



Collaboration for Research Integrity and Transparency

A PROGRAM OF YALE LAW SCHOOL, YALE SCHOOL OF MEDICINE AND THE YALE SCHOOL OF PUBLIC HEALTH

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Via Electronic Submission

Division of Dockets Management (HFA-305)
Food and Drug Administration
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Docket No. FDA-2018-D-0787

Yale Collaboration for Research Integrity and Transparency Comments on FDA’s Draft Guidance Entitled “Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank: Guidance for FDA Staff, Responsible Parties, and Submitters of Certain Applications and Submissions to FDA”

The Yale Collaboration for Research Integrity and Transparency (“CRIT”) submits these comments on the Food and Drug Administration’s (“FDA” or “the agency”) Draft Guidance entitled “Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank: Guidance for FDA Staff, Responsible Parties, and Submitters of Certain Applications and Submissions to FDA,” published on September 21, 2018 (“draft guidance”).¹

CRIT is an inter-disciplinary initiative of Yale Law School, Yale School of Public Health, and the Yale School of Medicine launched in 2016. CRIT is dedicated to promoting health by improving the integrity and transparency of biomedical and clinical research.

¹ 83 Fed. Reg. 47926-27 (Sept. 21, 2018). Agency/Docket No. FDA-2018-D-0787; Document No. 2018-20560



Collaboration for Research Integrity and Transparency

A PROGRAM OF YALE LAW SCHOOL, YALE SCHOOL OF MEDICINE AND THE YALE SCHOOL OF PUBLIC HEALTH

We appreciate FDA's draft guidance to the extent it marks an effort by the agency to begin enforcing responsible parties' statutory obligations to register and submit clinical trial data to the ClinicalTrials.gov Data Bank. However, we believe that the draft guidance does not go far enough to bring FDA, the National Institutes of Health ("NIH"), and the entire Department of Health and Human Services ("HHS") into compliance with the Food and Drug Administration Amendments Act of 2007 ("FDAAA"). We urge FDA, along with NIH and HHS, to issue a joint guidance document that more closely adheres to the letter and spirit of FDAAA and to promptly begin enforcement activity that meets the obligations imposed by Congress.

Although FDAAA was enacted in 2007, the draft guidance constitutes FDA's first and (to date) only guidance document detailing not only how it may *penalize* responsible parties' noncompliance with statutory and regulatory obligations but also whether and how it will *identify* noncompliance in the first instance.²

The procedures proposed in the draft guidance are inadequate for three reasons.

1. FDA Monitoring of Compliance Is Mandatory, Not Discretionary.

First, FDAAA unambiguously *mandates* that FDA monitor responsible parties' compliance with various reporting requirements, including trial registration, submission

² Draft guidance at 1-2 ("The guidance document addresses the following questions: How do the Centers intend to identify whether responsible parties have failed to submit required clinical trial registration and/or results information to the ClinicalTrials.gov data bank or submitted false or misleading information to the data bank, or whether submitters have failed to submit to FDA the certification required by section 402(j)(5)(B) of the PHS Act or knowingly submitted a false certification to FDA?").



Collaboration for Research Integrity and Transparency

A PROGRAM OF YALE LAW SCHOOL, YALE SCHOOL OF MEDICINE AND THE YALE SCHOOL OF PUBLIC HEALTH

of results, and certification.³ Yet the draft guidance appears to suggest that monitoring compliance is optional. “The Centers generally intend to identify violations of the FD&C Act’s requirements relating to the ClinicalTrials.gov data bank through evidence collected during inspections conducted as part of FDA’s Bioresearch Monitoring Program (BIMO). . . . In general, the Centers may also identify violations as a result of complaints received by the agency.”⁴ The guidance should be clarified to recognize that FDA’s responsibility to monitor compliance is mandatory, not discretionary.

2. Monitoring of Compliance through BIMO Is Inadequate.

Second, even if followed, the procedures outlined in the draft guidance will not adequately identify all responsible parties who are noncompliant with their reporting obligations because FDA will largely rely on its Bioresearch Monitoring Program (“BIMO”).⁵ We expect BIMO to be insufficient for this purpose in several ways.

³ See generally 42 U.S.C. § 282(j). For example, § 282(j)(3)(F) mandates that the “[t]he Commissioner of Food and Drugs shall notify the Director of NIH when there is an action described in subparagraph (E)(iv) or item (aa), (bb), or (cc) of subparagraph (E)(v)(I) with respect to an application or a report that includes a certification required under paragraph (5)(B) of such action [e.g., initial approval of a drug or device, or approval of a new use of a drug or device] not later than 30 days after such action.” Section 282(j)(5)(A)(ii) specifies that the FDA Commissioner, “as applicable, shall verify that the clinical trial information for each applicable clinical trial for which a grantee is the responsible party has been submitted under paragraphs (2) and (3) before releasing any remaining funding for a grant or funding for a future grant to such grantee.”

⁴ Draft guidance at 4.

⁵ FDA Compliance Program Guidance Manual 7348.810 Sponsors, Contract Research Organizations and Monitors (“Guidance Manual 7348.810”), available at <https://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/ucm133770.pdf> (last visited October 10, 2018). See draft guidance at 4 (“The Centers generally intend to identify violations of the FD&C Act’s requirements relating to the ClinicalTrials.gov data bank through evidence collected during inspections conducted as part of FDA’s Bioresearch Monitoring Program (BIMO). How FDA will collect information to assess compliance with these requirements is described in FDA’s Bioresearch Monitoring Compliance Program for Sponsors, Contract Research Organizations and Monitors.”).



Collaboration for Research Integrity and Transparency

A PROGRAM OF YALE LAW SCHOOL, YALE SCHOOL OF MEDICINE AND THE YALE SCHOOL OF PUBLIC HEALTH

For one, BIMO will not capture all relevant applicable clinical trials (“ACTs”). BIMO incorporates the HHS Final Rule (42 CFR Part 11) interpreting FDAAA, and this Final Rule improperly excludes any applicable clinical trial with a primary completion date before January 18, 2017 when the drug or device studied in the trial was approved after the primary completion date.⁶ To the extent that the Final Rule and, by extension, BIMO exclude such trials, they are inconsistent with the mandate of FDAAA.⁷ If FDA intends to rely on BIMO alone to identify potential violations of FDAAA’s reporting requirements, FDA will miss violations arising from applicable clinical trials with a primary completion date before January 18, 2017 and an approval date on or after January 18, 2017.

Second, BIMO will fail to capture additional relevant ACTs because BIMO inspections are triggered only under certain limited circumstances. The BIMO procedures specified in the section entitled “REGISTRATION OF STUDIES ON CLINICALTRIALS.GOV” appear to rely on a responsible party’s submission of Form FDA 3674 to trigger inspection of compliance with FDAAA’s registration and reporting requirements.⁸ Such reliance may improperly exclude ACTs that are subject to FDAAA’s requirements but that concern earlier-approved drugs and devices not covered by recent submissions of Form FDA 3674. In addition, to the extent BIMO ties

⁶ See Guidance Manual 7348.810 at 5 (citing and incorporating the Final Rule, including its definition of “applicable clinical trials” for which “clinical trial results in formation [must] be submitted,” codified at 42 CFR § 11.42).

⁷ See 42 U.S.C. § 282(j)(5)(E).

⁸ See Guidance Manual 7348.810 at 4-7.



Collaboration for Research Integrity and Transparency

A PROGRAM OF YALE LAW SCHOOL, YALE SCHOOL OF MEDICINE AND THE YALE SCHOOL OF PUBLIC HEALTH

inspection of compliance with FDAAA to site visits by field inspectors,⁹ BIMO is additionally insufficient because many relevant ACTs may not be subject to such visits.

Moreover, FDAAA requires a responsible party to *certify* to FDA, upon submitting any application for approval a drug (including biologics) or medical device, that the responsible party is in compliance with its registration and reporting obligations.¹⁰ FDAAA imposes on FDA an affirmative obligation to verify whether certifications filed with the agency are accurate or false, and to take appropriate enforcement action if false certifications are filed.¹¹ Yet BIMO specifies no particular procedure for verification of such certifications.¹²

For these reasons, FDA must expand its monitoring beyond inspections conducted as part of BIMO to capture *all* relevant ACTs and to revise the draft guidance accordingly.

3. FDA and NIH Must Work Together To Post Public Notices of Noncompliance.

Finally, the draft guidance must be revised to reflect the fact that FDA and NIH are required, by both FDAAA and the Final Rule, to work together to make specific, statutorily prescribed public notices of noncompliance.

FDAAA mandates that FDA and NIH must work together to post public notices of noncompliance on ClinicalTrials.gov. *See* 42 U.S.C. § 282(j)(5)(E)(i)-(v). In addition

⁹ *See* Guidance Manual 7348.810 at 1-3.

¹⁰ *See* 42 U.S.C. § 282(j)(5)(B).

¹¹ *See* 42 U.S.C. § 282(j)(5).

¹² *See* BIMO at Part III, 6-7.



Collaboration for Research Integrity and Transparency

A PROGRAM OF YALE LAW SCHOOL, YALE SCHOOL OF MEDICINE AND THE YALE SCHOOL OF PUBLIC HEALTH

to what FDAAA itself requires, the Final Rule clearly apportions responsibility to both NIH and FDA for monitoring and enforcement of compliance with clinical trial registration and results reporting. According to the Final Rule, NIH is responsible for administering the public ClinicalTrials.gov website, including accepting registration of clinical trials, granting or denying extensions to responsible parties' requirements for results reporting, receiving reports of trial results, determining whether reported results are adequate, referring possible noncompliant trials to FDA for investigation, and posting notices of noncompliance on ClinicalTrials.gov.¹³ According to the Final Rule, FDA is responsible for investigating noncompliance, reporting noncompliant trials to NIH for public posting, and otherwise enforcing compliance.¹⁴

Yet the draft guidance is entirely silent on public notices¹⁵ and entirely silent on FDA's broader obligation to work cooperatively with NIH (and other parts of HHS) to enforce the registration and reporting requirements. The draft guidance's silence on cooperation with NIH to issue public notices of noncompliance is particularly concerning because the NIH Director has indicated to Congress that FDA and NIH bear joint responsibility for verification and enforcement of compliance with FDAAA.¹⁶

¹³ See, e.g., 42 C.F.R. §§ 11.2, 11.4, 11.35, 11.44, 11.52, 11.54, 11.62, 11.64, 11.66.

¹⁴ See, e.g., 42 C.F.R. § 11.66.

¹⁵ The draft guidance contemplates notices of noncompliance sent directly to responsible parties, but not notices of noncompliance made available to the public at ClinicalTrials.gov.

¹⁶ "Both the NIH and FDA have responsibilities related to compliance and enforcement of the provisions of Section 801 of the FDAAA. FDA has authority to enforce the law's requirements for all applicable clinical trials and to assess civil monetary penalties for non-compliance. The NIH is responsible for verifying that NIH grantees have submitted the required information before releasing any remaining funds and for posting non-compliance information." Dr. Francis Collins, Director, National Institutes of Health, letter to Hon. Charles E. Grassley, Chair, Committee on the Judiciary, U.S. Senate (February 5, 2016), available at



Collaboration for Research Integrity and Transparency

A PROGRAM OF YALE LAW SCHOOL, YALE SCHOOL OF MEDICINE AND THE YALE SCHOOL OF PUBLIC HEALTH

The draft guidance should be revised accordingly. To the extent that FDA believes it is NIH's obligation, and not FDA's, to post public notices on ClinicalTrials.gov, the draft guidance should be revised to specify that each and every instance of noncompliance identified by FDA be reported promptly to NIH, so that NIH may post a public notice.

Having identified these specific inadequacies in the draft guidance, CRIT also expresses its concern over the general lack of effort made by FDA, NIH, and HHS, to date, to verify and enforce FDAAA requirements. As far as CRIT knows, the sole enforcement efforts by FDA and NIH to date consist of a "pilot enforcement project in 2013 and 2014 that resulted in the issuance of 14 pre-notice of non-compliance letters" by FDA.¹⁷ Since all 14 of the letter recipients subsequently complied with FDAAA requirements, no further action was taken. Notably, this pilot project was conducted years before the Final Rule became effective.

CRIT hopes that the draft guidance marks the beginning of genuine enforcement efforts. FDA, along with NIH and HHS, must, in appropriate cases, enforce compliance with FDAAA using all of the tools provided by the statute. Public notices of noncompliance are critical, as they permit numerous stakeholders—clinicians, researchers, professional societies and other guideline organizations, ethicists, journal

<https://www.grassley.senate.gov/sites/default/files/news/upload/2016-02-05%20NIH%20to%20CEG%20%28clinical%20trial%20reporting%29.pdf> (last visited October 11, 2018).

¹⁷ Dr. Francis Collins, Director, National Institutes of Health, letter to Hon. Charles E. Grassley, Chair, Committee on the Judiciary, U.S. Senate (February 5, 2016).



Collaboration for Research Integrity and Transparency

A PROGRAM OF YALE LAW SCHOOL, YALE SCHOOL OF MEDICINE AND THE YALE SCHOOL OF PUBLIC HEALTH

editors, others in the research community, agencies providing grant funding for clinical trials, patients, and others—reliable and transparent access to clinical research and results on the safety and effectiveness of medical products. Public notices of noncompliance promote more informed decision-making in clinical practice and ultimately better healthcare.

We thank the agency for the opportunity to comment.

Sincerely,

Margaret E. McCarthy
Executive Director