

ONE HUNDRED EIGHTEENTH CONGRESS
Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
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January 19, 2023

The Honorable Robert M. Califf, M.D.
Commissioner of Food and Drugs
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

The Honorable Lawrence A. Tabak, D.D.S., Ph.D.
Acting Director
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20892

Dear Commissioner Califf and Director Tabak,

I write regarding concerns about the lack of compliance by medical product sponsors with requirements to report certain clinical trial results information to the ClinicalTrials.gov database. The law requires that certain clinical trial sponsors report results to ClinicalTrials.gov to expand the knowledge base, support additional research, and provide important safety and efficacy information to health care providers and researchers. These important goals depend on adequate compliance with applicable requirements and appropriate enforcement.

According to a recent study, sponsors of 31 percent of registered trials required to report results have failed to report any results, and another 30 percent of sponsors of registered trials required to report results failed to do so on time, totaling 5,364 trials in violation of applicable reporting requirements, or 61 percent of such trials.¹ With respect to publicly-funded studies, a 2022 report from the Office of Inspector General (OIG) of the Department of Health and Human Services (HHS) found that, of 72 reviewed clinical trials funded by the National Institutes of Health (NIH), 37 (51 percent) failed to comply with applicable reporting requirements.² Despite these troubling results, the Food and Drug Administration (FDA) and NIH have only carried out limited enforcement activities for failure to comply with ClinicalTrials.gov requirements.³

¹ Nicholas J. DeVito & Ben Goldacre, *Evaluation of Compliance with Legal Requirements Under the FDA Amendments Act of 2007 for Timely Registration of Clinical Trials, Data Verification, Delayed Reporting, and Trial Document Submission*, 181 JAMA Intern. Med. 1128 (2021).

² HHS OIG, *The National Institutes of Health Did Not Ensure that All Clinical Trial Results Were Reported in Accordance with Federal Requirements* (August 2022), available at <https://oig.hhs.gov/oas/reports/region6/62107000.asp>.

³ *Id.*; FDA, ClinicalTrials.gov – Notices of Noncompliance and Civil Money Penalty Actions (<https://www.fda.gov/science-research/fdas-role-clinicaltrials.gov-information/clinicaltrials.gov-notices-noncompliance-and-civil-money-penalty-actions>) (Aug. 2, 2022).

Congress originally required NIH to establish a public database of clinical trials in 1997 to help patients find trials for serious illnesses.⁴ In 2007, the FDA Amendments Act (FDAAA) expanded the types of trials required to register as well as the types of information required to be submitted, including clinical trial results. The law also added a requirement for premarket submissions to include a certification of compliance with applicable ClinicalTrials.gov requirements, added prohibited acts and civil money penalties for failure to comply, and required the Secretary of HHS to further expand the registry and results data bank by regulation.⁵

Congress enacted these changes to increase the availability, transparency, and public scrutiny of clinical trial results, incentivize compliance, and facilitate enforcement in the event of noncompliance. Publicly reported clinical trial results serve as a resource for safety and effectiveness information for health care providers and researchers and has led to improved report quality. Publicly reported results have also expanded the public medical knowledge base, by providing easy access to key documentation and by facilitating research across all trials for particular diseases or types of products, which can lead to the identification of treatment gaps.⁶ Increased compliance with ClinicalTrials.gov requirements can also reduce unnecessary duplication of studies and increase participation in research.⁷

FDA and NIH both have a role in enforcement of ClinicalTrials.gov requirements. NIH's role comes from its control over funding for certain trials. The Public Health Service Act provides that, for trials funded in whole or in part by a grant from an HHS agency, the agency “shall verify” that required clinical trial information has been submitted before releasing any remaining or future funding to the grantee.⁸ NIH award terms and conditions specify expectations for trial registration and results reporting, and failure to comply provides a basis for enforcement actions, including trial termination.⁹

For most trials, enforcement is FDA's responsibility. The Public Health Service Act provides that, whenever the Secretary determines that any clinical trial information was not submitted as required, “the Secretary shall notify the responsible party” and give them an opportunity to remedy the violation within 30 days.¹⁰ FDA generally identifies violations via Bioresearch Monitoring (BIMO) inspections, which are typically associated with a research or marketing application, or through complaints to the agency.¹¹ When FDA believes there may be a violation, the agency first sends a Preliminary Notice of Noncompliance (Pre-Notice) describing the potential violation and giving the sponsor 30 days to address it and/or respond.¹² If violations persist, FDA may send a Notice of Noncompliance and pursue civil money penalties

⁴ Section 115 of the Food and Drug Administration Modernization Act of 1997, Public Law 105-115.

⁵ 42 U.S.C. § 282(j); 21 U.S.C. §§ 331(jj), 333(f)(3); 42 CFR part 11, 81 Fed. Reg. 64982 (2016).

⁶ Robert M. Califf, M.D. and Deborah A. Zarin, M.D., Invited Commentary, Health Care Policy and Law, *Trial Reporting and the Clinical Trials Enterprise*, 181 JAMA Intern. Med. 1128 (2021).

⁷ See HHS, *21st Century Cures Act, Section 2052 Report on Activities to Encourage Compliance with ClinicalTrials.gov Requirements* (2018).

⁸ 42 U.S.C. § 282(j)(5)(A).

⁹ See 45 CFR 75.371; NIH, *Policy on the Dissemination of NIH-Funded Clinical Trial Information* (last updated July 24, 2017), available at <https://grants.nih.gov/policy/clinical-trials/reporting/understanding/nih-policy.htm>.

¹⁰ 42 U.S.C. § 282(j)(5)(C)(ii).

¹¹ FDA Guidance, *Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank* (August 2020), available at <https://www.fda.gov/media/113361/download>.

¹² *Id.*

(which require an opportunity for a hearing before an administrative law judge under 21 CFR part 17), injunction, or criminal prosecution.¹³

While compliance with ClinicalTrials.gov reporting requirements has slowly but steadily improved since 2007, significant gaps remain.¹⁴ According to a 2021 study on all registered trials completed after January 2017 with data elements covered by applicable NIH regulations, sponsors of only 40 percent of trials required to report results did so within one year of completion, as required by law, and under 69 percent did so at any time.¹⁵ The study also found academic medical centers lagged behind other sponsors in the timeliness and completeness of trial reporting.¹⁶ According to a Universities Allied for Essential Medicines (UAEM) study of the top 40 publicly-funded U.S. research institutions (a mix of public and private universities), while the percentage of unreported university trials decreased between 2019 and 2021, 23 of these 40 institutions remain in violation of ClinicalTrials.gov requirements and over 100 trials still have results missing from the database.¹⁷ With respect to publicly-funded studies more generally, OIG found that sponsors of 37 of 72 NIH-funded clinical trials reviewed (51 percent), failed to comply with applicable reporting requirements (results were not submitted for 25 of the trials and results were submitted late for 12 of the trials).¹⁸

These studies show that sponsors of several thousand trials have been in violation of ClinicalTrials.gov reporting requirements, and yet it appears FDA and NIH have taken only modest compliance actions since reporting requirements first went into effect in 2007.

With respect to NIH enforcement for publicly-funded studies, OIG found that NIH notices of noncompliance “were not always effective at gaining compliance.” However, OIG concluded NIH “did not take any additional enforcement actions against responsible parties that failed to submit clinical trial results” beyond notifications of noncompliance, and “continued to fund new clinical trials” of noncompliant sponsors.¹⁹ OIG attributed the lack of sponsor compliance to NIH’s lack of enforcement, including citing a lack of adequate procedures for ensuring responsible parties submitted results of clinical trials, and NIH’s failure to act when there was noncompliance.²⁰

OIG recommended NIH improve its compliance procedures and activities and take enforcement actions against responsible parties that submit results late or fail to submit results at all. NIH agreed with this recommendation.²¹ In November, the Clinical Trials Registration and

¹³ *Id.*

¹⁴ See NIH, U.S. National Library of Medicine, Table, Number of Registered Studies with Posted Results Over Time, at <https://clinicaltrials.gov/ct2/resources/trends>, showing 55,723 studies with posted results as of October 11, 2022, up from 40,675 in 2020, 15,680 in 2015, and 1,139 in 2010.

¹⁵ See note 1. Of 27,645 covered trials, 8,863 were due to report results and only 3,499 did so on time; 6,099 reported at any time. The study did not include sponsors also in violation of registration requirements.

¹⁶ *Id.*; see also note 6.

¹⁷ See UAEM, *Clinical Trials Transparency at U.S. Universities* (2021), available at https://altroute.com/clinicaltrials/assets/download/Clinical_Trials_Transparency_Report_UAEM_v5.pdf.

¹⁸ See note 2.

¹⁹ *Id.*

²⁰ *Id.*

²¹ *Id.*

Results Reporting Taskforce reported that NIH increased outreach to institutions with overdue trial results and requested additional evidence of proper submissions to ClinicalTrials.gov.²²

Meanwhile, FDA, which bears responsibility for enforcing ClinicalTrials.gov requirements for a much larger number of trials, has also taken very limited action to ensure compliance. This is concerning considering that it is apparent when FDA takes action, it has great effect. FDA first began issuing Pre-Notice letters in 2013, six years after FDAAA was enacted.²³ FDA issued 15 such letters during a pilot conducted between 2013 and 2016, all of which were successful in achieving compliance.²⁴ Over the next five years, FDA issued more than 40 additional Pre-Notices, and over 90 percent of recipients reported missing information shortly after receiving these letters.^{25, 26} In April 2021, FDA issued its first Notice of Noncompliance and has since issued three more such Notices, all of which resulted in the reporting of missing information within a month of receipt.²⁷ However, these actions have only been taken with regard to a tiny fraction of the trials that have been or remain in violation of ClinicalTrials.gov requirements. Additionally, it appears FDA has not sent any compliance letters to NIH, despite the many trials NIH runs or oversees, and for which responsible parties have failed to comply with FDAAA requirements.²⁸

FDA has also not yet imposed any civil money penalties on any trial sponsors. The collection of these penalties would provide a stronger incentive for trial sponsors to comply.²⁹

Given the public health importance of compliance with ClinicalTrials.gov requirements, I ask that you provide responses to the following no later than February 17, 2023.

1. How many Pre-Notices and Notices of Noncompliance has FDA sent?
 - a. How many, or what percentage of, recipients have come into full compliance after receipt, and in what period of time?
 - b. Are there any Pre-Notice recipients that have not come into full compliance that have not received a Notice of Noncompliance? If so, please explain.

²² STAT, *After years of lax oversight, the NIH is starting to contact institutions about unreported clinical trial results* (<https://www.statnews.com/pharmalot/2022/11/07/nih-clinical-trials-transparency-fda-2/#:~:text=In%20recent%20weeks%2C%20the,the%20agency%20for%20lax%20oversight>) (November 7, 2022).

²³ See note 7. Although the NIH rule that became effective in 2017 expanded reporting requirements, certain requirements have been in effect since the enactment of FDAAA in 2007.

²⁴ See note 7.

²⁵ See FDA Statement from Janet Woodcock, M.D., *FDA Takes Action for Failure to Submit Required Clinical Trial Results Information to ClinicalTrials.gov* (April 28, 2021), available at <https://www.fda.gov/news-events/press-announcements/fda-takes-action-failure-submit-required-clinical-trial-results-information-clinicaltrials.gov> (stating that FDA had issued over 40 Pre-Notices to date); Reshma Ramachandran, M.D., et al., Viewpoint, *Strengthening the FDA's Enforcement of ClinicalTrials.gov Reporting Requirements*, 326 JAMA 21 (2021), available at <https://jamanetwork.com/journals/jama/article-abstract/2786399> (stating 58 Pre-Notices FDA issued between 2013 and 2021 were obtained via Freedom of Information Act requests, 57 of which regarded reporting requirements).

²⁶ Ramachandran et al., note 25. The missing information was submitted, on average, within three weeks.

²⁷ See notes 3 and 25.

²⁸ See Ramachandran et al., note 25.

²⁹ See note 17; UAEM Letter to Commissioner of Food and Drugs Robert M. Califf, M.D. (April 21, 2022), at https://assets.nationbuilder.com/uaem/pages/75/attachments/original/1650580897/Letter_to_FDA_Commissioner.pdf?1650580897.

- c. For any recipients of a Pre-Notice or Notice of Noncompliance that have not come into full compliance, has FDA taken any steps toward imposing civil money penalties or any other penalties? If not, why not? If so, how many sponsors and what steps has the agency taken?
 - d. How many Pre-Notices and Notices of Noncompliance are for trials that have at least some federal funding from an HHS agency? How many are for trials for which NIH is the responsible party?
 - e. Given the large number of trials that appear to be noncompliant and the success of FDA's Pre-Notices and Notices of Noncompliance, does FDA plan to send these letters more frequently in the future? If not, why not?
 - f. Are there ways FDA may be able to assess violations more efficiently, for example with the assistance of automated processes? Please explain.
- 2. For NIH-funded trials, what compliance and enforcement actions has NIH taken with respect to responsible parties that do not comply with ClinicalTrials.gov requirements?
 - a. What notices or other communications has NIH provided to responsible parties for noncompliance with ClinicalTrials.gov requirements? How many such communications has it provided in each year since these requirements have been effective?
 - b. How many, or what percentage of, recipients of such communications have come into full compliance after receipt, and in what period of time?
 - c. How many times has NIH withheld or blocked any funding due to noncompliance with ClinicalTrials.gov requirements? Please indicate timing, the number of sponsors and trials, and whether/when compliance was achieved.
 - d. Has NIH pursued any other remedies, e.g., under 45 CFR 75.371, for failure to comply with any ClinicalTrials.gov requirements? If so, please indicate the nature of the action, timing, the number of sponsors and trials, and whether/when compliance was achieved.
 - e. What actions has NIH taken, or will it take, in response to the August 2022 HHS OIG report to improve monitoring of ClinicalTrials.gov compliance, track trial funding, and increase intramural and extramural clinical trial results reporting?
- 3. FDA's 2020 guidance states it generally intends to identify ClinicalTrials.gov violations through evidence collected during BIMO inspections or through complaints received by the agency. Is it necessary to conduct an inspection or receive a complaint to determine whether a sponsor or trial is subject to and in compliance with ClinicalTrials.gov requirements, or is FDA able to more efficiently determine this through other means, such as review of sponsor submissions or communications with sponsors? How does FDA most commonly assess compliance?
- 4. FDA's 2020 guidance explains that the agency prioritizes enforcement activities based on product risk, public health need, compliance history, and whether there are additional violations of clinical investigation requirements. Please explain how FDA's compliance and enforcement actions to date have aligned with this prioritization, taking into account the trials for which FDA has and has not pursued such actions.
- 5. Has FDA approved or cleared premarket submissions that do not include the certification of ClinicalTrials.gov compliance required by section 402(j)(5)(B) of the Public Health Service Act? If so, what is the basis for taking such action?

Thank you for your prompt attention to this matter. Should you have questions about these requests, please contact Stephen Holland and Juan Negrete of the Committee Democratic staff at (202) 225-2927.

Sincerely,

A handwritten signature in blue ink that reads "Frank Pallone, Jr." The signature is written in a cursive, flowing style.

Frank Pallone, Jr.
Ranking Member