Analyzing Delays and Enforcement Challenges in FDA Clinical Trial Reporting Oversight - An Investigation of FOIA requests

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Objective

Our study investigates the impact of the FDA's timeliness and risk-based approach to enforcing clinical trial sponsor compliance as required by the Food and Drug Administration Amendments Act of 2007.

Background

Over 4,000 (23%) of applicable clinical trials (ACTs[1] as defined by 42 CFR 11.10) on the ClinicalTrials.gov database are missing results due to reporting deficiencies[2]. The FDA Amendments Act of 2007 (FDAAA) requires results reporting of all clinical trials funded by NIH to be submitted to ClinicalTrials.gov within 12 months of the primary completion date (42 CFR 11.44)[3]. FDAAA aims to ensure patient and physician access to clinical trial results, prevent scientific fraud, and avoid research duplication.

Pre-Notices are letters issued to trial sponsors who do not register an applicable clinical trial or submit required clinical trial information. The FDA will investigate cases of unaddressed Pre-Notices and potentially send a Notice of Noncompliance. If ACT sponsors do not address Notices within 30 days, the FDA may levy civil monetary penalties. However, FDA has not yet levied a single fine against a noncompliant trial sponsor.

The FDA's risk-based approach to monitoring clinical trials is designed to "ensure the rights, safety, and welfare of participants in the clinical investigation, and guarantee the integrity of data submitted to the FDA."[4] This guidance is intended to highlight recommendations the FDA intends to follow in its monitoring and issuance of Pre-Notices and Notices of Noncompliance.

Universities Allied for Essential Medicines (UAEM) is a non-profit health equity organization. UAEM's Clinical Trial Transparency Campaign has been actively involved in investigating how regulators enforce FDAAA and potential mechanisms to drive clinical trial resulting reporting compliance.

UAEM found in an earlier study that between 2013 and 2021 the FDA issued 57 Pre-Notices, which resulted in over 90% compliance and in cases where Pre-Notices were ignored by sponsors, 4 Notices of Noncompliance were issued in the same timeframe[5]. While underutilized, these Notices of Noncompliance yield high compliance.

Methods

Our study involved a comprehensive analysis of 32 cases of noncompliant trial sponsors. These cases were identified through FDA Freedom of Information Act (FOIA) requests. Four authors (MC, AW, BK, and MS) reviewed all inquiries. They extracted critical dates from each case, including: Study Start Date, Primary Completion Date, Deadline for Uploading Results, Date of Pre-Notice Issuance and Date of Notice of Noncompliance Issuance (if applicable).

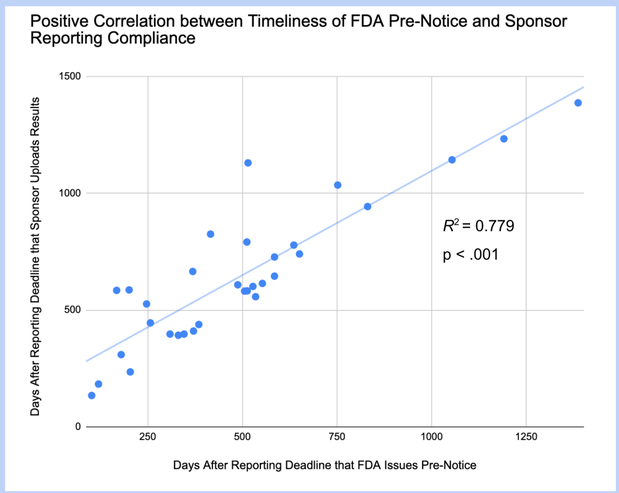

Figure 1: The correlation and significance between the amount of time for the FDA to issue Pre-Notices following missed results reporting deadlines and the time for sponsors to submit missing results is analyzed.

Figure 2: The amount of time for sponsors to reply to the FDA and submit results is contrasted between the sending of a Pre-Notice versus a Notice of Noncompliance.

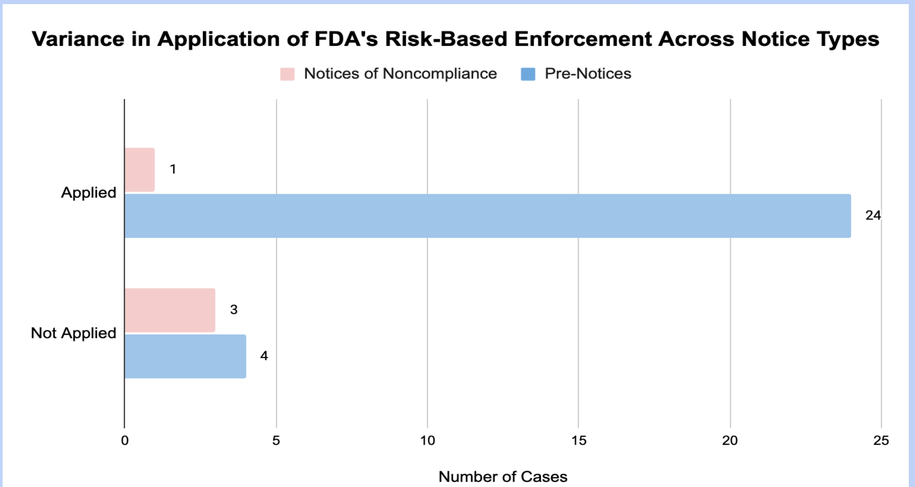

Figure 3: The application of FDA's risk-based approach was contrasted between Pre-Notices and Notices of Noncompliance.

Timeliness of Enforcement and Compliance with ClinicalTrials.gov Across Notice Types

Category	Median (Days)	IQR (Days)
Time after Reporting Deadline Until Pre-Notice is Issued	497	289
Time After First Pre-Notice Letter Until Sponsor Replied	48	51
Time After Pre-Notice Issued Until Sponsor Updates ClinicalTrials.gov	89	173
Time between Pre-Notice and Notice of Noncompliance	278	40.75
Time for Sponsor to Reply to Notice of Noncompliance	2	3
Time After Notice of Noncompliance that Sponsor Updates ClinicalTrials.gov	5.5	11.75

Table 1

We calculated the mean (standard deviation, SD) and median (interquartile range, IQR) for several key intervals. Investigating the role of timeliness in FDA Pre-Notices and Notices of Noncompliance on the timeliness of clinical trial sponsor reporting compliance. The Pearson correlation coefficient and p-value were calculated for: the number of days between the results reporting deadline (12 months after a study's primary completion date) and FDA Pre-Notice Issuance against the number of days between the results reporting deadline and sponsor submission of results. We performed a comparative review of the application of the FDA's Risk-Based Approach in the issuance of Notices of Noncompliance and Pre-Notices using qualifying criteria outlined by the FDA and study information on ClinicalTrials.gov.

Discussion

In our analysis, we found a strong positive correlation between the timeliness of FDA Pre-Notice issuance and sponsor compliance timeframes. As such, if the FDA sent Pre-Notices with greater expediency, noncompliant ACT sponsors would likely sooner address data submission issues. We also found that Pre-Notices are effective in improving compliance, yet Notices of Noncompliance yield faster responses and submission of results to ClinicalTrials.gov. These insights suggest that the FDA should increase the issuance of Notices of Noncompliance and Pre-Notices to promote greater transparency in results reporting.

Regarding the FDA's application of a risk-based approach, we found inconsistencies in utilization between notice types. While the majority of cases appeared to follow the FDA's risk-based approach, 22% of all notice types were issued for trials that did not adhere to the risk-based factors. Among the Notice of Noncompliance cohort, one study included the treatment of Acne Rosacea. These findings suggest that the FDA could allocate limited resources to prioritize enforcement for trials that pose greater risk to patients.

Our analysis was limited to the 32 cases obtained via FDA FOIA requests. In December 2023, shortly after our analysis was conducted, the FDA published all Pre-Notice letters sent, with the most recent ones having been sent out in September of this year. A future study could analyze these cases to determine how the FDA addresses outstanding ClinicalTrials.gov Quality Control Review issues and to evaluate changes in sponsor compliance patterns over time.

References

1. Food and Drug Administration Amendments Act, 42 CFR § 11.10 (2007)
2. Who's sharing their clinical trial results? The Bennett Institute for Applied Data Science, Oxford University https://fdaaa.trialstracker.net
3. Food and Drug Administration Amendments Act, 42 CFR § 11.44 (2007)
4. A Risk-Based Approach to Monitoring of Clinical Investigations, 2 (FDA 2023). https://www.fda.gov/media/121479/download
5. Ramachandran R, Morten CJ, Ross JS (11/12/2021). *Strengthening the FDA's Enforcement of ClinicalTrials.gov Reporting Requirements.* JAMA. https://pubmed.ncbi.nlm.nih.gov/34766971/

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