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Data Integrity in Clinical Trials Remains a Hot Issue in 2015

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Obtaining and maintaining data integrity in the global biopharmaceutical industry was one of the hot topics discussed at this year's FDLI Annual Conference. The issue of data integrity was a recurring theme in a number of presentations, and the morning of the first day of the conference, a plenary panel convened to discuss current concepts and trends in data integrity enforcement and compliance. The panel, moderated by Bob Rhoades, Quintiles, included a presentation on the Food and Drug Administration's (FDA) approach to oversight by Paula R. Katz, Director, Guidance and Policy, Office of Manufacturing Quality, CDER, FDA, as well as industry perspectives from Anton-Lewis Usala, CTMG, Inc., and George J. Serafin, Deloitte & Touche, LLP, and insight on legal issues from Cathy Burgess, Alston & Bird, LLP. Below is an overview of the issues discussed by the panel including some best-practices in assuring quality data from clinical research.

Ms. Katz indicated that, in recent years, FDA has increased its scrutiny of investigators, Sponsors, and other parties involved in clinical trials in order to ensure proper control and monitoring of data integrity systems and the implementation of procedures that ensure adequate and well-controlled studies.

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Obtaining adequate and reliable clinical trial data, while safeguarding human safety, is critical to obtaining FDA approval. Inadequate, false or manipulated data or clinical trial results can not only result in a rejected application, but also increased subject risk. Agency enforcement actions are also possible, including investigator or sponsor debarment. In the end, such actions serve as an impediment to FDA's ability to make accurate or informed decisions regarding the safety and efficacy of a sponsor's drug, biologic, medical device, or combination product.

The Complexity of Data Management

Data integrity remains a critical issue due to the length and complexity of clinical trials. In a typical clinical trial, extensive amounts of data have to be processed, analyzed, and monitored during and after the trial. Trials involve multiple parties, personnel, quality systems, technology, and procedures. Unintended errors can occur where the quality systems used are not properly controlled. Despite significant advances in electronic data capture, data integrity concerns can arise from inadequate training on continuously evolving technology. These include new complex technological platforms and diagnostic or treatment methods. Data error can also occur through human error or misconduct in the entry or supervision of a task, such as the taking of medical histories and recording of subject data.

Regulatory agency oversight of data integrity is growing as well. One example is the recent recommendation by the European Medicines Agency (EMA) to suspend the sale of several medicines for which clinical studies were conducted at an Indian Contract Research Organization (CRO), GVK Biosciences, P.L.[1] The inspection of GVK, led by the French Medicines Agency (ANSM),[2] revealed that electrocardiograms had been manipulated for a period of at least five years due to inadequate quality system and supervision maintained by the CRO. This discovery led to a review of clinical trial data related to 1,000 pharmaceutical medicines and a decision to halt European sales of 700 pharmaceutical products.

FDA's Role in Data Integrity

In order to assure that clinical investigations comply with regulatory standards during the entire clinical trial process, FDA does not only review clinical trial data submitted by a sponsor during the NDA process, but the agency also requires that investigators follow Good Clinical Practices (GCPs).[3] Sponsors of clinical trials are also required to disclose

details regarding the steps taken to ensure proper manufacturing.[4]

In addition to FDA's authority, Institutional Review Boards (IRBs)[5] and Data Safety Monitoring Boards (DSMBs),[6] if utilized in a clinical trial, also play a role in ensuring patient safety and data integrity.

FDA's role with regard to clinical trial phases of human drug development begins at an early stage when a compound has been tested for pharmacologic effect and an Investigational New Drug application (IND)[7] is submitted to the agency. Usually, clinical trials begin one month from submission of the IND, unless FDA issues an objection. The agency can place the IND on "clinical hold"[8] on a variety of grounds, depending on the phase of the trial.[9]

The IND submission will include a study protocol that must be followed during clinical investigation. If the clinical investigation is being conducted in a manner substantially different than that described in the protocol submitted in the IND, or the clinical investigation brings up safety concerns, FDA has the authority to order termination of the study.[10] When a New Drug Application (NDA) is submitted, FDA can order further studies of the product if the agency determines the data provided by the sponsor is insufficient.

FDA takes data integrity very seriously, as reflected in the number of post-inspection warning letters that the Office of Manufacturing and Product Quality has issued in the past two years. As mentioned during the FDLI session, nineteen Warning Letters[11] were issued in 2014, 11 of which disclosed data integrity issues. As of April 2015, five Warning Letters[12] had been issued relating to non-compliance with data integrity regulations. FDA has indicated that the agency will continue taking action against companies that either provide false data to the agency or file drug applications supported by inaccurate data because "false data is meaningless and endangers consumer and patient safety."[13]

Improving Data Integrity for Clinical Trials

The panelists indicated that there are several factors that, if developed and implemented, will help maintain adequate data and well-managed clinical investigations. Most importantly, a well-designed protocol with reliable quality metrics must be in place. If the protocol has errors or is ambiguous, the resulting clinical trials could become unreliable and the investigational product may fail to obtain FDA approval.

Developing and Implementing a Risk-Based Monitoring Plan

Sponsors are responsible for monitoring clinical investigations,[14] which includes reviewing the performance of the clinical investigator (CI) in carrying out the investigational plan and reviewing the evidence relating to the safety and efficacy of the investigational product. In recent years, FDA has encouraged sponsors to adopt risk-based monitoring plans and has issued guidance to that end.[15] Under such guidance, a sponsor must design a monitoring plan that identifies and analyzes risks and determines whether adjustments to levels of monitoring processes or practices are needed. Risk is measured by determining the threat that clinical trials pose to human subject

safety or data integrity. For example, assuring a study is blind at the site and sponsor level would be considered "critical data" in need of thorough monitoring. On the other hand, monitoring the storage of a product under investigation when the protocol does not provide specific handling instructions might be considered non-critical or an inferior risk to the study.[16]

In order to identify hazards and to screen out risks to human subject safety and data quality, FDA encourages sponsors to use innovation and modern methods and technology while conducting clinical trials.[17] One example is centralized monitoring. Centralized monitoring is an activity undertaken by the sponsor outside the clinical site, providing additional capabilities to the more traditional on-site monitoring practices. It fully relies on secure data transfer technology. Under such an arrangement, data generated on-site is automatically and securely transferred ensuring data quality and accuracy. Under the proper parameters, this is better than only using on-site data storage, as the system can rapidly generate statistics and identify, at a higher frequency, what needs to be reviewed, better monitored, trained or retrained or when an on-site monitoring visit needs to occur.[18]

Likewise, an important continuing trend is a sponsor's transfer of certain obligations, including monitoring obligations, to a contract research organization (CRO).[19] When this occurs, a CRO may take the lead in reviewing clinical trial data. The same is true when a DSMB is involved,[20] to ensure accurate and unbiased data and results. The sponsor still retains the obligation to oversee the CRO's monitoring on an ongoing basis and to review adverse events and assess data when working with a DSMB.[21]

Emerging high-tech approaches and technologies can also be implemented in order to increase clinical trial data integrity. These include mobile medical devices for subject monitoring and electronic platforms for patient recorded outcomes.

Setting Security Measures on Electronic Data Collection Documents

Confidentiality and accuracy of clinical trial data must be assured. Panelists emphasized the fact that documents that collect study data should be secured by the use of passwords or other security measures that block access to parties who may manipulate the results, as FDA inspections have, on occasions, identified fabricated or manipulated records reflecting more favorable results where adequate data collection security measures were not in place.

Designing and Implementing Corrective and Preventive Actions

Corrective and preventive action plans should be focused on product and process and on detecting or preventing potential non-conformities. To this end, the level of risk should be evaluated for each procedure and an evaluation should be tailored to each of them. Some processes or procedures might require more effort and meticulous control and investigation than others. Additionally, risk assessment should determine how controlling and monitoring practices should be

designed and implemented so as to prevent future data integrity problems.

In order to correct breaches of data integrity FDA suggests in its Warning Letters that, among other actions, drug developers conduct a review of documents, implement new controls, train or retrain personnel, or conduct any other actions that would correct the loss of integrity in data.

Delegating Tasks and Managing Personnel

It is the responsibility of the CI to ensure that the clinical research protocol is being adhered to, and that relevant FDA regulations and guidance are being correctly followed, to protect the rights, safety, and welfare of study subjects, and to personally supervise personnel working on delegated tasks.[22] The CI is also responsible for delegating to personnel qualified by education, training, and experience the performance of relevant tasks and supervision of the ongoing study. However, if the CI takes no leadership or management responsibility, adequate supervision may not be achieved and when this happens other factors may also impede adequate data collection.

Risk factors for data integrity breaches include inexperienced staff, large number of study subjects, lack of routine meetings with the investigational team scheduled by the CI, lack of procedures in place for addressing issues that might arise during the studies, or diffuse oversight, such as a single CI supervising several sites simultaneously, or overseeing several studies at multiple sites.[23]

Furthermore, it is the CI's responsibility to supervise personnel who have been employed by a Site Management Organization (SMO) and to carefully review, evaluate, and institute procedures to ensure authenticity and accuracy of data from studies that have to be conducted outside the investigator's site due to a lack of qualified personnel or necessary equipment.[24] Ideally, CIs and managers should take responsibility for and lead monitoring quality of data collection, analysis, transmission, and storage.

Training Personnel

Before starting and during clinical studies, sponsors should ensure that research nurses, database programmers, clinical data managers, and any person who works on the clinical investigation, should be trained to follow the protocol. sponsors should ensure that they understand their tasks, responsibilities, and the importance of being thorough. Likewise, personnel who do not follow the protocol should be removed to avoid future misconduct issues.[25] Personnel should be periodically trained and adequately supervised by the CI. Personnel should be aware of the necessity of reporting deviations or non-compliance issues to the sponsor, CI, or immediate manager or coordinator.

Conducting Independent Internal Investigations

Internal investigations should be conducted when issues arise and managers, coordinators, or anyone with a responsibility to take action has knowledge of any irregularity or misconduct, such as scientific misconduct, lack of informed consent of study subjects, or access to patient records that is prohibited under HIPAA.[26] It is important that the investigation is conducted by an independent person, company, or firm to avoid biased

conclusions. This third-party should understand the issue, the product, and the scope for investigation of the data necessary to provide additional disclosure.

Hiring Clinical Research Organizations

As noted above, it is common for sponsors to engage CROs to run their clinical trials. Among other things, CROs may assist in accelerating the recruitment and enrollment process and sponsors may leverage the data management systems made available by the CROs. CROs can also provide laboratory services, data management, and biostatistics, prescreen patients to assure they meet the protocol, and use appropriate software and licensing procedures. Nevertheless, before hiring a CRO, sponsors must recognize that they retain responsibility for the quality and integrity of the clinical trial data and the work performed by the CRO. Sponsors, therefore, must assure that the CRO chosen is the appropriate one for the planned studies. What sponsors should look at when choosing a CRO is the organization's experience on similar projects and teams, its site or geographical capacity, the existence of problem detection plans and corrective actions, and the quality systems used.

Hiring Third-Party Auditors

Another valuable measure is regularly hiring competent third-party auditors to investigate data management and procedures followed in and out of investigative sites, such as a sponsor's monitoring procedures, independent facilities that might conduct clinical chemistry testing, radiologic assessments or electrocardiograms, and other investigative sites that have appropriate equipment and personnel. Auditing issues arise when obtaining accurate information depends on comparing the data collected for the clinical investigation to other studies' data, since duplication of data may only succeed through audits of other companies' or competitors' data.

All these measures, if implemented, will likely increase the probability of more quickly identifying errors or data manipulation in time, thus leading to a more controlled data system, completion of a satisfactory FDA inspection and, finally, obtaining a product approval.

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1. EMA Website, http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/GVK_Biosciences/human_referral_000382.jsp&mid=WC0b01ac05805c516f.
2. Agence Nationale de Sécurité du Médicament et des Produits de Santé.
3. GCPs were issued by ICH and adopted by FDA as Guidance in 1996 – E6 Good Clinical Practice: Consolidated Guidance.
4. 21 C.F.R. 312.23(a)(6).
5. See 21 C.F.R. 56 for IRB responsibilities.
6. U.S. DHHS, FDA, CBER, and CDRH, Guidance for Clinical Trial Sponsors, *Establishment and Operation of Clinical Trial Data Monitoring Committees*, (October 2009).
7. 21 C.F.R. 312.1.
8. 21 C.F.R. 312.42.
9. 21 C.F.R. 312.42(b).
10. 21 C.F.R. 312.44(b)(4).
11. FDA Website, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/ucm380323.htm#DMPQ.
12. FDA Website, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/ucm432949.htm#DMPQ.
13. Howard Sklamberg, Deputy Commissioner for Global Regulatory Operations and Policy, FDA, Keynote Address, FDLI Annual Conference, April 21, 2015.
14. 21 CFR 312.50 and 21 CFR 312.56.
15. U.S. DHHS, FDA, CDER, CBER, CDRH, OGCP, and ORA Guidance for Industry, *Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring* (August 2013).
16. *Id.*
17. *Id.*
18. *Id.*
19. 21 C.F.R. 312.52.
20. Guidance for Clinical Trial Sponsors, *Establishment and Operation of Clinical Trial Data Monitoring Committees*.
21. 21 C.F.R. 312.32(b).
22. 21 C.F.R. 312.60. See also, U.S. DHHS, FDA, CDER, CBER, and CDRH, Guidance for Industry, *Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects* (October 2009).
23. *Id.*
24. *Id.*
25. See e.g., sponsor's removal obligations under 21 C.F.R. 312.56(b).
26. The Health Insurance Portability and Accountability Act of 1996.