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**Citizen Petition from Universities Allied for Essential Medicines North America
to the Food & Drug Administration
for Increased Enforcement of the ClinicalTrials.gov Reporting Requirements
in the Food and Drug Administration Amendments Act of 2007**

Table of Contents

Contents

A. Actions Requested.....	4
B. Statement of Grounds.....	4
I. Legal Grounds:.....	5
1. The Law of Citizen Petitions.....	5
2. The Law of ClinicalTrials.gov	6
3. The August 2020 Guidance.....	8
II. Factual Grounds:	10
1. Compliance with Clinical Trial Reporting Requirements Is Hugely Deficient	10
2. Compliance with Clinical Trial Reporting Requirements Is Deficient Because FDA’s Enforcement Has Been Minimal and Unfocused	12
3. FDA’s Minimal Enforcement Efforts Demonstrate That Enforcement Improves Compliance.....	14
4. Patients, Lawmakers and Researchers Agree that More and Better Enforcement Is Needed.....	15
5. UAEM Has Attempted to Bring These Problems to the Attention of the FDA, But Has Been Ignored.....	19
III. Argument and Relief Requested:	20
1. FDA Needs to Improve Its Efforts to Enforce Section 801 of FDAAA	20
2. FDA Should Issue New Guidance with a New Enforcement Prioritization Framework.....	21
a. Rescission of FDA’s 2020 Guidance and Issuance of New Guidance Are Appropriate	21
b. FDA’s New Guidance Should Commit the Agency to a New, Improved, and Expanded Enforcement Prioritization Framework	22
c. UAEM Recommends That FDA’s New Guidance Adopt UAEM’s Improved and Expanded Enforcement Prioritization Framework	23
UAEM’s Proposed Enforcement Prioritization Framework:	23
1. NIH-funded trials of FDA-approved products	23
2. Trials producing data which FDA relied upon when approving currently-FDA-approved products.....	25
3. NIH-funded trials of unapproved products	26
4. Phase IV trials of FDA-approved products subject to postmarketing commitments and requirements.....	26

5. Other trials of FDA-approved products	26
6. Trials for unapproved products of high importance.....	26
7. Remaining Phase III trials for unapproved products.....	27
8. Remaining Phase II trials for unapproved products	27
3. FDA Should Make Pre-Notices Public via a Public Dashboard	28
C. Environmental Impact	28
D. Economic Impact	28
E. Certification	28

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Universities Allied for Essential Medicines North America (“UAEM”) submits, under 21 C.F.R. § 10.30, this petition concerning 42 U.S.C. § 282, Section 801 of the Food and Drug Administration Amendments Act of 2007 (“FDAAA”). This petition requests that the Commissioner of Food and Drugs take three actions:

- (1) increase enforcement of the clinical trial results reporting requirements within FDAAA;
- (2) publish a new guidance document explaining how the Food and Drug Administration (“FDA”) will prioritize its enforcement efforts; and
- (3) create a public dashboard of Preliminary Notices of Noncompliance (“Pre-Notices”) sent to potentially noncompliant parties responsible for reporting clinical trial results

A. Actions Requested

UAEM requests that the Commissioner take the following administrative actions:

1. Order and organize offices to increase enforcement of 42 U.S.C. § 282(j), issuing more Pre-Notices and Notices of Noncompliance and imposing civil money penalties when appropriate;
2. Order the drafting and issuance of a new guidance document which explains how FDA will focus its enforcement efforts. This guidance should clearly outline a prioritization framework for the enforcement of 42 U.S.C. § 282(j); and
3. Create a public dashboard of Pre-Notices sent by FDA.

B. Statement of Grounds

UAEM is an international nonprofit organization committed to promoting health equity and access to medicines. Its efforts shape approaches to academic patenting and licensing, research and development, and access to biomedical research data.

UAEM North America brings this citizen petition as part of its ongoing initiative to increase data transparency in biomedical research.¹ In 2019 and 2021, UAEM North America published reports regarding the state of transparency in clinical trials.² The studies detailed in these reports generated data on compliance rates with clinical trial data-sharing rules among universities and other trial administrators. These studies found that despite some improvements in reporting rates over the past few years, noncompliance remains widespread.³ Individual

¹ *Clinical Trials Transparency: U.S. Universities Performance & Trends*, Universities Allied for Essential Medicines (Oct. 27, 2022), <https://www.altreroute.com/clinicaltrials/>.

² Universities Allied for Essential Medicines & TranspariMED, *Clinical Trials Transparency at U.S. Universities* (2019), <https://www.altreroute.com/clinicaltrials/assets/download/UniversityTransparencyReport2019.pdf>; Universities Allied for Essential Medicines, *Clinical Trials Transparency at U.S. Universities* (2021), https://www.altreroute.com/clinicaltrials/assets/download/Clinical_Trials_Transparency_Report_UAEM_v5.pdf.

³ UAEM, *supra* note 1 at 2; UAEM & TranspariMED, *supra* note 2 at 4.

members of UAEM North America have contributed to scholarship and public education about reporting noncompliance as well.⁴

I. Legal Grounds:

1. The Law of Citizen Petitions

Citizens' right to petition the government originates from the First Amendment. Originally understood as the right to petition the federal legislature and the courts, it has evolved to include the states and executive branch. The scope of citizens' right to petition the government was formalized and expanded in the Administrative Procedure Act ("APA").

Today, Section 553(e) of the APA states: "Each agency shall give an interested person the right to petition for the issuance, amendment, or repeal of a rule."⁵ According to the *Attorney General's Manual on the Administrative Procedure Act*,⁶ the APA broadly defines the term "rule" to cover a variety of agency actions, including numerous actions that are not subject to the APA's notice-and-comment rulemaking procedures. Such actions include agency interpretive rules and policy statements—categories that are often colloquially referred to as "guidance documents"—and rules of agency organization, procedure, and practice.⁷ Citizens may also petition agencies to enforce rules that agencies themselves have promulgated.⁸

This petition is directed at FDA. FDA has promulgated rule 21 C.F.R. 10.30 ("Citizen petition"), laying out a framework for petitions submitted to FDA and committing the agency to a response within 180 days of receipt of the petition. This petition has been prepared in accordance with this framework and follows its directives.

⁴ Livestream: *Protecting Patients Through Clinical Trials Transparency*, Action Network (Oct. 27, 2022), <https://actionnetwork.org/events/livestream-protecting-our-patients-through-clinical-trials-transparency?nowrapper=true&referrer=&source=>; Joe Rabinovitsj et al., Opinion, *COVID-19 lesson: New FDA chief, when chosen, must crack down on clinical trial transparency*, The Baltimore Sun (May 13, 2021), <https://www.baltimoresun.com/opinion/op-ed/bs-ed-op-0514-fda-importance-20210513-x6cuesxc2ze5rogpkwledqlem-story.html>; Christopher J. Morten et al., Opinion, *55 years to fulfill a records request? Clearly the FDA needs serious reform of its data-sharing practices*, Washington Post (Dec. 13, 2021), <https://www.washingtonpost.com/opinions/2021/12/13/55-years-fulfill-records-request-clearly-fda-needs-serious-reform-its-data-sharing-practices/>; Reshma Ramachandran et al., *Strengthening the FDA's Enforcement of ClinicalTrials.gov Reporting Requirements*, 326 JAMA 2131 (Nov. 12, 2021), https://scholarship.law.columbia.edu/faculty_scholarship/3314/; Anmol Gupta, *Canada has a problem with clinical trials: We cannot see them*, The Bell (Oct. 17, 2022), https://maxpolicy.substack.com/p/canada-has-a-problem-with-clinical?utm_campaign=post&utm_medium=web.

⁵ 5 U.S.C. § 553(e).

⁶ Tom C. Clark, *Attorney General's Manual on the Administrative Procedure Act* 38 (U.S. Dep't of Just., 1947).

⁷ Maeve P. Carey, Congr. Rsch. Serv., *Petitions for Rulemaking: An Overview* 4 (2020).

⁸ See, e.g., *Petition to the FDA to Initiate Disqualification Procedures Against Hennepin County Medical Center Researchers and IRB for Unethical High-Risk Clinical Trials*, Public Citizen (Nov. 17, 2021), <https://www.citizen.org/article/petition-to-the-fda-to-initiate-disqualification-procedures-against-hennepin-county-medical-center-researchers-and-irb-for-unethical-high-risk-clinical-trials/>.

2. The Law of ClinicalTrials.gov

Congress enacted Section 801 of FDAAA in 2007, requiring that the Secretary of the United States Department of Health and Human Services (“HHS”), “acting through the Director of NIH [National Institutes of Health],” expand the pre-existing clinical trials registry data bank “[t]o enhance patient enrollment and provide a mechanism to track subsequent progress of clinical trials.”⁹ Congress required the National Institutes of Health (“NIH”) to begin collecting and disseminating information not just on clinical trial registration, but also on trial design and results.¹⁰ Congress further mandated that “[t]he Director shall ensure that the registry data bank is made publicly available through the internet.”¹¹ The result of these directives is today’s ClinicalTrials.gov: the world’s largest publicly accessible database of clinical trial protocols, results, and other trial data.¹²

FDAAA and its implementing regulations impose reporting requirements¹³ on certain “responsible parties”¹⁴ for covered clinical trials, called “applicable clinical trials.”¹⁵ Prompt reporting of information is crucial to realize the policy goals behind FDAAA. As NIH announced when finalizing the rule implementing FDAAA:

Clinical trials are essential for the translation of research advances to new approaches to prevention and treatment. Volunteers who take part in clinical trials often do so with no assurance of personal benefit, but with the expectation that their involvement will add to the growing body of knowledge about health and disease, and thus may help others someday. For that to be realized, all trial results information needs to be publicly reported in a timely fashion—and yet we know that doesn’t always happen.¹⁶

FDA and its current Commissioner have similarly acknowledged the need for prompt, complete reporting of trial data to ClinicalTrials.gov to fulfill the legislative goals of FDAAA. FDA’s page

⁹ 42 U.S.C. § 282(j)(2)(A)(i).

¹⁰ 42 U.S.C. § 282(j)(3).

¹¹ 42 U.S.C. § 282(j)(3).

¹² Rebecca Williams, *Celebrating 20 Years of ClinicalTrials.gov and Looking to the Future*, National Institutes of Health (Jan. 7, 2020), <https://nexus.od.nih.gov/all/2020/01/07/celebrating-20-years-of-clinicaltrials-gov-and-looking-to-the-future/>.

¹³ 42 C.F.R. § 11.2-11.66 (The exact reporting requirements around clinical trials depend on the type of trial at issue).

¹⁴ U.S. Food & Drug Administration, Guidance Document, *Civil Money Penalties Relating to ClinicalTrials.gov Data Bank* at 3 (Aug. 2020) [hereinafter “FDA Guidance Document (2020)”] (defining a responsible party as the “individual or entity required to submit clinical trial information for an applicable clinical trial, as defined in 42 CFR 11.10(a).”)

¹⁵ For definition of the “applicable clinical trials,” see 42 U.S.C. § 282(j); 42 C.F.R. §§ 11.10(a), 11.42; *Seife v. U.S. Dep’t of Health & Human Servs.*, 440 F. Supp. 3d 254 (2020).

¹⁶ Kathy L. Hudson & Francis S. Collins, *Clinical Trials: Sharing of Data and Living Up to Our End of the Bargain*, NIH Director’s Blog (Sept. 16, 2016), <https://directorsblog.nih.gov/2016/09/16/clinical-trials-sharing-of-data-and-living-up-to-our-end-of-the-bargain/>; see also Clinical Trials Registration and Results Information Submission, 81 Fed. Reg. 64,981, 64,985 (Sept. 21, 2016) (describing the public health and scientific benefits of required disclosure of information on ClinicalTrials.gov).

on “FDA’s Role” in governing “ClinicalTrials.gov Information” recognizes that FDAAA was designed to “promote transparency of clinical research to trial participants and the public.”¹⁷ Commissioner Califf wrote in 2021:

Out-of-date, incomplete, or inaccurate trial information can distort understanding of the evidence base and the research landscape. The [ClinicalTrials.gov] database is not only an information resource for individual clinical trials, but also essential for identifying all trials studying particular research questions. For example, without ClinicalTrials.gov, there would be no way to know how many COVID-19 trials had been initiated, what drugs or other interventions were being evaluated, when the trials would be completed, and, ultimately, what the trials found.¹⁸

UAEM agrees wholeheartedly with Commissioner Califf’s conclusion that “the trial registration and results information in ClinicalTrials.gov is only as good as the quality, accuracy, and timeliness of the data submitted by researchers and trial sponsors.”¹⁹ The purpose of FDAAA cannot be actualized unless high-quality clinical trial results data are submitted consistently and promptly by trials’ responsible parties.

To ensure that FDAAA’s reporting requirements are met, Congress vested authority in HHS to take a wide range of measures to punish noncompliance by responsible parties, including mandatory withholding of grant funds,²⁰ imposing civil monetary penalties,²¹ and recommending criminal prosecution.²² The Secretary of HHS subsequently delegated this enforcement authority to the FDA Commissioner.²³ Thus, responsibility for the success of ClinicalTrials.gov today rests in FDA’s hands.

FDA in turn delegates some enforcement mechanisms to NIH by communicating to NIH which trial sponsors have received Notices of Noncompliance. NIH publishes this information on ClinicalTrials.gov for public access. NIH is further involved in the enforcement process by maintaining a list of delinquent trial sponsors (informally called the “Problems List”), which it may share with FDA.²⁴ NIH could play a larger role.²⁵ Acknowledging this, NIH committed

¹⁷ *FDA’s Role: ClinicalTrials.gov Information*, U.S. Food & Drug Administration (Mar. 7, 2022), <https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/fdas-role-clinicaltrialsgov-information>.

¹⁸ Deborah A. Zarin & Robert M. Califf, Invited Commentary, *Trial Reporting and the Clinical Trials Enterprise*, 181(8) *JAMA Intern. Med.* 1131-32 (2021), <https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2780023>.

¹⁹ *Id.*

²⁰ 42 U.S.C. § 282(j)(5)(A)(i); 42 C.F.R. § 11.66(c).

²¹ 21 U.S.C. § 333(f)(3).

²² 21 U.S.C. § 333(a); *see also* 21 U.S.C. § 336.

²³ Delegation of Authority, 77 Fed. Reg. 59196 (Sept. 5, 2012).

²⁴ NIH publishes a “PRS User’s Guide.” *PRS User’s Guide*, <https://prsinfo.clinicaltrials.gov/prs-users-guide.html>. (“PRS” refers to the ClinicalTrials.gov Protocol Registration and Results System.) According to Section 8.1.2 of the PRS User’s Guide, NIH maintains a list of trials with “FDAAA 801 Problems,” including trials missing results information: “PRS flags records for possible FDAAA or Final Rule issues (in the Problems column of the Record List on the PRS home page) to help Responsible Parties identify trials that are missing one or more FDAAA-required registration data elements.” *Id.*

itself in 2022 to increase enforcement by withholding research funding to institutions that do not comply with FDAAA.²⁶ This could be impactful because NIH is the largest public financial sponsor of all health research.²⁷

3. The August 2020 Guidance

In 2020, FDA issued a guidance document, *Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank* (“the 2020 guidance”), outlining its plans for enforcing clinical trial data reporting requirements under FDAAA.²⁸ The 2020 guidance specifies that it represents the collective thinking of FDA’s Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, and Center for Devices and Radiological Health (hereafter, “Centers”).²⁹

The 2020 guidance serves two overlapping purposes. First, it informs the parties responsible for reporting clinical trials’ data (“responsible parties”) of their obligations and potential liabilities under FDAAA and its companion provisions, detailing the process through which the Centers can notify responsible parties about noncompliance with reporting requirements and seek civil money penalties under § 303(f)(3) of the Federal Food, Drug, and Cosmetic Act (“FDCA”).³⁰ Second, the 2020 guidance informs the broader public of the agency’s methods for monitoring and enforcing noncompliance. According to the 2020 guidance, the Centers “generally intend to identify violations of [FDAAA’s] requirements relating to the ClinicalTrials.gov data bank through evidence collected during inspections conducted as part of FDA’s Bioresearch Monitoring Program (“BIMO”).”³¹ The 2020 guidance thus reveals that FDA has chosen to place responsibility for monitoring and enforcing compliance with ClinicalTrials.gov’s reporting requirements predominantly with BIMO.

According to FDA, BIMO “is a comprehensive program of on-site inspections, data audits, and remote regulatory assessments designed to monitor all aspects of the conduct and reporting of FDA regulated research,” and it implements this agenda through several multi-Center compliance programs.³² BIMO is part of FDA’s Office of Regulatory Affairs, FDA’s “lead office for all agency field activities.”³³ BIMO has many responsibilities other than

²⁵ Department of Health and Human Services Office of Inspector General, *The National Institutes of Health did not ensure that all clinical trial results were reported in accordance with federal requirements* 9-10 (Aug. 2022), <https://oig.hhs.gov/oas/reports/region6/62107000.pdf>.

²⁶ 42 U.S.C. § 282(j)(5)(A); Kathy L. Hudson & Francis S. Collins, *Sharing and Reporting the Results of Clinical Trials*, JAMA (Jan. 27, 2015), <https://jamanetwork.com/journals/jama/fullarticle/1939045>.

²⁷ Roderik F. Viergever & Thom C. C. Hendriks, *The 10 largest public and philanthropic funders of health research in the world: what they fund and how they distribute their funds*, 14 Health Rsch. Pol’y & Sys. 12, Table 1 (2016), <https://health-policy-systems.biomedcentral.com/articles/10.1186/s12961-015-0074-z#citeas>.

²⁸ FDA Guidance Document (2020).

²⁹ *Id.* at 1.

³⁰ *Id.* at 1-2.

³¹ *Id.* at 4.

³² U.S. Food & Drug Administration, *Bioresearch Monitoring Program Information* (Aug. 4, 2022), <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/fda-bioresearch-monitoring-information/bioresearch-monitoring-program-information>.

³³ U.S. Food & Drug Administration, *Office of Regulatory Affairs* (June 11, 2021), <https://www.fda.gov/about-fda/fda-organization/office-regulatory-affairs>.

stewardship of ClinicalTrials.gov. In fact, of the many compliance programs described on FDA's website as parts of BIMO's portfolio,³⁴ only one program focuses directly on data auditing, and the guidelines for that program do not discuss reporting requirements under FDAAA.³⁵

The 2020 guidance provides FDA's most detailed public statement on the agency's procedure for monitoring and enforcing compliance with FDAAA's clinical trial data reporting rules. The 2020 guidance reveals little concrete information on how BIMO and other FDA programs monitor compliance with FDAAA. However, the 2020 guidance does refer readers³⁶ to FDA's publication on FDA's Bioresearch Monitoring Compliance Program for Sponsors, Contract Research Organizations and Monitors, which confirms that evaluating compliance with FDAAA is part of the official inspection process that BIMO inspectors are supposed to perform.³⁷

According to the 2020 guidance, the procedure for enforcement is as follows. When a Center identifies a trial in potential violation of its reporting requirements, the first step of formal enforcement is sending a Preliminary Notice of Noncompliance ("Pre-Notice") Letter to the clinical trial's responsible party.³⁸ The Pre-Notice Letter notifies the responsible party of the potential violation and requests actions necessary to rectify the violation, such as submitting required clinical results information to the ClinicalTrials.gov data bank.³⁹ If thirty days pass without necessary action⁴⁰ from the clinical trial's responsible party, the Center "intends to review the information submitted to the ClinicalTrials.gov data bank for that applicable clinical trial, the application/submission in FDA files, and/or any other information available to the Agency, to determine whether such a violation exists."⁴¹ If the Agency determines that a violation does exist, FDA can then issue a Notice of Noncompliance under § 402(j)(5)(C)(ii) of the Public Health Service Act ("PHS Act"). After receiving a Notice of Noncompliance, the recipient has no more than thirty calendar days to come into compliance before civil money penalties may be imposed. Notably, if a party does remains noncompliant after thirty days, "the

³⁴ U.S. Food & Drug Administration, *Bioresearch Monitoring Program (BIMO) Compliance Programs* (Oct. 17, 2022), <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-program-manual/bioresearch-monitoring-program-bimo-compliance-programs>.

³⁵ U.S. Food & Drug Administration, *Compliance Program Guidance Manual For FDA Staff - Program 7348.808A* (Apr. 13, 2015), <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/fda-bioresearch-monitoring-information/compliance-program-guidance-manual-fda-staff-program-7348808a>.

³⁶ FDA Guidance Document (2020) at 4, n.16.

³⁷ U.S. Food & Drug Administration, *Compliance Program 7348.180: Chapter 48 - Bioresearch Monitoring* 18-21 (Sept. 15, 2021), <https://www.fda.gov/media/75916/download>.

³⁸ FDA Guidance Document (2020) at 6.

³⁹ *Id.* at 5.

⁴⁰ Necessary action can be defined as becoming compliant by reporting required clinical trial results data to ClinicalTrials.gov, or other paths to compliance such as requesting an extension for good cause or requesting a waiver of the requirements for submission of results information. FDA's April 15, 2022 letter to Ocugen is an example of a Notice of Noncompliance being sent after no necessary action was taken 30 days after FDA sent a Preliminary Notice of Noncompliance. Letter from Judith McMeekin, Associate Commissioner for Regulatory Affairs, FDA, to Vijay Tammarra, Senior Vice President, Global Regulatory and Quality, Ocugen (Apr. 15, 2021) (available at <https://www.fda.gov/media/157774/download>).

⁴¹ FDA Guidance Document (2020) at 6.

Center generally intends to seek civil money penalties, taking into account the type of noncompliance and the circumstances associated with the lack of remediation.”⁴²

Elaborating on FDA’s plan for enforcement, the 2020 guidance document briefly discusses its proposed method of evaluating potential violations. According to the 2020 guidance, “FDA intends to utilize a risk-based approach to determine the situations in which Pre-Notice Letters will be issued, consistent with FDA’s public health mission and how the Agency approaches its other compliance programs.”⁴³ Expanding upon its enforcement priorities, the guidance goes on to list broad areas in which FDA intends to focus its “enforcement and regulatory attention.”⁴⁴ These areas include situations in which 1) clinical trial registration or results information have not been submitted under § 402(j) of the PHS Act, 2) the responsible parties have a pattern of previous noncompliance, and 3) a noncompliant trial also flouts separate “statutory and/or regulatory requirements pertaining to the conduct of the trial.”⁴⁵

II. Factual Grounds:

1. Compliance with Clinical Trial Reporting Requirements Is Hugely Deficient

As of 2023, sixteen years after FDAAA went into effect, many responsible parties still fail to comply with the statute’s clinical trial reporting requirements. Ramachandran et al. summarized the poor state of compliance as of the beginning of 2021:

Recent estimates suggest that approximately 60% of trials fail to report results on time and more than 30%⁴⁶ (almost 3000 clinical trials with primary completion dates between January 18, 2017, and January 18, 2021) have not yet reported results. Among 3951 trials sponsored by industry, 43.2% complied fully with the FDAAA results reporting requirements. Among the top 40 US research universities (by number of trials subject to the FDAAA), only 17 complied fully with reporting of trial results.⁴⁷

As of February 2023, one independent watchdog estimates that there are currently thousands of responsible parties that have at least one trial out of compliance with FDAAA.⁴⁸

⁴² *Id.* at 7.

⁴³ *Id.* at 5.

⁴⁴ *Id.* at 5-6.

⁴⁵ *Id.* at 6.

⁴⁶ The estimate of more than 30% trials missing results as of early 2021 may be an overestimate because the responsible parties for some fraction of these trials may have received a “certification” from NIH authorizing the responsible parties to delay the submission of results information. *See, Frequently Asked Questions*, ClinicalTrials.gov (Aug. 2022), https://clinicaltrials.gov/ct2/manage-recs/faq#fr_35 (Certificate information is found under the question “When are results due for an applicable trial (ACT), if a certification of delay for an approved, licensed, or cleared product (‘certify new use’) has been submitted under 42 CFR 11.44(b)?”).

⁴⁷ Ramachandran et al., *supra* note 4.

⁴⁸ Bennet Institute for Applied Data Science, *FDAAA Trials Tracker* (last visited February 13, 2023), <https://fdaaa.trialstracker.net/rankings/>.

The medical literature is replete with additional data on the absence of important clinical trial data from ClinicalTrials.gov. For example, a recent study of trials in pancreatic adenocarcinoma over the past decade found that only 8% of applicable clinical trials in the paper’s sample had submitted trial results to ClinicalTrials.gov within a year of the trials’ primary completion date, contributing to a harmful lack of information for patients and doctors.⁴⁹ The authors observed that “[n]ot having access to trial results creates an even greater burden for rare and aggressive diseases such as [pancreatic adenocarcinoma] for which trials can be hard to conduct although new therapeutics are urgently needed.”⁵⁰

In 2021, Commissioner Califf himself noted that compliance with FDAAA’s results-reporting mandate was unsatisfactory, beset with “lingering deficiencies.”⁵¹ Commissioner Califf further warned that the results data missing from ClinicalTrials.gov could distort the medical literature: “incomplete reporting of studies sponsored by academic medical centers shows similar biases, including lack of publication of substantial proportions of studies and selective outcome and adverse event reporting.”⁵²

Underreporting of clinical trial results has serious and potentially life-altering consequences. Trials which expert reviewers deemed non-compliant for years include the trial NCT02049515, a Phase III extension trial of the FDA-approved drug duvelisib (COPIKTRA) indicated for the treatment of chronic lymphocytic leukemia or small lymphocytic lymphoma, a serious and life-threatening condition.⁵³ Patients prescribed duvelisib are those who have previously received multiple traditional cancer therapies before turning to duvelisib as a last resort. Providers and patients alike require data on duvelisib's efficacy and potential side effects to manage treatment and to potentially justify the drug’s high cost; some patients have out-of-pocket copays as high as \$4,000 a month.⁵⁴ Reporting the trial results would provide further evidence (and thus, reassurance) that the drug’s efficacy outweighs its serious risks.⁵⁵ Unfortunately, study results were not posted for more than two years after the trial reached its primary completion date on June 12, 2020.⁵⁶ The trial almost certainly missed the results reporting deadline established by FDAAA and the FDAAA Final Rule, and is therefore noncompliant with FDAAA.⁵⁷ The responsible party for this trial finally submitted results to

⁴⁹ Anna Pellat, Isabelle Boutron & Philippe Ravaud, *Availability of Results of Trials Studying Pancreatic Adenocarcinoma over the Past 10 Years*, 27 *Oncologist* e849 (2022), <https://academic.oup.com/oncolo/article/27/11/e849/6671771>.

⁵⁰ *Id.*

⁵¹ Zarin & Califf, *supra* note 18.

⁵² *Id.*

⁵³ NCT02049515 Study Details, *A Phase 3 Extension Study of Develisib and Ofatumumab in Patients With CLL/SLL Previously Enrolled in Study IPI-145-07*, ClinicalTrials.gov (last visited Nov. 21, 2022), <https://clinicaltrials.gov/ct2/show/NCT02049515>.

⁵⁴ Taylor Hartz, *Stem cell treatment offers hope--and high costs--for retired Farmington teacher with aggressive forms of cancer*, Hartford Courant (July 23, 2022), <https://www.courant.com/community/farmington/hc-news-john-berry-farmington-teacher-stem-cell-transplant-20220723-xgyxnlllefg65pmogi2u3o2hpe-story.html>.

⁵⁵ COPIKTRA Medication Guide, *Highlights of Prescribing Information*, FDA (Sept. 2018), https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211155s0001bl.pdf.

⁵⁶ <https://clinicaltrials.gov/ct2/show/NCT02049515>.

⁵⁷ 42 C.F.R. § 11.44 (Stating that clinical trials, “must be submitted no later than 1 year after the primary completion date of the applicable clinical trial”).

ClinicalTrials.gov on December 16, 2022, but the results were returned after NIH’s quality control review and remained unavailable to the public; results were finally posted on February 21, 2023, more than two and a half years after the trial’s primary completion date.⁵⁸ Patients and the broader public had to wait much longer than they should have for information on this costly but potentially life-saving treatment.

Some noncompliant clinical trials threaten the health and informational rights of particularly vulnerable patients, including children. For example, a January 2023 report led by Till Bruckner of TranspariMED and co-published by TranspariMED, UAEM, and the National Center for Health Research determined that as of January 24, 2023, 43 pediatric clinical trials had failed to report results data to ClinicalTrials.gov required under FDAAA *and* had failed to report results elsewhere, such as the medical literature.⁵⁹ These 43 identified noncompliant trials include trials addressing major pediatric health concerns such as infant heart surgery outcomes, premature birth, and Duchenne Muscular Dystrophy (a devastating and currently incurable condition). This group of 43 identified noncompliant trials also includes trials of opioid painkillers in children that have not reported their results, such as trials sponsored by Hikma Pharmaceuticals⁶⁰ and Endo Pharmaceuticals.⁶¹ Because the administrators of these pediatric clinical trials had not, as of January 2023, published their data in scientific literature, ClinicalTrials.gov is the only place for patients, their families, and their caregivers to find results. The lack of results from these trials on ClinicalTrials.gov highlights the problem of ongoing noncompliance with FDAAA. A STAT News story covering the January 2023 report observed that “a raft” of other studies have similarly shown “a failure by drug companies, universities, and academic medical centers to comply with disclosure requirements” under FDAAA.⁶²

2. Compliance with Clinical Trial Reporting Requirements Is Deficient Because FDA’s Enforcement Has Been Minimal and Unfocused

Compliance has lagged because enforcement has lagged. FDA’s efforts to compel delinquent trial sponsors to report outstanding clinical trial data have not been sufficient. FDA’s enforcement efforts have proven inadequate in two respects: FDA has not undertaken enough enforcement action, and the enforcement action FDA has taken has not been focused on obtaining data from the most important trials.

FDA’s enforcement efforts have been minimal overall. It has sent few Pre-Notices. From 2013 to April 29, 2021, FDA issued 58 Pre-Notices, 57 of which were for apparent noncompliance with results reporting requirements.⁶³ STAT News reported in January 2023 that

⁵⁸ <https://clinicaltrials.gov/ct2/show/NCT02049515>.

⁵⁹ Till Bruckner, *What happened to the 3,627 American children participating in these clinical trials?*, TranspariMED (January 22, 2023, updated January 24, 2023), <https://www.transparimed.org/single-post/fdaaa-pediatric>.

⁶⁰ <https://clinicaltrials.gov/ct2/show/NCT03429400>.

⁶¹ <https://clinicaltrials.gov/ct2/show/NCT04681027>.

⁶² Ed Silverman, *Many pediatric drug study results were never posted to a U.S. government database*, STAT News (Jan. 24, 2023), <https://www.statnews.com/pharmalot/2023/01/24/children-pediatrics-transparency-clinical-trials-fda-nih/>.

⁶³ Ramachandran et al., *supra* note 4.

FDA had sent a grand total of 92 Pre-Notices,⁶⁴ meaning that FDA sent only a few dozen Pre-Notices between April 2021 and January 2023. These numbers represent only a small fraction of the thousands of clinical trials that independent experts have identified as non-compliant during the same periods.⁶⁵ This may well be because BIMO investigates only a tiny fraction of applicable clinical trials and thus uncovered only a tiny fraction of the trials noncompliant with FDAAA.

FDA has also sent few Notices of Noncompliance. Of the 57 trial sponsors issued Pre-Notices between 2013 and April 29, 2021, just three received subsequent Notices of Noncompliance from FDA.⁶⁶ In other words, FDA elevated its enforcement efforts from the Pre-Notice to Notice of Noncompliance level on only three occasions between 2013 and 2021. Furthermore, FDA has yet to levy a single civil money penalty against a noncompliant responsible party.⁶⁷ To UAEM's knowledge, FDA has likewise never referred a responsible party for criminal prosecution or withheld grant money because of a responsible party's noncompliance with FDAAA.

Commissioner Califf himself chastised FDA (and NIH) in 2021 for failing to undertake any more than minimal enforcement effort, despite the thousands of applicable clinical trials out of compliance with their legal obligation to report results to ClinicalTrials.gov. Although independent researchers had “identified thousands of trials that are out of compliance owing to lack of results reporting, neither the FDA nor the NIH have used their regulatory authorities to impose monetary penalties or withhold grant support.”⁶⁸ Even in the face of criticism from the incoming commissioner, FDA has not significantly increased enforcement. At the end of 2021, FDA's Center for Drug Evaluation and Research reported that it had sent a total of 26 Pre-Notices.⁶⁹ While the pace of enforcement increased in 2021, it does not approach the level of enforcement needed to bring the majority of noncompliant trials into compliance.

FDA's enforcement efforts have not only been minimal; they have lacked focus. No Pre-Notices were sent to NIH, even though NIH, through its subsidiary institutes, is the legal sponsor for more trials than any other pharmaceutical company, university, or other major trial sponsor and is responsible for many trials that have failed to meet their reporting requirements under FDAAA.⁷⁰ Instead, most Pre-Notices were sent to private companies in the drug and medical device industry or, to a lesser extent, academic institutions.

⁶⁴ Silverman, *supra* note 62.

⁶⁵ 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(8) JAMA Internal Medicine 1128-1130 (May 24, 2021).

⁶⁶ Ramachandran et al., *supra* note 4.

⁶⁷ U.S. Food & Drug Administration, *ClinicalTrials.gov - Notices of Noncompliance and Civil Money Penalty Actions*, (Aug. 02, 2022), <https://www.fda.gov/science-research/fdas-role-clinicaltrialsgov-information/clinicaltrialsgov-notices-noncompliance-and-civil-money-penalty-actions>.

⁶⁸ Zarin & Califf, *supra* note 18.

⁶⁹ U.S. Food & Drug Administration, *Center for Drug Evaluation and Research Office of Compliance Compliance 2021 Annual Report* 32 (Apr. 2022).

⁷⁰ Charles Piller, *FDA and NIH let clinical trial sponsors keep results secret and break the law*, Science Insider, 13 Jan. 2020.

To UAEM's knowledge, there is currently little inter-agency communication between FDA and NIH. Without NIH regularly communicating to FDA which trial sponsors appear to be noncompliant based on its ClinicalTrials.gov database, FDA presumably has no systematic method for identifying noncompliant trials and no easy way to know when issuance of a Pre-Notice is appropriate.

The few Pre-Notices and Notices that FDA has sent have not targeted clinical trials addressing the most critical public health needs. For example, the three trials for which FDA issued Notices of Noncompliance in 2021 appear to be of modest importance from a medical point of view. Two of the three trials implicated in the Notices were a Phase II trial by Accutis of a topical treatment for acne rosacea,⁷¹ and a trial by an academic investigator studying a postoperative combination of ice and analgesic treatment.⁷² These trials were unlikely to produce results addressing pressing public health needs.⁷³ The third trial, a Phase II study of delantercept as a kidney cancer treatment, failed to obtain FDA approval after studies were shown to not demonstrate efficacy.⁷⁴ While information on delantercept and similar drugs may be pertinent to the treatment of serious health conditions, clinical trial data for unapproved medical products are less relevant to patients than data on the safety and efficacy of FDA-approved or soon-to-be approved products because these products will be available to many more patients. The Pre-Notices and Notices FDA has sent evidence that FDA's current enforcement framework lacks prioritization, allowing more clinically relevant trials to remain unreported without consequence.

In all of 2022, FDA sent just one Notice of Noncompliance, its fourth overall. This Notice was sent to Ocugen regarding a Phase III trial for an eye drop designed to treat dry eye syndrome.⁷⁵ Mirroring the lack of prioritization demonstrated by the previous three Notices, the data from this trial appear to be of significant but comparatively modest clinical importance.

3. FDA's Minimal Enforcement Efforts Demonstrate That Enforcement Improves Compliance

FDA has undertaken minimal and unfocused enforcement efforts despite clear evidence that enforcement incentivize compliance. Pre-Notices alone seem to be effective in compelling most delinquent parties to come into compliance – even without the issuance of a subsequent Notice of Noncompliance. As of August 17, 2021, all but 5 of the 57 Pre-Notice recipients had reported missing information to ClinicalTrials.gov.⁷⁶ The median time for data submission among Pre-Notice recipients was short: approximately 3 weeks.⁷⁷ Moreover, all responsible

⁷¹ Letter from Judith McMeekin, Associate Commissioner for Regulatory Affairs, FDA, to Rick Coulon, Accutis, Inc. (July 26, 2021) (available at <https://www.fda.gov/media/151081/download>).

⁷² Letter from Judith McMeekin, Associate Commissioner for Regulatory Affairs, FDA, to Andrey Petrikovets, M.D. (Aug. 31, 2021) (available at <https://www.fda.gov/media/151965/download>).

⁷³ See discussion *infra* B.III.c.6.

⁷⁴ Nick Paul Taylor, *Acceleron dumps dalantercept after kidney cancer trial fail*, Fierce Biotech, Jun. 13, 2017.

⁷⁵ Letter from Judith McMeekin to Vijay Tammara *supra* note 40.

⁷⁶ Ramachandran et al., *supra* note 4.

⁷⁷ *Id.*

parties that received Notices of Noncompliance reported their missing results to ClinicalTrials.gov, as certified by FDA in its response letters.⁷⁸

4. Patients, Lawmakers and Researchers Agree that More and Better Enforcement Is Needed

Far from being solely an academic issue, clinical trial transparency affects multiple stakeholders: patients, lawmakers, and clinical and academic researchers. One of the reasons ClinicalTrials.gov was established was to help patients find results of trials testing treatments for serious illnesses.⁷⁹ Some patients are interested in searching for drugs that have not yet been FDA-approved, but already show promising results. Increasingly, drug manufacturers are releasing select results of clinical trials through press releases, social media, and partnerships with patient advocacy organizations. Information posted on ClinicalTrials.gov in a standardized format provides a more comprehensive picture of a drug candidate than these other, often biased forms of data publication. Rigorous enforcement of FDAAA is necessary for patients to have an unbiased, standardized way to consume of clinical trial results. Patients cannot make fully informed decisions if promising trials are excluded from the database where data access is guaranteed.

Furthermore, all patients' interests are affected by noncompliance because clinical trial transparency plays a crucial role in ensuring drug safety and efficacy.⁸⁰ Research and development of drugs is tremendously costly. This puts responsible parties under pressure to report positive results. For example, important information on the safety and efficacy of drugs can be obscured when researchers do not disclose pre-specified outcomes, creating the common problem of outcome switching.⁸¹ Outcome switching occurs when "researchers fail to report the original outcomes that they had planned to measure and instead report different outcomes that are more favorable."⁸² A prominent example of outcome switching is GlaxoSmithKline's (GSK) Study 329 regarding the antidepressant paroxetine (Paxil). GSK employees distributed a GSK-funded medical article on Study 329 suggesting that paroxetine is well-tolerated and effective in young patients.⁸³ However, a later study by FDA indicated that the use of certain selective serotonin reuptake inhibitors such as paroxetine can lead to suicidal ideation and behavior in some young patients.⁸⁴ A renewed analysis of Study 329's data by a group of independent researchers of the showed that paroxetine was not effective in adolescents and can indeed lead to

⁷⁸ U.S. Food and Drug Administration, *supra* note 67, <https://www.fda.gov/science-research/fdas-role-clinicaltrials.gov-information/clinicaltrials.gov-notices-noncompliance-and-civil-money-penalty-actions>.

⁷⁹ *See, e.g.*, 42 U.S.C. § 282(j)(3)(B) ("The Secretary [of HHS], acting through the Director of NIH, shall ... expand the registry data bank to include the results of applicable clinical trials ... [and] ensure that such results are made publicly available through the Internet").

⁸⁰ Yale Collaboration for Research Integrity and Transparency, *Promoting Transparency in Clinical Research 4* (Nov. 2017).

⁸¹ Ben Goldacre et al., The COMPare Trials Project (2016), <https://www.compare-trials.org/project#whyitmatters>.

⁸² Yale Collaboration for Research Integrity and Transparency, *supra* note 80 at 8.

⁸³ Martin B. Keller et al., *Efficacy of Paroxetine in the Treatment of Adolescent Major Depression: A Randomized, Controlled Trial*, 40:7 J. of the Am. Acad. of Child & Adolescent Psychiatry 762, 763 (2001).

⁸⁴ U.S. Food & Drug Administration, *FDA Statement Regarding the Anti-Depressant Paxil for Pediatric Population* (June 19, 2003), <http://www.antidepressantsfacts.com/2003-06-19-FDA-Statement-talkpaper.htm>.

self-injury and suicidal ideation.⁸⁵ In fact, Study 329’s original trial protocol produced negative efficacy results, but the article’s authors hid this fact, publishing results which “reported different outcomes with better results, creating a distorted picture of the drug.”⁸⁶ Reporting the clinical trial data for this drug could have exposed these negative results sooner. As Commissioner Califf himself warned, responsible parties’ lack of compliance with FDAAA risks patient safety through biased “selective outcome and adverse event reporting.”⁸⁷

The painkiller drug celecoxib (Celebrex) also exemplifies the importance of comprehensive clinical trial result reporting. A high-profile article published in 2000 reported results from a celecoxib trial, the “CLASS trial,” concluding that after 6 months of treatment, celecoxib “was associated with a lower incidence of symptomatic ulcers and ulcer complications combined” compared with competitor painkillers ibuprofen and diclofenac, suggesting that celecoxib was a safer alternative.⁸⁸ This trial was funded by celecoxib’s manufacturers, Pfizer and Pharmacia, and the article was authored by Pharmacia employees and academic researchers who were also Pharmacia’s paid consultants.⁸⁹ FDA later disclosed additional trial showing patients outcomes through 12 months of treatment with celecoxib rather than merely 6 months. These data led independent researchers to question celecoxib’s purported safety benefits and the integrity of the 2000 article.⁹⁰ The independent researchers found that “the published CLASS trial differs from the original protocol in primary outcomes, statistical analysis, trial duration, and conclusions. In particular, the unpublished data [disclosed by FDA] show that by week 65, celecoxib was associated with a similar number of ulcer complications as [competitor painkillers] diclofenac and ibuprofen.”⁹¹ The New York Times later reported that internal Pfizer documents revealed how a Pfizer medical director acknowledged that the 2000 article was “cherry-picking the data” to create a misleading impression of celecoxib’s safety.⁹²

Aside from impacting patients’ health and safety, deficient clinical trial reporting also has a negative economic impact. This poses a concern for patients, policymakers, and taxpayers alike. Total drug spending in the United States was around \$500 billion in 2018 and is estimated to rise to \$863 billion by 2028.⁹³ Relying on incomplete trial data can lead the government and researchers to waste money on treatments that are unsafe or ineffective.⁹⁴ In a 2017 paper, researchers from the Yale Collaboration for Research Integrity and Transparency summarized

⁸⁵ Yale Collaboration for Research Integrity and Transparency, *supra* note 80 at 9.

⁸⁶ *Id.*

⁸⁷ Zarin & Califf, *supra* note 18 at 1131.

⁸⁸ Fred E. Silverstein, et al., *Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study*. 284 JAMA 1247, 1247 (2000). doi:[10.1001/jama.284.10.1247](https://doi.org/10.1001/jama.284.10.1247).

⁸⁹ *Id.*

⁹⁰ Jennifer Berg Hrachovec & Marc Mora, *Reporting of 6-month vs 12-month data in a clinical trial of celecoxib*. 286 JAMA 2398 (2001). doi:[10.1001/jama.286.19.2398](https://doi.org/10.1001/jama.286.19.2398).

⁹¹ *Id.*

⁹² Katie Thomas, *In Documents on Pain Drug, Signs of Doubt and Deception*, The New York Times (Jun. 24, 2012), <https://www.nytimes.com/2012/06/25/health/in-documents-on-pain-drug-celebrex-signs-of-doubt-and-deception.html>.

⁹³ Rena M. Conti et al., *Projections of US Prescription Drug Spending and Key Policy Implications*, JAMA Health Forum (Jan. 29, 2021), <https://jamanetwork.com/journals/jama-health-forum/fullarticle/2776040>.

⁹⁴ Yale Collaboration for Research Integrity and Transparency, *supra* note 80 at 16.

billions of dollars in wasted spending that could have been minimized by increased clinical trial data transparency:

Since 2002, governments around the world have been stockpiling antiviral medicines for the treatment of influenza based on information presented by manufacturers. Researchers associated with the Cochrane Collaboration tried for years to obtain complete clinical study reports on influenza medication trials from government regulators and pharmaceutical companies, and eventually were successful. In 2014, these independent researchers reviewed the clinical study reports from both published and unpublished clinical trial results, and concluded that Roche's oseltamivir (Tamiflu) and GlaxoSmithKline's zanamivir (Relenza) failed to prevent the spread of the flu, reduce admissions to the hospital, or minimize complications associated with the flu. By the time the study came out, the U.S. had spent more than \$1.3 billion developing and stockpiling 65 million treatments, and the UK spent £424 million stockpiling 40 million doses of Tamiflu alone. Across the globe, over \$20 billion in public money has been spent on stockpiling Tamiflu and Relenza.⁹⁵

Enforcing FDAAA could help ensure that it does not take 12 years until independent researchers have the opportunity to determine whether medical interventions produce their touted outcomes. In the case of oseltamivir (Tamiflu) and zanamivir (Relenza), this would have led to billions of dollars in savings.

Finally, incomplete clinical trial reporting hinders clinicians and researchers. Clinical practice guidelines are often informed by systematic reviews and meta-analyses of data pooled across multiple clinical trials. Incomplete clinical trial reporting makes it difficult for researchers to identify and include all relevant trials, particularly because nearly half of clinical trials do not publish their results in the medical literature.⁹⁶ A 2008 study on the selective publication of antidepressant trials illustrates this phenomenon:

Among 74 FDA-registered studies, 31%, accounting for 3449 study participants, were not published. Whether and how the studies were published were associated with the study outcome. A total of 37 studies viewed by the FDA as having positive results were published; 1 study viewed as positive was not published. Studies viewed by the FDA as having negative or questionable results were, with 3 exceptions, either not published (22 studies) or published in a way that, in our opinion, conveyed a positive outcome (11 studies). According to the published literature, it appeared that 94% of the trials conducted were positive. By contrast, the FDA analysis showed that 51% were positive.⁹⁷

⁹⁵ *Id.*

⁹⁶ Yale Collaboration for Research Integrity and Transparency, *supra* note 80 at 14.

⁹⁷ Erick H. Turner et al., *Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy*, 358 *New Eng. J. Med.* 252, 253 (Jan. 17, 2008).

To summarize, selective publication of trial results in the medical literature significantly skewed the perceived efficacy of the antidepressants. Incomplete results reporting may have resulted in patients receiving antidepressants that were ineffective or even unsafe for them. As the authors of the 2008 study wrote, “[b]y altering the apparent risk–benefit ratio of drugs, selective publication can lead doctors to make inappropriate prescribing decisions that may not be in the best interest of their patients and, thus, the public health.”⁹⁸

The results of unsuccessful trials are reported particularly infrequently. Increased reporting of unsuccessful trials would not only prevent the unnecessary repetition of such trials, which decreases wasteful spending on clinical trials and unnecessary risk to trial patients, but would also add to the scientific knowledge base. Negative results can be fruitful starting points for further research by other groups. Therefore, reporting requirements for unsuccessful trials must be enforced as well.

A prominent lawmaker agrees with these researchers that lack of enforcement of FDAAA is a problem. On January 19, 2023, U.S. House Representative Frank Pallone sent a high-profile letter to FDA that underscored the growing consensus that FDA needs to do more and better enforcement of FDAAA.⁹⁹ Representative Pallone sent the letter in his capacity as Ranking Member of the House Energy & Commerce Committee, which oversees FDA. Representative Pallone’s letter was sent both to FDA Commissioner Califf and NIH’s Acting Director, Lawrence Tabak. Representative Pallone opened his letter as follows:

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.

His letter went on to observe that FDA has taken minimal enforcement action despite widespread and documented noncompliance with FDAAA’s results reporting rules:

Meanwhile, FDA, which bears responsibility for enforcing ClinicalTrials.gov requirements for a much larger number of trials [than NIH] has [] taken very limited action to ensure compliance. This is concerning considering that it is apparent when FDA takes action, it has great effect.

⁹⁸ *Id.* at 259.

⁹⁹ <https://democrats-energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/Letter%20to%20FDA%20and%20NIH%20re%20CT-gov%20Compliance.pdf>. Rep. Pallone’s letter was also sent to NIH, and some of his letter’s concerns and questions are directed at that agency.

The letter then presents FDA with a summary of the agency’s minimal enforcement efforts. Some of this evidence was collected by representatives of UAEM.¹⁰⁰

Representative Pallone’s letter prompted a wave of media coverage,¹⁰¹ which has drawn new attention to the problem of FDA’s underenforcement of FDAAA. For example, on January 19, 2023, STAT News reported on Representative Pallone’s letter, noted that “critics say the NIH and FDA have too often failed to enforce the law and have pushed the agencies to boost oversight of clinical trial results and registrations.”¹⁰²

5. UAEM Has Attempted to Bring These Problems to the Attention of the FDA, But Has Been Ignored

UAEM has no choice but to file this citizen petition. UAEM made multiple previous efforts to bring its concerns about FDAAA enforcement to the FDA’s attention, but FDA rebuffed each of these efforts. On March 15, 2022, UAEM communicated with Andi Lipstein Fristedt, Deputy Commissioner for Policy, Legislation, and International Affairs at FDA, to begin a conversation. UAEM’s email outlined, inter alia, concerns about “how FDA’s enforcement of FDAAA could be improved.”¹⁰³ Though UAEM pressed for a meeting, James Flahive, Senior Advisor to the Office of the FDA Commissioner, wrote on behalf of Deputy Commissioner Fristedt that FDA officials were “not able to meet at this time.” Senior Advisor Flahive added that FDA would welcome written feedback in place of a conversation.¹⁰⁴

Between email exchanges, UAEM representatives wrote a formal letter to FDA Commissioner Califf on April 21, 2022 about the need for FDAAA enforcement and how current efforts were lacking.¹⁰⁵ UAEM emphasized its agreement with Commissioner Califf’s previous statements acknowledging the importance of “transparent, interchangeable information”¹⁰⁶ and

¹⁰⁰ See <https://democrats-energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/Letter%20to%20FDA%20and%20NIH%20re%20CT-gov%20Compliance.pdf> at nn. 25-29 (citing 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> and UAEM, Clinical Trials Transparency at U.S. Universities (2021), available at https://altroute.com/clinicaltrials/assets/download/Clinical_Trials_Transparency_Report_UAEM_v5.pdf).

¹⁰¹ See, e.g., <https://endpts.com/rep-frank-pallone-wants-fda-and-nih-to-act-on-pharmas-noncompliance-with-trial-records-law/>, <https://www.bmj.com/content/380/bmj.p235>.

¹⁰² <https://www.statnews.com/pharmalot/2023/01/19/clinical-trials-transparency-pallone-fda-nih/>

¹⁰³ Email from Christopher Morten to Andi Lipstein Fristedt Deputy Commissioner for Policy, Legislation, and International Affairs, FDA (March 15, 2022, 1:41 EDT) (on file with petitioners).

¹⁰⁴ Email from James Flahive to Reshma Ramachandran, Board of Directors, Universities Allied for Essential Medicines, North America (June 29, 2022, 3:46 EDT) (on file with petitioners).

¹⁰⁵ Letter from Nayva Dasari et al., Coordinating Committee, Universities Allied for Essential Medicines, North America to Robert M. Califf, Commissioner of FDA (Apr. 21, 2022), https://assets.nationbuilder.com/uaem/pages/75/attachments/original/1650580897/Letter_to_FDA_Commissioner_.pdf?1650580897.

¹⁰⁶ Derrick Gingery, *Califf Outlines Clinical Trial Reform Message, Which Could Travel With Him To Commissioner’s Office*, Pink Sheet Pharma Intelligence (Nov. 22, 2021), <https://pink.pharmaintelligence.informa.com/PS145289/Califf-Outlines-Clinical-Trial-Reform-Message-Which-Could-Travel-With-Him-To-Commissioners-Office>.

how clinical trial reporting is “fundamentally an ethical issue.”¹⁰⁷ UAEM addressed the lack of compliance across numerous trial sponsors (universities, public institutions, and the private sector) and how FDA has largely failed to deliver Notices of Noncompliance.¹⁰⁸ In its April 2022 letter, UAEM specifically requested “the opportunity to meet with [Commissioner Califf] to see if there may be ways for UAEM and the FDA to work collaboratively toward enabling greater compliance in registering and reporting clinical trials.”¹⁰⁹ FDA did not grant UAEM a meeting and did not provide UAEM with any substantive response to its letter.

Seeing as neither the letter nor the email exchanges resulted in a substantive response, UAEM is left with Senior Advisor Flahive’s request for written feedback. Accordingly, UAEM submits this citizen petition, written feedback as per FDA’s request.

III. Argument and Relief Requested:

1. FDA Needs to Improve Its Efforts to Enforce Section 801 of FDAAA

Insufficient enforcement of trial reporting has negative impacts on patient care and denies patients, clinicians, and researchers opportunities to identify and analyze relevant trial data. It leads to economic waste in an environment where the United States already spends significantly more on healthcare than all other Organization for Economic Co-Operation and Development (“OECD”) countries. Furthermore, it hampers quality control within the biomedical research community and slows the advancement of science.

We have presented evidence of how FDA’s enforcement of Section 801 of FDAAA has been insufficient and how this hurts interested parties.¹¹⁰ Out of thousands of estimated noncompliant trials, according to the FDAAA trials tracker, FDA sent only 57 Pre-Notices of Noncompliance between 2013 and April 2021. Of the 57 responsible parties that received these Pre-Notices, 52 had reported their missing results to ClinicalTrials.gov as of August 17, 2021,¹¹¹ meaning that at least five responsible parties remained noncompliant after far longer than 30 days since receipt of a Pre-Notice. Yet FDA has, as of writing in February 2023, sent a grand total of just four Notices of Noncompliance.¹¹² This suggests that FDA is not upholding the commitment made in the 2020 guidance that it will “conduct a further review and assessment of the clinical trial information submitted to ClinicalTrials.gov ... beginning 30 calendar days after the date a Pre-Notice Letter is received”;¹¹³ instead, it seems that FDA is failing to follow up promptly on some of its Pre-Notices. In short, over an eight-year period, FDA issued Pre-Notices to only a tiny fraction of a percentage of noncompliant trials, then issued Notices to only some

¹⁰⁷ Sara Reardon, *U.S. Toughens Rules for Clinical-Trial Transparency*, *Nature* (Sept. 16, 2016), <https://www.nature.com/articles/nature.2016.20616>.

¹⁰⁸ Letter from Nayva Dasari et al. to Robert M. Califf, *supra* note 105.

¹⁰⁹ *Id.*

¹¹⁰ *See supra* B.II.

¹¹¹ Ramachandran et al., *supra* note 4.

¹¹² U.S. Food and Drug Administration, *supra* note 67 (<https://www.fda.gov/science-research/fdas-role-clinicaltrials.gov-information/clinicaltrials.gov-notices-noncompliance-and-civil-money-penalty-actions>).

¹¹³ FDA Guidance Document (2020) at 5.

trials that still failed to comply post-Pre-Notice. Even considering that FDA has sent some additional Pre-Notices since April 2021, this meager enforcement effort is not sufficient. Moreover, FDA has yet to exercise its power to impose any penalties on non-compliant trial sponsors, including civil money penalties, criminal penalties, or withholding grant money.

Therefore, UAEM formally requests, as its first “action requested,” that FDA increase its enforcement of responsible parties’ reporting duties. Specifically, UAEM asks FDA to undertake the following three action steps to increase enforcement:

- 1) First, UAEM asks FDA to increase the number of Pre-Notices it issues, sending out a minimum of 250 such Pre-Notices annually, at least until compliance materially improves. As described above in section II(3), Pre-Notices are an effective enforcement tool. 90% of Pre-Notice recipients reported missing trial results, with a median time of three weeks.¹¹⁴ In fact, Pre-Notices appear so effective that a system that automatically sends out Pre-Notices based on data provided by NIH through ClinicalTrials.gov would likely bolster compliance immensely. It is likely that this action would help FDA easily meet the minimum threshold of issued Pre-Notices UAEM requests. FDA can revisit this minimum threshold number of Pre-Notices if and when compliance materially improves.
- 2) Second, UAEM asks FDA to be more stringent about issuing Notices of Noncompliance to those trial sponsors who fail to react to their Pre-Notices. FDA’s first four Notices were 100% effective in compelling responsible parties to comply with their trial reporting duties.
- 3) Finally, UAEM asks FDA to impose civil money penalties on those trial sponsors that refuse to comply even after receiving a Notice of Noncompliance.

The status quo—minimal enforcement action from FDA—fails to fulfill FDA’s administrative duty. Permitting responsible parties to evade compliance with FDAAA, a federal law, without tangible consequences sets a dangerous precedent with import far beyond the context of clinical trial data reporting.¹¹⁵

2. FDA Should Issue New Guidance with a New Enforcement Prioritization Framework

a. Rescission of FDA’s 2020 Guidance and Issuance of New Guidance Are Appropriate

FDA’s 2020 guidance, described above, provides responsible parties and the public at large with FDA’s most authoritative, concrete, detailed public statement on the agency’s procedure for monitoring and enforcing compliance with FDAAA’s clinical trial data reporting rules. Although the 2020 guidance is nominally nonbinding, it is, in effect, FDA’s official statement of the agency’s enforcement policy.

¹¹⁴ Ramachandran et al., *supra* note 4 at 2132.

¹¹⁵ Zarin & Califf, *supra* note 18 at 1131.

FDA's current guidance and the enforcement policy it embodies are insufficient. Enforcement actions have been scattered, unpredictable, and unfocused even though Pre-Notices and Notices of Noncompliance have been effective when issued. Therefore, as its second "action requested," UAEM asks FDA to rescind and replace the 2020 guidance with newly issued guidance. The new guidance should commit FDA to more vigorous enforcement. It should also articulate a new enforcement prioritization framework, as detailed below.

New guidance is the optimal way for FDA to articulate and publicize its new enforcement approach. Informal policy changes will not suffice. Because information about FDAAA's enforcement has historically been communicated through guidance documents, including the 2020 guidance and its preceding draft,¹¹⁶ issuing updated guidance in the same manner is appropriate. New guidance would properly inform and notify responsible parties and the public regarding FDA's new enforcement approach. Simply issuing new guidance could also meaningfully enhance compliance rates at minimal cost to FDA by reminding responsible parties of their duty to report trial results and of the potential consequences of noncompliance.

b. FDA's New Guidance Should Commit the Agency to a New, Improved, and Expanded Enforcement Prioritization Framework

FDA's 2020 guidance articulates a simple framework for prioritizing the agency's enforcement efforts. According to the 2020 guidance, FDA intends to focus its enforcement efforts on three categories of noncompliant applicable clinical trials. These three categories are:

- 1) trials that involve products "that potentially may pose a higher risk to human subjects or ... inten[d] to address significant public health need," including, for example, products which are "intended to treat a serious and/or life-threatening disease or condition and applicable clinical trials involving vulnerable populations (such as pediatrics), rare diseases, or emergency research conducted without informed consent under 21 CFR 50.24"¹¹⁷;
- 2) trials that involve responsible parties or submitters with a "pattern of previous noncompliance" with reporting or certification requirements pursuant to § 402(j) of the PHS Act and 42 CFR part 11;¹¹⁸ and
- 3) trials out of compliance with both § 402(j) of the PHS Act and "other statutory and/or regulatory requirements pertaining to the conduct of the trial."¹¹⁹

UAEM agrees that trials which meet any of these three criteria deserve prompt issuance of a Pre-Notice and, if noncompliance continues, a Notice of Noncompliance. UAEM's view is that Congress clearly intended for FDA, along with NIH, to monitor and enforce the compliance of every single applicable clinical trial. For reasons addressed in the previous section requesting

¹¹⁶ U.S. Food & Drug Administration, Draft Guidance for Food and Drug Administration Staff, Responsible Parties, and Submitters of Certain Applications and Submissions to the Food and Drug Administration, Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank, 83 Fed. Reg. 47926, (Nov. 20, 2018).

¹¹⁷ FDA Guidance Document (2020) at 5-6.

¹¹⁸ *Id.* at 6.

¹¹⁹ *Id.*

an increase in overall enforcement activity, comprehensive enforcement is a vital task. Commissioner Califf and other FDA officials should explore every option to allocate more agency resources to FDAAA enforcement so as to make comprehensive enforcement a reality.

At the same time, UAEM recognizes that the FDA requires resources to do its enforcement work. To the extent that FDA currently lacks resources to monitor and enforce compliance of every single applicable trial, FDA should prioritize its enforcement work, targeting the most important trials and trial results.

It is clear that the existing enforcement framework has not moved the parties responsible for some of the most important noncompliant trials to submit their missing results. As UAEM has explained above, FDA's minimal enforcement actions to date, which apparently follow the existing enforcement framework, have been incoherent. FDA's existing framework has failed to focus the agency's finite enforcement resources on obtaining and publishing the most important trial results.

FDA's new guidance should therefore commit the agency to a new, improved, and expanded enforcement prioritization framework. By "framework," UAEM means a detailed, organized, hierarchical list of enforcement priorities. Adopting and announcing such a framework will help FDA's enforcers focus on the most important missing trial results, help FDA integrate its monitoring and enforcement efforts with NIH, and help spur the parties responsible for the most important missing trial results to compliance.

c. UAEM Recommends That FDA's New Guidance Adopt UAEM's Improved and Expanded Enforcement Prioritization Framework

UAEM encourages FDA to replace the simple enforcement prioritization framework outlined in its 2020 guidance with an improved and expanded enforcement prioritization framework. UAEM provides a suggested framework here. The framework is ordered from highest priority to lowest priority, in UAEM's view. This framework is intended as a suggestion for how FDA can increase enforcement while incorporating the public health and welfare values expressed within. Issuing Pre-Notices and, as needed, Notices of Noncompliance for trials in any of the categories in this framework will promote public health, accelerate scientific research, and provide the other benefits of trial data sharing outlined above.

UAEM's Proposed Enforcement Prioritization Framework:

1. NIH-funded trials of FDA-approved products

FDA should first prioritize enforcement actions focused on NIH-funded trials of FDA-approved¹²⁰ products. By "NIH-funded" trials, UAEM means trials receiving intramural or extramural funds from NIH, including all trials sponsored by NIH or its grantees. There are several reasons to prioritize enforcement of FDAAA among this category of trials.

¹²⁰ By "FDA-approved," UAEM means not just drugs approved under 21 U.S.C. § 355 but also biologic products and medical devices approved, licensed, cleared, and registered under 21 U.S.C. §§ 360, 360e & 360j and 42 U.S.C. § 262.

First, since these trials are taxpayer-funded, public access to the data they generate is paramount. Prioritizing NIH-funded trials is a simple, categorical solution that would demonstrate FDA’s commitment to responsible stewardship of publicly funded research. Enforcement of reporting by NIH and its grantees could increase public approval of FDA’s enforcement efforts. Among responsible parties, both NIH¹²¹ and universities funded by NIH¹²² have lagged in reporting trial results to ClinicalTrials.gov, making them an urgent target for FDA enforcement.

Furthermore, because NIH funds are distributed based on merits closely scrutinized by NIH, NIH funding serves as a heuristic for identifying clinical trials which address the significant public health needs, such as those needs referenced in FDA’s first enforcement priority in the 2020 guidance.

Third-party research emphasizes the importance of NIH-funded trial data. For example, one group of researchers examined the citations in patents and publications of NIH funded research from American Medical Centers (“AMC”). They found “over a third of AMC grants resulted in publications that were cited in patents” and “about half of the new molecular entities approved over the 2000-2009 period had citations linked to NIH-funded AMC research.”¹²³ Similarly, in patents for new drugs approved by FDA between 1988 and 2005, almost two-thirds of all those receiving priority review (those drugs defined as the most innovative) cited research directly funded by the government.¹²⁴ Of the drugs approved by the FDA from 2008-2017, drugs that either “had origins in publicly supported research and development” or “originated in companies spun off from a publicly supported research program ... were more likely to receive expedited FDA approval or be designated first in class ..., indicating therapeutic importance.”¹²⁵ In short, NIH-funded trials are particularly likely to be of high importance to public health. Prioritizing NIH-funded trials is thus a simple and effective way to prioritize enforcement efforts. Indicating this enforcement priority in a guidance document would indicate FDA’s intent to optimize enforcement that promotes the public health needs identified by NIH.

Finally, prioritizing NIH-funded trials would serve FDA’s interest in increasing health equity and its obligation to adhere to the charge in the January 2021 Presidential *Executive Order On Advancing Racial Equity and Support for Underserved Communities Through the Federal*

¹²¹ Charles Piller, *supra* note 70 (<https://www.science.org/content/article/fda-and-nih-let-clinical-trial-sponsors-keep-results-secret-and-break-law>).

¹²² Universities Allied for Essential Medicines, *supra* note 1.

¹²³ Bhaven N. Sampat & Harold A. Pincus, *Citations in Life Science Patents to Publicly Funded Research at Academic Medical Centers*, 8(6) Clin. Transl. Sci. 759 (Dec. 2015), <https://pubmed.ncbi.nlm.nih.gov/26728947/>.

¹²⁴ Bhaven N. Sampat & Frank R. Lichtenberg, *What are the Respective Roles of the Public and Private Sectors in Pharmaceutical Innovation*, 30 Health Affairs 2 (2011),

<https://www.healthaffairs.org/doi/full/10.1377/hlthaff.2009.0917>. See also, Li et al., *The applied value of public investments in biomedical research*, 356 Science 6333 (Apr. 7, 2017),

<https://www.science.org/doi/10.1126/science.aal0010> (describing that between 1980 and 2007, 10% of government funded grants are directly cited by patents and 30% of grants are cited in research articles that are then cited by patents demonstrating the government funding often results in socially valuable outcomes such as medicines).

¹²⁵ Rahul K. Nayak et al., *Public sector financial support for late stage discovery of new drugs in the United States: cohort study*, 367 BMJ 5766 at *1 (Oct. 23, 2019), <https://www.bmj.com/content/bmj/367/bmj.l5766.full.pdf>.

*Government.*¹²⁶ NIH has demonstrated a commitment to increasing racial and socioeconomic justice in American healthcare since the order, and these priorities are realized in NIH’s approach to clinical trial administration and funding.¹²⁷ By prioritizing the enforcement of reporting requirements for trials run and funded by NIH, FDA can maximize the effect of NIH’s efforts to increase racial and economic justice in drug and medical device development.

Finally, UAEM specifically encourages FDA to make NIH-funded trials of FDA-approved products its highest priority for enforcement because FDA-approved drugs, vaccines, and devices are already in the widest use by patients and prescribers. When FDA approves drug and medical device products, it signals to clinicians and patients that adequate review to warrant market authorization has been conducted, confirming that the product is safe and effective when used as indicated and that the product's benefits outweigh its risks in being made available to patients. Thus, it becomes critical for patients and clinicians to have access to all results – both positive and negative – to make an informed decision about these products and assure themselves that they are using the product in a way consistent with the FDA’s approval decision.

2. Trials producing data which FDA relied upon when approving currently-FDA-approved products

a. Pivotal trials

Access to data from pivotal trials is particularly important because these data are paramount for the FDA approval process. These data not only reveal a drug’s safety and efficacy; they also provide the basis for FDA’s decision to approve a drug.¹²⁸ Pivotal trials are therefore essential to understanding how FDA approval works and to double-checking the FDA’s approval processes. Because FDA itself decides when a trial is pivotal and designates it accordingly, FDA understands the unique import of pivotal trials and the data they produce.

b. Non-pivotal supporting trials

Pivotal trials are not the only important trials that FDA reviews when deciding whether to approve a product. FDA also reviews data from non-pivotal trials, often called “supporting” trials. The multi-stage clinical trial process required by FDA evidences how FDA considers all pertinent trial data – not just data from pivotal trials but also supporting trial data – during the approval process. Although pivotal trials are particularly important, patients using FDA-approved products should have access to all data used to approve a product. Supporting trial data shape patient care, can reveal safety problems, and empower independent review of FDA’s decision making.

¹²⁶ Exec. Order No. 13.985, 86 Fed. Reg. 7009 (Jan. 20, 2021).

¹²⁷ Mike Lauer, *NIH Stands Against Structural Racism in Biomedical Research*, NIH Extramural Nexus (Mar. 1, 2021), <https://nexus.od.nih.gov/all/2021/03/01/nih-stands-against-structural-racism-in-biomedical-research/>.

¹²⁸ Joel Lexchin et al., *Regulators, Pivotal Clinical Trials, and Drug Regulation in the Age of COVID-19*, 51 Int. J. Health Serv. 1, 6 (Dec. 21, 2020) (The FDA emphasized that the term “pivotal trial” is not present in its regulations, but that it can be understood to refer to one or more trials that form the basis of its conclusion of substantial evidence of effectiveness).

3. NIH-funded trials of unapproved products

Since NIH invests in these trials using taxpayer dollars, the data produced by NIH-funded trials of unapproved products are of great interest to the public. For reasons detailed in the first enforcement criterion above, research funded by NIH is likely to address the nation's most important health needs. Although the trials in this category do not pertain to products already on the market, the importance of NIH-funded research and the fairness concerns raised by taxpayer funding warrant prioritization of these trials.

4. Phase IV trials of FDA-approved products subject to postmarketing commitments and requirements

Over the past several years, increased use of expedited review pathways, such as accelerated approval, has meant a smaller proportion of drugs is approved on the basis of high-quality pivotal trials showing clear evidence of safety and efficacy.¹²⁹ Instead, a growing proportion of drugs is approved on the basis of fewer, lower quality, or less convincing pivotal trial data. For example, as a condition for accelerated approval (and approval under some other expedited review pathways), FDA may require a manufacturer to run a Phase IV (post-approval) trial to generate more evidence of safety and efficacy. FDA also has separate authority to require other trials in specific cases, such as when there are concerns regarding the safety or efficacy of a drug in pediatric populations.¹³⁰

In this increasingly common approval and trial requirement scenario, the absence of high-quality pivotal trial data makes it more difficult for patients and clinicians to determine whether a drug is sufficiently safe and effective to warrant use in the months and years following approval. For this reason, access to the results of Phase IV trials conducted pursuant to post-marketing requirements and post-marketing commitments is crucial. The utility of post-marketing requirements is evidenced by the fact that FDA mandates them to demonstrate clinical benefits.¹³¹

5. Other trials of FDA-approved products

Enforcement is crucial for all trials of drugs and devices that are available to patients through FDA licensure, clearance, and/or approval. Because these drugs are directly available to patients and in widespread use, patients' right to information about the trials that supported their approval is important.

6. Trials for unapproved products of high importance

a. Trials for products with no proven alternative treatment

¹²⁹ Zhang et al., *Assessment of Clinical Trials Supporting US Food and Drug Administration Approval of Novel Therapeutic Agents, 1995-2017*, JAMA Network Open at 11 (Apr. 21, 2020).

¹³⁰ J. Wallach et al., *Postmarket studies required by the US Food and Drug Administration for new drugs and biologics approved between 2009 and 2012: cross sectional analysis*, 361 BMJ 1, 2 (April 16, 2018).

¹³¹ U.S. Food & Drug Administration, *Postmarketing Requirements and Commitments: Introduction* (Jan. 12, 2016), <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/postmarket-requirements-and-commitments>.

Enforcing reporting requirements for first-in-class drugs¹³² and other drug and device products without therapeutic alternatives (whether approved or unapproved) is important because patients may be solely reliant upon these treatment options. Patients' reliance makes it imperative that they, and the clinicians who care for them, have a clear understanding of their efficacy and safety. Consider, for example, the recent case of aducanumab for Alzheimer's disease: a first-in-class medicine with no therapeutic alternative.¹³³ Even before aducanumab's controversial approval, access to clinical trial results on the drug was crucial in helping clinicians understand that the drug did not demonstrate clinical efficacy and carried safety concerns.

b. Trials for products intended to address a public health emergency

Clinical trials for drugs intended to address public health emergencies, such as COVID-19, should be prioritized as well.¹³⁴ It is particularly important that the public be privy to data from these trials because data transparency could increase public trust in FDA (and NIH and the federal government more broadly) during public health emergencies. Data transparency can also empower citizens and scientists to make educated, data-backed decisions during crises.

c. Trials for products pertaining to diseases with a disproportionate impact on marginalized populations in the U.S. and abroad

FDA should prioritize trials pertaining to diseases with a disproportionate impact on marginalized populations in the U.S. and abroad. Prioritizing such clinical trials would align FDA's enforcement prioritization framework with the January 2021 Presidential *Executive Order On Advancing Racial Equity and Support for Underserved Communities Through the Federal Government*.¹³⁵ Prioritizing clinical trials that benefit historically marginalized communities could also enhance public trust in FDA by demonstrating its commitment to enhancing public health for vulnerable populations.

7. Remaining Phase III trials for unapproved products

Phase III trials are generally used to demonstrate the safety and efficacy of drug and medical device products through large-scale testing. Even if tested products are not ultimately approved, the results from such trials are important for informing further research and mitigating unnecessary repetition and waste in research and development.

8. Remaining Phase II trials for unapproved products

The results of Phase II trials are similarly important for preventing unnecessary repetition and waste in research and development. They represent the bulk of the remaining applicable

¹³² Joel Lexchin, *How Safe and Innovative Are First-in-Class Drugs Approved by Health Canada: A Cohort Study*, 12 *Healthcare Policy* 65, 66 (2016).

¹³³ G. Caleb Alexander et al., *Revisiting FDA Approval of Aducanumab*, 358 *New Eng. J. Med.* 769, 770 (Aug. 26, 2021).

¹³⁴ Commissioner Califf has himself noted as much. See Robert M. Califf, *Complete, Rapid Reporting of Clinical Trials: A Necessary Component of the Pandemic Response*, Medium (Jan. 4, 2021), <https://califf001.medium.com/complete-rapid-reporting-of-clinical-trials-a-necessary-component-of-the-pandemic-response-aa158eb1a1cb>.

¹³⁵ Exec. Order No. 13.985, 86 Fed. Reg. 7009, (Jan. 20, 2021).

clinical trials not captured by the above priorities. They, too, are subject to mandatory reporting under FDAAA.

3. FDA Should Make Pre-Notices Public via a Public Dashboard

Currently, FDA does not publish information about when and to whom it issues Pre-Notices, further reducing responsible parties' incentive to respond within 30 days. The public can track FDA's issuance of Notices of Noncompliance and civil money penalties on FDA's website,¹³⁶ but lacks information about the total number of Pre-Notices issued, which responsible parties have been targeted by Pre-Notices, and the time it takes for responsible parties take to respond. FDA can remedy this by creating a public dashboard of all enforcement actions taken, including Pre-Notices. This could be an expansion of the dashboard on Notices of Noncompliance and Civil Money Penalty Actions already hosted on FDA's website.¹³⁷ Section 801 of FDAAA made more clinical trials subject to reporting requirements partially to increase public access to information on clinical trials.¹³⁸ The ClinicalTrials.gov database is an essential tool for implementing of Section 801. The information on ClinicalTrials.gov is made public to provide information not only to healthcare providers and researchers, but also patients, loved ones, and other parties directly interested in clinical trial results reporting. Increased transparency of FDA's enforcement actions would help realize this objective of FDAAA and publicly demonstrate FDA's efforts to comply with federal regulations. Public attention to noncompliant trial sponsors who fail to respond to Pre-Notices in a timely manner may also help FDA's enforcement actions be more effective.

It is clear that Pre-Notices can be disclosed publicly. They do not contain trade secrets or confidential commercial information. FDA has already disclosed dozens of Pre-Notices to UAEM in response to a FOIA request.¹³⁹

C. Environmental Impact

UAEM claims a categorical exclusion under 21 C.F.R. § 25.30(a) and (b).

D. Economic Impact

Per 21 C.F.R. § 10.30, UAEM will submit an Economic Impact Statement upon request of the Commissioner.

E. Certification

The undersigned certify, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

¹³⁶ U.S. Food & Drug Administration, *supra* note 67 (<https://www.fda.gov/science-research/fdas-role-clinicaltrialsgov-information/clinicaltrialsgov-notices-noncompliance-and-civil-money-penalty-actions>).

¹³⁷ *Id.*

¹³⁸ *See, e.g.*, 42 U.S.C. § 282(j)(3)(B) (“The Secretary [of HHS], acting through the Director of NIH, shall ... expand the registry data bank to include the results of applicable clinical trials ... [and] ensure that such results are made publicly available through the Internet”).

¹³⁹ *See* Ramachandran et al., *supra* note 4.

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