Avoca Quality Consortium Leading Change Collaborative Forum

Meeting Highlights

Topic: How will the recent FDA BIMO guide update impact FDA inspections?

Meeting Date: February 15, 2022

Background Information

The emergence of the COVID-19 pandemic has caused the pharmaceutical industry to rapidly adapt its processes and technologies, including clinical trials. The AQC Leading Change Collaborative Forum features compelling topics designed to encourage provocative discussion. The priority is providing practical and actionable support and having immediate "peer-to-peer" benchmarking about how other organizations are managing the topic at hand, all while ensuring prioritization of patient safety, data integrity, and regulatory compliance.

In September of 2021, The US Food and Drug Administration (FDA) released updated Bioresearch Monitoring Program (BIMO) Compliance Program Guides. The changes to the Sponsor and CRO BIMO aligned with recent changes the way clinical trials are currently being conducted, including remote monitoring, increased outsourcing of various clinical trial activities, and clinical trials conducted outside the United States.

In the Sponsor and Contract Research Organization (CRO) BIMO, there were several updates. The following existing BIMO sections detailed additional inspection focus and scrutiny on:

- Selection and monitoring of clinical investigators
- Sponsor's oversight of CROs and other vendors
- Selection of monitors, monitoring procedures and activities
- Safety oversight
- Data Collection and Handling
- Electronic Records and Electronic Signatures

There were also some new sections detailing inspection checks on:

- Outsourced Services
- Safety Oversight
- Data and Safety Monitoring Board/Data Monitoring Committee

Discussion Summary

Panelists discussed what changes to FDA inspections have been seen or are anticipated following the release of BIMO and how they are preparing for these changes. The panelist touched on the enhanced and new BIMO topics listed in the previous sections. Below are a few discussion highlights.

Selection and Monitoring of Clinical Investigators

- Sponsors and CRO panelists experienced increased scrutiny on investigators, including documentation of the sponsor considering the FDA Debarment List and previous administrative and regulatory actions against the investigator. The inspectors also looked at investigators put on enrollment hold and changes to investigators. They wanted to understand and see documentation for these changes.
- Sponsor panelists commented on the increased focus for trials conducted outside the US. There is enhanced language in the BIMO for investigators not under the IND. While investigators for non-US sites do not sign a 1572, several sponsors have them sign a similar form. This provides the sponsor with information on the investigator's qualification and provides the site's written agreement to conduct the trial in accordance with GCP and local regulations.
- Sponsor training provided to the investigator before and during the trial was reviewed during recent inspections. Inspectors wanted to see protocol training and communication/training related to any protocol changes during the trial.
- A panelist reported that inspectors looked closely at termination at the site or at the study level. Inspectors asked for plans for subject transfer at the site level and required notifications for study and investigator terminations.

Outsourced Services and Sponsor's Oversight of CROs and Other Vendors

- One panelist said that the FDA inspector spent three days of the inspection focusing solely on outsourcing. The inspector wanted to see all contracts as well as all documentation that provided evidence that both the sponsor and the CRO were following the contract. The FDA inspectors want to understand processes and roles and responsibilities between the sponsor and CRO.
- Panelists commented that the FDA inspectors want to have a much better understanding of the interaction between the sponsor and CRO. They were interested in communication between them including governance minutes, oversight processes and documentation and types and frequency of communication at multiple levels.
- Panelists commented that because of the increased role of CROs and the increased focus on outsourcing, key CROs have become a very active partner in preparing for FDA inspections.
- A panelist said that in their vendor list, they include healthcare providers and facilities contracted to provide data relating to patient health status and/or the delivery of health care data collected to support a marketing application. This includes technology companies (e.g., eCOA). In addition to having them in the vendor list, they ensure contracts are in place and accessible during the inspection.
- Another panelist shared specific examples from recent FDA inspections: They had phlebotomy services that collected in-home PK and central lab samples and the company that was used to collect survival data on subjects in countries where this was permitted was listed as vendors in their CSR. They were asked to provide the contracts during inspection. They had not received any questions during an inspection but depending on the criticality of the data to endpoints, they anticipate that inspectors could

probe how the phlebotomists were qualified and trained on study specific procedures and request appropriate documentation including procedures to oversee/monitor the quality of those services.

Selection of Monitors, Monitoring Procedures, and Activities

- This section of the BIMO has been updated and recognizes monitors provide different functions (e.g., remote and onsite). There has been an increased focus on the monitoring plan and documentation that it was implemented as planned. With the increase in remote monitoring, inspectors are interested in the process by which this is conducted.
- Although there was always an expectation that key clinical activities and documentation would be completed in a timely manner, there is now increased focus on the timing and content; e.g., for Investigation Review Board approval and Informed Consent.
- Both sponsor and CRO panelists acknowledge that there has been a very high turnover of monitors. To address this, sponsors are carefully tracking monitor onboarding and offboarding throughout the trial and looking at how monitors are trained.
- A question was raised concerning delays caused by limited access to sites during the COVID-19 pandemic since remote monitoring and SDV at non-US sites in Europe is not permitted under EU General Data Protection Regulation (GDPR). A panelist responded that the FDA has been understanding delays in monitoring activities in such cases. The inspectors will ask for documentation as to what changes were made to accommodate activities due to the pandemic (e.g., trial staff reallocation to pandemic activities in the hospital; inability of monitors to get on sites) and to see appropriate updates to the monitoring plan.
- Panelists recommended having visit tracking systems that can differentiate between remote and on-site monitoring visits. Sponsors also need a way to track site status (e.g., sites which allow remote SDV and those who did not, when sites closed/reopened). One panelist stated that they used a combination of Excel tracking tools and CTMS to accomplish that task.
- Another panelist stated that they were recently asked about the impact of COVID-19 on subject visits and monitoring. Their strategy to update the monitoring plans to include remote visits was described in the CSR. The inspector did ask for additional information and documentation from the remote visits.
- There have been two new sections added to the BIMO on Data and Safety Monitoring Board/Data Monitoring Committee which will be areas of focus for the inspectors going forward.

Data Collection and Handling

- There was a lot of discussion and interest in many of the changes regarding data collection and handling. With the increased focus and complexity in data flow, two panelists suggested that sponsors talk the inspectors through a data flow diagram. The inspector will be interested in both sponsor and CRO systems. Patient reported outcomes also need to be included in the data flow.
- In addition to data flow and integrity, inspectors will want to understand system validation, security, change management, audit trails, inspector visibility, and control.
- Inspectors are interested in system procedures, who provided the training, and qualifications of the trainer.
- There has also been increased focus on audit trails, electronic records, and electronic signatures.

- There was also discussion on GxP and Non-GxP systems. Sponsors should have a comprehensive list of all systems. GxP systems should be included in the data flow diagram and validation documentation should be readily available.
- A question was raised about inspectors having access to audit trails deleted files (soft delete) which are available in electronic systems but only accessible by certain system administrator roles. One panelist responded that they do leverage the soft delete functionality but have not been asked for deleted documents or their process for handling such documents during an inspection. The inspectors were, however, very interested in the TMF audit trails. Another panelist commented that in an inspection going back to 2017, inspectors have requested the audit trail for deleted documents in the eTMF and an internal system utilized to analyze clinical trial data by their statisticians.

Safety Oversight

- This is a new section in the updated BIMO guide. One panelist described an inspection in 2021 in which a joint session was requested with both the Pharmacovigilance and Safety Management departments. The inspectors were interested in the interactions between PV, medical monitors, and clinical trial physicians for the safety oversight of the program.
- Inspectors asked questions about the risk management plan (RMP) as part of the GCP inspection. As leading practice, it is advised to have the right SMEs ready to talk to the RMP, which may be at the product or even indication level. The SME should be able to speak to the RMP at a broad level, but also explain how it translates to the protocol itself and how it is implemented. Aggregate reports preparation and signal detection are also typically done at the compound and program level. Again, SMEs need to be able to describe the overarching safety oversight activities and how the trial activities, documented in study plans, fit in.
- Another area of focus is unblinding of cases from a safety perspective. It is important to have documentation providing reasons for unblinding, e.g., in response to health authority request, submission, or investigator request. Especially in latter case, inspectors will want to understand reason why investigator requested to break the blind for one (or more) subjects.

Conclusion

Several AQC Member companies have been inspected since the September 2021 BIMO was released and have confirmed that the inspectors are following the updated BIMO. Based on their experiences, the panelists indicated that the most significant impacts of the update are:

- Increased scrutiny of investigators and monitoring activities
- Increased focus on outsourcing activities
- Increased focus on data collection and handling and suggestions to clearly define and leverage data flow diagrams
- Increase focus on overall safety oversight

If you are interested in learning more about the WCG Avoca Quality Consortium (AQC) or its Leading Change series, please contact Dawn.Auerbach@theavocagroup.com.