White paper

How Quality and Compliance Can Help Reduce the Cost and Time Involved in Executing Clinical Trials

Published Jointly By MasterControl Inc. and Fujitsu Limited

Introduction

Quality, compliance, time, and cost are all critical concerns for life science companies conducting clinical trials. Given the skyrocketing price of clinical research, coupled with the current global economic downturn, the cost sometimes trumps other concerns.

According to a study by Cutting Edge Information, a research firm serving the pharmaceutical, biotech, medical device, and healthcare delivery industries, the clinical-trial cost per patient has risen 70 percent between 2008 and 2011, with the largest increases being in Phase IIIa and Phase IIIb of clinical research. The study showed that both Phase IIIa and Phase IIIb costs were over $40,000 per patient during the 2008-2011 period compared with about $25,000 per patient before 2008.[1]

Considering the enormous cost of clinical research, life science companies and the contract research organizations (CROs) they hire are keen on reducing expenses. While cost cutting seems a logical approach, sponsors and CROs need to realize that reducing cost at the expense of quality and compliance can be self-defeating over the long haul if it means expensive corrective action and preventative action (CAPA) or downright failure to obtain accurate clinical research data.

Next to cost, most sponsors and CROs are concerned about the amount of time it takes to conduct a clinical trial, and rightly so. Ninety percent of clinical trials are delayed because of unrealistic timelines and difficulty in patient enrollment.[2]

Given their preoccupation with time and cost, many sponsors and CROs tend to overlook the fact that quality and compliance directly affect the time and cost involved in a clinical trial. It behooves sponsors and CROs to look at all four factors as interrelated.

Common Quality and Compliance Issues

The typical quality and compliance issues (such as those discussed below) that contribute to delays in clinical research and drive its cost higher can be found in the numerous warning letters issued by the U.S. Food and Drug Administration (FDA) every year. The warning letters mentioned below were issued as part of the FDA's Bioresearch Monitoring Program, which evaluates the conduct of clinical research to ensure the safety of subjects and the validity of data submitted in support of new drug applications.

- Deviations from the Clinical Trial's Protocol

No clinical trial can begin without a clinical study protocol. It is the study's blueprint for how the clinical trial will be executed. The clinical study protocol should ensure that the procedures being executed for the trial of the new drug under investigation are safe and that the patients participating in the study are protected.

One of the responsibilities of a clinical investigator is to report serious adverse events as they occur during the clinical trial. Failure to report serious adverse events (SAE) within the required timeframe is considered a serious deviation, as exemplified by an FDA warning letter to an investigator who failed to report an SAE to the CRO and the Institutional Review Board (IRB) within 24 hours as required by the study protocol.[3]

It took the investigator seven days to inform the CRO and the IRB about the SAE, a violation of 21 CFR 312.60 (responsibilities of investigators).

- Failure to Implement CAPA and Adhere to GCP Standards

A number of FDA regulations pertaining to clinical trials are known collectively as the Good Clinical Practice (GCP) regulations. In addition, the FDA has adopted the International Conference on Harmonization (ICH) E6 GCP Consolidated Guidance. Together, these GCP standards require that when quality issues arise, there should be a CAPA plan and implementation–including investigation of how widespread the problems are, correction of the problems, and corresponding efforts to help prevent their reoccurrence.

In a warning letter to a sponsor, the FDA cited several instances of failure to implement CAPA in relation to the administration of study drug in one investigation site.[4]

The FDA said the delays in administering study drug to nine subjects ranged from 48 hours to 11 days after randomization. Citing violations of 21 CFR 312.50 (responsibilities of sponsors) and 21 CFR 312.56 (review of ongoing investigations), the FDA said the study monitors "failed to fully recognize the significance of the clinical investigator's practice of repetitively delaying study drug dosing post randomization" and in addition, the investigator failed to "implement corrective actions to prevent this issue from recurring at the site." In the same warning letter, the FDA noted that another investigation site did not adhere to GCP guidelines for blinding procedures. It noted that the monitors' instructions to the site "were inconsistent with the International Conference on Harmonization GCP guidelines."

- Inadequate Recordkeeping and Ineffective Management of Essential Documents

Certain records and documents are required during the life of a clinical trial. Known as "essential documents," they are necessary to demonstrate compliance of the sponsor, investigators, and monitors, and to confirm the validity of the clinical research and the integrity of the data collected. All essential documents are subject to audit by the sponsor's auditor and inspection by regulatory agencies. The ICH E6 guidance categorizes essential documents according to these phases: before the clinical trial starts, during the clinical trial, and after the trial's completion. Furthermore, locations of the documents are often required at the clinical site, at the sponsor's location, or both.

The importance of vigilance in recordkeeping is highlighted in a warning letter to a clinical investigator who failed to maintain accurate study records.[5]

The warning letter noted inaccuracies in study medication worksheets and visit confirmation worksheets for a subject, as well as a lack of documentation verifying that a subject completing the study on an outpatient basis was contacted during the outpatient period as required by the study protocol. The letter also noted errors in drug disposition records and the lack of documentation showing that the data was rectified.

Similarly, another warning letter shows violations stemming from ineffective management of essential documents. In this letter the investigator was cited for discrepancies in informed consent records, duplicate case history records with dates that don't match, and a discrepancy in a patient's information that was handwritten.[6]

- Lack of Training on SOPs and Other Procedures

Effective, well-written standard operating procedures play a critical role in every clinical trial. Investigators, monitors, and support staff should be properly trained on the SOPs and any substantial amendments to the SOPs that apply to a clinical trial.

For example, in a warning letter to an investigator, the FDA highlighted the importance of training when the agency questioned

whether the pharmacist preparing study drugs had been properly trained in the safe handling and administration of cytotoxic agent.[7] In many instances, CAPAs involve re-training or ongoing training of staff on critical documents and procedures. Such was the case of an investigator whose warning letter noted the re-training of the clinical research staff on SOPs and GCP practices as part of CAPA implementation.[8]

Impact of Quality and Compliance

Quality and compliance go hand in hand in clinical trials. To comply with regulatory requirements, sponsors and CROs must implement and maintain quality assurance and quality control systems. "Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly," according to the ICH E6 guidance.

Monitoring and audits are performed to help ensure quality—to make sure that the clinical trial is conducted and documented in accordance with the study protocol and GCP standards and regulations.

Poor quality in conducting the clinical trial could mean noncompliance. It could potentially mean regulatory inspection and inaccurate data that could lead to wrong conclusions about the efficacy of the drug being investigated. Worse yet, poor quality might harm clinical trial subjects. Conversely, ensuring quality makes compliance smoother, which in turn could help reduce delays and lower the overall cost of clinical research.

Five Ways to Improve Quality and Compliance

Taking the common quality and compliance issues mentioned above as take-off point, here are some ways to improve quality in clinical research and ensure GCP compliance:

- Follow Study Protocol and SOPs Closely

The study protocol is the single most important document in any clinical trial. It defines "quality" for the trial in the sense that protocol adherence and uniformity of protocol implementation means "good quality," while protocol deviations contribute to "poor quality," some more serious than others. Adherence to protocol amendments is equally important throughout the life of a clinical trial.

The ICH E6 guidance defines an SOP as "detailed, written instructions to achieve uniformity of the performance of a specific function." SOPs are the procedures for implementing the study protocol. They instruct investigators, support staff, and participants how the clinical trial will operate. SOPs help ensure uniformity across all clinical trial sites, which is critical to achieving quality. They also provide the details on how GCP regulations and standards apply to the clinical trial and how to comply with them.

A clinical trial's success depends to a great extent on a foundation of well-written study protocol and SOPs. More importantly, each trial site must follow the study protocol and corresponding SOPs to exact specification, and in the event of deviation from procedures outlined, deviations should be documented thoroughly. One way to make sure that this happens is by training investigators and support staff on the protocol and SOPs and to conduct ongoing training with regard protocol amendments, as well as re-training in case of deviations.

- Manage Essential Documents Effectively

Regulatory agencies evaluate the conduct of a clinical trial and the data it generates by reviewing all essential documents. During inspection, those documents will be scrutinized. If a sponsor or a CRO is unable to produce a document during an inspection, then that document does not exist as far as the inspector is concerned. It is therefore critical that sponsors and CROs manage essential documents effectively.

The ICH E6 guidance states that trial master files (TMF), which contain essential documents, should be established at the beginning of a clinical trial. The guidance provides a list of essential documents that are required before a clinical trial starts, during the trial , and after a clinical trial.

While generating and keeping essential documents is very important, maintaining quality —the documents' accuracy, consistency, and reliability— is equally critical. Let's go back to the FDA warning letter (mentioned above), in which the investigator was cited for ineffective management of essential documents, including duplicate records and discrepancy in handwritten information.[9] An electronic system for managing TMF could easily remedy such problems. A robust TMF management system makes it easy to search, track, and retrieve documents, and therefore easy to spot duplicate records and discrepancies in information. Any handwritten information would be entered into the system, making tracking and double checking of information faster and easier.

- **Prompt Issue Management, including CAPA Implementation**

It is a well-known fact that no clinical trial is free of quality issues. Quality issues are unavoidable, perhaps inevitable, during the life of a clinical trial. What is important is that sponsors and CROs address them promptly and properly so they will not occur again and that the scope of the impact of the issue is clearly understood and when possible reduced.

The ICH GCP guidelines state that clinical trial deviations should be documented and a corrective action taken. In addition, the ICH E6 consolidated guidance states that the implementation and maintenance of quality assurance (QA) and quality control (QC) systems are part of the sponsor's responsibilities. CAPA is an important part of maintaining QA and QC systems.

The depth of a CAPA investigation and implementation should match the risk. The ICH GCP guidelines acknowledge that not all clinical trial deviations significantly affect the scientific value of the trial results. The guidelines outline the types of protocol deviations that should be reported as "serious breaches" and require appropriately serious CAPAs.

- **Choose the Right CROs and Vendors**

Sponsors are increasingly outsourcing segments of their clinical research to contractors. Many CROs perform multiple aspects of clinical research, while others specialize in certain services. Depending on a sponsor's needs, it might hire a CRO that can do everything, or it might hire a vendor just for electronic data capture or just statistical analysis, etc. In addition, the sponsor may enlist the services of a contract manufacturing organization (CMO), a site management organization (SMO), contract auditors, and an IRB, among others.

Choosing the right contractor is critical to the success of a clinical research. But for sponsors, how do you choose the right CRO and other vendors? If you are a CRO, how do you increase your chances of being chosen by a sponsor? A study by the University of the Sciences in Philadelphia and TTC, a drug development data company, showed that there was a general agreement between the reasons cited by sponsors in choosing CROs and what CROs thought were the reasons they were chosen by pharmaceutical companies. There were five key reasons:

chemistry between sponsor and CRO, CRO experience, project execution plan, problem-solving processes, and other criteria (including a CRO's geographic scope and price of services).[10]
The criteria for choosing a CRO or vendor will obviously vary. However, a good qualification criteria and plan should be easy to adapt and use across the spectrum of vendors (CRO, CMO, SMO, etc.) that a sponsor wants to hire.

- Assess CROs and Other Vendors

Assuming that a sponsor has selected the right CRO for its clinical research, how would the sponsor make sure that the CRO will perform as expected? On the part of the CRO, how can it be sure that the investigational sites it has chosen on behalf of the sponsor will perform accordingly? Auditing of CROs and other vendors play a significant role in ensuring quality of the execution of the clinical trial. Sponsors should conduct periodic assessments or audits to make sure the CRO and other vendors are complying with GCP standards. These audits can be spelled out in a quality agreement between the sponsor and the CRO or vendor.
Sponsors also need a CRO/vendor oversight program to ensure a smooth relationship. The program should reflect the regulatory requirements that apply to the contractors and the expectations of the sponsor. It should include a process for escalation of issues and a CAPA plan.
The CRO oversight program should include monitoring and reporting of quality issues in real time, or as close to real time as possible. Some electronic systems can achieve this by consolidating the different tools being used by each CRO for reporting and communication into a single platform. Consolidation will not only allow the sponsor to be able to monitor each CRO's activities in real-time (or close), but also to reduce the sponsor's risk by performing more accurate and effective assessment against each CRO along with regular audits.
Time is of essence when dealing with serious deviations; any delay in addressing such issues increases risk. A tool such as an electronic audit system can help sponsors manage regular audits effectively by providing automatic audit scheduling and assignment of tasks. A robust system will integrate the audit process with other quality processes to allow the sponsor to monitor the CRO or specific clinical trial sites in real time, or as close to real time as possible, by tracking serious quality issues (e.g., audit findings, deviations) that could escalate to CAPA. An effective system will provide analytics and reporting capability to help assess CRO or vendor performance. It is important to choose an electronic system that the sponsor and the CRO can share. Choose a system that will allow the sponsor and the CRO to collaborate during the life of a clinical trial. The system should provide automatic notifications and reporting capability. For example, if a clinical research associate (CRA) working for the CRO enters a monitoring report into the system, and issues are identified from the report, the system will automatically notify the manager at the sponsoring company. The manager will be able to review and address the issues in real time or as soon as possible.

Conclusion

It is impossible to tell from FDA warning letters whether study protocol deviations, or failure to adhere to GCP standards, and other violations were caused somehow by the desire to reduce cost and time in clinical research. But it is apparent that instances of poor quality can lead to noncompliance, which in turn leads to CAPAs or even re-inspection in some cases, all of which result in delays and extra cost.
While it makes good business sense to cut cost and time, sponsors and CROs should do so without sacrificing quality and compliance. In fact, prioritizing quality ultimately helps cut the cost and time involved in clinical research because it helps avoid, or at least minimize, deviations that require costly and time-consuming CAPAs.

References

1. "Per Patient Clinical Trial Costs Rise 70% in Three Years," press release from Cutting Edge Information. Press release viewed on May 1, 2012, at http://www.marketwire.com/press-release/per-patient-clinical-trial-costs-rise-70-in-threeyears-1538269.htm
2. Alberto Grignolo, "The Clinical Trials Transformation Initiative," Annali dell Istituto Superiore de Sanita, 2011, Vol. 47, No. 1, page 15. The article cited data from the Tufts Center for the Study of Drug Development.
3. FDA warning letter to Vaughn Mancha Jr., Feb. 2, 2011. Warning letter viewed on April 23, 2012, at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm244336.htm
4. FDA warning letter to Johnson & Johnson Pharmaceutical Research and Development LLC, Aug. 10, 2009. Warning letter viewed on April 23, 2012, at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm177398.htm
5. FDA warning letter to Saroj Brar, March 20, 2008. Warning letter viewed on April 23, 2012, at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048366.htm
6. FDA warning letter to Linda Bosserman, July 19, 2011. Warning letter viewed on April 23, 2012, at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2011/ucm264129.htm
7. FDA warning letter to Joel Picus, Sept. 20, 2010. Warning letter viewed on April 23, 2012, at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm227878.htm
8. FDA warning letter to Linda Bosserman, July 19, 2011. Warning letter viewed on April 23, 2012, at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2011/ucm264129.htm
9. FDA warning letter to Linda Bosserman, July 19, 2011. Warning letter viewed on April 23, 2012, at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2011/ucm264129.htm
10. Harold E. Glass & Daniel P. Beaudry, "Key Factors in CRO Selection," Applied Clinical Trials, Sept. 2010. Article viewed on April 20, 2012 at http://www.appliedclinicaltrialsonline.com/appliedclinicaltrials/CRO%2FSponsor/Key-Factors-in-CRO-Selection/ArticleStandard/Article/detail/687151

About MasterControl

MasterControl produces software solutions that enable regulated companies to get their products to market faster, while reducing overall costs and increasing internal efficiency. MasterControl securely manages a company's critical information throughout the entire product lifecycle. Our software is known for being easy to implement, easy to validate, and easy to use. MasterControl solutions include quality management, document management, product lifecycle management, audit management, training management, document control, bill of materials, supplier management, submissions management, and more. Supported by a comprehensive array of services based on industry best practices, MasterControl provides our customers with a complete information management solution across the enterprise. For more information about MasterControl, visit www.mastercontrol.com or call 1.800.825.9117 (U.S.); +44 (0) 1256 325 949 (Europe); or +81 (03) 5422 6665 (Japan).

About Fujitsu Limited

Fujitsu is the leading Japanese information and communication technology (ICT) company offering a full range of technology products, solutions, and services. Over 170,000 Fujitsu people support customers in more than 100 countries. We use our experience and the power of ICT to shape the future of society with our customers. Fujitsu Limited (TSE:6702) reported consolidated revenues of 4.5 trillion yen (US$55 billion) for the fiscal year ended March 31, 2011. For more information, please see http://www.fujitsu.com.

Contact
FUJITSU Limited
Address: Shiodome City Center, 5-2, Higashi-shimbashi 1-chome, Minato-ku, Tokyo 105-7123, Japan
E-mail: contact-web-life@cs.jp.fujitsu.com

© Copyright 2012 Fujitsu Limited, the Fujitsu logo is trademark or registered trademark of Fujitsu Limited in Japan and other countries. Other company, product and service names may be trademarks or registered trademarks of their respective owners.