the features listed above can quickly access areas of risk throughout the life of a clinical trial. Having real-time information on the status of a trial provides an organization with the ability to react quickly and proactively to events that may compromise the quality of a trial both in the short term and long term. A good quality management system can also reduce cost overall as an organization can take a more "risk-based approach" to quality management as recommended by the FDA in a recent Draft Guidance released in August 2011 entitled "Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring" released in August 2011.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf

Conclusion

All of the information regarding an issue or deviation should be well documented to include investigation of root cause, impact, frequency, corrective and/or preventative actions taken, as well as risk to patient safety if applicable. Without extensive documentation of issues found in a clinical trial, it is impossible to obtain a true risk assessment and overall quality impact of deviations in a clinical study, especially in a large scale study. Regardless of the level of perceived severity of a deviation, it is critical that it be documented even if only to state that the issue was found, and an immediate action was taken to correct the issue and the issue has been closed. This information will be critical for tracking and trending, and can play a significant role in identifying issues at a high level that may be missed by clinical monitors at the site level. In order to close the loop on any issue found it is important that a deviation be closed out using an issue resolution plan for minor deviations and a corrective and/or preventative plan for major deviations. How a company identifies the differences between minor and major deviations is a decision that must be discussed and agreed upon by quality functional representatives and communicated to all involved in quality activities. By doing so, the company can be assured that its investment in the costly clinical trial is concluded with the collection of adequate and accurate data in compliance with GCP requirements to establish safety and/or efficacy of the product under investigation.

About MasterControl

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