BLA REGULATORY

PHARMAFOCUS

Weekly Newsletter - One Topic at a Time

2025 wk-issue 07, 20 Mar. 2025

About Us

BLA Regulatory is located in the State of Maryland, conveniently close to the FDA's headquarters. We offer U.S. agent services for all types of FDA-regulated products, including drugs, cosmetics, medical devices, and more. Our team can guide you through the entire application and registration process to ensure FDA compliance. Please visit our office website for more information or if you need any assistance.

Understanding Protocol Deviations for Clinical Investigations in the US

Clinical trials follow strict protocols to ensure accuracy, safety, and compliance with regulations. However, in reality, these protocols are not always followed exactly as planned. Changes, known as protocol deviations, happen for various reasons—patients may struggle with visit schedules or medications, and study staff may need to adjust procedures to manage real-world challenges.

Protocol deviations are a leading cause of FDA enforcement actions, with about 30% of warning letters issued due to non-compliance with study protocols (1). While some deviations are minor, others can impact the reliability of study results, patient safety, and overall trial success.

In this article, we break down why protocol deviations happen, their consequences, and how to prevent them. We also want to highlight the release of FDA's Industry Guidance titled "Protocol Deviations for Clinical Investigations of Drugs, Biological Products, and Devices: Guidance for Industry in December 2024" (3). Understanding the requirements can help researchers and sponsors run smoother, more compliant clinical trials.

Common Causes of Protocol Deviations

Several factors contribute to the occurrence of protocol deviations:

- Complex Protocol Designs: Protocols with numerous endpoints, procedures per visit, and extensive eligibility criteria increase the likelihood of deviations.
- Geographical Dispersion: Trials conducted across multiple countries and sites face challenges in maintaining consistent protocol adherence.
- Inadequate Training (2): Insufficient training of clinical staff on protocol specifics can lead to misunderstandings and errors.
- Patient Non-Compliance: Participants may unintentionally deviate from protocols due to misunderstanding instructions or personal circumstances.

Prevalence of Protocol Deviations

A study conducted by the Tufts Center for the Study of Drug Development (Tufts CSDD) in 2022 showed that out of 187 protocols, phase II and III protocols have a mean total of 75 and 119 protocol deviations, respectively, involving nearly one-third of all patients enrolled in each clinical trial (Table 1).

Oncology clinical trials have the highest relatively mean number of protocol deviations affecting more than 40% of patients enrolled in each trial (Table 2).

Table 1: Mean total number of protocol deviations per protocol by phase

Protocols (n=187)	Total mean number of deviations per protocol	Proportion of patients with protocol deviations (%)
Phase I	8.7	15.3%
Phase II	75.3	30.0%
Phase III	118.5	32.8%

Table 2: Mean total number of protocol deviations per protocol by major disease category

Combined phase II/III protocols (n=139)	Oncology	Non-oncology	Rare disease indications	Non-rare disease indications
Mean number of protocol deviations	108.8	91.9	78.1	98.7
Proportion of patients with protocol deviations (%)	46.6%	27.4%	27.7%	32.1%

The number of endpoints, the number of procedures per visit, and the number of countries were modestly positively associated with and predictive of, the incidence of deviations per protocol. A strong positive relationship was shown between the number of investigative sites and the number of protocol deviations. The findings in this study provide useful measures that sponsor companies can use to benchmark their own protocol deviation experience and determine whether remediation is warranted (1).

Consequences of Protocol Deviations

The impact of protocol deviations can be substantial:

- **Data Integrity**: Deviations can compromise the reliability of study data, potentially leading to invalid conclusions.
- **Regulatory Actions** (2): Failure to adhere to protocols is a leading cause of regulatory enforcement actions, including warning letters from authorities like the FDA.
- **Increased Costs and Timelines** (2): Addressing deviations often requires additional monitoring, retraining, and potential protocol amendments, all of which can extend study timelines and escalate costs.

Strategies to Prevent Protocol Deviations

Implementing effective prevention strategies is essential:

- **Simplify Protocol Design**: Streamlining protocols by minimizing unnecessary complexity can reduce the risk of deviations.
- **Comprehensive Training** (2): Ensuring all clinical staff receive thorough training on protocol requirements enhances adherence.
- **Enhanced Monitoring**: Regular and rigorous monitoring can identify potential deviations early, allowing for prompt corrective actions.
- **Patient Engagement**: Educating and supporting participants fosters better compliance with protocol requirements.

FDA's New Guidance on Protocol Deviations for Clinical Investigations

The U.S. Food and Drug Administration (FDA) released a pivotal guidance document titled *"Protocol Deviations for Clinical Investigations of Drugs, Biological Products, and Devices: Guidance for Industry in December 2024"* (3). This guidance provides critical insights for sponsors, clinical investigators, and institutional review boards (IRBs) on handling unexpected changes in study procedures. Here's the gist:

How will it help?

- It helps define, identify, and report protocol deviations consistently.
- Stresses the need for consistent classification, reporting, and documentation.

When with it help?

- Protocol deviations are usually unintentional and found after they happen.
- Intentional deviations should be rare and need prior approval from sponsors and IRBs.

What are the highlights?

A. Protocol Deviations

- **Important Deviations**: Big issues that affect data quality or participant safety, like missing safety tests or giving the wrong treatment.
- **Minor Deviations**: Smaller issues that don't have a major impact, like slight delays in scheduled visits.

B. Roles and Responsibilities

- **Investigators**: Protect participants and report all deviations to sponsors and IRBs.
- **Sponsors**: Monitor studies, ensure protocols are followed, and report major issues to the FDA. They should also train investigators.
- **IRBs**: Review and approve deviations to ensure safety and study integrity.

C. Protocol Amendments and Changes

- Changes to protocols need IRB and sometimes FDA approval. Urgent changes to eliminate immediate hazards can be made without prior approval but must be reported as deviations.

The guidance also provides recommendations on how to prevent or minimize deviations when they occur. The goal is to ensure reliable study results while keeping participants safe.

If you have questions about how this guidance affects your study protocols or require assistance with FDA regulatory compliance, BLA Regulatory is here to help. Our team of experts can provide tailored solutions to ensure your clinical investigations meet regulatory standards. For the latest updates on regulatory news and industry best practices, subscribe to our newsletter and follow us on LinkedIn.

Disclaimer: This newsletter is for informational purposes only and does not constitute legal or regulatory advice. Please refer to the official FDA guidance document for detailed recommendations

References:

1. Getz, K., Smith, Z., Jain, A., & Krauss, R. (2022). Benchmarking Protocol Deviations and Their Variation by Major Disease Categories. Therapeutic innovation & regulatory science, 56(4), 632–636.
2. Beth Harper. (2022). Reducing Protocol Deviations with Training-Based Metrics. Retrieved on March 13, 2025.
3. U.S. Food & Drug Administration. Protocol Deviations for Clinical Investigations of Drugs, Biological Products, and Devices. December 2024. Retrieved on February 27, 2025.