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Role of quality assurance and quality control in clinical trials – Need for harmonization

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ABSTRACT

Clinical trials may be defined as biomedical or health related research studies in human beings that follow a pre-defined protocol. Clinical trials are the link between the results of preclinical testing and actual clinical practice. They are conducted to collect the data necessary to provide information for academia, industry and regulators and it is only through trials that progress is made on new medicines including drugs, vaccines, and devices, as well as improved treatments for diseases. Clinical trials involves interplay between clinical investigators (often referred as Principal Investigator or PI), patients, sponsors, control research organization (CRO), clinical laboratories with the overall objective of improving healthcare to ensure subject safety, validity, accuracy and credibility of data generated. To ensure that these concerns are adequately addressed in a study, regulations and guidelines have been developed like following the protocol, complying with regulatory and Good Clinical Practice (GCP) standards, collecting and reporting quality data and overall monitoring of the progress of trial. Maintaining accuracy and quality throughout the clinical study is a continuous dynamic process. There is increasing focus on having quality system in place throughout the planning stages of clinical trials with specific standards for each clinical trial process to produce a more reliable and useful end product – high quality data without compromising the rights and welfare of human subjects. Globalization, outsourcing and increasing complexity of clinical trials have made the target of achieving global quality challenging. Although the study requirements are carefully set forth initially, expectation and requirements can change during a study and coordination and harmonization throughout the trial is essential.

Keywords: Clinical trials, academia, industry, regulators, control research organization (CRO), Good Clinical Practice (GCP).

INTRODUCTION

Clinical trials process begins with the development of a study protocol and ends with the preparation of a clinical study report. The selection of investigators sites, the recruitment of study subject and completion of case report forms (CRF) constitute the most important parts of this process. As clinical trials operate on a "project" mode and involve several parties, processes, and regulations, it is necessary to outline the roles and responsibilities of each of the constituents of the trial well before the study begins. Essential documents, individually and collectively permit evaluation of the conduct of the trials and quality of the data generated, and serves to demonstrate compliance of the Principal Investigator, sponsor, and the Contract Research Organization (CRO) with GCP and other regulatory requirements. It is said that "if it is not documented, it does not happen" and according to International Conference on Hormonisation (ICH) – GCP guidelines, essential documents, are those documents that individually and collectively permit the evaluation of the conduct of a trial and the quality of the data produced. Quality of a clinical trial rests on ensuring that the data and reported results all credible and accurate and the rights, integrity and confidentiality of trial subjects are protected. The sponsor is responsible for quality assurance (QA) and quality control (QC) of the clinical trial. Much of the literature on quality assurance and quality control has arisen in the context of clinical trials, focusing on maximizing the quality of the data through standardized study - wide and local protocols, training of study personnel and data management systems[1-9].

DISCUSSION

Quality control is one of the most important aspects of any study as the integrity of the conclusions drawn by a study are in large part determined by the quality of the data collected. Minimizing all the potential sources of error is of paramount importance in conduct of clinical trial. There are actually two basic components of Quality control viz. Quality Assurance and Quality Control. Quality Assurance (QA) is a wide-ranging concept which covers all matters which individually or collectively influence the quality of a product. It is the sum total of the organized arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use while as quality control consists of those activities that take place during and after data collection to identify and correct any errors or discrepancies in the data that have been collected. It is concerned with sampling, specifications and testing and with the organization, documentation, and release procedures which ensure that the necessary and relevant tests are actually carried out and that the materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. 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 and reported in compliance with the protocol, GCP and the applicable regulatory requirements(s) [10-15]. An integral component of quality assurance is the training and certification of study personnel in accordance with the study protocol[2,3,16,17,18,10,11,19,20]. Once data collection begins, quality control procedures developed as part of the quality assurance processes must be implemented. Thus the goal of the quality control procedures is to identify and correct sources of bias in the data both during and after the data collection. Manuals should also be reviewed so that any sections that are ambiguous or subjected to misinterpretation can be clarified[20].

QUALITY ACTIVITIES DURING THE TRIAL

There are a number of Quality Assurance (QA) activities throughout the conduct of a trial. The most significant activity is adverse event reporting by the investigator to the sponsor and as appropriate to the ethical committee (EC), verification of data versus source documents, analysis of data queries and drug accountability. The sponsor should facilitate all the reporting to all related investigator(s) and to the regulatory authority of all adverse drug reactions - both critical and unanticipated. Ethical committee should be communicated about any unexpected and related adverse events that can impact the overall risk benefit balance. The intention of trial monitoring is to confirm the rights and interests of the subjects are protected, the trial data are exact, absolute and provable from source documents and the conduct of the trial is in confirmation with the protocol, with GCP and with the appropriate regulatory requirements. Monitors appointed should be suitably trained and be well known with the test article(s), the protocol, the written instructed consent document, the sponsor's SOPs, GCP and the appropriate regulatory requirement(s). The monitor should give a written report to the sponsor following each trial site inspection or trial related communication. Data management of clinical trials is very important and highly controlled, because the data gathered will be utilized for statistical analysis and report writing and will subsequently be put through regulatory review. The data management team sends data queries to the study site and the decisions are sent back to the data management team by the monitor[21].

Internal audits of the site selection and management procedures need suitable staff and guarantee that the trial was carried out in compliance with the procedure and suitable regulations. Site performance is assessed by an internal process evaluations following the trial have commenced taking into regard such trial related items[22]. Some common deficiencies observed during site inspection include failure to follow the investigational plan and signed investigator statement/agreement, protocal deviations, inadequate record keeping, inadequate accoutability for the investigational product, inadequate subject protection including informed consent issues, adverse event recording and reporting.[23,24].

Over the year, these have remained the areas of deficiencies at the investigator sites. However, the sponsor and its team monitors play a significant role in the site performance. In FDA inspections ,some of the common sponsor deficiencies were inadequate monitoring, failure to secure investigator compliance, failure to submit progress reports, failure to notify FDA, investigators or internal review boards (IRBs), failure to obtain signed investigator agreement, failure to obtain FDA or IRB approval and unqualified monitors[25].

The FDA warning letters also cite deficiencies in monitoring[26]. As the quality of a clinical trial depends on ensuring protection of human subjects, the functioning of the IRB also needs to be reviewed[23,27]. Standards need to be developed and implemented for each clinical trial process[28,29] and the quality system requirements include personal roles and responsibilities, training policies and procedures, quality assurance and auditing, document management, record retention and reporting, corrective and preventive action (CAPA). Thus quality system should deal with all types of errors likely to occur in clinical trials i.e. design, procedural, recording and analytical[28].

QUALITY – NEW REGULATORY APPROACHES AND INITIATIVES

Upto now, quality management was often uneven e.g. there was quality verification at the beginning of novel research development, and one more at the closing stages through peer review publications. But throughout the balance of the research procedure, quality management was repeatedly left to the researchers and their institutions[29]. The FDA is developing new approaches on risk based evaluation planning[30] which include Center for Drug Evaluation and Research (CDER) risk based site selection tool,

IRB inspection model, bioequivalence examination model and Sponsor /CRO surveillance review model.

The FDA is programming to switch its inspection focus, which is currently post New Drug Approval (NDA) submission, to clinical trial inspection, supervision in real time to make surveillance inspections of sponsors and clinical investigators during the trial and appraisal of the sponsor quality systems and sponsor quality management plan at end of phase II.

Another more important FDA initiative is the Clinical trials transformation initiative (CTTI) which was set up in 2008 by the FDA and Duke University as a public private partnership. The CTTI, a public private partnership involving industry, government, patient advocates, trade organizations, professional societies, academia, and non-academic investigators and more than 60 interested parties with an aim to identify practices that, through broad adoption will increase the quality and competence of clinical trials[31]. The CTTI has characterized quality as "the ability to efficiently answer the intended question about the benefits and risks of a medical product or process, at the same time assuring protection of human subjects[32]. The CTTI has initiated several projects to identity practices that will increase the quality and efficiency of clinical trials. One of the first projects designed and accepted under this initiative is "Effective and Efficient Monitoring as a component of Quality assurance in the conduct of Clinical Trials". Even though present regulations need sponsors to guarantee proper monitoring of clinical investigations of products subjects to Investigational New Drug Applications and Investigational Device Exemptions, monitoring process that are unsuccessfully and overly burdened may intentionally give to poor data quality[33]. The CTTI has made suggestions to build quality into scientific and operational design in the conduction of clinical trials, some of which are: concentrate on what matters, develop a quality plan focusing or areas of serious risk for generating errors that matters, prospectively measure error rates of critical parameters, monitoring approach, improved training and procedures and report quality problems found, actions taken, converse their effect on the analysis and explanation of results. This FDA's recent steps highlight the significance of prospectively building quality into scientific and operational design and the conduct and monitoring of clinical trial[34].

CONCLUSION

Quality assurance and quality control procedures span the entire course of the study and include a multitude of tasks. Such tasks are delegated to various committees and / or are undertaken by participating centers, all of which must take responsibility for understanding, implementing and following through on all procedures that maximize data quality. The procedures should be designed to ensure that the data being produced are in fact reliable, valid on the appropriate scale, and do not reflect bias of the instrument or bias that may arise in subgroups of population being studied. The quality of the quality assurance/quality control process is highly correlated with the quality of communication with and between centers and all researchers. Maintaining standardization of procedures across centers and analytical procedures are integral part of quality control demanding continuous vigilance from the key state holders - investigators and sponsors and harmonizing the activities.

REFERENCES

[1] Freedland KE, Carney RM. Data management and accountability in behavioral and biomedical research. Am Psychol 1992; 47: 640-5.

[2] Gassman JJ, Owen WW, Kuntz TE, et al. Data quality assurance, monitoring, and reporting. Control Clin Trials 1995; 16(2 Suppl): 104S-36S.

[3] Prud'homme GJ, Canner PL, Cutler JA. Quality assurance and monitoring in the Hypertension Prevention Trial. Hypertension Prevention Trial Research Group. Control Clin Trials 1989; 10(3 Suppl): 84S-94S.

[4] Karrison T. Data editing in a clinical trial. Control Clin Trials 1981; 2: 15-29.

[5] Marinez YN, McMahan CA, Barnwell GM, et al. Ensuring data quality in medical research through an integrated data management system. Stat Med 1984; 3: 101-ll.

[6] Bagniewska A, Black D, Molvig K, et al. Data quality in a distributed data processing system: the SHEP Pilot Study. Control Clin Trials 1986; 7: 27-37.

[7] Severe JB, Schooler NR, Lee JH, et al. Ensuring data quality in a multicenter clinical trial: remote site data entry, central coordination and feedback. Psycho pharmacol Bull 1989; 25: 488-90.

[8] Sforza VA. Quality data: what are they? Ann 1st Super Sanita 1994; 30: 439-43.

[9] Hohnloser JH, Puerner F, Soltanian H. Improving coded data entry by an electronic patient record system. Methods Inf Med 1996; 35: 108-11.

[10] Canner PL, Borhani NO, Oberman A, et al. The Hypertension Prevention Trial: assessment of the quality of blood pressure measurements. Am J Epidemiol 1991; 134: 379-92.

[11] Keltner JL, Johnson CA, Beck RW, et al. Quality control functions of the Visual Field Reading Center (VFRC) for the Optic Neuritis Treatment Trial (ONTT). Control Clin Trials 1993; 14: 143-59.

[12] Habig RL, Thomas P, Lippel K, et al. Central laboratory quality control in the National Cooperative Gallstone Study. Control Clin Trials 1983; 4: 101-23.

[13] Correa A, Stewart WF, Yeh HC, et al. Exposure measurement in case-control studies: reported methods and recommendations. Epidemiol Rev 1994; 16: 18-32.

[14] Bergman LR. Measurement and data quality in longitudinal research. Eur Child Adolesc Psychiatry 1996; 5(Suppl 1): 28-32.

[15] Johstone FD, Brown MC, Campbell D, et al. Measurement of variables: data quality control. Am J Clin Nutr 1981; 34(Suppl 4): 804-6.
[16] Tillotson JL, Gorder DD, DuChene AG, et al. Quality control in the Multiple Risk Factor Intervention Trial Nutrition Modality. Control Clin Trials 1986; 7(3 Suppl): 66S-9OS.
[17] Dischinger P, DuChene AG. Quality control aspects of blood pressure measurements in the Multiple Risk Factor Intervention Trial. Control Clin Trials 1986; 7(3 Suppl): 137S-57S.
[18] Cooper GR, Haff AC, Widdowson GM, et al. Quality control in the MRFIT local screening and clinic laboratory. Control Clin Trials 1986; 7(3 Suppl): 158S-65S.
[19] Neaton JD, Duchene AG, Svendsen KH, et al. An examination of the efficiency of some quality assurance methods commonly employed in clinical trials. Stat Med 1990; 9: 115-24.
[20] van der Putten E, van der Velden JW, Siers A, et al. A pilot study on the quality of data management in a cancer clinical trial. Control Clin Trials 1987; 8: 96-100.
[21] FDA ORA Quality Manual. http://www.fda.gov/AboutFDA/Centers Offices/ORA/UCM 135836.htm
[22] A Guided Self-Assessment for Human Research Protection Programs. http://www.hhs.gov/ohrp/qi/.
[23] Salewski JP. FDA Expectations of Clinical Trials and Investigators. [Last accessed 2011 Mar 1]. Available from: http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/Spotlighto nCPIProjects/UCM236735.ppt.
[24] US FDA Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors FDA Inspections of Clinical Investigators..http://www.fda.gov/downloads/RegulatoryInformation /Guidances/UCM126553.pdf.
[25] Lou A. Preparing for an FDA Medical Device Sponsor Inspection. [Last accessed on 2011 Jul 28]. Available from: http://www.fda.gov/downloads/Training /CDRHLearn/UCM176843.pdf .
[26] Korieth K. Spike in warning letters sends tremors through industry. Centerwatch Mon. 2010; 17: 1–9.
[27] Lou A. Preparing for an FDA Institutional Review Board Inspection. [Last accessed on 2011 Jul 28]. Available from: http://www.fda.gov/Training/CDRHLearn/ ucm180891.htm.
[28] Kleppinger CF, Ball LK. Building Quality in clinical trials with use of a quality systems approach. Clin Infect Dis. 2010; 51(Suppl 1): S111–6.
[29] Research needs quality management. Article, quality management. http:///www.therqa.com/ assets/js/tiny_mce/plugins/ilemanager/iles/Committees/Quality/Research_needs_quality_management_syst em.pdf.
[30] Ann Meeker-O'Connell. Enhancing clinical trial quality: CDER perspective. http:///www.fdanews.com /ext/iles/conference/FIS10Presentations/MeekerOConnell-Harmonizing RegulatoryApproaches.pdf.
[31] Clinical Trials Transformation Initiative (CTTI): Conducting Multicenter Clinical Trials: New Recommendations and Tool for Research. http://www.ctti-clinicaltrials.org/.
[32] Clinical Trials Transformation Initiative. Scope statement. http://www. trialstransformation.org/scope.
[33] Code of Federal Regulations Title 21. US Food and Drug Administration, Department of Health and Human Services. Subchapter H: medical devices. Part 812 – investigational device exemptions. Subpart C: responsibilities of sponsors. Sec 812.40. General responsibilities of sponsors. http://frwebgate. access.gpo.gov/cgi-bin/get cfr.cgi?TITLEp21@PARTp812&SECTIONp40&TYPEp TEXT
Arun Bhatt. Quality of clinical trials: A moving target. Perspectives in Clinical Research. 2011.