

# DEVICE CLINICAL TRIALS REGULATORY CONSIDERATIONS

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**Abstract:** *The U.S. Food and Drug Administration's (FDA's) Bioresearch Monitoring (BIMO) program is a comprehensive program of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of agency-regulated research. This article provides an overview of the BIMO program, especially in relation to the Center for Devices and Radiological Health. It focuses on the responsibilities of sponsors and clinical investigators, including responsibilities that must be met at the clinical investigator sites. FDA's perspective on quality and integrity, that quality data is essential to data integrity, is highlighted. Inspectional findings and case examples are provided.*

FDA's BIMO program is a comprehensive program of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA-regulated research. Each FDA center has a BIMO division, branch, or staff, depending upon its size. Each center determines which clinical sites, sponsors, and institutional review boards need to be audited and issues assignments to the districts. FDA investigators in the field conduct the audits. Sometimes headquarters personnel go out with FDA investigators to assist them, for training purposes, or to stay current. Sometimes reviewers go out on an inspection for training purposes or because their expertise may be needed for that particular inspection.

Table 1 provides an overview of BIMO's objectives, the types of research it covers, and the types of inspections it conducts. BIMO's program objectives are to verify the quality and integrity of data and protect the rights and welfare of human research subjects. Any research that is intended to be

submitted to the FDA for review and approval (e.g., Investigational New Drug [IND] application or Investigational Device Exemption [IDE]) is subject to the BIMO program. This includes clinical and non-clinical data. The BIMO program covers laboratory facilities, clinical investigator sites, institutional review boards (IRBs), and sponsors/monitors/CROs (contract research organizations). This article focuses on audits of clinical investigator sites and sponsors/monitors/CROs.

BIMO's compliance programs, guides for FDA investigators on what to cover during an inspection, are a very good source of information ([http://www.fda.gov/ora/compliance\\_ref/bimo/default.htm](http://www.fda.gov/ora/compliance_ref/bimo/default.htm)). There are four guides: Good Laboratory Practice (CP 7348.808); Institutional Review Boards (CP 7348.809); Sponsors, CROs, and Monitors (CP 7348.810); and Clinical Investigators (CP 7348.811). There is also a compliance program for bio-equivalence.

**TABLE 1**  
**An Overview of BIMO**

#### **Objectives**

- To verify the quality and integrity of data
- To protect the rights and welfare of human research subjects

#### **Types of Research Covered**

- Any research that is intended to be submitted to the FDA for review and approval:
  - o Clinical data
  - o Non-clinical data

#### **Types of Inspections Conducted**

- Laboratory facilities
- Clinical investigator sites
- IRBs
- Sponsors/monitors/CROs

Within the Center for Devices and Radiological Health (CDRH), after the clinical module of a Pre-Market Application (PMA) comes in, my staff meets with the Office of Device Evaluation reviewer(s) assigned to that application. The reviewer has 180 days to review the application. In the meantime, we issue inspection assignments to the field investigators. We usually select three clinical investigator sites, at least one IRB, and the sponsor if the sponsor has not been inspected recently.

The inspectors conduct their inspections and send establishment inspection reports back to us. Our staff reviews those reports and makes a final determination as to whether we need to send compliance correspondence. This could be an Untitled Letter, which says that there were some minor deficiencies that we noticed and here are the deficiencies, or a Warning Letter, which says, "you really have a problem here, and it impacts data reliability or human subject protection." These are the problems that were found during the inspection, and we want to hear from you within 15 days." Staff at headquarters, inspectors in the districts, and the reviewing divisions work as a team in making review and approval decisions. Once our staff goes over the establishment inspection reports and handles the compliance aspects, we also provide a complete package of feedback to the reviewing division.

The basic regulations related to the BIMO program are found in 21 CFR:

- Part 812: - IDE Regulations (devices)
- Part 312 - IND Regulations (drugs and biologics)
- Part 50 - Protection of Human Subjects
- Part 56 - Institutional Review Boards
- Part 58 - Good Laboratory Practices
- Part 54 - Financial Disclosures by Clinical Investigators
- Part 11 - Electronic Records and Electronic Signatures.

It is in everybody's best interest that data from research trials be of good quality and have integrity. Clinical and non-clinical data must have data quality and integrity. For example, we have seen instances where animals have died due to toxicity, and this was not reported to us. As a result, subsequent clinical trials in humans lack integrity. We are all interested in doing the best job that we can to protect human subjects.

### **Sponsor Responsibilities**

Sponsors must label their investigational products appropriately, indicating that they are investigational products (812.5). They must not commercialize investigational products (812.7), and they must ship investigational products only to clinical investigators at clinical sites that are involved in the study. They must keep good documentation.

In the world of devices, there are significant risk and non-significant risk studies. The significant risk studies are studies that can present greater risks either by virtue of the product or the procedures that are involved with the investigational product. It is very important to obtain FDA and IRB approval (812.42) before starting a significant risk study. A non-significant risk study requires only IRB approval. The clinical investigator is responsible for obtaining IRB approval. The sponsor is responsible for submitting the IDE for approval.

The sponsor must know where the investigational product is going and where it is being distributed and to whom (812.43). If the devices are disposed of or not used, that must be documented. We have seen many examples where device sponsors did not have adequate control of their investigational product. They keep poor records. When we go out and audit, if we cannot figure out where the devices went, we question the reliability of the data in the application submitted to the center. This means that the firm may

have delays in getting its product approved. That is why it is very important to meet the requirements and keep track of investigational devices and how they are distributed.

The sponsor must select qualified investigators (812.43) and disseminate appropriate information to investigators (812.45). The sponsor must monitor the study (812.46) to oversee it and to bring clinical investigators back into compliance when necessary.

The sponsor must monitor and report adverse effects (812.46). We have seen instances where sponsors were late in submitting their Adverse Effect reports and Anticipated Device Effect reports to the center while their application is under review. At other times, sponsors do not capture adverse effects right away. They might be in a source record somewhere, but they are neither in the case record form (CRF) nor reported to us. It is very important that sponsors be timely and report any unanticipated device effects. Clinical investigator sites must keep accurate and timely records and provide the IRB and sponsor with the information they need. The sponsor must maintain adequate records (812.140) and submit progress reports and final results (812.150).

Common sponsor/CRO/monitor deficiencies are:

- Inadequate monitoring
- Inadequate documentation of monitoring activities
- Inadequate test article accountability
- Failure to report unanticipated adverse events.

In fiscal year 2001, approximately 40% of sponsors failed to ensure proper monitoring of their clinical investigator sites. Of these, 50% failed to ensure clinical investigator compliance. In the two previous years (fiscal years 1999 and 2000), 50% and 30% of sponsors failed to ensure proper monitoring of their clinical investigator sites,

respectively, and 43% and 70% failed to ensure clinical investigator compliance, respectively.

### **Clinical Investigator Responsibilities**

Clinical investigators must assure initial and continuing (at least once a year) IRB review and approval before the study starts. We found many cases where clinical investigators start studies before getting subjects' informed consent.

Clinical investigators must follow the investigational plan and the investigator's agreement (devices) or the FDA 1572 form (drugs and biologics). They should read this before they sign it.

Clinical investigators must provide an adequate informed consent process. When we conduct inspections, we rarely have the time and resources to get into the informed consent process. But it is very important for researchers to be sensitive to informed consent, so that subjects understand what the research is all about, are fully informed, and have a chance to ask questions and get them answered. All of this must happen before the study starts, before the subjects sign the informed consent form.

Clinical investigators must maintain adequate records. There are times when we go out to inspect sites and find few source documents. In a recent case with few source documents, we stopped the review of the application. Clinical investigators must maintain test article accountability and report adverse events.

Common clinical investigator deficiencies are:

- Failure to follow the study protocol
- Inadequate informed consent
- Inadequate record keeping
- Inadequate test article accountability
- Failure to report adverse events.

Please note that many inspections do not have problems like these.

### **Quality and Integrity**

In the research world, we know that quality data are important. We know that quality data are essential to data integrity. Quality data are: accurate, complete, traceable, legible, attributable, and entered in a timely manner. On inspections, I have seen data where a patient was assessed on a given day, and the date and protocol aspects covered were entered, but this information was not transferred to the CRFs right away. Six months later, when the adverse effects and other data were transferred, mistakes were made and carried into the data that were reported to FDA; it was the domino effect.

Good Clinical Practices (GCPs) and International Standards Organization (ISO) standards cover quality policy, management, assurance, control, and audit. International Conference on Harmonization (ICH) GCPs cover pharmaceutical products. ISO is conducting an international harmonization process for devices.

My staff and others in the center have been working internationally to get a device clinical research monitoring standard adopted. We hope to get that to the point where it will be in sync with ICH GCPs. It will not say the same thing as ICH GCPs because much of those are specific to drugs and drug regulation.

ISO 9000 and 9001 are general standards about quality management systems. Many firms are implementing quality management systems. The FDA is working on an internal quality management system.

To ensure as much as you can that you have quality data and data of integrity at your clinical research site, you must have some sort of quality policy. Determine the objectives and responsibilities of

your work and implement them. Implementation includes quality planning, quality control, quality assurance, and quality improvement.

Quality control is building in quality and monitoring. Quality assurance is ensuring that things are being done accurately, that the trial is performed, and that the data are generated, documented, recorded, and reported in compliance with regulatory requirements. You audit to ensure that the source data are being captured and transferred accurately and that the protocol is being met. If you find non-compliance, mistakes, or problems, you identify them, correct them, and figure out a way to try to keep them from re-occurring.

Data quality and integrity are very important. Sponsors are required to monitor their studies. It is in their best interests to audit their studies and to have an overall quality assurance component to identify and correct problems.

The FDA's Application Integrity Policy evolved as a result of the generic drug crisis, in which fraudulent information was being submitted to the FDA in applications. This fraudulent information related to manufacturers and some FDA reviewers who were accepting bribes. Many people went to jail. The Application Integrity Policy deals with the integrity of data and information in applications that are submitted to the FDA for review. If we have a significant question about the reliability of data, and we see a pattern or practice of wrongful acts in that application or a systemic problem with a firm, we stop review of the data. Sometimes fraud is involved and sometimes it is not. We have applied the Application Integrity Policy in cases of pervasive sloppiness, out of control systems, no quality assurance, inability to locate records, and so forth.

### Case Examples

The names in these case examples are fictitious. There are many sponsor/investigators in the device world, such as CellFinder, Inc. This sponsor/investigator had an IVD product for the detection of disease/antibiotics and had three 510(k)s under FDA review. The CDRH reviewer told the BIMO Division that the data looked too good. When he called the firm, they sent him another set of data within 24 hours. The district inspector and one of our staff members went out and audited the company. We found data that had been altered to increase the number of positive results in the study. We also found no source documentation for much of the data in the 510(k) submissions. This was an in vitro diagnostic product, so there was a package insert that was not followed for performance testing, and some materials supplied with the test kits were not used for performance testing. There was much falsification and many fraudulent activities associated with this study.

There were many consequences for the sponsor. One of its 510(k) submissions was withdrawn. One 510(k) submission was found to be not substantially equivalent. We invoked the Application Integrity Policy and stopped review of the applications. The firm was required to submit a corrective action plan that was acceptable to CDRH. We are working with the firm on that plan and the field is working with us.

OncoScreen, Inc. is a positive case example. OncoScreen submitted a PMA supplement for an in vitro diagnostic device. The supplement involved 1,000 subjects at 33 clinical sites. We went out on a routine inspection and found that they had a standard operating procedure for monitoring that they followed. They audited their sites every two months, using in-house staff. When they found

non-compliance, they did a quality assurance review and took care of the problem.

OncoScreen dropped two sites and documented the reasons (lost or late delivery of subject samples and an insufficient number of subjects). They hired an independent consultant to duplicate database entry to verify its accuracy.

OncoScreen had conducted pre-study visits and training. Before the study started, the firm got signed investigator agreements and IRB approval. The firm had good storage and test article accountability, proper labeling on test articles, and prompt response to clinical investigators' non-compliance. OncoScreen's outcomes were a prompt and successful BIMO inspection and approval of their supplement within five months. Its device is now marketed worldwide with the additional indication for use.

### CDRH BIMO Activities

In the past fiscal year, CDRH's BIMO Division conducted 51 research misconduct investigations.

The results included: notification to disqualify the sponsor-investigator, withdrawal of a sponsor's 510(k), closing of one sponsor's three IDEs, and rejection of site data.

CDRH conducted 238 BIMO inspections in fiscal year 2001: 7 GLP, 59 IRB, 58 sponsor/monitor/CRO (4 outside the U.S.), and 114 clinical investigator (10 outside the U.S.). CDRH issued 15 warning letters and 97 untitled letters. Our division focuses on sponsor/monitor inspections and conducts more of these inspections than other FDA centers.

CDRH is continuing to look at inspectional improvements and is conducting inspections earlier during the device research phase. Internally, we want to continue to improve our interactions with the reviewing divisions. We also participate with the other centers and the Office of the Commissioner in policy-making, guidance preparation, regulation preparation, and so forth. We continue to educate. Table 2 provides useful references.

**TABLE 2 - Useful References**

- CDRH Bioresearch Monitoring: [www.fda.gov/cdrh/comp/bimo.html](http://www.fda.gov/cdrh/comp/bimo.html)
- Office of Good Clinical Practices: <http://www.fda.gov/oc/gcp/default.htm>
- Regulatory Procedures Manual Subchapter 10: Application Integrity Policy: [http://www.fda.gov/ora/compliance\\_ref/rpm\\_new2/rpm10aip.html](http://www.fda.gov/ora/compliance_ref/rpm_new2/rpm10aip.html)
- Disqualified/Restricted Clinical Investigator List: [http://www.fda.gov/ora/compliance\\_ref/bimo/dis\\_res\\_assur.htm](http://www.fda.gov/ora/compliance_ref/bimo/dis_res_assur.htm)
- FDA Guidance: Information Sheets: <http://www.fda.gov/oc/ohrt/irbs>
- Guidance for Industry and FDA Staff: Preparing Notices of Availability of Investigational Medical Devices and for Recruiting Study Subjects: <http://www.fda.gov/cdrh/comp/2229.html>
- IDE Protocol Changes: [www.fda.gov/cdrh/ode/guidance/1337.pdf](http://www.fda.gov/cdrh/ode/guidance/1337.pdf)
- Regulating IVD Studies: <http://www.fda.gov/cdrh/comp/ivdreg.html>