READY ROOM

What's New with the BIMO Compliance Program Manual for Sponsors and CROs?

In September 2021, the US Food and Drug Administration (FDA) published the first update to its Bioresearch Monitoring Compliance Program Manual for Sponsors and Contract Research Organizations since 2017. This document, which serves as FDA's Standard Operating Procedure for conducting a GCP inspection, is a critical resource for sponsors and CROs preparing for inspections. Other than the switch from serif to sans serif, what's new? Let's jump in.

Highlights

- More detail on inspection of **site selection procedures**, including review of investigator qualifications and debarment procedures
- New section on **outsourced services** with focus on detailed written agreements; inspectors are required to verify that agreements specify responsibilities for complying with FDA regulations as well as approval responsibilities for study activities
- Added emphasis on **sponsor oversight**, including escalation plans and audits
- New steps for evaluating whether monitoring included source verification of data changes and how monitors ensured confidentiality and security of records during remote monitoring
- New **DSMB/DMC** section
- Greatly expanded **safety** section, including steps for reviewing aggregate reporting procedures, surveillance activities, risk management, and criteria for selection of medical monitors
- More detailed **data handling** section with focus on validation, user access control, and change control of study-specific systems as well as data integrity during transfers and transformations

Definition of Sponsor

- A note on the title page states that the term "sponsor" is intended to refer to the "entity that initiates and takes responsibility for clinical and nonclinical investigations and/or has been so identified by FDA through receipt of an investigational exemption or application for research or marketing permit." "Sponsor" is also used to refer to a Contract Research Organization to whom sponsor responsibilities have been transferred.

List of Regulations

- Page 6 provides a "non-exhaustive" list of clinical trial regulations.

Pre-Announcement

- The 2021 update changes the time between announcement and inspection from "as short as possible" to "no less than 5 calendar days."

483s

- Both the previous and updated versions state, with slightly different wording, that when deviations from FDA regulations are observed, the FDA investigator must issue an FDA 483 at the conclusion of the inspection. The 2021 version continues, somewhat contradictorily, "Any observations that may constitute **significant deviations** from the regulations should be listed on the FDA 483. Those inspectional observations that represent **less significant deviations** from regulations should be discussed during the close out discussion with management and reported in the EIR" (emphasis ours). A bolded statement in the 2017 version, "Approaches that differ from those described in FDA's guidance documents should not be listed on the 483 unless they constitute deviations from the regulations," has been omitted from the 2021 version.

  This update also directs the FDA investigator to "inform the sponsor that they may submit a written response to the FDA 483 to the appropriate ORA OBIMO division correspondence email box regarding any inspection observations listed on the FDA 483," with advice that if an adequate response is received within 15 business days or inspection close, it may "impact FDA's determination of the need for subsequent action."

Organization and Personnel

- The 2021 version adds a new requirement for the FDA investigator to confirm there are no staff with responsibilities for which they are not qualified.

  When sponsors have contracted responsibilities to CROs, this section now directs the FDA investigator to notify the center, which may decide to follow up with the CRO.

Clinicaltrials.gov

- The 2021 update adds a step for the inspector to determine whether a certification to delay results, extension request, or request for a waiver from the requirement to submit results to clinicaltrials.gov has been submitted to clinicaltrials.gov.

Selection and Monitoring of Clinical Investigators

- The 2021 update now adds "site number and site location" to the list of sites to be collected by the FDA investigator. Inspectors are also directed to determine whether any waivers from 1572 signature requirements were granted by FDA. The list also now includes identification of foreign investigators who did not conduct the study under an IND; identification of clinical investigators who were terminated or placed on enrollment hold; and identification of "any healthcare providers or facilities contracted to provide data relating to patient health status and/or the delivery of health care collected to support a marketing application."

  This section gives examples of sponsor criteria for selecting investigators, requires a close look at investigator qualifications to conduct the study, and specifies that inspectors should look for sponsor procedures for checking debarment lists for prospective investigators. The update also provides a more detailed list of documents that sponsors should provide to investigators prior to study start.

  While the previous version directed inspectors to review the process for handling "serious" deviations from the protocol/regulations, the update indicates that the process for handling all deviations should be reviewed.

  The update adds a step for the inspector to identify changes to "clinical investigators" (the manual does not specify that this is limited to Principal Investigators)

Outsourced Services

- The 2021 update adds a new section, Outsourced Services, that pulls some content from the previous version of the Organization and Personnel section, but adds a significant amount of new content.

  Inspectors are now directed to review sponsor procedures for vendor evaluation and selection and to verify that sponsors have selected vendors "based on their ability to comply with FDA regulations and follow GCP standards." This version also asks the inspector to review any preferred or prequalified vendor list that the sponsor maintains and to evaluate the criteria for inclusion on that list.

  Whereas the 2017 version directed the inspector to review written agreements transferring responsibilities to a CRO, the 2021 version asks inspectors to obtain copies of all versions of written agreements, including master service agreements, statements of work, quality agreements, and service-level agreements for critical services, providing the following examples: "Site monitoring, drug management, data handling (e.g., EDC systems, Interactive Response Technology (IRT) systems), ePRO, registries used to capture clinical trial data, and other clinical outcome assessments (COAs), electronic system vendors, data management, statistical analysis, central laboratories, and safety management."

  Inspectors are asked to determine whether written agreements specify responsibilities for complying with FDA regulations and "who has the ultimate responsibility for approving final decisions related to each of the individual trial-related activities outlined in these written agreements."

  Per the 2021 update, inspectors are also required to determine whether CRO employees are appropriately qualified and whether they were appropriately trained on protocol-specific topics.

Continued on next page >

Outsourced Services *continued*

- Inspectors are asked to review audit SOPs, communication plans, escalation plans, and contingency plans, focusing on whose SOPs were followed and which processes were followed to address deviations. Inspectors will focus on sponsor oversight of CROs, including oversight plans and audits. This update also codifies FDA's typical practice of requesting audit certificates but not audit reports "unless directed by the assigning center."

Selection of Monitors

- This short section adds a step for the inspector to obtain a list of "individuals performing monitoring activities." The step for determining allocation of responsibilities gives remote monitoring and unblinded monitoring as new examples of different types of responsibilities.

Monitoring Procedures and Activities

- This section has a new preface that name-checks risk-based monitoring and also references the relatively new GCP requirement for a monitoring plan.

  The subsection on Monitoring Procedures now includes steps for reviewing changes to the monitoring plan and also references on-site co-monitoring visits, which are described as evaluation or oversight activities.

  The subsection on Monitoring Activities references both the Trial Master File and the Clinical Trial Management System as sources of monitoring records. The steps formerly under the heading Review of Site Records are now included under Monitoring Activities. A new step requires inspectors to evaluate whether monitoring included verification of data changes. A step to determine whether non-site personnel made changes to data has been moved to a different section.

  This section also includes a new step to evaluate remote monitoring activities: "Determine how monitors accessed clinical site records and ensured the security and confidentiality of the records was maintained (e.g., was the monitor given direct access to the site records via an online portal, were access controls used, were copies sent via a secured email)."

Quality Assurance Activities

- Specific steps from the previous version of the manual – determine how the quality unit operates, obtain written SOPs, describe separation of functions between auditing and monitoring, and compare list of audited studies with sponsor's records – have been omitted from the 2021 update, replaced by a statement that the inspector should "review and confirm" audit certificates but not other audit documentation "unless directed by the assigning center."

Safety and Adverse Event Reporting

- The first two steps of this section have been rewritten to focus more on the process for safety data collection and reporting, in addition to the previous focus on compliance with regulations. Inspectors are now asked to review the sponsor's SOP for safety reporting against FDA criteria and confirm it was followed for all cases. Two new sections have been added to examine other aspects of safety.

Data and Safety Monitoring Board/ Data Monitoring Committee

- This new section directs the inspector to review the DSMB/DMC charter and procedures for reviewing data and communicating decisions. The inspector also confirms that all committee members received training, an activity that is not always explicitly documented.

Safety Oversight

This new section is a significant addition to the manual. The subsection starts with review of relevant plans, including risk management, safety monitoring, and/or safety management plans. The second subsection specifies reviews of safety team roles and responsibilities; procedures for review of aggregate safety data, surveillance, and safety risk management; and criteria for selection of medical monitors.

The third subsection examines safety case processing and reporting in detail, including aggregate reporting across programs. This topic was a standard point of inquiry in inspections prior to the manual update, but was not previously detailed in the manual.

The fourth section looks in detail at safety endpoints and adjudication processes.

The fifth section addresses communication of safety data from investigator-initiated studies, and the last section looks at literature review processes.

Data Collection and Handling

This section, which was previously concerned with the correspondence between studies conducted and data submitted to the NDA or BLA, has been almost entirely rewritten to focus on end-to-end data collection procedures.

The inspector is instructed to take a deeper dive if "significant issues and deviations…are observed during the routine review" – for example, protocol deviations or dosing errors that occurred due to computerized system errors, accidental unblinding, or confidentiality breaches. New inspection activities specified here include review of data flow from source to Clinical Study Report; determining whether "source data" is adequately defined in the protocol and plans; and review of validation of data transfer activities.

Inspectors are also advised to review a "sample of helpdesk tickets" to identify whether software issues were adequately followed up, including root cause analysis and corrective/preventative actions. Any "significant concerns" in this area will prompt a more thorough review of the sponsor's procedures for electronic systems validation, training, technical support, security, and change controls. Where vendor systems are used, the inspector is to "determine whether the sponsor performed independent UAT prior to system implementation."

Inspectors are instructed to pay attention to study-specific blinding procedures, as well as general procedures for handling accidental unblinding. Steps for reviewing user access control procedures are included in the subsection on blinding.

Steps for determining roles, responsibilities, and controls for correcting data have been moved from the Monitoring Procedures and Activities section to this section, with additional steps for evaluating authorization for data changes; determining whether systems permitted other users to make changes; and review of audit trails to evaluate whether changes were made according to plans. The audit trail review also looks at whether eCRF data were entered "contemporaneously at the time of collection" and whether the audit trail can be turned off.

This section also adds an in-depth look at data lock procedures as well as changes made after lock.

Another new subsection addresses reconciliation, integration, and transformation of data. Inspectors may compare raw data to transformed data to verify that transformations were made according to plans. Inspectors may review conformance with SDTM and ADaM standards as well as access controls for repositories holding raw data and analysis datasets.

Finally, this section examines record retention, disaster recovery, and business continuity plans.

Electronic Records and Electronic Systems

- This section has been moved forward to follow the related Data Collection and Handling section. The prologue, slightly rewritten, retains the commitment to exercise "enforcement discretion regarding certain Part 11 provisions for validation, record copying, record retention, and audit trails." Some of the detail in the previous version of the manual has been moved to the Data Collection and Handling section; this section now asks the inspector to identify systems used to manage "critical data and study procedures" and to determine processes for electronic signatures in those systems, focusing on uniqueness, controls, and signature components.

Records Custody and Retention

- This section has been renamed and reworded without substantive changes in content: Inspector are to verify that the sponsor maintained required records for the full retention period.

Financial Disclosure

- The same four points from the 2017 version are retained in the update. Inspectors are now directed to determine not just if, but "how" the sponsor received prompt updates regarding relevant changes in financial disclosure.

Investigational Product

- The former "Test Article" section has been renamed "Investigational Product," a welcome change to clinical study teams unfamiliar with the former term. The step to determine if test article met release specifications has been removed. The steps on accountability have been rewritten slightly; now, instead of determining whether sponsor records are "sufficient to reconcile test article usage," inspectors are asked to determine whether sponsor records "demonstrate reconciliation of the shipment, receipt, and disposition of the investigational product."

Emergency Research

- The update now includes a step for determining if the sponsor obtained written authorization from FDA before proceeding. The step for determining whether the sponsor provided public disclosure to the communities in which the investigation was conducted has been expanded to include review of pre-investigation consultation and post-investigation results disclosure.

International Data

- A new beginning to this section notes that inspections conducted by foreign regulatory authorities should be noted in the inspector's report. Text about criteria for accepting non-IND, non-US clinical studies as support for an IND or NDA has been removed. The section now requires inspectors to determine how the sponsor collected 1572 information from sites that did not sign a 1572. It notes that sponsors may request a waiver from the IRB requirements in the 1572, so that sites can sign the 1572, or a waiver from the signature requirements, in which case supporting documentation should be reviewed. Such supporting documentation may include a completed but unsigned 1572 or an alternative form.

Nonclinical Laboratory Studies

- This section now includes more detailed steps for review of nonclinical studies that fall under the scope of the inspection, such as steps to review the sponsor's procedures for monitoring the laboratory and overseeing the study.