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FDA Inspections

Findings for Clinical Investigators

IMARC examined the warning letters posted on the FDA's website to compile the top findings from BIMO inspections. This year, we are reflecting on the top findings of previous years and discussing trends seen in 2018.

Established in 1977 by the FDA, the Bioresearch Monitoring (BIMO) program protects the safety and welfare of study participants and ensures adequate levels of data integrity. BIMO completes routine and for-cause inspections of clinical investigative sites to assess compliance and enforce FDA regulations. Investigators that are found to have serious deficiencies or violations may receive an FDA warning letter.

Why Might a Clinical Investigator Receive a Warning Letter?

The FDA Inspections of Clinical Investigators Guide states that a warning letter is issued for violations of regulatory significance "which may lead to enforcement action if not promptly and adequately corrected." The recipient of the warning letter is requested to secure voluntary compliance, correct the violations and provide an adequate written response to the agency.

Recent Trends in Warning Letters

Reflecting on the previous five years (2013-2017) of published BIMO metrics, an average of 1,137 BIMO inspections were conducted, which includes the inspection of clinical investigators (CI), IRBs, sponsors, monitors, CROs, and Good Laboratory Practice. As shown in the table below, the percentage of clinical investigator inspections has increased overall, while the warning letter frequency has fluctuated over time.

Fiscal Year	Number of Total Inspections	Percent of CI Inspections	CI Warning Letters
2017	965	73%	6
2016	1055	73%	6
2105	1113	74%	5
2014	1326	54%	12
2013	1224	54%	8

While the number of inspections varied each year, there has been a noticeable consistent trend in the inspection findings. Each year, the FDA cites the same clinical investigator deficiencies from the BIMO inspections.

Listed are the top three warning letter findings for clinical investigators in the past five years

1. Failure to ensure that the investigation was conducted according to the investigation plan

Examples include:

- Failure to perform study visits at the location specified in the protocol
- No investigator oversight of inclusion/exclusion criteria
- Patient self-reported items were instead carried out by study personnel

2. Failure to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual in the investigation

Examples include:

- Failure to report adverse events accurately and correctly to the IRB
- Revisions on source worksheets were unclear
- Failure to document dates related to serious adverse events

3. Failure to maintain adequate records and accountability for the investigational product

Examples include:

- Records of the investigational product, including dates, quantity, and use by subjects, were not maintained
- Failure to maintain any drug disposition records or product accountability log
- Failure to produce the unused supply of investigational product or drug with no other records indicating the use or disposal of the unused supply

Honorable Mentions

Failure to protect the rights, safety and welfare of clinical trial subjects

Examples include:

- Failure to report serious adverse events (SAEs) according to the protocol
- Failure to provide timely treatment to subjects experiencing symptoms

Failure to obtain informed consent in accordance with 21 CRF Part 50

Examples include:

- A consent form was used that was not approved by an IRB
- Failure to document or maintain documentation of subjects' consent

While looking at the 2018 preliminary BIMO findings from inspections, the metrics (including 483 findings) demonstrate similar clinical investigator deficiencies to those seen in past years. During the 2018 BIMO inspections, 400 violations were cited for clinical investigators. See the table below for the frequency of each clinical investigator violation found during the BIMO 2018 inspections. The most frequent inspection observation in 2018 remained to be "failing to follow the investigation plan," with 118 instances occurring.

Clinical Investigator Violation Observed	Frequency
FAILURE TO FOLLOW THE INVESTIGATIONAL PLAN	30%
FAILURE TO ADEQUATELY MAINTAIN CASE RECORDS	17%
FAILURE TO MAINTAIN IRB RECORDS	4%
FAILURE TO MAINTAIN PROPER RECORDS OF DRUG DOSES	3%
CONFLICT OF INTEREST	1%
FAILURE TO OBTAIN PROPER INFORMED CONSENT	1%
FAILURE TO DISPOSE OF UNUSED DRUGS PROPERLY	1%

Are there improvements your study team can attain to avoid these year-to-year trending deficiencies?