Impact of protocol deviations on the clinical study

A protocol is a critical clinical document that should be followed during the conduct of the clinical study. Hence, it is essential that any deviations to the protocol-mandated procedures study are identified, reviewed, reported, and corrective and preventive actions as appropriate are taken to ensure patient safety and maintain data integrity. Protocol complexity has been increasing over the last few years which has impacted subject recruitment, increased in protocol deviations, and delayed study completion. This has increased the workload of study team and affected study conduct and performance. In addition, clinical study regulation and governance have also become more challenging.[1]

As per the ICH E3 guidelines, protocol deviations are any change, divergence, or departure from the study design or procedures defined in the protocol. It defines protocol violations as change, divergence, or departure from the study requirements, whether by the subject or investigator, that resulted in a subject's withdrawal from study participation.[2] Important or significant protocol deviations are the ones that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being for a particular study. These are study specific and are determined by study design, the critical procedures/data, and the planned analyses of study data.[2,3]

Kulkarni *et al.* in this issue have reported the results of an audit conducted on the 80-postgraduate dissertations.[4] They found that 73.75% of them were observational studies and 10% were interventional studies. Potentially, vulnerable populations were included in 25% of the studies. The authors have classified the deviations which were found as noncompliance, protocol deviations, and protocol violations. Kulkarni *et al.* have reported that most of the deviations (42.5%) were due to nonreporting and incomplete documentation of the deviations (33.3%).[4]

The deviations in a study could be related to the sponsor or the investigational team. These could be caused due to (1) poor and/or complex study design, (2) inadequate description of study procedures, (3) stringent requirements for study visits, (4) unrealistic window periods for study conduct, (5) inadequate site staff training or understanding of the protocol requirements, (6) lack of infrastructure, resources, and trained staff at the site, and (7) lack of clinical study oversight by the sponsor or the Investigator.[5] Economics of drug development demands faster recruitment and completion of studies, which could potentially also cause protocol deviations. Additionally, the need to publish and unreasonable expectations have been identified as other causes.[1]

Protocol deviations can impair the data quality and integrity, can affect rights, safety, and welfare of the participants and can undermine the scientific validity and reliability of the study data. Deviations are one of the most common causes of Food and Drug Administration (FDA) inspection warning letters.[6] A warning letter is issued for violations that may lead to enforcement action if not promptly and adequately corrected. Warning letters are issued to achieve voluntary compliance and include a request for correction and a written response to the agency. FDA may initiate a process to disqualify the clinical investigator from receiving investigational new drugs and/or biologics if disqualified under part 312, or investigational devices if disqualified under part 812, if the investigator has repeatedly or deliberately failed to comply with applicable regulatory requirements or has deliberately or repeatedly submitted false information to the sponsor or FDA in any required report. During inspection, the regulators would check if protocol deviations were documented and reported appropriately.[7]

Protocol deviations can be decreased by:

1. Training: Deviations caused by investigational staff are mostly due to poor training and can be reduced by training the site team on the therapy area and the protocol[1]
2. Monitoring: Regular effective monitoring focussing on critical data and critical processes in is essential to ensure compliance to protocol. Risk-Based Monitoring and centralized monitoring can complement and reduce the extent and/or frequency of on-site monitoring and help distinguish between reliable data and potentially unreliable data. Statistical approached in review of accumulating data study data, which from centralized monitoring can be used to identify missing data, inconsistent data, data outliers, unexpected lack of variability, and protocol deviations[8]
3. Protocol complexity: The protocols are becoming more and more complex and demanding.[6,9] During protocol

development, keeping a focus on critical data and critical processes affecting human protection and data integrity would improve the understanding of the sponsor and the investigator teams about the key protocol aspects, example, selection criteria, end points, safety reporting. Oversight by ethics committee: Site monitoring visits by Ethics committee (EC) is of utmost importance in the detection of protocol deviations. ECs should conduct both initial and ongoing review of clinical drug trials and high-risk biomedical research and ensure that the investigator and her team conduct the study in compliance with the approved protocol.

Despite increased focus on monitoring, audits and regulatory inspections, protocol deviations remain a major challenge in conduct of clinical studies. Reduced protocol complexity, use of electronic data capture, risk:-based monitoring, quality management system, standard operating procedures, and training of sponsor and investigator teams will go a long way in reducing protocol deviations, improving data integrity, and ensuring the protection of study participants.

Disclosure

The insights stated in this article are author's personal opinion and does not reflect those of the current and previous employers.

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