



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health  
Bethesda, Maryland 20892

February 5, 2016

The Honorable Charles E. Grassley  
Chairman  
Committee on the Judiciary  
United States Senate  
Washington, D.C. 20510

Dear Mr. Chairman:

I am writing in response to your letter of December 23, 2015, about an article published by *STAT* in December on clinical trial reporting requirements in Section 801 of the Food and Drug Administration Amendments of 2007 (FDAAA). I share your commitment to ensuring the rapid sharing of information about clinical trials.

Your letter raised six specific questions about how clinical trial information is being reported and posted to ClinicalTrials.gov. Responses to those questions are enclosed.

The National Institutes of Health (NIH) firmly believes, as I know you do, in the significant benefits of public access to clinical trial information. Thus, we remain deeply committed to carrying out the mandate set out for us in Section 801. Not only does public access provide a way for the public to identify trials in which they may be eligible to participate, it also helps inform future research, improve study design, and prevent duplication of unsafe or unsuccessful trials. In addition, we recognize that there is an important ethical dimension to dissemination of clinical trial results because individuals who volunteer to participate in such studies, and who may assume risks related to that participation, trust that what we learn will contribute to knowledge about human health. We also know that enhancing transparency can affirm public trust in clinical research.

I would like to update you on the efforts we have made in the last year to advance the implementation of Section 801. As you know, Section 801 included a provision calling on us to make certain determinations via rulemaking, including whether to require submission of results from applicable clinical trials of products that are unapproved, unlicensed, or uncleared. Given that the rationale for requiring access to trial results applies just as much, if not more, to trials of products that are not yet on the market, the Notice of Proposed Rulemaking (NPRM) that we issued in November 2014 included a requirement to submit results from trials of those products (<https://www.gpo.gov/fdsys/pkg/FR-2014-11-21/pdf/2014-26197.pdf>). To address concerns that such a requirement would undermine commercial competitiveness, we proposed allowing a longer time period for results submission (up to two years beyond the one-year deadline for trials involving approved products). The NPRM has provided additional guidance to the regulated community about which trials are subject to the law as well as details about the registration and results data elements that are to be submitted.

The NPRM comment period closed in March 2015, and we received roughly 900 comments, the vast majority of which were supportive of the NPRM proposals. About 100 submissions discussed specific provisions of the NPRM and some suggested changes. We are currently working with the Food and Drug Administration (FDA) to consider the public comments and develop the final rule.

Further reflecting our commitment to ensuring access to clinical trial information, the NIH issued a draft policy in tandem with the release of the NPRM that will hold NIH-funded clinical trials to an even higher standard of transparency (<https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-019.html> and <https://www.federalregister.gov/articles/2015/02/13/2015-02994/announcement-of-a-draft-nih-policy-on-dissemination-of-nih-funded-clinical-trial-information>). The draft policy called for the registration and results submission to ClinicalTrials.gov of **all** NIH-funded clinical trials, regardless of phase or type of intervention. If implemented in accordance with the specific roles and terms described in the draft policy, this would mean that NIH-funded phase 1 trials of products regulated by the FDA and trials of interventions that do not involve FDA-regulated products, e.g., behavioral or surgical interventions, will also be required to register and submit results. The NIH policy is a further recognition that the dissemination of research results is both fundamental to our research mission and particularly important when the research involves clinical trials. We intend to issue a final policy along with the final rule.

Although reporting of clinical trial information to ClinicalTrials.gov is not yet what it should be, our data suggest that the rates of results reporting over the last several years are improving. We believe some of the improvement may be attributed to greater awareness of the reporting requirements due to outreach efforts, particularly with the attention raised by the publication of the NPRM and the draft NIH policy. We expect that the publication of the final rule will lead to still further improvement because there will be greater clarity provided about which clinical trials are subject to the law, when results must be reported, and when and how to seek a certification to delay submission. The regulatory provisions will help us identify applicable clinical trials more easily, detect when their results are due, and remind responsible parties of their obligations. As a result, the final rule will also facilitate taking enforcement actions against responsible parties when compliance is not achieved. When the NPRM and draft policy were released for public comment, we highlighted NIH's commitment to ensuring that clinical trial transparency is fully realized for the benefit of research participants, patients, and the general public (<http://jama.jamanetwork.com/article.aspx?articleid=1939045>). I can assure you that we are as resolved as ever to bringing this vital public health law and policy to fruition.

We appreciate your ongoing interest in and support for transparency of clinical trial information.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Francis S. Collins".

Francis S. Collins, M.D., Ph.D  
Director

Enclosure

## NIH Responses to Questions Raised by Senator Grassley's Letter of December 23, 2015

- 1. For the last two years that data are available (calendar, fiscal or whatever period of account used), how many clinical trials of all types should have had information reported to NIH? Please categorize the type of responsible party for these clinical trials (industry, hospitals, academic institutions, federal government etc.).*

Due to current ambiguities in the law and an absence of independently verifiable information about all existing clinical trials being conducted worldwide, it is not possible to determine, with certainty, which trials registered with ClinicalTrials.gov are “applicable clinical trials” under the Food and Drug Administration Amendments Act of 2007 (FDAAA) or whether all applicable clinical trials are registered. We used the existing imperfect data available to us on ClinicalTrials.gov to identify trials that we believe are highly likely to be applicable clinical trials. We refer to these as “probable applicable clinical trials” (ACTs) or “pACTs.” In calendar years (CY) 2014 and 2015, there were 10,025 trials registered at ClinicalTrials.gov that appear to meet the criteria of an applicable clinical trial subject to FDAAA.<sup>1</sup> Of these pACTs, 4,802 (48 percent) were funded by industry, 739 (7 percent) by the NIH, and 4,484 (45 percent) by other (academic, non-profit, other government organizations).

In general, results of an applicable clinical trial of a drug, biologic, or device that is approved, licensed, or cleared by the Food and Drug Administration (FDA) must be submitted by the Responsible Party no later than 12 months after the Primary Completion Date, but can be up to 3 years after the primary completion date for certain ACTs. Applicable clinical trials that evaluate drugs or devices that are not yet approved by the FDA are not currently required to submit results. One challenge in determining which trials require results is knowing, based on the information in a study record on ClinicalTrials.gov, whether the trial involves an unapproved product. Sponsors may submit a “certification” to indicate that the trial reached its Primary Completion Date before the drug, biologic, or device was approved, licensed, or cleared by the FDA. However, if this certification is not filed (which is not currently required), it is not possible to detect with the existing data elements if the trial involves an unapproved product and therefore is excluded from the results submission requirements. In our estimates below, however, we assume that studies involve approved products (and thus must submit results) unless they have filed a certification.

To estimate the number of registered pACTs that should report results over a 2-year period, we identified pACTs with results due in CY 2013 or CY 2014 (i.e., pACTs completed in CY 2012 or CY 2013). Using these two years allows for enough time to enable us to study late submissions, as requested (and as discussed in the recent report in *STAT*),<sup>2</sup> and to allow for completion of the review process. The review process in place at ClinicalTrials.gov is designed

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<sup>1</sup> Probable applicable clinical trials (pACTs) subject to FDAAA were derived from the following data elements currently available in ClinicalTrials.gov: Study Type = Interventional AND Phase ≠ 0 or 1; AND (IND/IDE = Yes OR Intervention Type = Drug, Biologic, or Device AND Location = at least 1 site in U.S.) AND Primary Completion Date > December 2007.

<sup>2</sup> It should be noted that the report in *STAT*, as with other similar articles, is necessarily hampered by not having access to certain existing data that is not publicly posted and by the absence of certain data on all existing trials (as discussed above).

to determine whether the submitted results information is adequate for posting (i.e., information appears valid, is meaningful, logical, and internally consistent). This review process frequently identifies issues that require correction before the record can be posted on ClinicalTrials.gov. Thus, there may be more than one submission round and it takes time for the Responsible Party to resolve all issues.

Since the launch of the results database in September 2008, we estimate that the overall rate of results reporting for pACTs that have been completed is 64 percent. By sector, the rates are 71 percent for industry trials, 61 percent for extramural NIH-funded trials, 93 percent for intramural NIH-funded trials, and 46 percent for other government and academic trials. For pACTs that may have results due in CY 2013 and CY 2014 the rates are summarized in Table 1.

Table 1. Registered probable applicable clinical trials (pACTs) that may have results due in CY 2013 or CY 2014 and overall estimated rate of results submission					
Data as of 12/30/2015	# Registered pACTs That May Have Results Due in CY 2013 or CY 2014				
Organization Type	Total	Results Posted	Results Submitted (Not Yet Posted)	Delayed Results*	Results Posted or Submitted OR Delayed Results**
Industry	4,001	1,854	201	571	2,626 (66%)
Other	1,888	627	215	18	860 (46%)
NIH	891	473	84	20	577 (65%)
Total	6,780	2,954	500	609	4,063 (60%)

\* Trials for which the Responsible Party submitted a certification or extension request to delay results.

\*\* Trials for which summary results are posted on ClinicalTrials.gov OR submitted and not yet posted (including those pending first review, failed first review and pending subsequent review, waiting for Responsible Party to resubmit), OR certification or extension request to delay results.

**2. For the same two years as question 1, how many of the required clinical trial reports were received on time? How many have not been received at all? Of those that were received late please provide an average and/or mean time until the required materials were received.**

In general, results must be submitted no later than 12 months after the Primary Completion Date, but can be up to 3 years after the Primary Completion Date for certain ACTs. However, if the drug, biologic, or device evaluated in the trial was not approved, licensed, or cleared, then results may not be due at all as trials of unapproved products are not required to have results submitted. If the product does gain FDA approval, licensure, or clearance, then results are generally required to be submitted within 30 days of such an action. It is, therefore, possible that results submitted after the Primary Completion Date are being submitted on time in accordance with the requirements of the FDAAA.

Of the estimated 6,780 pACTs that may have results due in CY 2013 or CY 2014, 60 percent (n=4,063) had either submitted results or a certification or extension request to delay results

submission. Of these, 2,954 records have results posted on ClinicalTrials.gov and 39 percent (n=1,161) of these records with results posted were received on or before one year after the Primary Completion Date. Of those records that were submitted more than one year after the Primary Completion Date (n=1,793), the average and median number of days late was 233 days and 182 days (Interquartile Range 76–133), respectively. Additional details about the distribution are available in Table 2.

Table 2. Timing of submission of results information for pACTs that may have results due in CY 2013 or CY 2014 and with results posted on ClinicalTrials.gov		
Data as of 12/30/2015	# Registered pACTs That May Have Results Due in CY 2013 or CY 2014	
Results Submission Date as Compared to 1 Year After Primary Completion Date*	Total pACTs with Results Posted (n=2954)	Percent of Total pACTS with Results Posted
On time or early	1,161	39.4%
Up to 1 month late	225	7.6%
2 - 3 months late	282	9.6%
4 - 6 months late	384	13.0%
7 – 12 months late	506	17.2%
More than 12 months late	396	13.4%

\* Results submitted more than one year after the Primary Completion Date (e.g., 30 days after product approval) may still be on time in accordance with the current FDAAA requirements.

**3. For the same two years as question 1, what was the average time it took from receipt of clinical trial data for NIH to post the information in the registry data bank?**

When a study record with results is submitted, it is reviewed by a ClinicalTrials.gov staff member before it is posted. This review focuses on apparent validity (when possible), meaningful entries, logic and internal consistency, and formatting.<sup>3</sup> The Responsible Party may be asked to clarify items or make corrections to the record before it is posted. Based on current volume and staffing, this review may take up to 30 days. It then takes additional time for the Responsible Party to address the issues and resubmit the record. In general, about one quarter to one third of the time it takes from initial submission to posting is accounted for by the ClinicalTrials.gov review process and the remaining time is the time required for the Responsible Party to adequately revise and resubmit the study record.

For the 2,954 pACTs that may have results due in CY 2013 or CY 2014 and that have results posted, the average time from the submission of results information to the posting of results information was 93 days. The median time was 55 days (Interquartile Range 29–113). Once a record is determined to meet the review criteria, it generally takes 2-5 days to be processed and posted on ClinicalTrials.gov.

<sup>3</sup> ClinicalTrials.gov Review of Results Submissions:  
<https://prsinfo.clinicaltrials.gov/ResultsDetailedReviewItems.pdf>

**4. *For the same two years as question 1, how timely and how often did NIH post the required notices that submissions were late or not received at all?***

To date, no notices have been posted, as the posting of a notice of violation requires other regulatory action to occur before such notice can be posted. However, there has been much activity by both NIH and FDA to inform people of the ClinicalTrials.gov requirements and responsibilities. These efforts have taken place since FDAAA was passed and have included outreach and follow-up with the clinical trial community.

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. In order to inform a full enforcement program, FDA undertook a pilot enforcement project in 2013 and 2014 that resulted in the issuance of 14 pre-notice of non-compliance letters. Each of the recipients of the letters subsequently submitted results to ClinicalTrials.gov, and no further regulatory action by FDA was needed nor was it necessary for the NIH to post notices of non-compliance.

**5. *Over the last five years, what efforts, if any, has NIH made to see that violations of these reporting requirements resulted in penalties being assessed for the responsible party? Have any penalties been assessed for violations of the clinical trial reporting requirements over the last five years?***

No penalties have been assessed over the last five years. The final rule will facilitate taking enforcement actions against responsible parties when compliance is not achieved. These compliance actions may include withholding funding when the trial is NIH funded. When the trial is subject to Section 801, the FDA may assess monetary penalties after other regulatory actions are taken. When a trial is subject only to NIH policy, we will be able to use our own enforcement tools, which include withholding funding of future grants, to ensure compliance.

**6. *Please describe the steps NIH has taken and will take to see that clinical trials conducted by its own scientists, as well as those conducting work under an NIH grant, will comply with these reporting requirements.***

The NIH and ClinicalTrials.gov staff have taken a number of steps to educate grantees on the FDAAA submission requirements. There is comprehensive information on the ClinicalTrials.gov web site under the Submit Studies section (<https://clinicaltrials.gov/ct2/manage-recs>), as well as on the NIH Office of Extramural Research (OER) web site for grantees ([https://grants.nih.gov/ClinicalTrials\\_fdaaa/](https://grants.nih.gov/ClinicalTrials_fdaaa/)). This information not only describes the FDAAA requirements, but also provides detailed information on how to establish an account, register a study, and submit results. These requirements are also covered at the NIH OER Regional Seminars that train grantees on NIH grant obligations. ClinicalTrials.gov staff frequently speak at conferences to educate those involved in clinical research on the reporting requirements. In addition, NIH and ClinicalTrials.gov staff publish

related research articles in widely disseminated journals in order to reach a diverse audience (<https://clinicaltrials.gov/ct2/resources/pubs>).

To further assist responsible parties in complying with the FDAAA, ClinicalTrials.gov staff have developed reports that are accessible to account holders in the data submission system, known as the Protocol Registration and Results System (PRS). The system provides reports to account holders on the status of the records in their account and records with “problems” are easily identifiable on the home page after logging in. These “problem” records include those that may require updates (under FDAAA records must be updated at least once per year) and records that may be overdue for results submission. In addition to the reports available within the system in real-time, ClinicalTrials.gov sends automated reminders every six months to Responsible Parties when there are records in their accounts that are flagged as needing updates or that may need results entered.

PRS has also undergone extensive evaluation and revision to make the process for submitting results as straightforward as possible. However, because many investigators (primarily from academic institutions) are using the system for the first time it can be a steep learning curve. To address this, ClinicalTrials.gov has invested in training individuals at academic institutions who can be a resource for their investigators. This training has been in the form of two-day train-the-trainer workshops in which practical, hands-on training is provided to give trainees an in-depth understanding of FDAAA and experience in using the data entry system to fulfill the results submission requirements. While this training has been successful, many institutions still do not have a resource person(s) available to investigators. To fill this gap, ClinicalTrials.gov staff also provides one-on-one assistance to any investigator or data submitter who may need help. A staff member will host a teleconference (or series of teleconferences) to understand what results information the investigator has available and walk them through the results submission process from start to finish. Over the past year, ClinicalTrials.gov has hired additional results reviewers to expand this successful one-on-one assistance program.