What Changes From Current Practice Are Proposed in the NPRM?

The Notice of Proposed Rulemaking (NPRM) proposes several changes to current requirements and practices for submitting data to ClinicalTrials.gov under FDAAA. The most significant of those proposed changes are summarized below. The NPRM also provides greater explication of many elements of current requirements and practices. For a complete discussion of the proposed changes from current requirements and practices, please review the NPRM itself, which is available in docket number NIH-2011-0003 at www.regulations.gov. Comments on the NPRM may be submitted to the docket for consideration by the agency as it prepares the final rule.

Under the proposed rule:

1. **Additional data elements would be required for registration and results submission**. Some data elements that are currently optional in ClinicalTrials.gov would be required, and some new data elements not yet available in ClinicalTrials.gov would be required. *See* proposed sections 11.28 and 11.48. Tables 1 and 2 summarize the proposed changes to registration and results data elements, respectively

2. **Results information would be required for ALL applicable clinical trials that are required to register,** not just those for which the drugs or devices studied are approved, licensed, or cleared. *See* proposed section 11.42. The proposed timeline for submitting results information is specified in proposed section 11.44.

3. **An expanded access record would be required if a drug studied in an applicable clinical trial is available through an expanded access program.** The data elements to be submitted as part of an expanded access record are listed in proposed section 11.28(c) of the NPRM. Multiple applicable clinical trials could link to the same expanded access record if they all study the same drug.

4. **Some data elements would have to be updated more frequently**. While most updates to submitted data elements would be required once a year, several data elements would need to be updated 15 or 30 days after a change. *See* proposed section 11.64. Table 3 provides a summary of the data elements with shorter update times.

5. **Determining whether a clinical trial is an applicable clinical trial (ACT) would be based on registration data elements.** A responsible party would no longer be asked to submit a separate data element to indicate whether a clinical trial is an ACT. Instead an algorithm based on registration data elements would determine whether a clinical trial meets the definition of an ACT. Several new registration data elements are proposed to assist in this determination. *See* proposed section 11.22(b).

6. **Corrections to submitted information would be required within 15 days.** Responsible parties would be required to correct within 15 days any errors that are identified during NLM's quality review or subsequently. *See* proposed section 11.66.

Table 1. Proposed Changes to Clinical Trial Registration Information Data Elements (Proposed §11.28(a))

The table below lists the clinical trial registration information data elements that the NPRM proposes to require responsible parties to submit to ClinicalTrials.gov. The "Currently Required" column shows the data elements that currently must be submitted in order for registration information to be accepted by Clinical Trials.gov. The "Currently Optional" column shows other data elements that may be submitted now. The "Added by NPRM" column shows new data elements that would be required under the NPRM. All data elements currently collected in ClinicalTrials.gov, i.e., the "Currently Required" and "Currently Optional" elements, are collected under OMB PRA clearance OMB Control No: 0925-0586.

Required in NPRM	Provision No. in §11.28(a)	Currently Required	Currently Optional	Added by NPRM	Comments
Descriptive Information					
Brief Title	(1)(i)	X			
Official Title	(1)(ii)		X		
Brief Summary	(1)(iii)	X			
Primary Purpose	(1)(iv)		X		Specifically enumerated in FDAAA
Study Design	(1)(v)	X			Propose changing from requiring at least one subelement to requiring all subelements
Interventional Study Model			X		Subelement of Study Design, (1)(v)
Number of Arms			X		Subelement of Study Design, (1)(v)
Arm Information (e.g., Label, Type, Description, Designation)			X		Subelement of Study Design, (1)(v)
Allocation			X		Subelement of Study Design, (1)(v)
Masking			X		Subelement of Study Design, (1)(v)
Single Arm Controlled?				X	Propose adding to assist in determining if a trial is an ACT
Study Phase	(1)(vi)	X			Propose removing "Phase 0" as an acceptable entry (consistent with FDA terminology)
Study Type	(1)(vii)	X			
Whether the Study is a Pediatric Post-market Surveillance of a Device	(1)(viii)			X	Cleared by OMB [Control No: 0925-0586] but not yet implemented in CT.gov
Primary Disease or Conditions Being Studied in the Trial	(1)(ix)	X			
Intervention Name	(1)(x)	X			
Other Intervention Name(s)	(1)(xi)		X		
Intervention Description	(1)(xii)		X		

Required in NPRM	Provision No. in §11.28(a)	Currently Required	Currently Optional	Added by NPRM	Comments
Intervention Type	(1)(xiii)	X			
Studies an FDA-Regulated Device	(1)(xiv)			X	Propose adding to assist in determining if a trial is an ACT
Studies an FDA-Regulated Drug	(1)(xv)			X	Propose adding to assist in determining if a trial is an ACT
U.S. FDA Approval, Licensure, or Clearance Status	(1)(xvi)			X	Cleared by OMB [Control No: 0925-0586] but not yet implemented in CT.gov.
Product Manufactured in the U.S.	(1)(xvii)			X	Propose adding to assist in determining if a trial is an ACT
Study Start Date	(1)(xviii)		X		Specifically enumerated in FDAAA
Completion Date	(1)(xiv)	X			Name changed from "primary completion date," consistent with statute
Enrollment	(1)(xx)		X		Specifically enumerated from FDAAA (as "target number of subjects")
Primary Outcome Measures (Name, Description, Time of Assessment)	(1)(xxi)	X			No longer require designation of outcome measure as "safety issue"
Secondary Outcome Measures (Name, Description, Time of Assessment)	(1)(xxii)	X			No longer require designation of outcome measure as "safety issue"
Recruitment Information					
Eligibility Criteria	(2)(i)	X			
Gender	(2)(ii)	X			
Age Limits	(2)(iii)	X			
Accepts Healthy Volunteers?	(2)(iv)		X		Specifically enumerated in FDAAA
Overall Recruitment Status	(2)(v)	X			
Why Study Stopped?	(2)(vi)		X		Required if Overall Recruitment Status changes to "terminated," "suspended," or "withdrawn."
Actual Enrollment	(2)(vii)		X		Currently an "update" to Enrollment, but propose separating out for clarity
Individual Site Status	(2)(viii)	X			
Availability of Expanded Access	(2)(ix)		X		Specifically enumerated in FDAAA.
Location and Contact Information					
Name of the Sponsor	(3)(i)	X			
Responsible Party, by Official Title	(3)(ii)	X			

Required in NPRM	Provision No. in §11.28(a)	Currently Required	Currently Optional	Added by NPRM	Comments
Facility Information (Facility Name, Facility Location, and Facility Contact or Central Contact)	(3)(iii)	X			
Administrative Data					
Unique Protocol Identification Number	(4)(i)	X			
Secondary IDs (including ID Type)	(4)(ii)		X		Specifically enumerated in FDAAA ("other unique protocol identification numbers, if any). Propose requiring ID Type (e.g., grant number, other registry number) for each Secondary ID submitted
Food and Drug Administration IND or IDE number (Center, Number, Sequence)	(4)(iii)	X			Propose requiring sequence number to be included for IDEs
Record Verification Date	(4)(v)	X			
Responsible Party Contact Information	(4)(vii)	X			
Human Subjects Protection Review Board Status	(4)(iv)	X			Currently required only for trials without an IND or IDE. NPRM proposes it for all trials.

Notes.

- Definitions for these proposed clinical trial registration information data elements and subelements are provided in §11.10(b).
- "Studies an FDA-Regulated Device" and "Completion Date" are currently both labeled as "(1)(xiv)" in the draft NPRM and are listed as such in Table 1 for consistency. The correct provision number for "Completion Date" is "(1)(xix)."
- For a pediatric postmarket surveillance of a device or an expanded access program that is not a clinical trial (as defined in the NPRM), the responsible party would be required to submit a more limited set of the above data elements (see proposed §11.28(b) and (c)).
- Four current registration data elements are not included in the table because they are not proposed to be required by the NPRM. These data elements are: applicable clinical trial, delayed posting, oversight authorities, and human subjects protection review board information

Table 2. Proposed Changes to Clinical Trial Results Information Data Elements (Proposed §11.48(a))

The table below lists the clinical trial results information data elements that the NPRM proposes to require responsible parties to submit to ClinicalTrials.gov. The "Currently Required" column shows the data elements that currently must be submitted in order for results information to be accepted by Clinical Trials.gov. The "Currently Optional" column shows other data elements that may be submitted now. The "Added by NPRM" column shows new data elements that would be required under the NPRM. All data elements currently collected in ClinicalTrials.gov, i.e., the "Currently Required" and "Currently Optional" elements, are collected under OMB PRA clearance OMB Control No: 0925-0586.

Required by the NPRM	Provision No. in §11.48(a)	Currently Required	Currently Optional	Added by NPRM	Comments
Participant Flow					
Participant Flow Arm Information (arm/group title)	(1)(i)	X			
Pre-assignment Information	(1)(ii)		X		Propose requiring to describe significant events affecting the number of human subjects enrolled in the clinical trial but not assigned to an arm
Participant Data	(1)(iii)	X			
Demographic and Baseline Characteristics					
Baseline Characteristics Arm/Group Information	(2)(i)	X			
Overall Number of Baseline Participants	(2)(ii)	X			
Baseline Measure Information	(2)(iii)	X			
Age		X			Subelement of Baseline Measure Information, (2)(iii)
Gender		X			Subelement of Baseline Measure Information, (2)(iii)
Other			X		Propose requiring other baseline measures used in the analysis of outcome measures; Subelement of Baseline Measure Information, (2)(iii)
Name and Description of the Measure, including any categories	(2)(iii)(A)	X			
Measure Type and Measure of Dispersion	(2)(iii)(B)	X			
Unit of Measure	(2)(iii)(C)	X			
Baseline Measure Data	(2)(iv)	X			
Outcomes and Statistical Analyses					
Outcome Measure Arm/Group Information	(3)(i)	X			

Required by the NPRM	Provision No. in §11.48(a)	Currently Required	Currently Optional	Added by NPRM	Comments
Analysis Population Information	(3)(ii)	X			
Number of Participants	(3)(ii)(A)	X			If unit analyzed is other than human subject, must specify the unit of analysis (e.g., eyes, lesions)
Number of Units Analyzed	(3)(ii)(B)	X			If unit analyzed is other than human subject, must specify the unit of analysis (e.g., eyes, lesions)
Analysis Population Description	(3)(ii)(C)		X		Propose requiring if analysis population differs from number of subjects assigned to the arm.
Outcome Measure Information	(3)(iii)	X			
Name of the Specific Outcome Measure	(3)(iii)(A)	X			
Description of the Metric Used	(3)(iii)(B)		X		Proposed to improve the specificity of information provided about the outcome measurement
Time Point(s) at which the Measurement was Assessed	(3)(iii)(C)	X			
Outcome Measure Type	(3)(iii)(D)	X			
Outcome Measure Reporting Status	(3)(iii)(E)	X			
Measure Type (including Measure of Dispersion/Precision)	(3)(iii)(F)	X			
Unit of Measure	(3)(iii)(G)	X			
Outcome Measure Data (number or descriptive statistics)	(3)(iv)	X			
Statistical Analyses	(3)(v)		X		Currently optional, but elements below are required if statistical analyses submitted
Statistical Analysis Overview (including identification of arms compared, type of statistical test conducted, and, for a non-inferiority test, a description that includes power calculation and non-inferiority margin)	(3)(v)(A)	X			Propose adding requirement to include a power calculation and non-inferiority margin for a non-inferiority test.
Statistical Test of Hypothesis (p-value and procedure used)	(3)(v)(B)	X			
Method of Estimation (estimation parameter, estimated value, and confidence interval)	(3)(v)(C)	X			
Adverse Event Information					

Required by the NPRM	Provision No. in §11.48(a)	Currently Required	Currently Optional	Added by NPRM	Comments
Table of all serious adverse events grouped by organ system, with the number and frequency of each event by arm or comparison group	(4)(i)(A)	X			
Table of all adverse events, other than serious adverse events, that exceed a frequency of 5 percent within any arm of the clinical trial, grouped by organ system, with the number and frequency of each event by arm or comparison group.	(4)(i)(B)	X			
Each table to include the following data elements:					
Adverse Event Arm/Comparison Group Information (Title and Description)	(4)(ii)(A)	X			
Total Number Affected, by Arm or Comparison Group	(4)(ii)(B)	X			
Total Number at Risk, by Arm or Comparison Group	(4)(ii)(C)	X			
Total Number Affected, by Organ System	(4)(ii)(D)			X	Propose adding to improve understanding/ comparability of AE information across arms
Total Number at Risk, by Organ System	(4)(ii)(E)			X	Propose adding to improve understanding/ comparability of AE information across arms
Adverse Event Information	(4)(ii)(F)	X			
Descriptive term for the adverse event	(4)(ii)(F)(1)	X			
- Organ system associated with the adverse event	(4)(ii)(F)(2)	X			
Adverse Event Data	(4)(ii)(G)	X			
- Number of human subjects affected by such adverse event	(4)(ii)(G)(1)	X			
- Number of human subjects at risk for such adverse event	(4)(ii)(G)(2)	X			
Additional Adverse Event Description	(4)(ii)(H)		X		Propose requiring if AE collection is based on a definition different from that proposed in NPRM
Administrative Information					
Results Point of Contact	(5)(i)	X			
Certain Agreements	(5)(ii)	X			

Notes.

- The NPRM proposes that results information (as listed in Table 2) be submitted for applicable clinical trials of unapproved/unlicensed/uncleared products as well as for applicable clinical trials of products that are approved, cleared or licensed.
- The NPRM would continue to permit responsible parties to voluntarily submit non-serious adverse events that occur with a frequency of 5% or less in any arm of the trial. The responsible party would continue to be required to indicate any alternative threshold used.
- Three results data elements that are currently optional in ClinicalTrials.gov and not required by the statute are not listed in the table because they are not proposed in the NPRM. These elements are timeframe for AE collection, assessment type, and total number of events. The NPRM requests comment on the potential benefit and burden of requiring them.

Table 3. Proposed Data Elements for More Rapid Updating (Proposed §11.60)

Proposed section 11.64 of the NPRM specifies that all clinical trial information submitted to ClinicalTrials.gov must be updated not less than once every 12 months, unless there are no changes to report. The NRPM further proposes that some data elements be updated more rapidly, as summarized in Table 2 below. The NPRM also proposes that all registration data elements be reviewed and updated, as necessary, at the time clinical trial results information is submitted. See sections III.C.13 and IV.D.3 of the preamble and proposed section 11.64 for a more complete elaboration and specification of these proposed requirements.

Data Element	Proposed deadline for updating (i.e., not later than the specified date)
Study Start Date	30 days after the first subject is enrolled (if the first human subject was not enrolled at the time of registration).
Intervention Name	30 days after a nonproprietary name is established.
Availability of Expanded Access	30 days after expanded access becomes available (if available after registration) or is terminated; and 30 days after an NCT number is assigned to a newly created expanded access record. [1]
Expanded Access Status	30 calendar days after a change in the availability of expanded access.
Overall recruitment status	30 calendar days after any change in overall recruitment status [2]
Individual site status	30 days after a change in status of any individual site
Human subjects review board status	30 calendar days after a change in status
Completion date	30 days after the clinical trial reaches its actual completion date
Responsible party, by official title	not later than 30 calendar days after a change in the responsible party or the official title of the responsible party
Responsible party contact information	30 calendar days after a change in the responsible party or the contact information of the responsible party
U.S. FDA approval clearance or licensing status	15 calendar days after a change in status has occurred
Any changes pursuant to a protocol amendment	30 calendar days after a protocol amendment is approved by a human subjects protection review board, if a protocol is amended in such a manner that changes are communicated to human subjects in the clinical trial.
Record verification date	Immediately, any time the responsible party reviews the complete set of submitted clinical trial information for

	accuracy, even if no other updated information is submitted at that time

Notes:

1. If expanded access to a drug becomes available after a clinical trial of that drug has been registered and an expanded access record has not yet been created, the responsible party must also, not later than 30 calendar days after expanded access becomes available, submit the data elements listed in proposed §11.28(c) to create an expanded access record.
2. If Overall Recruitment Status is changed to "suspended," "terminated," or "withdrawn," the Why Study Stopped data element must be submitted at the time the update is made. If Overall Recruitment Status is changed to "terminated" or "active, not recruiting," the Actual Enrollment data element must be submitted at the time the update is made.