WHITE PAPER

Data Integrity in Clinical Trials & IRT: FDA & MHRA concerns

Data integrity is the frequently represented topic concerning pharmaceutical manufacturing, at the same time being critically important in the context of clinical trials. Data integrity issues related to Good Clinical Practice (GCP) can at times be more crippling to a company than Good Manufacturing Practice (GMP) data integrity issues. In the case of severe GCP data integrity issues, the FDA can completely reject the data submitted in new drug applications, supplemental drug applications, and abbreviated new drug applications. This can significantly set back the study drug's clinical development program and cost the sponsor substantial time, money, and reputational credibility, not to mention the delay in patient access to new drugs.

As clinical trial methodologies and new technologies are deployed, data integrity and the safety of clinical trial participants remain at the forefront of regulatory oversight, officials from the US Food and Drug Administration (FDA) and the UK's Medicines and Healthcare products Regulatory Agency (MHRA) wrote in an article published in Clinical Pharmacology & Therapeutics.

David Burrow, director of the office of scientific investigations at the CDER of the FDA, mentions "Data integrity, it's not black or white. It's an incredible continuum. There are shades of gray. The shades of gray here are what drive the conversation. Those shades of gray right now, are things that we are going to start to paint in color."

Impacts on Data Integrity

Several areas were identified as key topics that influence data integrity. They ranged from unblinding, vendor selection, data management, to audit trails. We will discuss a couple of areas here related to IRT

a) Unblinding

In these days of interactive response technology (IRT), the maintenance of the blind is managed systematically. The series of events, from treatment assignment to the final analysis of data, can be reviewed on the indisputable audit trail timeline. In terms of blinding, the authors used the example of inspectors identifying a poorly designed interactive response technology (IRT) reporting system that resulted in unblinding.

"The IRT produced blinded and unblinded reports, and while access controls for the two reports were assigned and restricted to either blinded or unblinded study personnel, as appropriate, both reports contained IMP [investigational medicinal product] lot numbers which could be used to unblind the treatment assignment. A review of the system access logs also revealed that blinded study personnel had been able to access and view unblinded IRT reports," as stated by some experts.

All stakeholders who are responsible for the treatment schedule of a blinded trial should particularly pay attention to the enforcement of the blind. Systems that have unblinding materials should be validated with clearly defined roles that have been tested for integrity assurance. Data repositories, laboratory data, IP management systems, and any essential document that may reveal the treatment assignments needs to be managed by process and system for blind assurance. Following that, the data breaches related to the blind must be raised and promptly handled. The organizational culture need to be willing to allow the recognition of errors and not punish for reporting them once found.

b) Audit trail

As an example of deficiencies with audit trails, the regulators explained how a clinical investigator inspection for a pivotal, randomized, double-blind, pharmacokinetic (PK) study, showed that the regulator's review of the data listings in the clinical study report, as compared to source data, revealed that several study subjects appeared to have received opposite treatments (i.e., active drug instead of placebo), mixed treatments (i.e., active drug and placebo), or opposite dietary conditions (i.e., dosing under fed conditions instead of fasted conditions or vice versa) during the study.

The audit trail data available to inspectors are considered to be of significant value in the assessment of security, control, and potential for abuse, but the inability in interpreting the details is challenging to an inspection. Clear and human-readable codes are needed for both the sponsor and the regulator; otherwise, it is not usable. Stephen Vinter, operations manager for the MHRA's Good Laboratory Practice Monitoring Authority (GLPMA), also advised avoiding merged cells in an Excel spreadsheet, as they disrupt the audit trail.

The message deducted is that audit trails should and will be used for the revelation of digital revisions and can ensure compliance or for discrepancy revelation by anyone using a system. The problem is that it may reveal more than expected. An inspection is not a good time for surprises.

Understanding Data Integrity

Data Integrity is maintained only when all details furnished during the initial process remains accurate and exact all through the product lifecycle. An integrated data can be categorized through the ALCOA system, which stands for attributable, legible, contemporaneous, original and accurate. It can be further elaborated as:

- **ATTRIBUTABLE:** Complete responsibility and accountability can be placed on the person who is in charge of the completion of the task.
- **LEGIBLE:** Clear and concise data to be easily read, understood, and stored for future references.
- **CONTEMPORANEOUS:** The time of data creation should match with the time of the activity.
- **ORIGINAL:** Authenticity of the data needs to be maintained throughout the lifecycle.
- **ACCURATE:** Both the data and the task needs to have a resemblance.

Conclusion

Maintaining data integrity tends to be of the highest concern within the industry. IRT systems that you use for randomization and clinical supplies need to be verified, not just as part of vendor qualification or during UAT, whenever there is a change request implemented or protocol change occurs. Ensure vendors follow the process and maintain full documentation of every change. Don't maintain the status quo with the vendor and ensure these are checked continually as part of your Oversight.

"Quality means doing it right when no one is looking" ~ HENRY FORD

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