UCDAVIS HEALTH

Compliance Department
RESEARCH COMPLIANCE MEMORANDUM

To: UCD Health Chairs & Chief Administrator Officers
From: Nirali Patel, Compliance Manager
Kathy Olson, Research Compliance Analyst
Re: Department of Health and Human Services Final Rule & National Institutes of Health Complementary Policy
Date: January 18, 2017

Introduction

In 2000, ClinicalTrials.gov was created to establish a registry of clinical trials involving investigational drugs as a result of the Food and Drug Administration Modernization Act of 1997 (FDAMA). Subsequently, the FDA Amendments Act of 2007, Section 801 (FDAAA 801) required additional types of trials to register on the ClinicalTrials.gov website and submit certain data elements.

Recently, in September 2016, the Department of Health and Human Services (DHHS) issued a Final Rule clarifying and expanding the registration and results information submission requirements under FDAAA 801. In parallel to the Final Rule, the National Institutes for Health (NIH) issued a complementary policy outlining the requirements for registering and submitting results information to ClinicalTrials.gov. Both the Final Rule and the NIH Policy have effective dates of January 18, 2017, and will impact all new studies and some existing studies at UD Davis Health. The following is a summary of the registering and data submission requirements contained in the Final Rule and NIH Policy that impact many of our researchers.

1. Which trials must register and submit results on ClinicalTrials.gov?

Under the new rules, the studies that must register and report results on ClinicalTrials.gov are[1]:

A. Clinical trials funded in whole or in part by NIH, only when the NIH application/proposal or IRB approval is received on or after January 18, 2017[2]; and

B. Applicable Clinical Trials (ACT), which include:
- Studies initiated after September 27, 2007, or initiated on or before that date and were still ongoing as of December 26, 2007;
- Interventional Studies or Studies that involve a pediatric postmarket surveillance of a device[3];
- Studies involving a U.S. FDA Regulated Drug, Biologic, or Device Product;
- Studies that do not include Phase 1 (drug and biological product);

[1] Note: While not discussed in detail in this memorandum, studies that intend to publish in journals governed by the International Committee of Medical Journal Editors (ICMJE) are also required to register on ClinicTrials.gov and may have additional requirements pursuant to ICMJE guidelines. For more information, please see: http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

[2] Trials that use NIH-supported infrastructure but receive no other NIH funds for the conduct of a specific clinical trial are not subject to the NIH Policy.

[3] *See* 42 CFR 11.22(b)(1)(i)

- Studies where the primary purpose is not device feasibility (device products); and
- Studies where any of the following apply: (1) Trial site has one or more locations in the United States, (2) trial is conducted under an FDA investigational new drug application or investigational device exemption, or (3) trial involves a drug, biologic, or device that is manufactured in the United States or its territories and is exported for research.

2. Who is responsible for complying with these rules?

A single Responsible Party must be designated to register and submit results information via the ClincalTrials.gov website. The Responsible Party is defined as:

- The sponsor of the clinical trial; or

- The principal investigator (PI), if designated by a sponsor, grantee, contractor, or awardee, so long as the PI is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of requirements for the submission of clinical trial information.

Practically, it is crucial for researchers to understand whether a trial sponsor will be complying with the requirements or if the study personnel (i.e., the Principal Investigator) are responsible for compliance.

3. What are the registration and results requirements?

Under the new rules, there are two primary categories of required activities on ClinicalTrials.gov: (A) Registration and (B) Results Submissions.

A. Registration

All eligible studies must register online at ClincalTrials.gov[4]. The studies that must register include: all ACTs with a *study start date*[5] on or after January 18, 2017; and all NIH funded studies where the NIH application/proposal or IRB approval was received on or after January 18, 2017.

Studies must register no later than 21 days after the first subject enrollment[6]. Registration information must also be updated no less than once every 12 months, although certain information may be required to be updated more frequently[7]. In addition, an expanded access registration is required if an investigational drug product studied in an applicable drug clinical trial is available through an expanded access program. Only one expanded access record will be created for each investigational drug product, although multiple applicable clinical trials can be linked to the same record if they study the same product. For more information, *See* 42 CFR 11.28 (c) of the Final Rule.

[4] *See* https://clinicaltrials.gov/ct2/manage-recs/how-register#StepsForRegistering
[5] Study Start Date is the estimated date on which the clinical trial will be open to enrollment of human subjects, or if the clinical trial has enrolled the first human subject, the actual date on which the first human subject was enrolled. *See* 42 CFR 11.10(b)(16)
[6] *See* Appendix A for registration data requirements.
[7] *See* Appendix B for submission timing requirements.

B. **Results**

In addition to meeting the registration requirements, certain studies must also input results information on the ClinicalTrials.gov website. These studies include: ACTs with a *primary completion date*[8] on or after January 18, 2017; and all NIH funded studies where the NIH application/proposal or IRB approval was received on or after January 18, 2017. Studies must generally report results within 1 year of the primary completion date[9]. Data must be updated no less than once every 12 months, although certain information may be required to be updated more frequently[10].

4. What are the possible penalties for non-compliance?

Failure to comply with the Final Rule and NIH Policy requirements may have significant implications for both researchers and the institution. Possible penalties include: criminal proceedings, civil penalties up to $10,000 per day, and the withholding or loss of DHHS and NIH funds for individual researchers and the institution.

Additional Resources:

The Final Rule: https://www.federalregister.gov/documents/2016/09/21/2016-22129/clinical-trials-registration-and-results-information-submission.

Final Rule information, resources and training: https://prsinfo.clinicaltrials.gov

NIH Policy: https://federalregister.gov/d/2016-22379

[8] Primary Completion Date is (1) Date the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, (2) If multiple primary outcome measures, the date on which data collection is completed for all of the primary outcomes, or (3) Estimated date updated to actual primary completion date.

[9] *See* Appendix C for reporting results data requirements, and 42 CFR 11.48 for more information on when delays are allowed.

[10] *See* Appendix B for submission timing requirements.

Appendix A

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		

Source: https://clinicaltrials.gov

Appendix A

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

Source: https://clinicaltrials.gov

Appendix A

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).

Source: https://clinicaltrials.gov

Appendix A

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).

Source: https://clinicaltrials.gov

Appendix B

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.

Source: https://clinicaltrials.gov

Appendix C

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)

Source: https://clinicaltrials.gov

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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		

Source: https://clinicaltrials.gov

Appendix C

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

Source: https://clinicaltrials.gov

Appendix C

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		

Source: https://clinicaltrials.gov

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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.

Source: https://clinicaltrials.gov