April 11, 2023

The Honorable Frank Pallone, Jr.
Ranking Member
U.S. House of Representatives
Washington, DC 20515

Dear Ranking Member Pallone:

Thank you for your letter of January 19, 2023, regarding reporting of certain clinical trial results information to the ClinicalTrials.gov database. The Food and Drug Administration (FDA) and the National Institutes of Health (NIH) support and share the goal of increasing transparency of information about clinical trials through the ClinicalTrials.gov databank, which in turn may promote more efficient allocation of research funding by identifying gaps and avoiding duplication of effort. The databank may also help reduce publication and outcome reporting bias.

When considering the summary results information available on ClinicalTrials.gov, it is important to recognize that the information required to be submitted is not intended to be as comprehensive as the safety and efficacy data that are submitted to and reviewed by FDA as part of a medical product marketing application.

Because the information available on ClinicalTrials.gov is only a subset of the information submitted to FDA in a marketing application, it is generally not possible to draw conclusions about either the safety or the efficacy of FDA-regulated medical products based solely on the limited subset of public information that is available on ClinicalTrials.gov for any specific trial.

We offer responses to your specific questions below:

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?**

   Response:
   As of February 14, 2023, FDA has sent a total of 92 Pre-Notice of Noncompliance Letters (Pre-Notice Letters). Following publication of the Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11) in 2016, FDA implemented processes and procedures for identifying and evaluating potential noncompliance or noncompliance with the clinical trials registration and results information submission requirements. Subsequent to the implementation of those processes and procedures, FDA issued 77 Pre-Notice Letters and four Notices of Noncompliance regarding potential noncompliance and noncompliance, respectively, with the clinical trials registration and results information submission requirements. In addition, prior to implementation of the ClinicalTrials.gov Final

Rule, FDA issued 15 Pre-Notice Letters for potential noncompliance with the clinical trials registration or results information submission requirements.

The Pre-Notice Letters have been largely effective. Over 90 percent of Pre-Notice Letter recipients have submitted the required clinical trial information without the need for further action by FDA. The median time for responsible parties to submit the required clinical trial information is 26 days. In the few instances where FDA has issued a Notice of Noncompliance, the Notices have also been extremely effective. All of the Notice of Noncompliance recipients subsequently submitted the required clinical trial information.

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.

Response:

As of February 14, 2023, all Pre-Notice Letter recipients that FDA subsequently determined were not in compliance with the clinical trials registration and/or results information submission requirements have received a Notice of Noncompliance. FDA is currently reviewing and assessing the clinical trials referenced in six Pre-Notice Letters to determine whether there has been a violation and if so, FDA will issue a Notice of Noncompliance Letter to any non-compliant responsible party.

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?

Response:
To date, Pre-Notice Letters sent to responsible parties have been largely effective in securing compliance. Four responsible parties who did not come into full compliance following receipt of a Pre-Notice Letter received Notices of Noncompliance, and all four have submitted the required clinical trial information. FDA has not pursued civil money penalties (CMPs) or any other actions against such responsible parties.

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?

Response:
To the best of our knowledge, FDA has not issued any Pre-Notice Letters or Notices of Noncompliance to responsible parties with federal funding from an HHS agency or for which NIH was a 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?

Response:
When evaluating compliance rates, it is important to recognize that not all clinical trials registered on ClinicalTrials.gov are applicable clinical trials subject to the clinical trials registration and results information submission requirements. The databank includes a substantial number of records to which these requirements do not apply, such as observational studies, behavioral intervention studies, and phase 1 drug trials, among others. Indeed, the majority of trials registered on the ClinicalTrials.gov databank are not applicable clinical trials subject to the clinical trials registration and results information submission requirements.

For trials subject to the clinical trials registration and results information submission requirements, issuing Pre-Notice Letters for potential noncompliance and, where a decision of noncompliance has been made, Notices of Noncompliance, have been largely effective in securing compliance and improving submission of clinical trial information to ClinicalTrials.gov more broadly. As noted above, over 90% of Pre-Notice Letter recipients have submitted clinical trial information without the need for further action by FDA. FDA's approach to compliance and enforcement of the clinical trials registration and results information submission requirements is consistent with other FDA compliance programs, which generally prioritize activities using a risk-based approach. When deciding where to focus limited compliance resources, FDA considers which activities are likely to have the greatest public health impact and balances resource allocation to ClinicalTrials.gov with resource needs for other compliance programs, such as evaluating inspection reports of clinical investigators and other establishments to determine whether there appear to be violations of the law.

FDA continues to develop its ClinicalTrials.gov compliance program and is always looking at ways to refine its processes for identifying potential noncompliance and issuing Pre-Notice Letters and Notices of Noncompliance. We have taken several actions to enhance our compliance and enforcement program since the final ClinicalTrials.gov regulations went into effect in January 2017, including developing an internal analytics platform that supports Center surveillance activities related to ClinicalTrials.gov and establishing routine cross-Center compliance and enforcement policy coordination. These process improvements have increased program efficiency. However, there are no specific budget resources dedicated solely to ClinicalTrials.gov enforcement. As a result, Center staff must balance their ClinicalTrials.gov work with all other components of FDA's Bioresearch Monitoring (BIMO) program that may have greater and more direct public health impact.

f. Are there ways FDA may be able to assess violations more efficiently, for example with the assistance of automated processes? Please explain.

Response:
FDA continues to explore opportunities to assess violations of the clinical trials registration and results information submission requirements more efficiently, including by enhancing our internal analytics platform that supports Center surveillance activities related to ClinicalTrials.gov. This internal analytics platform incorporates data from FDA systems and

from ClinicalTrials.gov, providing one tool that Center BIMO staff can use to identify trials that appear to be subject to clinical trials registration and results information submission requirements and that may be noncompliant with those requirements. Although this internal analytics platform has made it easier to identify potential noncompliance, staff still must review non-public information to verify whether the clinical trials registration and results information submission requirements apply to each specific trial. This non-public information may be submitted to FDA in a variety of formats and is not typically readily accessible as data, thus requiring manual review. To the extent that automation or other IT solutions could make this information more readily available, it may further streamline surveillance activities. FDA is exploring such IT enhancements to our internal analytics platform. However, automation alone may not eliminate the need for manual review and confirmation.

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?**

Response: NIH is actively implementing processes to verify compliance with clinical trials registration and results information submission requirements by NIH grantees, including additional enhancements in response to an HHS Office of the Inspector General audit. Driving NIH's compliance activities is an automated quarterly report which identifies NIH grant awards registered in NIH's Human Subjects System (HSS), for which the results expected date has passed, so that NIH may identify and address potential noncompliance.

As of February 14, 2023, NIH Institutes and Centers (ICs) have sent initial notices of potential noncompliance letters to recipients for 317 clinical trials. The NIH Office of Policy for Extramural Research Administration (OPERA) has sent additional notices of potential noncompliance to recipients for 48 clinical trials where results information was not submitted in response to the initial NIH IC notice.

   b. **How many, or what percentage of, recipients of such communications have come into full compliance after receipt, and in what period of time?**

Response: As of February 14, 2023, of the 317 trials for which initial notices of potential noncompliance were sent to recipients, 267 trials (81.2 percent) were subsequently determined to be compliant. Specifically, of those, results information was submitted to ClinicalTrials.gov for 233 trials, and 34 trials were found to be compliant based upon further review and receipt of additional information from the recipient.

Of the 317 clinical trials referenced above, results information has not been submitted for 50 trials. Of those, 36 are within their allotted timeframe for providing a response, and with

regard to 14, NIH is proceeding towards enforcement action, which could include holds on current funding or withholding of future funding.

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.**

Response: As of February 14, 2023, NIH has not withheld or blocked any funding due to noncompliance with the clinical trials registration and results information submission requirements.

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.**

Response: NIH has not pursued any other remedies for failure to comply with any clinical trials registration and/or results submission requirements; however, NIH does take its responsibilities in facilitating compliance with these requirements seriously and is working to identify and resolve any instances of noncompliance.

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?**

Response: NIH has worked in close collaboration with partners within the HHS Office of General Counsel and the Food and Drug Administration to standardize NIH's approach across its ICs for verifying extramural grant recipient compliance with both the NIH Policy and regulatory requirements pursuant to the Food and Drug Administration Amendments Act (FDAAA) of 2007. The processes and enhancements NIH has implemented provide a robust and automated system for centralized tracking of registration and results reporting information, enabling NIH to take action upon the notification of a potential violation. To support its process, the NIH has enabled new internal quarterly reporting to NIH ICs of all NIH grant-funded clinical trials that have not submitted results information to ClinicalTrials.gov by the required deadline. In addition, FDA refers reports of potentially noncompliant clinical trials with an apparent association to NIH, so that NIH can verify if the clinical trial has NIH grant-funding to take further appropriate action.

The Intramural Research Program (IRP) developed and published NIH Policy Manual Chapter 3007 (MC 3007), "Clinical Trial Registration and Results Information Reporting." It establishes responsibilities and procedures for registration and results information reporting of IRP-conducted or supported clinical trials to ClinicalTrials.gov and establishes consequences in the event of noncompliance. As of February 14, 2023, since the implementation of MC 3007 in January 2022, all intramural trials that have results expected have submitted results information to ClinicalTrials.gov. The IRP's

experience to date with MC 3007 suggests the new policy is an effective tool to facilitate intramural compliance with reporting requirements.

NIH will continue to assess compliance statistics over time to ensure that responsible parties of NIH-funded clinical trials comply with requirements under the NIH Policy and regulations issued pursuant to FDAAA.

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?**

   Response: No, it is generally not necessary to conduct an inspection or receive a complaint to determine whether a sponsor or trial is subject to and in compliance with the clinical trials registration and results information submission requirements. FDA's primary means to identify potential noncompliance is through surveillance, which typically does not involve inspection. One surveillance approach includes use of an internal analytics platform that incorporates data from ClinicalTrials.gov and FDA systems to identify potential cases of noncompliance, which are then further evaluated by staff to confirm applicability of the requirements and whether potential noncompliance exists, and to prioritize compliance and enforcement action based on risk criteria.

   FDA has, however, integrated ClinicalTrials.gov compliance as a fundamental part of our BIMO inspection programs (e.g., inspections conducted of sponsors for review of information submitted to research and marketing applications). We have generally found a very high-level of compliance during inspections. Similarly, FDA reviews individual complaints received about potential noncompliance, but those types of complaints are small and have resulted in only three Pre-Notice Letters being issued.

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.**

   Response:
   FDA's risk-based approach to ClinicalTrials.gov compliance has been evolving over the last several years, and FDA continues to refine its processes for identifying studies for which ensuring compliance with the clinical trials registration and results submission requirements may be of greatest public health benefit. Although many of the Pre-Notice Letters and Notices of Noncompliance issued meet the risk-criteria, we continue to improve the alignment of our surveillance activities with those criteria.

FDA's current approach to compliance and enforcement of the clinical trials registration and results information submission requirements is consistent with other FDA compliance programs, which generally follow a risk-based approach to prioritization of activities. Examples of risk-based factors that FDA now uses when evaluating potential noncompliance with the requirements include:

- The vulnerability of the population under study in the clinical trial (for example, pediatric or cognitively impaired participants);
- The nature of the product involved in the trial (for example, cytotoxic, permanent implant, new molecular entities, new therapeutic biological products);
- Whether the product involved in the trial is intended to address a significant public health need (e.g., COVID-19, monkeypox);
- The risks to subjects participating in the trial;
- Whether the product involved is approved or unapproved;
- Whether ClinicalTrials.gov noncompliance exists in conjunction with noncompliance with other statutory or regulatory requirements pertaining to the conduct of the trial; and
- Trials for which FDA requires submission of an application (e.g., investigational new drug application (IND) or investigational device exemption (IDE) application), because these are inherently higher risk studies.

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?**

Response: FDA would like to clarify that, although section 402(j)(5)(B) of the Public Health Service (PHS) Act requires that a certification of ClinicalTrials.gov compliance accompany certain drug, biological product, and device applications and submissions, neither Title VIII of FDAAA, nor section 402(j) of the PHS Act, nor the implementing regulations in 45 C.F.R. part 11, provide a legal basis for FDA to refuse to approve, license, or clear marketing applications or submissions based on the absence of the certification, nor does such a legal basis exist in the Federal Food, Drug, and Cosmetic (FD&C) Act or its implementing regulations. However, failing to submit or knowingly submitting a false certification to FDA is a prohibited act under section 301(jj)(1) of the FD&C Act.

Consistent with our approach across compliance programs, FDA utilizes a risk-based approach to determine whether to take regulatory or enforcement action. For example, when considering whether to take action, FDA prioritizes failure to submit the certification required under section 402(j)(5)(B) of the PHS Act in conjunction with noncompliance with other statutory and/or regulatory violations over failure to submit the certification without other noncompliance. This risk-based approach helps ensure that any regulatory or enforcement action is consistent with FDA's public health mission and how it approaches other compliance programs when potential or actual non-compliance is identified.

Thank you, again, for contacting us regarding this important matter.

Sincerely,

Andi Lipstein Fristedt
Deputy Commissioner for
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U.S. Food and Drug Administration

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