

Draft Questions and Answers on the Clinical Trials NPRM

1. Why is HHS just issuing the NPRM now? Hasn't FDAAA been in place since 2007, and haven't researchers already been registering and reporting results at ClinicalTrials.gov for several years?

The NPRM is being issued both to clarify the registration and results requirements established by FDAAA and to address specific issues that the law directs HHS to consider via rulemaking. Those issues include:

- whether summary results information must be submitted for applicable clinical trials for which the products under study are still unapproved, uncleared, or unlicensed,
- whether written summaries of the trial and its results must be submitted as part of results reporting, and
- whether the full protocol or other information on the protocol must be submitted with results information to assist users in understanding the results of a clinical trial.

While responsible parties have been submitting registration and results information to ClinicalTrials.gov pursuant to FDAAA since December 2007 and September 2008, respectively, the NPRM clarifies a number of the statutory requirements, which clinical trials meet the definition of an applicable clinical trial and are subject to FDAAA), who will be considered the responsible party who must submit required information, what constitutes an adequate description of a “study design”, which baseline measures must be submitted as part of results information, how does a responsible party submit a request to extend the deadline for results submission.

2. The law required regulations to be in place by 2010 - what took so long?

FDAAA specifies that regulations were to be issued on certain issues within three years of enactment; these include whether to require summary results submission for unapproved, uncleared, and unlicensed products, whether to require submission of written summaries of the clinical trial and its results, and whether to require submission of the full protocol or other information on the protocol to assist in understanding the results of a clinical trial. These are complex issues on which public comment was gathered during a public meeting organized in April 2009.

Many additional issues also needed to be clarified via a regulation to facilitate compliance and enforcement, such as what information must be provided, which clinical trials are subject to FDAAA, and who will be considered the responsible party for submitting information. The law itself is complex and close collaboration with FDA was needed to ensure consistency of our regulatory proposals with relevant FDA regulations and procedures. Development of the NPRM therefore took considerable time.

We note that even as the draft regulations were under development, NIH expanded the ClinicalTrials.gov registry and results data bank so that responsible parties could meet their

obligations under the law. We have used the experience gained in operating ClinicalTrials.gov since enactment of FDAAA to inform the proposals contained in this NPRM.

3. What is new in the NPRM? What are the most significant proposals in the NPRM?

Among the more significant changes to current practice, the NPRM:

- Proposes to require results information to be submitted for *all* registered applicable clinical trials, regardless of whether the drugs, biological products, or medical devices under study have been approved, licensed, or cleared by the FDA. Under FDAAA results information is required only for registered applicable clinical trials for which the studied drugs, biological products, or devices have been approved, licensed, or cleared for marketing by the FDA.
- For applicable clinical trials of unapproved, unlicensed, and uncleared products that are still under development, the NPRM would permit results submission to be delayed as long as 3 years after the completion date of the trial.
- In addition, the NPRM proposes certain additional data elements, not listed in the statute, that must be submitted at the time of registration or results submission to provide a more complete description of the trial and assist users in interpreting the results.
- The NPRM also proposes that some submitted information be updated more frequently than is current practice.
- The NPRM would also require a responsible party to submit or link to an existing expanded access record if a drug studied in an applicable clinical trial is available outside the clinical trial through an expanded access program of updates that must occur.

A list of major changes is available here: ([link to docket](#)) or at [ClinicalTrials.gov](#).

4. How long after the 90 day comment period do you expect a final rule?

We will move as quickly as possible after the public comment period ends to consider the comments and prepare a final rule. The amount of time that will take will depend on the number of comments received and the issues they raise, but NIH will give the NPRM a very high priority.

5. Why are phase 1 trials of FDA-regulated drugs and biologics and small feasibility studies of devices not covered by FDAAA? Why are behavioral interventions or observational studies not subject to FDAAA?

That is a question that only Congress can answer. The NRPM follows the definition of an applicable clinical trial specified in FDAAA, which includes interventional studies of drugs and biological devices and specifically excludes phase 1 studies.

6. How many phase 1 clinical trial protocols are under way in a given year?

We can't answer that question definitively. Phase 1 studies are not required to register with ClinicalTrials.gov. Still, of the 20,000 studies registered with ClinicalTrials.gov in 2013, approximately 2,600 were listed as phase 1 (including phase 0) studies of drugs or biological

products. FDA would have information on the number of phase 1 clinical trials that were submitted under an IND in a given year.

7. Does ClinicalTrials.gov contain registration and results for all clinical trials conducted anywhere in the world?

No. ClinicalTrials.gov is the largest and most complete clinical trial registry and results database in the world, with more than 170,000 registered clinical studies being conducted in the US and in more than 180 countries – and summary results of more than 13,000 of those studies. But it does not include all clinical trials. Under FDAAA only those trials that meet the definition of an “applicable clinical trial” and were initiated after Sept 27 2007 or ongoing as of December 26, 2007 are required to register – and only those for which the products under study are approved, licensed, or cleared by the FDA have to submit summary results. [Applicable clinical trials consist of controlled, interventional studies (clinical trials) of FDA-regulated drugs and devices, (including pediatric postmarket surveillance of a device) other than phase 1 studies of drugs and small feasibility studies of devices]. In addition, many investigators register studies in response to other policies, including that of the International Committee of Medical Journal Editors, which requires trial registration prior to enrollment of the first subject a prerequisite for considering a manuscript for publication. Many other institutions also have policies to encourage trial registration.

8. How many clinical trials are registered annually in ClinicalTrials.gov? How many of these are NIH-funded trials?

In 2013, about 20,000 clinical studies were newly registered with ClinicalTrials.gov. Most of these (about 80 percent) do not appear to be subject to FDAAA, e.g., because they are phase 1 trials, small feasibility studies of devices, trials of other types of interventions, such as behavioral or surgical interventions, or observational studies, or they do not appear to be subject to FDA regulation. About 1,300, or 7 percent, of the 20,000 indicate they received NIH support of some kind. Some of the data elements we are proposing to require at the time of registration would help us generate more precise estimates of the numbers of registered trials that are subject to FDAAA and/or are supported by NIH.

9. How many currently registered applicable clinical trials are also required to submit results? How many have not done so?

Currently, summary results information must be submitted to ClinicalTrials.gov only for applicable clinical trials of drugs, biological products, or devices that have been approved, licensed, or cleared for marketing by the FDA. Based on information available in ClinicalTrials.gov today, XX registered trials appear to be applicable clinical trials that are more than 12 months beyond their completion date. But we do not have information in ClinicalTrials.gov to know whether the products under study are approved, licensed, or cleared for marketing by the FDA or whether a study is investigating a new use of a product. Hence, we cannot determine from information available in ClinicalTrials.gov itself how many of these clinical trials owe results information. The information we propose to collect in the NPRM will enable us to develop more precise estimates of the levels of compliance with the FDAAA and

regulatory requirements. The NPRM also proposes that results information be required of applicable clinical trials of unapproved, unlicensed, and uncleared products, although it proposes to allow the deadline for results submission to be delayed with certification that the product(s) studied in the clinical trial are still under development and/or are being studied for a new use.

10. Why weren't trials of unapproved products required to report results before the NPRM?

FDAAA specifies mandatory results reporting only for trials of drugs, biological products, and medical devices that had been approved, licensed, or cleared by the FDA. FDAAA directs the Secretary to determine via rulemaking whether to require the submission of results information for applicable clinical trials of products that are not approved, licensed, or cleared, and, if so, to establish the timeline for such submissions. Consideration of this issue entails weighing the public health benefits of access to such information against commercial interests in keeping such summary results proprietary. The NPRM proposes to require the submission of results information for trials of unapproved products, which we believe has considerable public health benefit – not the least of which is to avoid unnecessary duplication of trials, including trials of products that have been shown to be unsafe or ineffective. But also to provide access to information that is known about similar or related products and to address well-supported concerns that negative trial results are less likely to be published. Importantly, making the results publicly accessible acknowledges society's ethical responsibility to the individuals who volunteered in these studies with an understanding that their participation would contribute to advancing medical knowledge.

To balance commercial interests, we propose to provide industry with an opportunity to delay results submission by as much as two years beyond the initial deadline (of 12 months after the completion date) if they certify that they are continuing to develop the product and may seek marketing approval at a future date (i.e., they have not abandoned product development). This provides up to three years of exclusivity to the summary results information before it would have to be submitted to ClinicalTrials.gov.

11. How many more trials will be required to report results under the requirements in the proposed rule?

We estimate in the NPRM that the proposed rule would require results submission for approximately 7,400 clinical trials per year. This compares to an estimate of 1,845 clinical trials under the existing information collection. In 2013, ClinicalTrials.gov received approximately summary results of XXXX clinical trials.

12. Who is responsible for enforcing the requirements for submitting information to ClinicalTrials.gov?

FDAAA establishes two sets of possible enforcement actions for noncompliance.

(1) Under provisions of the Food and Drug Administration Amendments Act of 2007 (FDAAA), and through a delegation of authority from the Secretary of Health and Human Services, FDA

has authority for certain enforcement activities. The failure to submit required clinical trial information or the submission of false or misleading information to the ClinicalTrials.gov database under FDAAA, is a “prohibited act” under the Federal Food, Drug, and Cosmetic Act (FD&C Act). There also are provisions for assessment of civil money penalties for violations of the provisions of the FD&C Act related to ClinicalTrials.gov. FDA has the authority to enforce the FD&C Act.

(2) NIH and other federal agencies that fund applicable clinical trials also have enforcement responsibilities under FDAAA. If an applicable clinical trial is funded in whole or in part by a grant from NIH or any agency of HHS, the agency must verify that clinical trial information for each applicable clinical trial for which a grantee is the responsible party has been submitted before releasing any remaining funding for a grant or funding for a future grant to such grantee. The agency must provide notice to such a grantee and allow 30 days to correct noncompliance and submit the required clinical trial information.

Non-compliance must be made public through a notification in ClinicalTrials.gov record. Regarding NIH-funded trials, NIH is developing procedures to monitor compliance and meet our obligation under the law to verify the submission of required information. We will communicate our compliance plans to the NIH-funded community separately at a future date. Right now, we are looking to clarify the regulatory requirements and seek public comment on the proposals contained in the NPRM. The NPRM will both establish the basis against which compliance will be measured and proposes the submission of certain data elements that would enable more accurate and meaningful monitoring of compliance

13. What aspects of compliance and enforcement will change with publication of the NPRM?

Regarding NIH-funded trials, NIH is developing procedures to monitor compliance and meet our obligation under the law to verify the submission of required information. We will communicate our compliance plans to the NIH-funded community separately at a future date. Right now, we are looking to clarify the regulatory requirements and seek public comment on the proposals contained in the NPRM. The NPRM will both establish the basis against which compliance will be measured and proposes the submission of certain data elements that would enable more accurate and meaningful monitoring of compliance.

14. How have HHS, FDA or NIH enforced the law to date?

As a general matter, NIH, FDA, and HHS have worked with industry, academia, and other government agencies in a variety of ways to encourage compliance with the statutory provisions. These have included presentations at numerous conferences, responding to media inquiries, publishing articles, and sending general letters to submitters and grantees. Information is included in grant notices, grant agreements, and announcements specifically identifying requirements related to ClinicalTrials.gov, including the obligation to certify in annual grant reports that the responsible party has submitted clinical trial information as required by FDAAA. NIH has focused on educating the affected stakeholders about their legal requirements, enhancing the ClinicalTrials.gov system, and drafting the NPRM. Our efforts to inform affected

stakeholders about the FDAAA requirements has aimed to improve compliance by ensuring that they understand the requirements and procedures for submitting the required information to ClinicalTrials.gov. Effective enforcement relies on clear requirements; we expect that publication of the final rule will facilitate enforcement.

Other steps that NIH and FDA have taken to increase compliance are listed here

NIH:

- *Working with NIH institutes and centers to inform NIH-funded clinical investigators about their statutory obligations;*
- *Revising the NIH grants website (used by other agencies, including FDA) to include specific information concerning the requirements related to submitting information to ClinicalTrials.gov;*
- *Based on a review of certain ClinicalTrials.gov databank information NIH sent a series of communications (identified as “nudging” messages) to ClinicalTrials.gov record holders identifying issues that may have needed updating in the record holders’ data submission*

FDA:

- *implementing the requirement to submit a Certification of Compliance, Form FDA 3674, with certain submissions to FDA;*
- *promulgating a rule at 21 CFR 50.25(c) which requires a specific statement relating to posting of clinical trial information at ClinicalTrials.gov be included in informed consent documents for applicable clinical trials;*
- *training clinical investigators on the statutory requirements;*
- *training FDA staff on the requirements related to ClinicalTrials.gov;*
- *including information relating to the statutory requirements in various FDA guidances; and,*
- *undertaking cooperative efforts with NIH to inform ClinicalTrials.gov record holders of statutory responsibilities and potential non-compliance.*

Information on FDA’s role in ClinicalTrials.gov can be found at <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/FDAsRoleClinicalTrials.govInformation/default.htm>.

15. Has FDA assessed any civil money penalties under the statute?

This question should be directed to the FDA.

16. Has NIH withheld funding for a grantee that was out of compliance with FDAAA?

To date, NIH has not withheld any funding for a grantee that was out of compliance with FDAAA requirements. As with any compliance and enforcement effort associated with a new statutory responsibility, significant efforts have been devoted to providing information and

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assistance to the affected parties to encourage compliance and to ensure an understanding of the responsibilities. Final rulemaking will help to clarify the statutory provisions and requirements and enable additional enforcement of the statute.

17. ClinicalTrials.gov contains records for NIH-supported trials for which no results have been submitted. Why hasn't NIH withheld funding from these grantees?

The databank contains many trials that are not subject to the FDAAA statutory provisions. The type of trial, the dates during which the trial was conducted, and other factors determine whether a particular clinical trial must be registered, and there are additional provisions that determine whether a responsible party for an applicable clinical trial must submit results for posting. Under the statute, results submission is required only for certain applicable clinical trials of products that have been approved, licensed, or cleared by FDA. In addition, there are specific statutory limitations on the posting of clinical trial information for certain applicable device clinical trials. It also is possible that results have been submitted but not yet posted on the public databank record.

It is often not possible to determine which parties may be noncompliant based solely on the information in the record that is publicly posted on the ClinicalTrials.gov website. Significant analysis is necessary to evaluate whether a responsible party has not complied with the statutory requirements; this analysis may involve consideration of non-public information submitted to FDA under FDA's regulations and other provisions of the FD&C Act, as well as information that may be held by NIH that is not publicly posted.

18. There have been published articles describing clinical trials which do not have results posted to ClinicalTrials.gov. Do those articles contain accurate data about which trials are out of compliance?

NIH and FDA are aware of a number of articles that describe apparent discrepancies in the reporting of results for clinical trials registered on ClinicalTrials.gov. It is important to recognize that the databank contains many trials that are not subject to the FDAAA statutory provisions. The type of trial, the dates during which the trial was conducted, and other factors determine whether a particular clinical trial must be registered. Under the statute, results submission is required only for certain applicable clinical trials of drugs, biological products, and devices that have been approved, licensed, or cleared by FDA. In addition, there are specific statutory limitations on the posting of clinical trial information for certain applicable device clinical trials.

19. Prayle, et al published data in the British Medical Journal (BMJ) showing that only 22% of the trials subject to FDAAA had reported results within one year of completion of the trial. Did you review this article and why haven't you done anything about these records?

FDA conducted a preliminary analysis of the data that were relied on and made publicly available by the authors of the BMJ article. FDA can tell you more about the specifics of their analysis and their results.

QAs on the Draft Policy

1. Why was the draft policy developed?

The policy was developed to increase the transparency of NIH-funded clinical trials. Public access to clinical trial information drives scientific progress and optimizes the return on the nation's investment in clinical trials. It helps inform future research, improve study design, and prevent duplication of unsafe and unsuccessful trials. Dissemination of positive and negative clinical trial results can also inform patient care. In addition, 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, trust that what we learn will contribute to generalizable knowledge about human health. Finally, enhancing transparency also increases public trust in clinical research.

The policy will ensure ~~for~~ that all NIH-funded clinical trials, whether funded through grants, contracts, or the intramural research program, are held to the same high standard for registration and results reporting as those subject to FDAAA. Recent studies have added to a growing body of evidence that an unacceptable number of NIH-funded clinical trial results are not being published. The policy provides another avenue for investigators to disseminate their results.

2. How is the draft policy different from the FDAAA NPRM?

The draft policy applies to all NIH-funded awardees and investigators conducting clinical trials, funded in whole or in part by NIH, regardless of the study phase, or type of intervention. The FDAAA NPRM applies only to applicable clinical trials, whether NIH-funded or not. However, the draft policy is also complementary in that it will expect investigators to submit the same type of registration and results information and in the same timeframes as investigators subject to the law.

3. Why are you issuing this as a policy not a regulation?

A policy approach is standard for NIH, and we have used it before to promote broad access to research results. Examples include the NIH Data Sharing Policy, Model Organism Sharing Policy, and Genomic Data Sharing Policy.

4. The draft policy says that NIH “expects” investigators to register and submit results to ClinicalTrials.gov. Why not make it a requirement? How will the expectation be enforced?

While the policy is an expectation, once an applicant accepts NIH funding, policy expectations become a term and condition of award. We anticipate that the scientific community will recognize the value of registration and results submission and willingly fulfill the terms of the policy. However, should an investigator fail to meet reporting deadlines or

to respond to efforts to remedy non-compliance, NIH may take enforcement actions, including termination of funding, consistent with 45 CFR 74.62 and/or other authorities.

5. Why does the draft policy require registration and results submission for phase 1 clinical trials? Why doesn't the NPRM include phase 1 trials?

There are a number of reasons why sharing clinical trial results is important, and they all apply to phase 1 trials as well as later stage trials (which generally involve more participants). Sharing information about phase1 trials has a particular ethical imperative given that they focus on assessing the safety of the intervention. The NPRM does not include phase 1 trials because FDAAA excludes them from the requirement. We recognize that private sector commercial interests must also be considered in the development of laws that apply across all types of funders and performers of research. Since the NIH policy applies only to NIH-funded investigators, those considerations do not apply in most situations. .

6. Since the draft policy applies to phase 1 trials, but the NPRM does not, will the private sector have concerns about collaborating with NIH funded investigators in the development of new interventions?

We don't anticipate that the NIH Policy will discourage public-private partnerships. Considerable information about NIH-funded phase 1 trials is already in the public domain via our grants information system, and this transparency has not been an impediment to public-private partnerships. Also, most phase 1 trials are likely to involve unapproved products or new uses of approved products, and, if the sponsor intends to continue development, with an eye toward submitting a marketing application, they will have an opportunity to delay results submission as long as 3 years after the completion date of the trial. These time frames provide sufficient time to pursue any intellectual property filings deemed necessary. For clinical trials funded through SBIRs that are not subject to FDAAA, the timeframe for reporting results will follow the SBIR Policy Directive, which generally prohibits the agency from releasing SBIR data for at least four years from completion of the study unless the awardee consents to an earlier release. However, NIH will encourage SBIR awardees to adhere to the Policy's reporting timeframes.

7. The draft policy applies to NIH-funded investigators "who have committed to NIH that they will comply with this policy." How is this commitment obtained and documented?

The commitment is reflected in the institutional official's signature on applications to NIH, and is a term and condition of award that takes effect as soon as the awardee accepts NIH funds.

8. What will happen if an investigator fails to comply?

We anticipate that the scientific community will recognize the value of registration and results submission and willingly fulfill the terms of the policy. While we do not anticipate the need for extensive enforcement actions, if an investigator fails to meet reporting

deadlines or to respond to efforts to remedy non-compliance, NIH may take enforcement actions, including termination of funding, consistent with 45 CFR 74.62 and/or other authorities. Intramural investigators will be required to follow the policy, and there will be similar consequences for failing to do so, e.g., suspension of support. NIH-funded investigators who are out of compliance with the NIH policy will not, however, be subject to the civil monetary penalties in FDAAA unless they are also subject to FDAAA.

9. Why is the clinical trial definition in the NIH draft policy different from the definition in the FDAAA NPRM?

The wording of the two definitions is slightly different because the NIH definition of clinical trial, which is what is used in the policy, more clearly reflects the scope of NIH-funded clinical trials. For example, NIH supports trials involving behavioral interventions. Behavioral interventions are not regulated by FDA and, therefore, are not subject to the registration and reporting requirements under FDAAA.

10. Who is responsible for registration and results submission under the NIH policy, the institution or the investigator?

Both have responsibilities under the draft NIH policy. The investigator, who is responsible for the conduct of the trial and the data gathered from it, is responsible for carrying out the registration and results submission. The extramural institution that receives an award is accountable for ensuring that NIH policy expectations are fulfilled. An NIH funded trial that meets the definition of an applicable clinical trial described in the NPRM and is required to be registered or have results submitted under the NPRM must be registered and have results submitted by the responsible party, as that term is defined in the NPRM.

11. What effect does submission of results to ClinicalTrials.gov have on the ability to publish of the trial results?

The submission of clinical trial results to ClinicalTrials.gov should have no effect on the ability to publish an analysis of the trial results in a scientific journal. The International Committee of Medical Journal Editors issued a policy in 2004 that requires registration of a clinical trial in a public registry, such as ClinicalTrials.gov, in order to be considered for publication. The ICMJE policy also encourages the posting of clinical trial results in public registries and states that a public posting of results will not be considered a prior publication of those results if they are presented in a structured format. See <http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html>

12. The draft policy does not spell out the details of what information should be submitted. How will investigators know what to submit?

Clinical trials covered by the policy will be expected to submit the same type of registration and results data and in the same timeframes as the trials subject to FDAAA. The specific

registration and results information to be submitted will be indicated at the ClinicalTrials.gov site.

13. When will the draft policy be finalized? What will the effective date be?

The draft policy, like the NPRM, is being issued for a 90-day public comment period. NIH will consider the public comments before finalizing the policy. The effective date of the final Policy will be determined after the public comment process is completed.

14. We have heard investigators complain about how long it takes to submit their results to ClinicalTrials.gov. They say the database is hard to use. Shouldn't the database be redesigned before moving forward with this policy?

The data submission system is undergoing important upgrades, and additional resources are being devoted to improving the data submission process to streamline the data submission task. These improvements will be helpful to current users as well as investigators who will be expected by the policy to submit results. While we know that summarizing clinical trial results is not always a simple task, it is important that those results be made available for all of NIH-funded clinical trials.