10. Emerging regulatory expectations for technologies

With the ever-evolving technology landscape, there is a greater need for CDM to ensure the effective management of data quality and integrity through those multiple technologies and data sources. As presented at the 2019 SCDM Annual Conference in Baltimore by regulators from the FDA and the Danish Medicines Agency[20], there are regulatory expectations from sponsors to ensure clarity of the dataflow and ongoing review of data and metadata. In a world where e-Source is becoming the norm, those reviews are critical to identify potential issues regarding data quality, completeness and overall compliance to protocol and regulations.

10.1 Audit Trail

Sponsors are expected to have procedures for risk-based routine audit trail reviews. As more trial data are collected as e-Source across numerous systems, this is becoming increasingly important. Without these procedures, sponsors can miss important non-compliance issues that could only be evidenced through metadata. In addition, it is likely that GCP inspectors will be enquiring more about these procedures as well as requesting access to audit trial data during inspections.

During the SCDM Conference, regulators shared issues identified by audit trail and metadata review during GCP inspections. Reviews revealed that:

- Data entry was not performed by authorized individuals
- ePRO data was entered within an unreasonably short period of time: ePRO was entered in less time compared to the time it should take for the site to complete 1) the assessment with a trial subject and 2) entering data in the ePRO system.
- e-Source primary efficacy data was not entered directly into the application by sites per protocol (i.e., alternative source data existed). Additionally, discrepancies were detected when the inspectors retrieved the 'true' source data to verified ePRO data.
- Site entry occurring during the same time/day for a group of subjects.

These issues could have easily been identified before the inspection with the right data review strategies. Such issues have the potential of delaying drug approval by months as inspection findings must be properly answered prior to approval. They can even question the reliability of trial results and lead to the exclusion of site data from statistical analysis.

Please note that efforts are underway from the e-Clinical Forum and SCDM Audit Trail Task Force to publish an industry position paper on audit trail processes.

10.2 Inspection readiness considerations

The evolution of technologies and regulations have a direct impact on inspections. The multiplicity of systems used in clinical trials and the increasing volume of data collected beyond EDC are driving inspectors to focus on system and data lineage. During inspections, CDM organizations need to be able to clearly articulate their data flow, risk-based data review plan, system access and validations strategies. Inspectors may want to review processes, study documentation, systems validation packages and get systems demonstrations. They may even request access to systems, the eTMF, and data to freely assess compliance with protocol and regulations.

Beyond traditional inspection readiness, CDM organizations may want to consider the following:

- Sponsors need to simply and clearly illustrate the **end-to-end data flow** for a trial. CDMs should consider including a data flow diagram**,** with supporting explanations, in their DMP. Alternatively, they could create a separate data lineage plan, describing all the elements of data, from acquisition and data delivery to statistical analysis, that make up the study. Ideally, this would include all transformations and derivations.
- Proactively adjust **system decommissioning** strategies: Due to an increasing need for inspectors to access dynamic data and audit trails in the data collection tool, there should be consideration of a fit-for-purpose approach to decommissioning systems. For example, consider decommissioning non-submission studies within 4 months of database lock or upon CSR completion, whichever occurs first. For Phase III submission/pivotal studies, consider decommissioning EDC, eCOA, IxRS and similar systems after the first regulatory approval or first sponsor inspection, whichever occurs first.
- Anticipate **requests from inspectors to have access to systems**: Processes should be in place to describe access during an inspection whether it is at site or sponsor level. This should include an auditor read-only role, an expectation of training, how system access requests are submitted, and what roles are involved, as well as a process to revoke system access after the inspection. Training should be fit-for-purpose (e.g., 10-15 mins) and access should be granted as soon as possible: within 24 hours, where feasible, for example.
- Consider **system access for site vs sponsor inspections**: The process for granting inspectors a level of access should be relevant to the type of inspection being undertaken. For sponsor-level inspection, the sponsor should be ready to provide access to all sites and studies, whereas site-level inspection access should be restricted to the relevant site.
- **Anticipate site data archival challenges** (No more CD readers and USB Keys failing): As traditional CDs are being replaced by USBs, site archival continues to be a challenge:
    1. Are sites storing and retaining physical media appropriately?
    2. Is security placed on archives by sponsors making site access easy?
    3. Where are sites managing cross study archive credentials?
    4. Will data archived on physical media be readable over time?
    5. Is PDF the right way to archive data?

The list of challenges is long. Access to searchable data and audit trails from site archives is crucial during inspections and inspectors are growing tired of searching for audit trails in patient specific PDFs. There should be consideration of a cloud-based solution allowing sites to access to all data sources (e.g., EDC, eCOA, central labs, sensors, etc.) without the challenges of traditional hard media. This would enable sites working with multiple sponsors on many studies to have one centralized method of retrieving **dynamic** data and audit trail archives during an inspection without requesting last-minute support from the sponsor.

- **Readiness for site inspections**: CDM involvement in site level inspections has been growing over the last few years. Those include the review of systems and data flows. CDM organizations need to increase the scope of inspection readiness activities and consider site-level inspection readiness plans which include site specific dataflows.

While inspection readiness is important, the best readiness strategy is to foster QbD in all aspects of our work. If all processes, study and system documents are clear and well organized in the eTMF, inspection readiness activities will be more focused and less labor intensive.