Changes from Current Practice Described in the Final Rule

Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11)

The final rule describes the requirements and practices for submitting information to ClinicalTrials.gov under FDAAA. Some of the changes from current practice are summarized below. For a complete discussion of the requirements and changes from current practices, please review the final rule itself, which is available in docket number NIH-2011-0003 at www.regulations.gov.

Under the final rule:

1. **Additional data elements are required for registration and results information submission**. Some data elements that are currently optional when submitting information to the ClinicalTrials.gov Protocol Registration and Results System (PRS) will be required, and some new data elements not yet available in the PRS will be required. The full protocol and statistical analysis plan (if separate from the protocol) will also be required with results information. *See* 42 CFR 11.28 and 11.48. Tables 1 and 2 summarize the changes to registration and results information data elements, respectively.

2. **Results information is required for ALL applicable clinical trials that are required to register,** not just those for which the drug, biological, or device products studied are approved, licensed, or cleared. This requirement applies to applicable clinical trials with a primary completion date on or after January 18, 2017. *See* 42 CFR 11.42. The standard deadline for results information submission is no later than one year after the primary completion date; the final rule permits delayed submission of results information under certain circumstances. The timelines for submitting results information are specified in 42 CFR 11.44.

3. **An expanded access record is required if an investigational drug product studied in an applicable drug 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 42 CFR 11.28(c) of the final rule. This requirement must be fulfilled by responsible parties who are both the manufacturer of the investigational product and the sponsor of the applicable clinical trial. Only one expanded access record will be created for each investigational drug product; multiple applicable clinical trials will link to the same expanded access record if they all study the same investigational drug product.

4. **Some data elements must be updated more frequently than the standard 12 months**. Several data elements must be updated within 30 days of a change, and one in 15 days. *See* 42 CFR 11.64(a). For clinical trials initiated on or after January 18, 2017, Table 3 provides a summary of the data elements with shorter update times.

5. **Responsible parties can evaluate whether a clinical trial is an applicable clinical trial (ACT) based on required registration data elements.** A responsible party will be able to evaluate, based on their registration information, whether or not their study is an ACT. Several new required registration data elements will assist in this evaluation. *See* 42 CFR 11.22(b).

6. **Corrections to submitted information will be required within 15 days (for registration information) and 25 days (for results information).** Responsible parties will be required to correct or address within 15 days (for registration information) and 25 days (for results information) any apparent errors, deficiencies and/or inconsistencies that are identified during NLM's quality control review process. *See* 42 CFR 11.64(b)(1). Responsible parties will also be required to correct or address any errors that they identify on their own, including after quality review by NLM is complete. *See* section 11.64(b)(2).

Table 1. Final Rule Clinical Trial Registration Information Data Elements That Apply to Applicable Clinical Trials Subject to 42 CFR 11.28(a)(2)

The table below summarizes the clinical trial registration information data elements in 42 CFR 11.28(a)(2) that responsible parties must submit to ClinicalTrials.gov for applicable clinical trials (ACTs) initiated on or after January 18, 2017. The "Required" column shows the data elements required for registration information submission to be accepted by the ClinicalTrials.gov Protocol Registration and Results System (PRS) before the changes in the final rule. The "Optional" column shows other data elements that could be submitted to the PRS before the changes in the final rule.

Data Elements Required in Final Rule	Provision No. in 42 CFR 11.28(a)(2)	ClinicalTrials.gov PRS Pre-Final Rule Status		Comments
		Required	Optional	
Descriptive Information				
Brief Title	(i)(A)	X		Also provide acronym for title, if any
Official Title	(i)(B)		X	
Brief Summary	(i)(C)	X		
Primary Purpose	(i)(D)		X	Specifically enumerated in FDAAA. Added "device feasibility" to assist in determining if a trial is an ACT.
Study Design	(i)(E)	X		Changed from requiring at least one sub-element to requiring all sub-elements
Interventional Study Model			X	Sub-element of Study Design, (i)(E)
Number of Arms			X	Sub-element of Study Design, (i)(E)
Arm Information (e.g., Label, Type, Description, Designation)		X	X	Sub-element of Study Design, (i)(E). Included both required and optional components before the final rule.
Allocation			X	Sub-element of Study Design, (i)(E)
Masking			X	Sub-element of Study Design, (i)(E)
Study Phase	(i)(F)	X		For an applicable drug clinical trial, removed "Phase 0" for consistency with FDA terminology (designate as "Phase 1")
Study Type	(i)(G)	X		

Data Elements Required in Final Rule	Provision No. in 42 CFR 11.28(a)(2)	ClinicalTrials.gov PRS Pre-Final Rule Status		Comments
		Required	Optional	
Pediatric Postmarket Surveillance of a Device Product	(i)(H)			For an applicable device clinical trial that is a Pediatric Postmarket Surveillance of a Device Product
Primary Disease or Condition Being Studied in the Trial, or the Focus of the Study	(i)(I)	X		
Intervention Name(s)	(i)(J)	X		For each intervention studied
Other Intervention Name(s)	(i)(K)		X	For each intervention studied
Intervention Description	(i)(L)		X	For each intervention studied
Intervention Type	(i)(M)	X		For each intervention studied
Studies a U.S. FDA-regulated Device Product	(i)(N)			Assists in determining if a trial is an ACT
Studies a U.S. FDA-regulated Drug Product	(i)(O)			Assists in determining if a trial is an ACT
Device Product Not Approved or Cleared by U.S. FDA	(i)(P)		X	If any studied intervention is a device product.
Post Prior to U.S. FDA Approval or Clearance	(i)(Q)			Optional for an applicable device clinical trial that studies at least one device product not previously approved or cleared by the U.S. FDA
Product Manufactured in and Exported from the U.S.	(i)(R)			Assists in determining if a trial is an ACT. Required only if the entry for U.S. Food and Drug Administration IND or IDE Number data element indicates that there is no IND or IDE for the clinical trial, and the entry(ies) for Facility Information include no facility locations in the United States or its territories.
Study Start Date	(i)(S)		X	Specifically enumerated in FDAAA
Primary Completion Date	(i)(T)	X		Name changed from “completion date” in statute for easier recognition, but definition remains consistent with FDAAA.
Study Completion Date	(i)(U)		X	Assists in determining when obligation to update or correct clinical trial information ends

Data Elements Required in Final Rule	Provision No. in 42 CFR 11.28(a)(2)	ClinicalTrials.gov PRS Pre-Final Rule Status		Comments
		Required	Optional	
Enrollment	(i)(V)		X	Specifically enumerated in FDAAA (as "target number of subjects")
Primary Outcome Measure Information (Name, Description, Time of assessment)	(i)(W)	X		For each primary outcome measure
Secondary Outcome Measure Information (Name, Description, Time of assessment)	(i)(X)	X		For each secondary outcome measure
Recruitment Information				
Eligibility Criteria	(ii)(A)	X		
Sex/Gender	(ii)(B)	X		
Age Limits	(ii)(C)	X		
Accepts Healthy Volunteers	(ii)(D)		X	Specifically enumerated in FDAAA
Overall Recruitment Status	(ii)(E)	X		
Why Study Stopped	(ii)(F)		X	Required if Overall Recruitment Status changes to "terminated," "suspended," or "withdrawn."
Individual Site Status	(ii)(G)	X		
Availability of Expanded Access	(ii)(H)		X	Specifically enumerated in FDAAA. If expanded access is available for an investigational drug product (including a biological product), an expanded access record must be submitted in accordance with § 11.28(c).

Data Elements Required in Final Rule	Provision No. in 42 CFR 11.28(a)(2)	ClinicalTrials.gov PRS Pre-Final Rule Status		Comments
		Required	Optional	
Location and Contact Information				
Name of the Sponsor	(iii)(A)	X		
Responsible Party, by Official Title	(iii)(B)	X		
Facility Information (Facility Name, Facility Location, and Facility Contact or Central Contact)	(iii)(C)	X		
Administrative Data				
Unique Protocol Identification Number	(iv)(A)	X		
Secondary ID (including ID Type)	(iv)(B)		X	Specifically enumerated in FDAAA ("other unique protocol identification numbers, if any"). ID Type required (e.g., grant number, other registry number) for each Secondary ID submitted.
U.S. Food and Drug Administration IND or IDE number (Center, Number, Serial Number)	(iv)(C)	X		Serial number required for INDs
Human Subjects Protection Review Board Status	(iv)(D)	X		
Record Verification Date	(iv)(E)	X		
Responsible Party Contact Information	(iv)(F)	X		

Notes:

- Definitions for these clinical trial registration information data elements and sub-elements are provided in 42 CFR 11.10(b).
- For a pediatric postmarket surveillance of a device that is not a clinical trial or an expanded access program (as defined in the final rule), the responsible party would be required to submit a more limited set of the above data elements (see 42 CFR 11.28(b)(2) and (c)).
- Four registration data elements available in ClinicalTrials.gov before the final rule are not included in the table because they are not required by the final rule. These data elements are: FDA-regulated intervention, Section 801 clinical trial oversight authorities, and human subjects protection review board information (other than Human Subjects Protection Review Board Status).

Table 2. Final Rule Clinical Trial Results Information Data Elements That Apply to Applicable Clinical Trials Subject to 42 CFR 11.48(a)

Table 2 summarizes the clinical trial results information data elements in 42 CFR 11.48(a) that responsible parties must submit to ClinicalTrials.gov for applicable clinical trials (ACTs) with a primary completion date on or after January 18, 2017. The "Required" column shows the data elements required for results information to be accepted by the Clinical Trials.gov Protocol Registration and Results System (PRS) before the changes in the final rule. The "Optional" column shows other data elements that could be submitted to the PRS before the changes in the final rule.

Data Elements Required in Final Rule	Provision No. in 42 CFR 11.48(a)	ClinicalTrials.gov PRS Pre-Final Rule Status		Comments
		Required	Optional	
Participant Flow				
Participant Flow Arm Information	(1)(i)	X		
Pre-assignment Information, if any	(1)(ii)		X	
Participant Data (number of human subjects that started and completed the clinical trial, by arm)	(1)(iii)	X		If assignment is based on a unit other than participants, also include a description of the unit of assignment (e.g., eyes, lesions) and number of units that started and completed the clinical trial, by arm
Demographic and Baseline Characteristics				
Baseline Characteristics Arm/Group Information	(2)(i)	X		
Baseline Analysis Population Information	(2)(ii)			
Overall Number of Baseline Participants	(2)(ii)(A)	X		
Overall Number of Units Analyzed	(2)(ii)(B)			If the analysis is based on a unit other than participants, a description of the unit of analysis (e.g., eyes, lesions)
Analysis Population Description	(2)(ii)(C)		X	If the Overall Number of Baseline Participants (or units) differs from the number of human subjects (or units) assigned to the arm
Baseline Measure Information	(2)(iii)	X		
Age		X		Sub-element of Baseline Measure Information, (2)(iii)
Sex/Gender		X		Sub-element of Baseline Measure Information, (2)(iii)
Race, ethnicity (if collected under the protocol)			X	Sub-element of Baseline Measure Information, (2)(iii)

Data Elements Required in Final Rule	Provision No. in 42 CFR 11.48(a)	ClinicalTrials.gov PRS Pre-Final Rule Status		Comments
		Required	Optional	
Other measure(s)			X	Sub-element of Baseline Measure Information, (2)(iii). Any other measure(s) that were assessed at baseline and are used in the analysis of the primary outcome measure(s).
Name and Description of the Measure, including any categories that are used to submit Baseline Measure Data	(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		
Number of Baseline Participants (and Units)	(2)(v)			If different from Overall Number of Baseline Participants or Overall Number of Units Analyzed
Outcomes and Statistical Analyses				
Outcome Measure Arm/Group Information	(3)(i)	X		
Analysis Population Information	(3)(ii)	X		
Number of Participants Analyzed	(3)(ii)(A)	X		
Number of Units Analyzed	(3)(ii)(B)	X		If the analysis is based on a unit other than participants, a description of the unit of analysis (e.g., eyes, lesions)
Analysis Population Description	(3)(ii)(C)		X	If Number of Participants Analyzed or Number of Units Analyzed differs from the number of human subjects or units 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	
Time Point(s) at which the Measurement was Assessed	(3)(iii)(C)	X		
Outcome Measure Type	(3)(iii)(D)	X		
Measure Type and Measure of Dispersion or Precision	(3)(iii)(E)	X		

Data Elements Required in Final Rule	Provision No. in 42 CFR 11.48(a)	ClinicalTrials.gov PRS Pre-Final Rule Status		Comments
		Required	Optional	
Unit of Measure	(3)(iii)(F)	X		
Outcome Measure Data	(3)(iv)	X		
Statistical Analyses	(3)(v)		X	Optional in PRS before the final rule, but elements below were required if statistical analyses submitted
Statistical Analysis Overview (including identification of arms compared, type of statistical test conducted, and, for a non-inferiority or equivalence test, a description that includes the power calculation and non-inferiority or equivalence margin)	(3)(v)(B)(1)	X		
One of the following, as applicable:	(3)(v)(B)(2)			
Statistical Test of Hypothesis (p-value and procedure used)	(3)(v)(B)(2)(i)	X		
Method of Estimation (estimation parameter, estimated value, and confidence interval (if calculated))	(3)(v)(B)(2)(ii)	X		
Adverse Event Information				
Information to describe the methods for collecting adverse events	(4)(i)			
Time Frame	(4)(i)(A)		X	
Adverse Event Reporting Description	(4)(i)(B)		X	If adverse event information collected in the clinical trial is collected based on a different definition of adverse event and/or serious adverse event defined in 42 CFR Part 11
Collection Approach	(4)(i)(C)		X	The type of approach taken to collect adverse event information, whether systematic or non-systematic

Data Elements Required in Final Rule	Provision No. in 42 CFR 11.48(a)	ClinicalTrials.gov PRS Pre-Final Rule Status		Comments
		Required	Optional	
Information for completing three tables summarizing anticipated and unanticipated adverse events collected	(4)(ii)			
Table of all serious adverse events grouped by organ system, with the number and frequency of each event by arm or comparison group	(4)(ii)(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)(ii)(B)	X		
Table of all-cause mortality, with the number and frequency of deaths due to any cause by arm or comparison group	(4)(ii)(C)			
Information for each table specified in paragraph (4)(ii)	(4)(iii)			
Adverse Event Arm/Group Information	(4)(iii)(A)	X		
Total Number Affected, by Arm or Comparison Group	(4)(iii)(B)	X		
Total Number at Risk, by Arm or Comparison Group	(4)(iii)(C)	X		
Adverse Event Information for the two tables described in paragraphs (4)(ii)(A) and (B)	(4)(iii)(D)	X		Does not apply to the table of all-cause mortality
Descriptive term for the adverse event	(4)(iii)(D)(1)	X		
Organ system associated with the adverse event	(4)(iii)(D)(2)	X		
Adverse Event Data for the two tables described in paragraphs (4)(ii)(A) and (B)	(4)(iii)(E)	X		Does not apply to the table of all-cause mortality
Number of human subjects affected by such adverse event	(4)(ii)(E)(1)	X		
Number of human subjects at risk for such adverse event	(4)(ii)(E)(2)	X		

Data Elements Required in Final Rule	Provision No. in 42 CFR 11.48(a)	ClinicalTrials.gov PRS Pre-Final Rule Status		Comments
		Required	Optional	
Protocol and Statistical Analysis Plan				
Protocol and Statistical Analysis Plan	(5)			A copy of the protocol and the statistical analysis plan (if not included in the protocol)
Administrative Information				
Results Point of Contact	(6)(i)	X		
Name or official title of the point of contact	(6)(i)(A)	X		
Name of the affiliated organization	(6)(i)(B)	X		
Telephone number and email address of the point of contact	(6)(i)(C)	X		
Certain Agreements	(6)(ii)	X		

Notes:

- The final rule requires 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 final rule will continue to permit responsible parties to submit non-serious adverse events that occur with a frequency of 5% or less in any arm of the trial, but would continue to require them to indicate any alternative threshold used.

Table 3. Data Elements for More Rapid Updating for Clinical Trials Initiated On or After January 18, 2017 (42 CFR 11.64(a)(1)(ii))

For clinical trials initiated on or after January 18, 2017, section 11.64(a)(1)(ii) of the Final Rule specifies update requirements. In general, clinical trial information submitted to ClinicalTrials.gov must be updated not less than once every 12 months. The Final Rule further requires that some data elements be updated more rapidly, as summarized in Table 3 below. In addition, the Final Rule requires that if a protocol is amended in such a manner that changes are communicated to human subjects in the clinical trial, updates to any relevant clinical trial information must be submitted not later than 30 calendar days after the protocol amendment is approved by a human subjects protection review board. See section IV.D.3 of the preamble and 42 CFR 11.64 for a more complete elaboration and specification of these requirements.

Data Element	Deadline for Updating (i.e., not later than the specified date)
Study Start Date	30 calendar days after the first subject is enrolled (if the first human subject was not enrolled at the time of registration).
Intervention Name(s)	30 calendar days after a nonproprietary name is established.
Availability of Expanded Access	30 calendar days after expanded access becomes available (if available after registration); and 30 calendar 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.
Expanded Access Type	30 calendar days after a change in the type(s) of available expanded access.
Overall Recruitment Status	30 calendar days after a change in overall recruitment status. [2]
Individual Site Status	30 calendar days after a change in status of any individual site.
Human Subjects Protection Review Board Status	30 calendar days after a change in status.
Primary Completion Date	30 calendar days after the clinical trial reaches its actual primary completion date.
Enrollment	At the time the primary completion date is changed to "actual," the actual number of participants enrolled must be submitted.
Study Completion Date	30 calendar days after the clinical trial reaches its actual study completion date.
Responsible Party, by Official Title	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 for the responsible party.
Device Product Not Approved or Cleared by U.S. FDA	15 calendar days after a change in approval or clearance status has occurred.
Record Verification Date	Any time the responsible party reviews the complete set of submitted clinical trial information for accuracy and not less than every 12 months, even if no other updated information is submitted at that time.

Notes:

1. If expanded access to an investigational drug product becomes available after a clinical trial of that drug product has been registered and an expanded access record has not yet been created, a responsible party who is both the manufacturer of the investigational product and the sponsor of the applicable clinical trial must also, not later than 30 calendar days after expanded access becomes available, submit the data elements in accordance with §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.