

Quality Management in Clinical Trials

Clinical trials are conducted to collect the data necessary to provide information for academia, industry, and regulators to make decisions about the safety and efficacy of the disease, illness, or preventative medicines under study. To ensure investigators are following the protocol, complying with regulatory and Good Clinical Practice (GCP) standards, and collecting and reporting quality data, sponsors of clinical trials monitor the progress of clinical trials performed by the investigators during the clinical trial. The core components of monitoring are to ensure patient protection and to validate integrity of the data. Monitoring involves periodic on-site visits by monitors each year for the duration of a study as part of a quality process. Significant findings identified as a result of monitoring are escalated for review by the sponsor's Clinical Teams and Quality Assurance (QA) Departments, which may then be managed as a suspected significant deviation. Risk assessments and evaluations are then conducted. There are circumstances where decisions have to be made with regard to taking remedial actions, which may include notifying regulatory authorities and ethics committees of any significant regulatory and/or GCP requirements. At all times, the safety and rights of subjects are the top priority for the trial sponsor.

Components for Quality

Clinical research quality is designed and embedded in the clinical trial processes and study protocol well in advance of enrollment of the first patient. Components of the quality process related to clinical trial sites include:

- Creating, implementing, and upholding standard operating procedures (SOPs) for trial execution
- A quality scientific and medical design of the protocol
- Clinical investigator and site pre-assessment and selection
- Regulatory agency and ethics committee approval
- Developing and providing appropriate informed consent (language, transparency of benefits and risks) and obtaining ethics committee approval of the informed consent process
- Investigator meetings and training
- Adequate recording and reporting of data
- Periodic monitoring
- Audits

Appropriate planning before the trial, adequate oversight and monitoring during the trial, and verification to ensure accurate reporting of results at the conclusion of the trial, create a framework for assuring quality in clinical studies.

This systematic approach recognizes quality must be integrated into the entire clinical study process, not just through testing or oversight during the course of the trial. The twin goals are to ensure subject protection and to deliver high quality data:

“...data that can be used without further revisions or data that will produce conclusions and interpretations that are equivalent to those that would be derived from error-free data, that is, data that are accurate, reliable, and fit for use.”¹

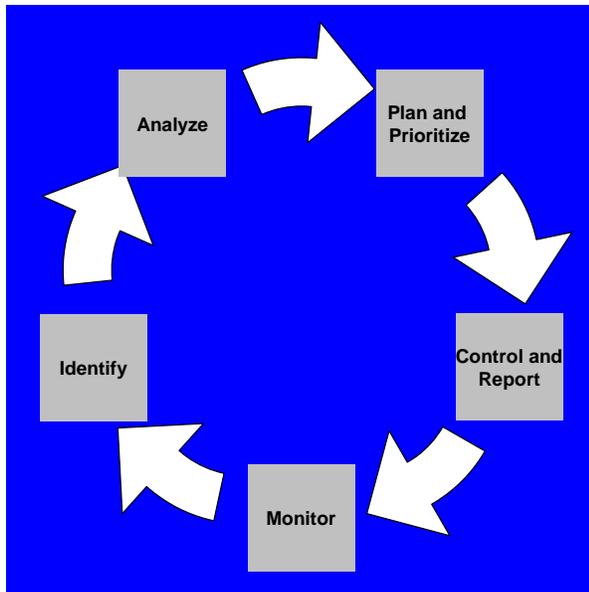
At the core of the clinical trial process is the reliance on the conduct, ability and diligence of the individual investigators to carry out or oversee the trial. Investigators must ensure adherence to the study protocol, regulatory requirements, and GCP standards in conducting the trial. Sponsors of clinical research have a broad range of obligations including responsibly selecting, training, and supporting investigators and monitors. These obligations have a direct impact on thousands of patients enrolled in clinical trials globally. However, as levels of knowledge, local regulatory requirements and standards and access to care vary internationally, quality assurance can sometimes present challenges.

The Risk Management Framework

At any given time, some sponsors may be conducting hundreds to thousands of clinical trials in locations around the world. To anticipate, prevent, and address protocol, regulatory, and/or GCP non-compliance issues, should they arise, the sponsor company uses a best practice risk management framework that considers all parts of the process, which lists controls and then tests the strength of the controls. Each potential risk is prioritized to enable the QA team to focus their efforts on particular parts of the study trial process.

¹ Davis, J, Nolan, V, Woodcock, J, and Estabrook, R. Editors “Assuring Data Quality and Validity in Clinical Trials for Regulatory Decision Making. A Workshop Report.” The Institutes of Medicine. National Academies Press, Washington, DC, 1999.

http://books.nap.edu/openbook.php?record_id=9623&page=R1



Prioritizing Risk

The five steps of continuous quality management begin with planning and prioritizing. Each consequence is assigned a severity (S), likelihood of occurrence (O) and detectability (D).

The Risk Priority Number is calculated²:

$$= S \times O \times D$$

Because potential risks are quantified, reducing the likelihood of occurrence, as in the control and report and monitoring phases, and the ability to detect problems, as in the identify phase, enable the analysis phase.

Data Integrity

Part of being proactive is to detect possible issues before they actually occur, however, with all best intentions that may not happen. In a recent case in Central Europe, Pfizer's Quality Assurance team faced a situation where the routine monitoring uncovered data collection irregularities consisting of questionable data entries. In this case, one of the study's primary components was the use of patient diaries. Subjects enrolled in this trial were asked to record specific information related to the trial in a diary over the course of predetermined periods. The information related to the medical condition under investigation and was to be recorded chronologically (in real-time) by the subject under each of the specified columns within a single line for each event occurrence, which resulted in several lines of entry per day. The diary design required recording in a left to right fashion, under the respective column, the time of the event, the completion of a specified scale related to the event, etc.

During the course of the quality related activities of a monitoring visit, the monitor noticed that some of the entries within a given subject's diary page had been filled out with different handwritings. In some cases, within the real-time, single entry line for each event, different colors of ink were used in a way that was inconsistent with how the diary was expected to be completed. In a significant number of the cases, the hand writing and ink pen color were the same for each line entry within an entire given column, but the handwriting

² "How to build risk management into clinical trials," WCI Group white paper. Accessed 12/1/08. <http://www.wcigroup.com/Repository/White+Papers/How+to+build+Risk+Management+into+Clinical+Trials.htm>

and/or ink pen color varied between the columns of the daily diary, which gave the impression that the daily diaries were completed separately for an entire column and not chronologically for each entry line.

The monitor reported the entries in question within Pfizer and after an initial assessment of the reported facts a decision was made for the conduct of a QA visit to the study site in question, for an assessment of the conduct of the study at the site with a primary focus on the alleged diary data recording irregularities.

The Quality Assurance Visit

The QA visit started with separate interviews with the clinical investigator and sub-investigator, who were the only site staff directly involved with the conduct of the clinical trial related activities. The QA team asked questions related to how the trial protocol had been executed to determine the various steps they took to implement the protocol. Interviews were also conducted with the study monitor to determine how the monitoring activities took place and to answer specific questions related to the data irregularities that they observed. Pfizer's QA team was looking to understand the flow of the study related activities at this particular site, not to assign blame or "critique" the performance of the investigators or site.

In the process of hearing the site's explanations of their processes and their concerns about the trial execution, it became apparent that some entries and/or corrections in some of the diaries were made by the sub-investigator and not the patients themselves, in accordance with protocol. The sub-investigator acknowledged he had made changes or additions to some subject diaries based on information shared with him during the subject visit. In other words, he said he was simply recording the information a subject gave him during the visit that supposedly should have been recorded in the diary one to three days prior to the subject visit. He had thought modifying or adding to the diary was in accordance with the protocol. The investigator soon realized during the course of the conversation, and in reflecting on earlier conversations with the study monitor, he had not been following the protocol by making those corrections and entries.

Significantly, none of the subjects whose diaries included changes or additions by the sub-investigator would have met the original requirements for enrolling in the study (called the protocol inclusion criteria) without those changes or additions made by the sub-investigator.

What Happens Next?

In the case of an identified quality issue, as was uncovered by the monitor and the QA review, two courses of action are undertaken. First, the data in question must be addressed. Secondly a determination has to be made about the continued participation of the investigator/trial site.

Ensuring quality data

The Clinical Study Report (CSR) is the report that summarizes the clinical data. It includes the entire protocol, sample case report forms, investigator information, all information related to the investigational product being studied as well as any statistical analyses, publications, tables or other data. It is an integrated report that contains all study related information and is provided to regulators, after conclusion of every study.³

In the CSR, questionable data is typically removed from the efficacy portion of the study analysis, to ensure that such analysis is reliable, and the report will explain why this data was excluded. The data may still be used for safety analyses. In some instances the study analysis is performed with and without the questionable data to provide the regulators with both results for consideration. Transparency of both the data, and the processes for analyzing the data is essential for regulators to understand the ethical conduct of the trial.

Determining the status of the site

After the QA audit, the next step was for that Pfizer audit team to debrief the clinical study team about the findings. The clinical team then has to make a decision as to what to do next. A variety of actions can be taken:

- The site, or sites, with identified issues can be closed; or
- The sites can be continued, but with increased monitoring; or
- The investigator at the site, can be retrained
- Other action may need to be taken, especially if the problems are seen as issues with the protocol or the training

If the decision is made to close the site because of non-compliance to Good Clinical Practice, Pfizer would alert the local regulatory authorities, and any other relevant regulators about the decision.

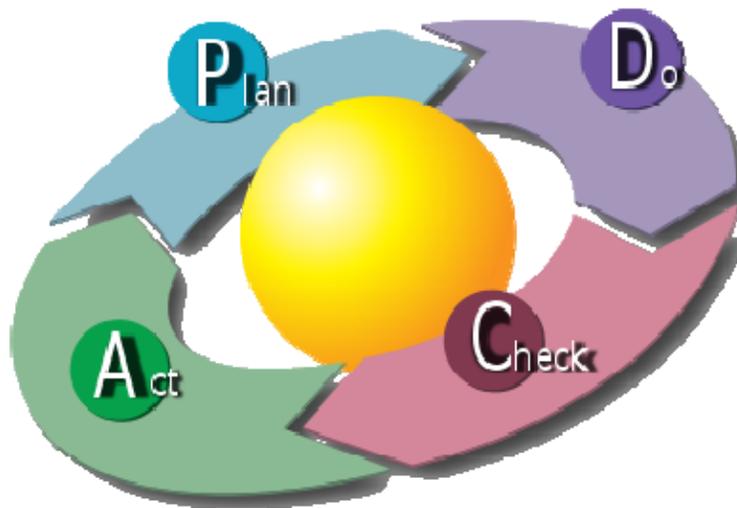
³ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), "E3: Structure and Content of Clinical Study Reports," Nov. 1995. <http://www.ich.org/cache/compo/475-272-1.html#E3>

Additionally, Pfizer will notify the ethics committee (EC) or institutional review board (IRB) about the data irregularities it uncovered, and document the issues in the CSR. These actions are taken to provide transparency to the regulators and to provide the EC/IRB with details pertaining to significant Good Clinical Practices non-compliance.

Pfizer's Approach to Quality

An effective quality assurance program means a range of possible risks may be prevented. In other cases, monitoring studies uncovers risks that trigger the occurrence of an audit, as in the patient diary case example. To ensure quality is inherent in every aspect of the process, the Shewhart model is often considered the best guide. Popularized by the father of quality control, Dr. Edward Deming, the model is at the core of Pfizer's QA processes. Plan, do, check, act are the essential steps for quality assurance in clinical studies across the world.

The Shewhart Model of Quality Assurance



Discussion Questions

1. Pfizer and other companies are trying to employ risk-based monitoring, which would target monitoring at higher risk sites. How would you determine if a site is high, medium or low risk?
2. What are the benefits and risks associated with risk-based monitoring, in terms of ensuring quality in clinical trials?
3. Should a sponsor try to find monitors for a trial that are familiar with local practices, or should the same monitors look at data at sites in different countries to ensure consistency?
4. Sponsors usually have detailed monitoring reports prepared, and in the case of audits, detailed audit reports. Should sponsors share those with regulators, when problems arise? What would the benefits and risks, if any, be in sharing such reports routinely?
5. If some data from a site is found to be unreliable, should data from the entire site be excluded from the analysis (but noted for the regulators), or included in the analysis?