

Facilitating the FDA Bioresearch Monitoring Inspection for Sponsor/monitors

a report by

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The US Food and Drug Administration's (FDA) Bioresearch Monitoring (BIMO) programme is a comprehensive arrangement of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA-regulated research. BIMO was established to assure the quality and integrity of data submitted to the FDA in support of new product approvals and to provide for protection of the rights and welfare of human subjects participating in FDA regulated research. It has become the cornerstone of the FDA's pre-approval process for the introduction of new medical devices into the US marketplace.

FDA-regulated research involves several entities – the sponsor, study monitors, study investigator(s), study subjects and Institutional Review Boards (IRB). These entities must work together closely to accomplish an appropriate scientific evaluation of investigational devices for their targeted indications. 21 CFR Part 812.³ provides definitions for each entity, which are generalised as follows.

- A sponsor is a person or an organisation that initiates, but does not actually conduct, the study of an investigational device.
- A monitor is an individual designated by a sponsor to oversee the progress of an investigation.
- An investigator is an individual who actually conducts a clinical investigation. The investigator provides immediate direction with respect to test device administration or dispensation to study subject(s). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of that team.
- A subject is a human being who participates in an investigation. A subject may be healthy or may have a medical condition or disease.
- An IRB is any board, committee, or other group

formally designated to review biomedical research involving subjects. The IRB must be established, operated and functioning in conformance with 21 CFR Part 56 (Institutional Review Boards).²

BIMO's programme is implemented in the US and internationally via compliance programmes applying to non-clinical testing labs (GLP), clinical investigators, sponsor/monitors and IRBs.

This article focuses exclusively on steps that can be taken to facilitate an efficient sponsor/monitor compliance inspection.

Sponsor Obligations

The FDA has defined the following specific obligations for clinical study sponsors:³

- obtain FDA approval, where necessary, prior to study initiation;
- manufacture and label investigational products appropriately;
- initiate, withhold or discontinue clinical trials as required;
- refrain from commercialisation of investigational products;
- control the distribution and return of investigational products;
- select qualified investigators to conduct studies;
- disseminate appropriate information to investigators;
- select qualified persons to monitor study conduct;
- monitor clinical investigations adequately;
- evaluate and report adverse experiences;

1. 21 CFR Part 812: Investigational Device Exemptions

2. 21 CFR Part 56: Institutional Review Boards

3. FDA Compliance Program Guidance Manual: CP 7348.810

- maintain adequate study records; and
- submit study progress reports and final results.

At the time of a BIMO inspection, documentation on-hand should reflect the sponsor's conformance with these obligations. In the sections that follow, suggestions are provided for the development and organisation of documentation that will provide evidence regarding compliance with the FDA's requirements. Ideally, these steps should be taken before the study is initiated and internal audits of the programme maintenance should be performed periodically.

Project Organisation and Personnel Assessment

One of the first priorities for BIMO inspectors is to determine how the clinical programme is organised and how responsibilities were assigned. To facilitate an efficient assessment, it is recommended that sponsors do the following.

- Establish and maintain a written summary of key study activities and associated responsibilities. Each responsibility should be assigned to the sponsor or other contract personnel/facilities. Joint responsibilities are expected; however, the summary should clearly indicate who is responsible for approval of protocols, plans, etc.
- If a contract research organisation (CRO), central laboratory/reading centre, or other contract resources are used to support study-related activities, document their study responsibilities via a written agreement. Maintain copies of these agreement(s) and any amendments that occur during the project.
- Develop and maintain organisation chart(s) for the clinical research department, which includes the team(s) for the project under inspection. The duration of many device trials can be lengthy and personnel changes within the team are common. To minimise confusion regarding responsibilities throughout the project, organisation charts should clearly reflect changes in team membership and the dates on which changes were effective. The organisation charts should be supported by easily accessible team member résumés and summaries of relevant training. Again, due to the lengthy duration of many device trials, it is recommended that a programme be implemented to update team member résumés annually.
- Develop and maintain a list of all study investigators with whom investigator agreements were executed. To facilitate the

efficient comparison of subject records, it is helpful to supplement this list with study enrollment numbers by investigator. The list should reflect the date of exit/entry for all investigators.

Clinical Investigator Selection and Monitoring

The inspector will be interested to review documentation regarding study investigators – their qualifications, investigator agreement, relevant information provided by the sponsor to support their decision to participate in the study, and compliance with FDA regulations.

This review can be streamlined via the development and maintenance of an organised filing system for each study investigator. It is recommended that files be subdivided into logical subsections where information such as the following could be filed.

- Protocol – original protocol and amendments, along with the associated fully-executed signature page(s).
- Report of prior investigations (if applicable) – original report and updates, along with signature page(s) reflecting investigator receipt.
- IRB approvals – IRB membership list(s) or multiple assurance number and documentation of approval of investigator(s), protocol(s) and consent document(s). If applicable, subject recruitment or information materials and declarations of translation may also be included.
- IRB correspondence – periodic progress reports submitted, notification of adverse events (AE) and miscellaneous correspondence.
- Investigator agreements - original fully-executed non-disclosure and investigator agreement(s), along with the investigator's financial disclosure, *curriculum vitae* and medical license. Any amendments to the original agreements should also be included.
- Monitoring – documentation of each monitoring visit using an easy to view log, and associated site visit reports.
- Product accountability – documentation reflecting investigational product shipment, receipt, use or return.
- Study management logs – signature authorisation logs identify each study staff member and their responsibilities; screening/enrollment logs

identify sequentially each person screened for the study, their enrollment status and reason(s) for exclusion, if applicable; calibration logs provide documentation of calibration or service for key instruments/equipment used for study-related measurements.

- Memos to file.
- Sponsor-investigator correspondence – between the sponsor or its representative and the investigator.
- Adverse event correspondence.
- Internal correspondence – among the sponsor or sponsor-representatives related to the study.

Occasionally, investigator agreements are executed with investigators who are not formally activated for study participation. It is recommended that study files be maintained for these investigators as well.

Monitoring Procedures and Activities Assessment

Review of study monitoring procedures and activities is likely to be one of the most time-consuming activities conducted by the inspector. At this stage of the inspection, the sponsor should be prepared for a detailed review of inspector-designated monitoring reports and subject records, as well as all unanticipated adverse device effects or serious adverse events. In preparation for this review, the following steps should be implemented.

- Prepare and maintain written study monitoring procedures and plans. These documents should be subject to change controls. The study monitoring plan may include, at minimum, information regarding clinical monitor training and responsibilities, monitoring procedures to be used and checklists or logs to confirm procedural compliance, study definitions, and guidelines for reporting protocol deviations and adverse events, etc.
- Subject data line listings should be prepared to provide efficient comparison with related case report forms (CRF). A line listing physically resembling the CRF promotes uniformity in the review process and, because not every subject's data is likely to be reviewed, data line listings should be segregated by subject.
- Some amount of the subject data received on CRFs is subject to further clarification and possible change after the data has been reviewed by the sponsor. These questions and their responses should be documented, chronologically

ordered and readily available with the CRFs to support differences between line listings and the associated CRFs. It is also suggested that a log be developed to track queries generated and their resolution to confirm that all questions asked were satisfactorily answered.

- Develop and maintain a log of unanticipated adverse device effects and serious adverse events reported by study sites. The log might also contain the following important milestones – date each event was reported by the site, date of IRB notification, date of FDA reporting, and date of notification of other investigators (if applicable).
- Develop and maintain a log of protocol deviations. This enables a quick assessment of protocol non-compliance by investigator.

Data Collection and Handling Assessment

The BIMO inspector will need to substantiate the integrity of the sponsor's data collection, management and analysis activities in support of the PMA submission. This process can be facilitated via the following steps.

- Develop and maintain a list of all clinical studies included in the PMA submitted. If there were studies done with the device that were not reported in the PMA, be prepared to address these and indicate the reason why.
- Prepare and maintain written plans describing data management systems and procedures, as well as for the statistical analysis. The data management plan should describe procedures for data collection, maintenance and analysis and should include annotated CRFs, database field definitions, automated edit checks and database validation plan(s). If remote data capture was used for the project, the plan should address 21 CFR Part 11 requirements for software, data collection and computerised system security. The statistical analysis plan should describe the study population(s) to be analysed, how visit windows will be applied, general analysis, conventions to be used and subject disposition definitions. The plan should also identify variables to be analysed and explain analysis methodology. Ideally, the plan should include sample tables and supporting listings to be generated.
- Maintain well-labelled data listings supporting study tabulations submitted in the PMA. These listings should have been previously confirmed with subject data on file.

Investigational Product Accountability Assessment

The last general area of focus for the inspector will be the control of the investigational product used for the clinical study. The inspector's review can be facilitated by the following.

- Develop and maintain written procedures describing requirements for investigational product manufacture, release and storage. Ideally, these procedures will include checklists or logs to enable verification that procedures have been followed.
- Labelling and distribution of investigational devices must also be strictly controlled to eliminate the possibility of unauthorised distribution or use. To provide confirmation, maintain a detailed log of product shipment, use, return or disposal. Log entries should be supported by detailed documentation reflecting product quantities/lots shipped and confirmed received by study sites. If product is returned by the site, documentation should reflect the quantity/lot involved, with sponsor confirmation of such. Any discrepancies should

be resolved and documentation associated with resolution should be maintained.

- Investigational product records should be maintained in a logically organised fashion; e.g., by sterilisation lot, so the inspector can readily review adherence to established procedures and standards.

Conclusion

The suggestions provided are intended to provide stimulus for planning medical device clinical programme operations to facilitate an efficient project and a smooth BIMO inspection. ■

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